“THE CAVEATS OF DRUG-ELUTING STENTS”

A CRITICAL APPRAISAL OF THE SAFETY CONCERNS

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“THE CAVEATS OF DRUG-ELUTING STENTS”

A CRITICAL APPRAISAL OF THE SAFETY CONCERNS

De waarschuwingen voor het gebruik van met medicijnen gecoate stent

Een kritische evaluatie van de zorgen omtrent veiligheid

Proefschrift

ter verkrijging van de graad van doctor aan de

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op gezag van de rector magnificus

Prof.dr. S.W.J. Lamberts

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Voor Lisanne

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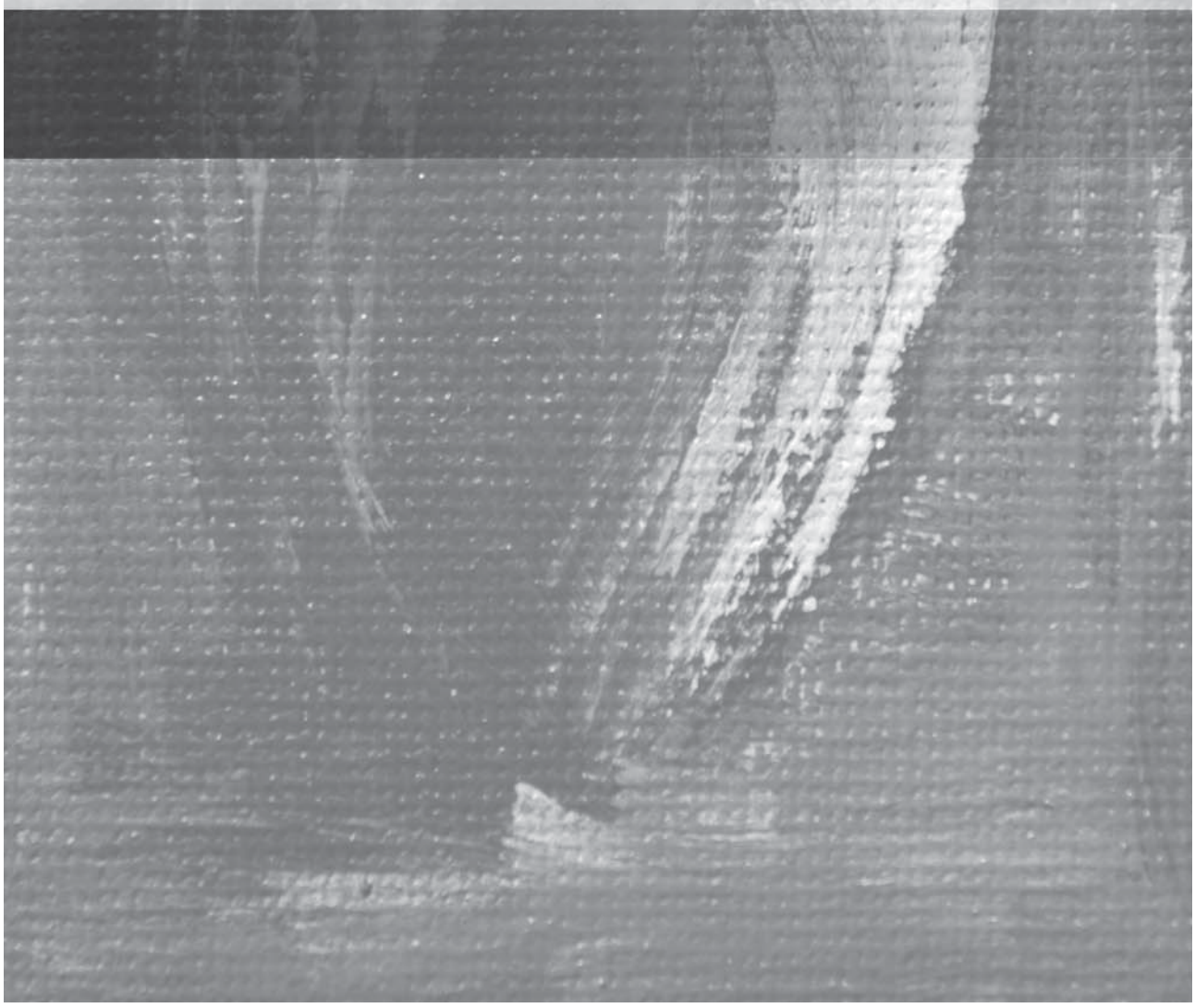
Chapter 1

General introduction and outline of the thesis



General introduction and outline of the thesis

Coronary heart disease has been the leading cause of death in developed countries for many years.[1] At the same time, the developments in the field of interventional cardiology occurred at an incredible speed and it took no more than 15 years for the first balloon-mounted stent by Palmaz et al. in 1985 to evolve into a modern first generation drug-eluting stent (DES). As early as 1999, stenting comprised 84.2% of percutaneous coronary interventions (PCI).[2] In the same year, several preclinical studies reported that sirolimus (rapamycin), a macrocyclic lactone that inhibits cytokine-mediated and growth-factor–mediated proliferation of lymphocytes and smooth-muscle cells, reduced neointimal proliferation (i.e. renarrowing of the vascular lumen at the site of stent implantation, leading to recurrence of angina - the largest limitation of stenting thus far).[3-5] In 2002, the first DES, coated with sirolimus, were introduced into clinical practice in order to reduce restenosis which occurred in 15% to 25% of patients receiving bare-metal stents.[6, 7] Subsequent trials with different types of DES confirmed their efficacy in this regard.[8] In 2002, the pivotal RAVEL trial reported that none of the patients in the sirolimus-stent group, as compared with 26.6% of those in the standard-stent group, had restenosis of 50 percent or more of the luminal diameter (P<0.001).[6]

The success of DES can be reflected by the fact that the entire interventional cardiology community quickly embraced the DES as the ultimate manner to prevent restenosis following PCI. The use of the first generation DES even increased up to 100% in some centers in Europe and the US as soon as 2003, no more than one year after their commercial introduction in 2002 and despite the lack of long-term data on safety and efficacy.

To assess the performance of DES in a "real world" setting, far beyond the scope of the pivotal randomized trials, the Thoraxcenter decided to implant these devices in all patients suitable for stent implantation, irrespective of clinical or angiographic findings. From the moment of the commercial introduction of the sirolimus-eluting (Cypher®, Cordis Corporation, a Johnson and Johnson company, Waterloo, Belgium) stent on April 16, 2002, the Thoraxcenter adopted a policy of an unrestricted sirolimus-eluting stent use until February 23, 2003, when the paclitaxel-eluting stent (TAXUS™ Express2™ or Liberté™, Boston Scientific, Natick, MA) replaced the Cypher as the device of first choice. All patients treated in this period were included in the RESEARCH and T-SEARCH registries respectively.[9, 10]

Despite the initial booming success, several caveats regarding the use of DES emerged. Late stent thrombosis, acute closure of the in-stent vascular lumen due to thrombotic material, was reported as early as 2004, typically in patients discontinuing dual antiplatelet therapy.[11] At the European and World Congress of Cardiology in Barcelona 2006, a threesome of proceedings hypothesized that the use of DES was even associated with increased rates of death and myocardial infarction as compared to bare metal stents.[12-15]

The aims of the current thesis are multiple. The primary goal was to study the long-term safety and efficacy of DES in real world clinical practice with specific attention for high-risk patient and lesion subsets, caveats and cost-effectiveness.

Part I, including chapters 1 and 2, is a preface to the current developments and problems in the DES field. Part II reports on the long-term follow-up of the RESEARCH and T-SEARCH registries. While Chapter 4 reports the 2-year follow-up of the T-SEARCH registry, the 3 and 4 follow-up of the RESEARCH registry are described in Chapters 5 and 6 respectively. In Part III and IV of this thesis, the long-term relative benefits and limitations of DES in specific patient and lesion subsets not previously described, are assessed. Chapter 7 reports on the outcome of DES in patients on dialysis, Chapter 8 specifically focuses on patients presenting with acute myocardial infarction, and Chapter 9 and 10 deal with diabetics. In Part IV, focussing on specific lesion subsets, Chapter 11 reports on the usability of sirolimus-eluting stents for comprehensive bifurcation stenting. Additionally, chapter 12, 13, 14 and 15 focus on the long-term performance of both sirolimus and paclitaxel-eluting stents in very small vessels (2.25mm), chronic total occlusions, aorto ostial lesions, and coronary artery bypass grafts respectively.

Following the specific attention to several sub-

group analysis, Part VI reports on the first caveat of drug-eluting stents, namely stent thrombosis. Part IV opens with Chapter 16, which puts the problem into perspective. Chapter 17 consists of the landmark paper of a collaborative study of the Thoraxcenter together with the University Medical Center in Bern Switserland on the long-term incidence of stent thrombosis in real world clinical practice and is followed by Chapter 18 extending the follow-up from 3 to 4 years. Finally, Chapter 19 goes into further detail on the importance of thrombus burden in patients presenting with ST-segment elevation myocardial infarction.

After having assessed the occurrence of stent thrombosis following DES implantation, Part VII reports on the long-term safety as expressed by hard clinical endpoints. Chapters 20 and 21 include patient-level based data meta-analyses of the pivotal randomized controlled Cypher and TAXUS trials respectively with 4-years of follow-up. In Chapter 22 an epidemiological analysis was performed with specific attention to long-term safety in an extended RESEARCH and T-SEARCH population, including 6.219 consecutive all-comers treated with bare-metal, sirolimus-eluting, and paclitaxel-eluting stents in a sequential fashion. Closing Part VII, Chapter 23 contains the official ESC forum report of a meeting on Drug-Eluting Stents held on September 27-28 2007, in Nice, France.

In the spirit of the continuing struggle of PCI to compete with the golden standard for treatment of multivessel coronary artery disease, coronary artery bypass graft surgery (CABG), Part VIII encloses several chapters on the relative outcome of PCI with DES for multivessel disease as compared to CABG. Chapter 24 opens Part VIII by providing a state-of-the-art overview of the pros and cons of both treatment modalities up to 2006. Chapter 25 contains a meta-analysis of the five-year follow-up to the pivotal randomized PCI-CABG trials with 5-years of follow-up. Following this pooled analysis, including exclusively PCI patients treated with bare-metal stents, Chapters 26-29 focus on the outcomes of patients treated with sirolimus-eluting stents for multivessel disease as part of the Arterial Revascularization Therapies Study (ARTS), Part II. The overall 3-year follow-up is covered by Chapter 26, whereas Chapter 27, 28 and 29 reports on the impact of body mass index, diabetes and quality of life on the long-term outcomes.

A specific topic that gathered attention in the last years was the cost-effectives of DES. Chapter 30, embedded in Part IX of this thesis, includes a cost-effectiveness analysis based on the 2-year results on the RESEARCH registry.

Finally, going beyond the scope of the conventional riskfactors, increasing attention has gone to the impact of psychological factors on the performance of patients treated with PCI. Part X includes 3 chapters reporting on the influence of Type-D-personality, fatigue, depression, hopelessness and anhedonia on the long-term outcome of patients treated with DES as part of the RESEARCH and T-SEARCH registries in Chapters 31 to 33 respectively.

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Chapter 2

Drug-eluting stent update 2007 – Part I

A survey of current and future generation drug-eluting stents: meaningful advances or more of the same?

Daemen J, Serruys PW

Circulation 2007; 116(3):316-28

Drug-Eluting Stent Update 2007

Part I: A Survey of Current and Future Generation Drug-Eluting Stents: Meaningful Advances or More of the Same?

Joost Daemen, MD; Patrick W. Serruys, MD, PhD

Analyst projections for the drug-eluting stent (DES) market estimated that the total number of DES implanted in 2010 would go beyond 4.5 million worldwide. Although the initial results seemed promising, longer-term follow-up in a broader range of patients revealed some pitfalls. Delayed neointimal growth, enhanced platelet aggregation, a local hypersensitivity reaction against the polymer coating, stent fracture, and a failure of sirolimus-, paclitaxel-, and tacrolimus-eluting stents to reduce neointimal hyperplasia at 90 and 180 days in animals, when the drug was completely eluted from the stent, are just several examples.[1–8]

The number of stents currently under investigation is substantial. They are all loaded with drugs that interfere with pathways in the process of inflammation and neointimal proliferation. However, the process of restenosis is a sequence of complex events that has been only partly elucidated over the last 2 decades.[9] Locally acting DES provide the opportunity to interfere with the various mechanisms responsible for each step in the restenotic cascade, and a wide variety of different agents are currently available. Although only sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) have received US Food and Drug Administration (FDA) approval to date, multiple alternative devices are attempting to find their way to achieve the same goal, namely a reduction of restenosis and the need for repeat interventions.

Established and Investigational Drugs

Six Limus family–related drugs are currently being studied in DES, namely sirolimus, everolimus, biolimus A9, zotarolimus, tacrolimus, and pimecrolimus. Sirolimus, everolimus, biolimus A9, and zotarolimus all bind to the FKBP12 binding protein, which subsequently binds to the mammalian target of rapamycin (mTOR) and thereby blocks the cell cycle mainly of the smooth muscle cell from the G1 to S phase. The mechanisms of action of tacrolimus and pimecrolimus are different. Both drugs bind to FKBP506. The tacrolimus/pimecrolimus FKBP506 complex subsequently inhibits the calcineurin receptor, which leads to decreased cytokine expression on the cell surface membrane and results in an inhibition of T-cell activation and lower smooth muscle cell selectivity (Figures 1 and 2).

A non-Limus family–related drug widely studied for its efficacy in coronary stents is paclitaxel. Its effect has been mainly explained by its ability to stabilize microtubules and thereby inhibit cell division in the G0/G1 and G2/M phases.

Sirolimus

The first of the Limus family drugs used on endovascular prosthesis was sirolimus, a natural macrocyclic lactone that is able to inhibit mTOR.[10,11] Sirolimus proved to possess potent antiproliferative and immunosuppressive effects. Several successive studies proved the efficacy of the SES (Cypher, Cordis Corp, Warren, NJ), a polymer-coated bare metal Bx Velocity (Cordis Corp) balloon expandable stent, in populations that ranged from highly selected patients with single lesions to unselected all-comers.[12–18] The Cypher stent was the first DES to receive both Conformité Européenne (CE)-mark and FDA approval in April 2002 and 2003, respectively (Figure 3). Because of the polymer, 75% of the drug is slowly released over the first 10 days. Nevertheless, the antirestenotic properties of the SES proved to persist much longer.[19] Because there was no significant change in neointimal thickening between 2 and 4 years in the First in Man (FIM) trial and given the continued clinical superiority of SES after 4 years in a pooled analysis of the 4 pivotal randomized Cypher trials (RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions [RAVEL], SIRolImUS-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions [SIRIUS], Canadian [C]-SIRIUS and European [E]-SIRIUS), it seems reasonable to rule out a late catch-up in restenosis; at least so far, because both the clinical and angiographic end points continue to slowly accrue over time.[14,20]

Everolimus

A second derivative of the Limus family is everolimus, a sirolimus analog with a single minimal alteration in its

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(*Circulation.* 2007;116:316-328.)

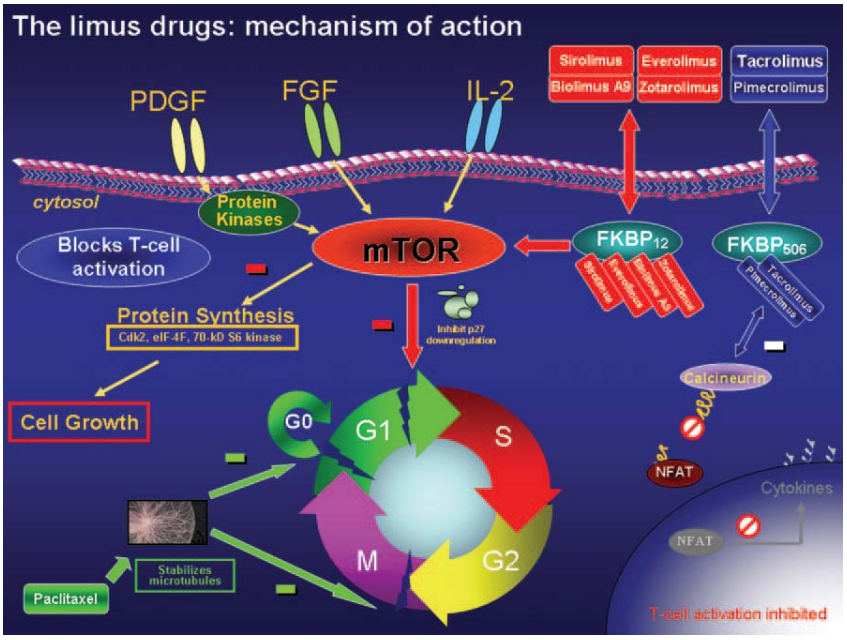

Figure 1. Mechanisms of action of sirolimus, everolimus, Biolimus A9, zotarolimus, tacrolimus, and pimecrolimus. PDGF indicates platelet-derived growth factor; FGF, fibroblast growth factor; FKBP, FK binding protein; G, growth; M, mitosis; S, synthesis; and NFAT, nuclear factor of activated T cells.

molecular structure (position 40), without a chemical modification of the mTOR binding domain[21] (Figures 1 and 2). Of interest is that, when implanted in rabbit iliac arteries, a more rapid endothelialization was observed in the everolimus-eluting stent as compared with sirolimus-, zotarolimus-, or paclitaxel-eluting stents, demonstrated by a complete endothelialization of the struts with exhibition of cd31 (antigen surface marker of good endothelial functionality) in the cells at 14 days (R. Virmani, MD, unpublished data, 2006).

The Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions First (SPIRIT) trial proved the superiority of everolimus embedded in a durable polymer on a cobalt chromium stent as compared with bare metal stents (BMS).[22,23] In the recently completed SPIRIT-II trial, the everolimus-eluting XIENCE V stent (Advanced Cardiovascular Systems, an Abbott Vascular Company, Santa Clara, Calif) proved to be superior to the PES for reduction of both late loss and binary restenosis.[24] Subsequently, the SPIRIT-III trial has randomized 1002 patients in the US to treatment with either an everolimus XIENCE V stent or a PES. As part of the SPIRIT-III study, additional patients will also be enrolled in 4 registry arms in Japan, 1 each for stents that are 38 mm, 2.25 mm, and 4.0 mm long. Additionally, the SPIRIT-IV and SPIRIT-V studies will provide further clinical data.

Zotarolimus

A third descendant of the Limus family, also with a change on position 40, that is used on coronary stents is zotarolimus (ABT-578, Abbott Pharmaceuticals, Abbott Park, Ill), which likewise contains antiproliferative and antiinflammatory effects, but zotarolimus is suggested to have higher tissue retention compared with the SES (Figures 1, 2). Of note, recent data on endothelial function after stent placement in porcine coronaries showed a normally functioning endothelium 1 and 3 months after zotarolimus-eluting stent implantation, whereas a dysfunctional endothelium was observed after both Cypher and Taxus implantation.[25]

In the ENDEAVOR I and II trials, the phosphorylcholine polymer-based cobalt-alloy Driver coronary stent (Medtronic Vascular, Santa Rosa, Calif), loaded with zotarolimus, proved to be superior to BMS in both angiographic and clinical end points.[26,27] Recently presented 2- and 3-year follow-up data of the ENDEAVOR I and II trials proved sustained superiority in the reduction of target lesion revascularization (TLR) with remarkably low rates of total stent thrombosis (0.3%) and no cases of stent thrombosis after 30 days. The ENDEAVOR III trial was a prospective randomized comparison of the Endeavor zotarolimus-eluting stent and the SES (n=436). At 8 months, the Endeavor stent failed to meet its noninferiority end point in terms of late lumen loss. Of note, the rates of death, myocardial infarction, and target vessel

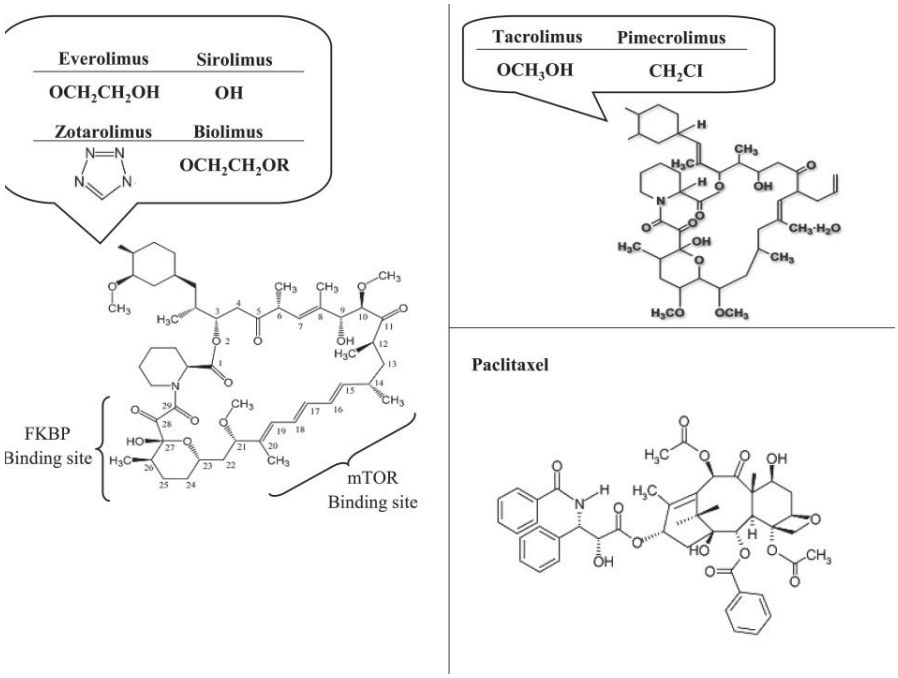

Figure 2. Molecular structure of sirolimus, everolimus, biolimus, zotarolimus, tacrolimus, and pimecrolimus.

revascularization were equal in both groups.[28] A possible explanation for the lack of noninferiority of the Endeavor stent might be the rate of elution. The Cypher stent elutes 75% of its drug within the first 10 days; in the Endeavor stent this took only 2 days.

Another zotarolimus-eluting device is the Zomaxx Tri-Maxx stent (Abbott Pharmaceuticals, Abbott Park, Ill.), which has a trilayer pharmacoat that consists of a phosphorylcholine basecoat and topcoat wrapped around a zotarolimus layer with elution rates comparable to the Cypher stent. The platform used was a stainless steel/tantalum/stainless steel triplex stent. Although the 4-month results of the Zomaxx-IVUS trial (n=40), which showed a late loss of 0.20 mm, were promising, its manufacturer Abbott recently announced it would discontinue the Zomaxx program after the disappointing results of the Zomaxx-I trial. At 9 months, the Zomaxx stent was associated with a significantly higher late loss and binary restenosis rate compared with the Taxus stent.[29]

Biolimus

Biolimus A9 is a highly lipophilic sirolimus analog that inhibits T cell and smooth muscle cell proliferation (Figures 1 and 2). The Stent Eluting A9 Biolimus Trial in Humans (STEALTH) trial was the FIM study to assess the safety and efficacy of the poly-lactic acid bioabsorbable-polymer-coated Biolimus A9–eluting BioMatrix stent (Biosensors International, Singapore). A stainless steel S-stent was the basis for a biodegradable polymer coating that released its drug gradually over 6 to 9 months. The STEALTH-I trial randomized 120 (1:2) patients to treatment with a control bare metal S-stent or a Biolimus A9–eluting stent. Although the 12-month clinical event rates were similar between both groups, treatment with the Biolimus A9 stent was associated with a 57% lower rate of binary restenosis and 65% lower rate of late lumen loss compared with the BMS group at 6 months.[30] The recently presented 9-month results of the Nobori-I trial, which randomized (2:1) patients to either a PES (n=35) or the Biolimus-eluting stent (n=85), showed significantly less late lumen loss in the Biolimus arm as compared with the Taxus arm.[31]

Pimecrolimus

Although a part of the Limus family, pimecrolimus does not block mTOR and inhibits to a much lesser degree the endothelial cell proliferation (Figures 1 and 2).[32] The active pharmaceutical ingredient of pimecrolimus is Elidel, an FDA-approved drug developed by Novartis Pharmaceuticals Corp, East Hanover, NJ) for the treatment of atopic dermatitis. The FIM study to evaluate the safety and efficacy of a pimecrolimus-eluting stent is currently ongoing.[33]

Status of current and investigational devices

Manufacturer	Name	Drug	Stent material	Polymer	Status
Cordis/J&J	Cypher Select	Sirolimus	Stainless steel	Durable	FDA/CE Mark
Boston Scientific	Taxus Liberté	Paclitaxel	Stainless steel	Durable	FDA/CE Mark
Medtronic	Endeavor	Zotarolimus	Cobalt chromium	Durable	CE Mark
Abbott	ZoMaxx	Zotarolimus	Tantalum/stainless steel	Durable	trial
Abbott	Xience V	Everolimus	Cobalt chromium	Durable	CE Mark
Biosensors	BioMatrix	Biolimus-A9	Stainless steel	Bioabsorbable	CE Filed
Conor	CoStar	Paclitaxel	Cobalt chromium	Bioabsorbable	CE Mark
Sahajanand	Supralimus	Sirolimus	Stainless steel	Bioabsorbable	CE Mark
Sahajanand	Infinnium	Paclitaxel	Stainless steel	Bioabsorbable	CE Mark
Terumo	Nobori	Biolimus-A9	Stainless steel	Bioabsorbable	trial
Sorin	Janus	Tacrolimus	Stainless steel	None	CE Mark
Orbus Neich	Genous	EPC capture	Stainless steel	Durable	CE Mark
Biotronik	?	AVT-03	Absorbable metal (Mg)	-	trial
Abbott	-	Everolimus	Biodegradable	-	trial

Figure 3. CE or FDA approval of current and investigational devices.

Tacrolimus

Tacrolimus (FK506) is a water-insoluble macrolide immunosuppressant produced by streptomyces tsukubaensis (Figures 1 and 2). Tacrolimus is also known as Prograf, a drug widely used to prevent allograft rejection after organ transplantation. Tacrolimus is a noncytotoxic T cell inhibitor, which holds cells in the G0 or resting phase. In this situation, cells are able to function but unable to replicate. The end result of tacrolimus is a reduction in activation of cytokine genes. In contrast to sirolimus, tacrolimus demonstrates far more potent inhibition of smooth muscle cells rather than endothelial cells.[4,34]

The multicenter European Direct Stenting of De Novo Coronary Artery Stenosis With Tacrolimus-Eluting Versus Carbon-Coated Carbostents (JUPITER)–II trial (n=332) was conducted to compare the safety and effectiveness of direct stenting with a Janus tacrolimus-eluting stent (Sorin Biomedica Cardio, Saluggia, Italy) versus the mechanical platform with no drug-eluting capability from which the Janus stent (Tecnic CCS coronary carbostents) was derived. In the Janus tacrolimus-eluting stent, the drug is embedded in reservoirs carved on the outer stent surface to release the drug only toward the vessel wall and possesses an integral thromboresistant carbofilm coating on the whole stent surface. Remarkable was that at 1 year no cases of stent thrombosis were reported in the polymer-free tacrolimus-eluting stent arm. However, the 6-month in-stent late lumen loss of 0.65 mm for the Janus was equal to the Tecnic carbostent; therefore the study failed to meet its primary end point.[35] The currently ongoing 3-arm Inova trial is evaluating the efficacy of a Janus Carbofilm–coated SRT stent platform with different formulations of tacrolimus: (1) pure tacrolimus (3.3 $\mu g/mm^2$); (2) tacrolimus with 20% ascorbyl palmitate (2.3 $\mu g/mm^2$); (3) tacrolimus with 20% PVP Kollidon 17 (2.3 $\mu g/mm^2$). Along these lines, the Japanese company Kaneka is evaluating the efficacy of a tacrolimus when applied on a cobalt chromium platform with a poly-DL-lactide-co-glycolide biodegradable polymer.

Paclitaxel

Although not a member of the Limus family, the PES (Taxus, Boston Scientific, Natick, Mass) was the second DES to receive FDA approval, 1 year after the SES. Paclitaxel was first found by The National Cancer Institute in a search for naturally occurring agents with strong antiproliferative qualities. Paclitaxel stabilizes microtubules and thereby inhibits cell division in the G0/G1 and G2/M phases (Figure 1). The randomized TAXUS-I trial (2003) was designed as a FIM phase I feasibility study and proved that a polymer-coated PES was superior to BMS at 6 and 12 months of follow-up.[36] Thereafter, the TAXUS family trials expanded with the II, IV, V, and VI trials and confirmed the superiority of PES as compared with BMS in more complex patients and lesions.[36–39] Recently, the TAXUS-V-ISR (in-stent restenosis) trial compared the efficacy of a slow-release polymer-based PES with brachytherapy for in-stent restenotic lesions. At 9 months, the use of PES was associated with lower rates of clinical and angiographic restenosis and an improved event-free survival.[40] The TAXUS clinical trial program, which assessed the TAXUS Express stent system from single to complex lesions, was followed by the TAXUS ATLAS and Olympia programs, which transferred the established polymer drug combination to a new stent platform, the Liberté stent.[41,42]

Another new device coated with paclitaxel is the Asian Infinnium (Sahajanand Medical Technologies, Gujarat, India) stent. The stent has a biodegradable hemocompatible polymer

coating and lower strut thickness (0.084 mm compared with 0.14 mm for Cypher) designed to reduce vessel trauma. The coating consists of slow, medium, and fast release polymer layers. The multicenter open-label registry Safety and Efficacy of Infinnium: A Paclitaxel-Eluting Stent (SIMPLE-I) trial (n=282) was the first to test the efficacy of this new device. The SIMPLE-I trial was followed by the multicenter, single-arm, prospective SIMPLE-II trial (n=103) to further investigate the safety and the efficacy of the Infinnium stent.[43] With little late loss at 6 months (0.38 mm) and a binary restenosis rate of 7.3%, the device was the first indigenously designed and evaluated "low-cost" DES from Asia to receive CE mark approval.

New Coatings

After disappointing results with the use of carbon-, platinum-, and gold-coated stents, the polymer was hypothesized to be an appealing alternative carrier to reduce restenosis and thrombosis and to guarantee controlled drug-release kinetics.[44] Soon, the first-generation polymer-coated SES and PES proved to be more effective than their non–polymer-coated counterparts.[45–48] Nevertheless, a major limitation is that many polymer coatings are not entirely inert, and hypersensitivity reactions against the polymer have been frequently reported.[1,3,49] In line with this data, long-term adverse effects such as increased inflammation of the vessel wall, a thrombogenic response, and induced apoptosis of smooth muscle cells have been described.[50,51]

To reduce the inflammatory reaction, which is partially caused by the polymer, Medtronic recently developed a novel co-polymer, the "Endeavor Resolute", for extended release of zotarolimus in a next-generation DES. The new BioLinx polymer system contains a C10 polymer, which is lipophilic/hydrophobic and stimulates a controlled drug release, a C19 polymer, which is primarily hydrophilic and thus more biocompatible and helpful in drug elution, and finally polyvinyl pyrrolidone, which is hydrophilic, increases the initial drug burst, and enhances the elution rate. Porcine coronary implants (n=25) showed no difference in inflammatory response after implantation of the Endeavor Resolute or a control BMS and a 100% re-endothelialization. Four-month follow-up in the first 30 patients revealed an in-stent late loss of 0.12 mm, and no target vessel revascularization or stent thrombosis were observed.[52]

In a search for more biocompatible coatings, hydroxyapatite was found to be a valuable alternative as a polymer surrogate. Hydroxyapatite is a well-known and excellent bioceramic that closely resembles biological apatite (bone); it is biocompatible, bioactive, and bioresorbable, and it forms the basis of a polymer that is only 200 nm thick.[53] Furthermore, its porous structure makes it an ideal drug carrier. Likewise, a new spongious nanocarbon coating constructed of porous, glassy, pyrolytic carbon, which guarantees extraordinary elasticity, was recently developed. Lastly, the Intracoronary Stenting and Angiographic Restenosis–Test Equivalence Between 2 Drug-Eluting Stents (ISAR-TEST) study recently showed that a polymer-free, microporous, sirolimus-coated Yukon stent (Translumina, The Drug-Eluting System Company, Hechinger, Germany) was not inferior to a polymer-based PES in the reduction of restenosis.[54]

Another alternative for the polymer is a heparin coating. Heparin-coated stents proved to be superior to both balloon angioplasty and BMS. In 1996, the Belgium Netherlands Stent II (BENESTENT II) randomized trial proved the superiority of heparin-coated stents as compared with balloon angioplasty. A more recent registry even proved a significant reduction in stent thrombosis in the heparin-coated stent as compared with a standard BMS.[55] Sahajanand Medical Technologies Pvt. Ltd. (Saiyedpura, Surat, India), recently designed a dual-layer heparin-SES, which combines the antiproliferative action of sirolimus with the excellent biocompatibility and hemocompatibility of the heparin coating. Both drugs elute almost simultaneously, whereas heparin will give effect for almost 50 days and sirolimus for 60 days.

A completely new concept is heparin-coupled with poly-L-lactic acid to create a so-called absorbable "heparinized" polymer, which in turn can serve as a drug reservoir.

Indeed, the most commonly studied biodegradable polymers are derived from lactic and glycolic acid. Biodegradation is achieved by hydrolytically unstable linkages (esters) in the backbone of the polymer, which results in surface erosion. The rate of erosion or biodegradation can be altered by the molecular weight of the polymer and the number of unstable linkages. Furthermore, the drug-release profile can be adjusted by alteration of the biodegradation profile of the polymer.

New Platforms

Several limitations and side effects have been associated with coronary stenting. First, stents cause permanent physical irritation with the risk of long-term endothelial dysfunction or inflammation.[9] Second, stents possess a high thrombogenicity.[56] Third, stents create an inability for the vessel to remodel and act in a normal physiological way.[4] Finally, stents create difficulties for possible future bypass surgery and noninvasive imaging. The first bioabsorbable stents were made of poly-L-lactic acid and recently studied in porcine models.[57] The first successful in-human experience with a poly-L-lactic acid stent was described by Tamai et al in 2000.[58] The study included 15 patients treated with a monopolymer poly-L-lactic acid Igaki-Tamai stent (Igaki Medical Planning Co, Ltd, Kyoto, Japan) with a zigzag helical coil pattern. The stent expanded by itself at a temperature of 37°C. Angiographic restenosis rate and TLR was 10.5%, which thereby proved that its use was feasible, safe, and effective in humans.

The 30-day results of the FIM ABSORB trial (n=30) are worth mentioning. The BVS stent (Figure 4) (Bioabsorbable Vascular Solutions, Guidant Corp, Indianapolis, Ind), the world's first fully absorbable DES, which consists of a bioabsorbable polylactic acid polymer that contains everolimus (98 $\mu g/cm^2$ of surface area) and a bioabsorbable BVS polylactic acid stent platform, proved to be associated with a 100% procedural success rate and a major adverse cardiac event rate of 0%. Furthermore, the stent recoil of 6.85% was comparable to the 4.27% seen with the XIENCE V metal stent.[59–61]

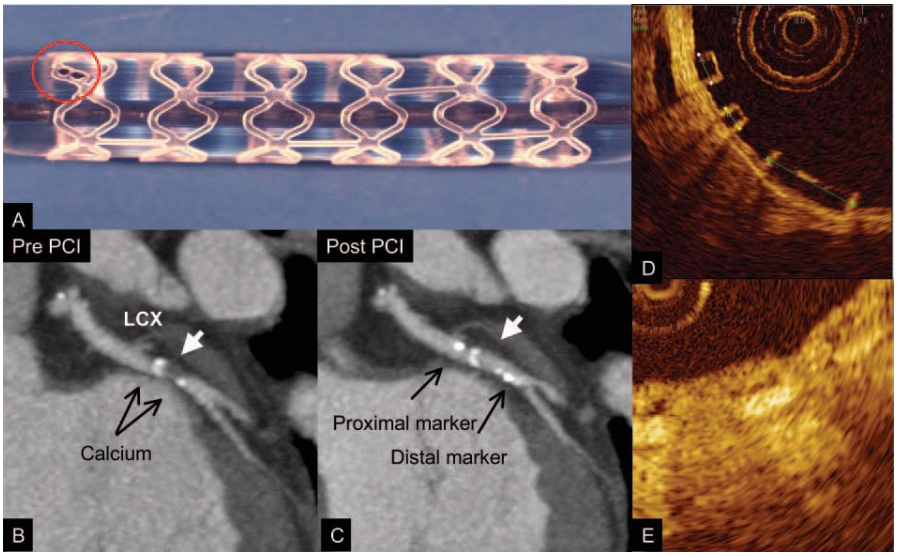

Figure 4. The BVS fully absorbable DES. A, Bioabsorbable BVS polymer and platform. Note the radiopaque marker at the top left. B, 64-slice MSCT scan shows a significant stenosis in the LCX with 3 calcium spots. C, MSCT posttreatment with a BVS stent. Note that only the markers are visible. D and E, OCT images show the BVS stent struts immediately after implantation (D) and covered with a new endothelial layer at 6 months follow-up (E). BVS indicates Bioabsorbable Vascular Solutions; MSCT, multislice coronary tomography; and OCT, optical coherence tomography.

REVA Medical, Inc. (San Diego, Calif) is presently investigating a fully absorbable polymer stent with a "slide & lock" design; sliding parts with monodirectional lockouts that are hypothesized to result in a nearly negligible stent recoil (Figure 5). The stent consists of a radiopaque tyrosine-derived polycarbonate backbone. The composition of the polymer, comprised of 3 basic components, allows the resorption time to be varied by a change in the ratio of these components. Both a bare and a paclitaxel-eluting version, in which the polymer is mixed with the drug, will become available. The Randomized Endovascular Study of the REVA Bioresorbable Stent (RESORB) clinical trial has been recently designed to assess the safety of this new platform.

Another alternative for the metallic backbone of the stent was found in magnesium. Magnesium, with antithrombotic, antiarrhythmic, and antiproliferative properties, is one of the first natural body components to be used as a basis for a bioabsorbable stent. Several experimental studies to evaluate the efficacy of a magnesium alloy stent degradable by biocorrosion have been performed. Heublein et al described the use of a coronary stent prototype that consisted of the noncommercial magnesium-based alloy AE21 (contains 2% aluminum and 1% rare earth metals) with an expected 50% loss of mass within 6 months in 11 domestic pigs (Figure 6). Quantitative angiography at follow-up showed a significant 40% loss of perfused lumen between 10 and 35 days caused by the loss of mechanical integrity of the stent.[62] One year later, the use of a bioabsorbable magnesium alloy–based stent with a controlled corrosion in 20 patients with critical limb ischemia was described. At 9 months, a 90% vessel patency was observed.[63] As a result of the successful FIM trial (n=5) by Erbel and colleagues, the enrollment in the larger worldwide PROGRESS-AMS study has been recently completed.[64] The 4-month results showed a late loss of 1.08± −0.49 and an ischemia-driven TLR rate of 23.8%, which was comparable to those reported with the use of BMS.

New Concepts

An appealing new concept is the dual DES. In line with the previously mentioned dual-layer heparin-SES, Abbott's Zodiac program incorporates a trilayer stent that embeds both zotarolimus and dexamethasone. Dexamethasone is a potent antiinflammatory agent that is used for a variety of inflammatory and immune diseases. Glucocorticoids suppress the production and effects of humoral factors involved in the inflammatory response, inhibit leukocyte migration to sites of inflammation, and have a rather low effect on endothelial (≈35%) and smooth muscle cell (≈60%) proliferation.[65–68] Although the Study of Antirestenosis With the BiodivYsio Dexamethasone-Eluting Stent (STRIDE) trial, the FIM pilot trial that evaluated the safety and efficacy of a dexamethasone-eluting stent (BiodivYsio Matrix LO stent, Biocompatibles, Ltd., Farnham, UK) demonstrated an acceptable binary restenosis rate of 13.3%,[69] the preliminary 6-month results of the larger-scale Drug-Eluting Stents for In-Stent Restenosis (DESIRE) trial showed a clinically driven target

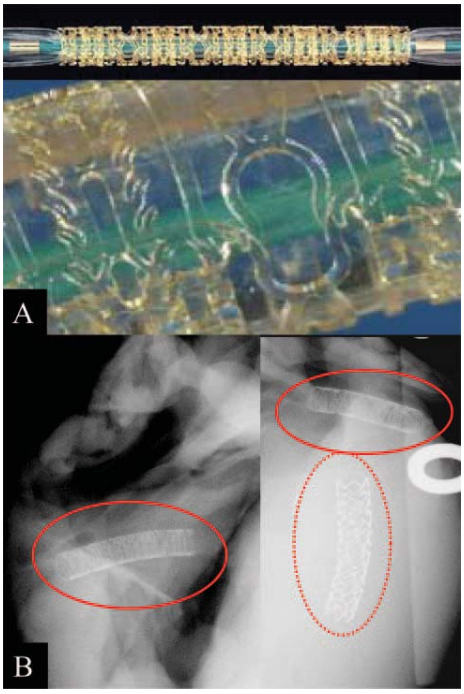

Figure 5. A, REVA's "slide & lock" design. Sliding parts with monodirectional lockouts result in nearly negligible stent recoil. B, Excellent radiopacity of the tyrosine-derived polycarbonate backbone. Two REVA stents (left side and top right side) and one metal control stent (bottom right side).

vessel recascularization rate of 9.5%, which was ≈50% higher than the target vessel recascularization rates in the TAXUS-IV and SIRIUS trials.[70] The final results were never published, and it is to be expected whether the simultaneous inhibition of smooth muscle cell proliferation and endothelial inflammation by zotarolimus and dexamethasone in the Zodiac program will turn out to be successful.

Promising results are also expected from the Randomized, Multicenter Study of the Pimecrolimus-Eluting (Corio) and Pimecrolimus/Paclitaxel–Eluting Coronary Stent System (SymBio) in Patients With De Novo Lesions of the Native Coronary Arteries (GENESIS) trial, which will compare a dual paclitaxel/pimecrolimus-eluting stent with a stent that elutes only pimecrolimus. Additionally, a dual sirolimus/genistein-eluting stent is currently under investigation (Figure 7). Genistein is a potential isoflavone, which possesses dose-dependent antiplatelet and antiproliferative properties and inhibits collagen-induced platelet aggregation responsible for primary thrombosis. The stent consists of 5 layers that contain an alternating blend of sirolimus and genistein and a drug-free top layer. The unique biodegradable heparinized polymer blend includes poly-L-lactide, poly-DL-lactide-co-glycolide and polyvinyl pyrrolidone. A complex elution pattern aims to provide both smooth muscle cell proliferation by sirolimus and short- and long-term thrombus formation by genistein.

The Prohealing Approach

Endothelial progenitor cells have been identified as a key factor in the reendothelialization process after stent implantation.[71] To accelerate the process of endothelialization and thereby reduce the risk of thrombosis and restenosis, the Genous Bioengineered R stent (OrbusNeich, Fort Lauderdale, Fla) was developed. The Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth (HEALING)-FIM (n=16) was the first clinical study to evaluate the use of an endothelial progenitor cell (EPC)-captured stent, which was developed with immobilized antibodies targeted at EPC surface antigens. Six-month angiographic outcomes showed a binary restenosis rate of 13.3% with an associated late loss of 0.63±0.52. Nine-month outcomes showed that its use was safe and feasible (major adverse cardiac event and cerebrovascular events rate was 6.3%).[72] The HEALING-II study (n=63) extended these results in a nonrandomized multicenter trial. The initial results reported a zero incidence of major adverse cardiac events at 30 days and 6-month in-stent restenosis rates of 17.2% with an associated in-stent late luminal loss 0.78±0.39. Of interest is the late loss at 18 months, which decreased to 0.59±0.06 mm.[73] Of note, 2 things have to be mentioned. First, the patient's total number of circulating EPCs were shown to be of critical importance for the efficacy of the EPC-captured stent. This can be illustrated by the results of the HEALING-I; late loss in patients found to have low levels of circulating EPCs was more than double that of patients with normal circulating EPC levels. Second, the total number of circulation EPCs can be increased by an optimal usage of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins).[74]

Following the dual-elution trend, recent developments have been made on an EPC-DES combination. A concept of a stent with a biodegradable, abluminally focused drug on a Genous-coated platform with an additional drug component integrated throughout the polymer backbone. The stent should be able to enhance drug delivery at the abluminal site, to inhibit neointimal proliferation, and to simultaneously possess CD34 endothelial cell capture activity at the endoluminal site to enhance reendothelialization.

New Techniques of Elution

The Conor Medstent (Conor Medsystems, Inc., Menlo Park, Calif) was the first stent specifically designed for drug-delivery, and it guaranteed an expanded drug capacity and controllable release kinetics. The stent was equipped with hundreds of laser-cut holes, and the drug could be deposited in multilayered degradable polymer inlays.

The Paclitaxel in Stent Controlled Eluting Study (PISCES) study was the FIM study to evaluate the safety and potential efficacy of a 316L stainless steel Conor stent system with an erodable polymer with complete elution of low doses of paclitaxel. The study included 6 groups distinguished by different paclitaxel-doses with fast or slow and unidirectional

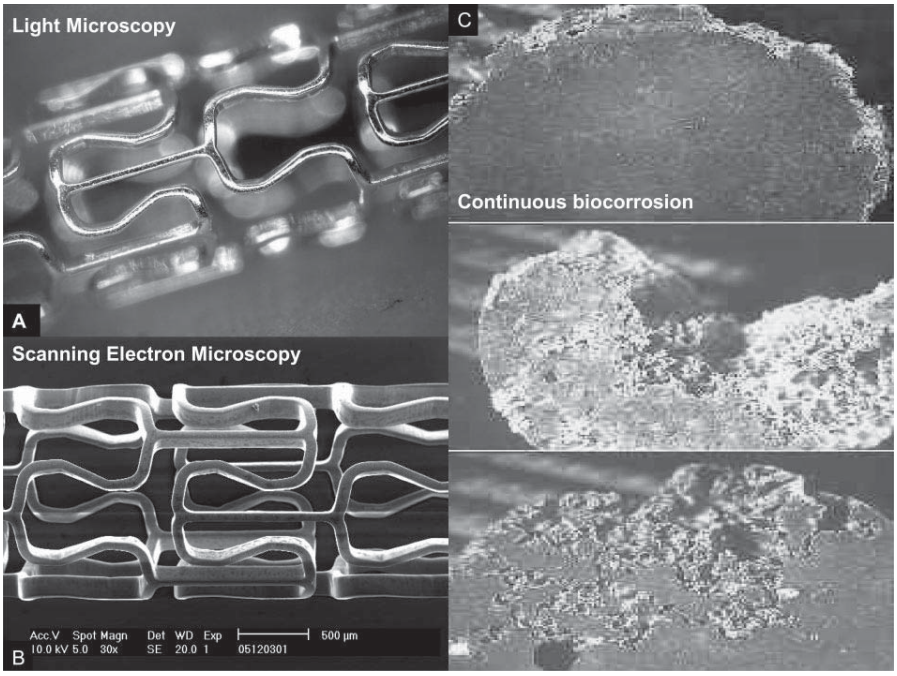

Figure 6. Light microscopy (A) and scanning electron microscopy (B) images of the magnesium-based alloy AE21 stent.

or bidirectional release kinetics. At 30 days, the lowest in-stent late loss (0.38 mm and 0.30 mm) and volume obstruction (8% and 5%) were observed in the 10-μg and 30-μg doses groups, respectively, both with unidirectional release.[75,76] The PISCES study was followed by the Study of Controlled Elution of Paclitaxel for the Elimination of Restenosis (SCEPTER) trial, a safety and effectiveness study intended to justify market clearance in the European Community and incorporate 2 arms of 130 patients.[77]

The Conor Cobalt Chromium Stent With Antiproliferative for Restenosis (COSTAR)-I trial evaluated the use of an equally effective, more flexible, and more deliverable cobalt chromium COSTAR paclitaxel-eluting coronary stent system. The stent uses a poly-lactic-co-glycolic acid bioabsorbable polymer, limited to the small wells embedded in the stent where the drug is loaded, which thereby leaves the actual stent surface free of polymer.[78] The small-scale dose-finding COSTAR-I trial (n=87) was directly followed by the European Cobalt Chromium Stent With Antiproliferative for Restenosis (EuroSTAR) trial and the COSTAR-II trial. The EUROSTAR trial showed that the Costar stent system was highly deliverable and radiopaque, and it permitted high rates of acute success and direct stenting. One-year clinical follow-up data showed a 2.8% and 3.4% incidence of TLR in the 10-μg and 30-μg groups, respectively, associated with an in-stent late loss of 0.25 mm and 0.36 mm.[79] On the basis of these results, the cobalt chromium COSTAR paclitaxel-eluting coronary stent recently received CE mark approval.

Furthermore, the deliverability of the stent has proven to be of great importance. With the growing complexity of the lesions treated percutaneously, there exists a need for devices with better deliverability and higher flexibility. For that reason, both the Taxus Liberté (Boston Scientific) and Cypher Select (Cordis) were developed.

To improve the efficacy of stenting of specific lesions like bifurcations, the multicenter Axxess Plus Biolimus Stent in LMCA Bifurcations Trial (AXXENT) registry (n=33), was conducted to evaluate the safety and efficacy of the DEVAX–AXXESS bifurcation stent (Devax, Inc., Irvine, Calif) for use in the left main coronary artery. Procedural success rates have been shown to be high, and with a 30-day major adverse cardiac event rate of 6.1%, the early results looked encouraging.[80] Recently the DIVERGE trial has been conducted to further assess the efficacy of this specific bifurcation device. Comparable dedicated bifurcation devices are the Multilink Frontier (Abbott),[81] which was designed to preserve side-branch access; the Invatec system (Invatec srl, Roncadelle, Italy) with axial and rotational self-positioning properties; the Nile CroCo (Minvasys, Gennevilliers, France), which allows instant poststent "kissing balloon" dilatation; the Petal (Boston Scientific) with a side aperture and deployable struts; the Sideguard (Cappella, Inc, Auburndale, Mass), a Nitinol self-

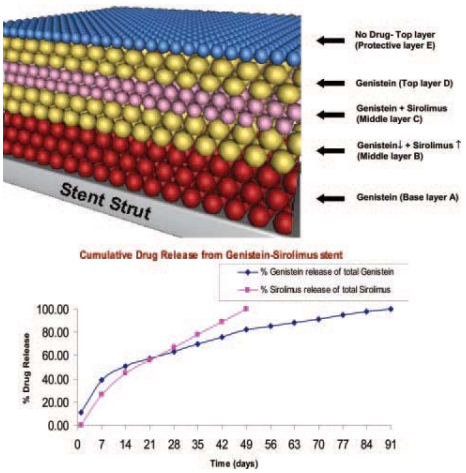

Figure 7. Design of the genistein-sirolimus dual-eluting stent. Total drug dose: 2.51 mg/mm^2 (112 mg genistein and 76 mg sirolimus content on 16-mm stent). Unique biodegradable heparinized polymers blend includes poly-L-lactide, 50/50 poly-DL-lactide-co-glycolide, and polyvinyl pyrrolidone. Elution profile: Initial high dose of genistein for 2 days to prevent platelet aggregation. (Top layer D). Concurrent release of genistein and sirolimus from layer C between 3 to 9 days will target primary thrombus formation and intimal cell proliferation. Slow release of genistein and sirolimus (Layer B) between 10 to 49 days to prevent mainly cell proliferation. Finally, slow release of genistein (Layer A) from 50 to 89 days will prevent late thrombosis up to 3 months.

expanding device on a single-catheter delivery system; and the Tryton stent (Tryton Medical, Inc, Newton, Mass).

A promising new concept is the Xtent modular system for long lesions, multiple lesions, and multivessel disease (Figure 8). The Biolimus A9 polylactic acid bioabsorbable polymer-coated stent (Biosensors International) has a modular design and consists of multiple 6-mm cobalt chromium stent segments that are interdigitated, which allows for in situ customization of stent length. The delivery system consists of a balloon that can be shortened and reused during the procedure, which may eliminate the need to use a separate postdeployment balloon and may result in significant device cost savings, reduced catheter exchanges, and shorter procedure times. The device is currently under investigation in the CUSTOM-II trial, which aims to extend the promising results of the CUSTOM-I registry.

Finally, an ultralow-profile, self-expandable, thin strut stent mounted on a guide wire (CardioMind, Sunnyvale, Calif) is in development for specific use in small vessels.

Current Clinical Results

Although many of the investigated devices have been shown to be effective in the reduction of restenosis and the need for repeat revascularization, drug-coated devices like those coated with batistimat, actinomycin, or tacrolimus, or taxol-dipped stents failed to show superiority compared with BMS.[48,82–84] The relative efficacy of the more successful DES cannot be easily assessed because they are most often compared with BMS. Randomized trials such as the Prospective, Randomized, Multi-Center Comparison of the Cypher Sirolimus-Eluting and the Taxus Paclitaxel-Eluting Stent Systems (REALITY), Paclitaxel and Sirolimus Stents in the Real World of Interventional Cardiology (TAXI) study, Drug-Eluting Stent for Complex Lesions: Cordoba–Las Palmas Study (CORPAL), Sirolimus-Eluting Stent Compared with Paclitaxel-Eluting Stent for Coronary Revascularization (SIRTAX) study, Intracoronary Stenting and Angiographic Results—Drug-Eluting Stents for In-Stent Restenosis (ISAR-DESIRE) trial, and the ISAR-Diabetes trial directly compared SES and PES in a wide variety of patient and lesion types.[85–90] The Basel Stent Kosten Effektivitäts Trial (BASKET) assessed the cost-effectiveness of SES and PES combined versus BMS.[91] Both the SIRTAX and ISAR-DESIRE showed TLR rates that favored SES.[88,89] However, the TAXI, REAL-

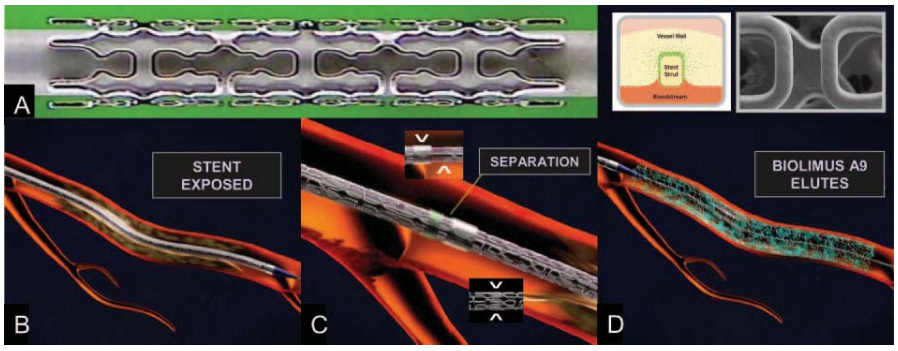

Figure 8. The Xtent modular system for long lesions, multiple lesions, and multivessel disease. A, 6-mm CoCr segment; 1 device contains 6 to 10 segments (diameters: 2.5, 3.0, and 3.5 mm). B, The delivery system consists of a balloon that can be shortened and reused during the procedure. C, A modular design that consists of multiple 6-mm CoCr stent segments customized to fit the lesion length. D, Biolimus A9 elutes from a polylactic acid bioabsorbable polymer.

ITY, ISAR-DIABETES, and CORPAL studies did not show a significant difference between both devices.[85–87,90] Of note, because of a lack of angiographic follow-up, a large reference vessel diameter, and only 50% of randomized patients, the results of the TAXI trial should be interpreted with care. Two recent meta-analyses showed that the use of SES was associated with lower angiographic restenosis rates and a lower incidence of target vessel recascularization as compared with PES.[92,93] Of note, no significant differences were found in the incidence of death or myocardial infarction between both groups. Among the PES registries, the TAXUS Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registry is worth mention because it was one of the first studies to reflect real-world clinical practice. The recently published 2-year results did not show a significant difference between PES and SES in any of the clinical end points.[94] The much larger Strategic Transcatheter Evaluation of New Therapies (STENT) registry also did not show a significant difference between both devices at 6 months in 6659 patients.[95]

Currently, a variety of trials that compare the Taxus and CYPHER stents to several newcomers are in progress. In the Prospective, Multicenter, Randomized Trial of Zotarolimus- and Paclitaxel-Eluting Stents in Patients With Coronary Artery Disease (ZOMAXX-I) (n=396), which compared the zotarolimus-eluting Zomaxx stent to a PES, the Zomaxx stent was shown to be associated with a significantly higher late loss at 9 months and thereby failed to meet its primary end point.[29] The CObalt chromium STent with Anti-proliferative for Restenosis (COSTAR)-II trial, which used the CONOR platform, is an ongoing, prospective, randomized controlled trial that will include ≈2000 patients at 85 international sites that compare the use of the COSTAR stent to a TAXUS stent.[78,96,97] Medtronic's Patient-Related OuTcomes with Endeavor versus Cypher stenting Trial (PROTECT) is currently enrolling 8000 patients to compare the safety and efficacy of the Endeavor zotarolimus-eluting stent to the Cypher stent, with stent thrombosis as one of its primary end points at 3 years.

Also currently ongoing are 2 prospective, randomized, multicenter trials that compare the Biolimus A9–eluting Biomatrix (Biolimus-eluting stent) with a Cypher SES (Limus Eluted From a Durable versus Erodable Stent Coating (LEADERS) trial; n=1700) and to a Taxus PES (Nobori-I study; n=360). The recently presented 9-month results of the Nobori-I showed significantly less late lumen loss in the Biolimus arm as compared with the Taxus arm.[31] Finally, the large-scale SPIRIT III, which was designed for further evaluation of the efficacy of the XIENCE V everolimus-eluting stent, has finished enrollment of its randomized arm.

Conclusions

As with any new device in medicine, the applauded 2 pioneer DES Cypher and TAXUS were shown to possess some side effects as well, some of which only arose very recently.

Currently, various innovative DES types are emerging and will become available in the coming years with the intention to avoid the current pitfalls. Abolition of neointimal hyperplasia is no longer the ultimate goal and has been replaced by the development of more biocompatible and bioabsorbable stents that facilitate adequate endothelialization.

Recently, the FDA acknowledged a cause of concern for late adverse events after stent implantation and called for long-term monitoring of safety outcome. It is hoped that the testing of possible remedies to the current deficiencies of the first-generation DES will not be paradoxically hindered by more stringent regulatory measures as a penalty for the late recognition of their inherent limitations.

Disclosures

None.

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KEY WORDS: angioplasty ■ atherosclerosis ■ catheterization ■ coronary disease ■ restenosis ■ stenosis ■ stents

Chapter 3

Drug-eluting stent update 2007 – Part II
"Unsettled issues"

Daemen J, Serruys PW

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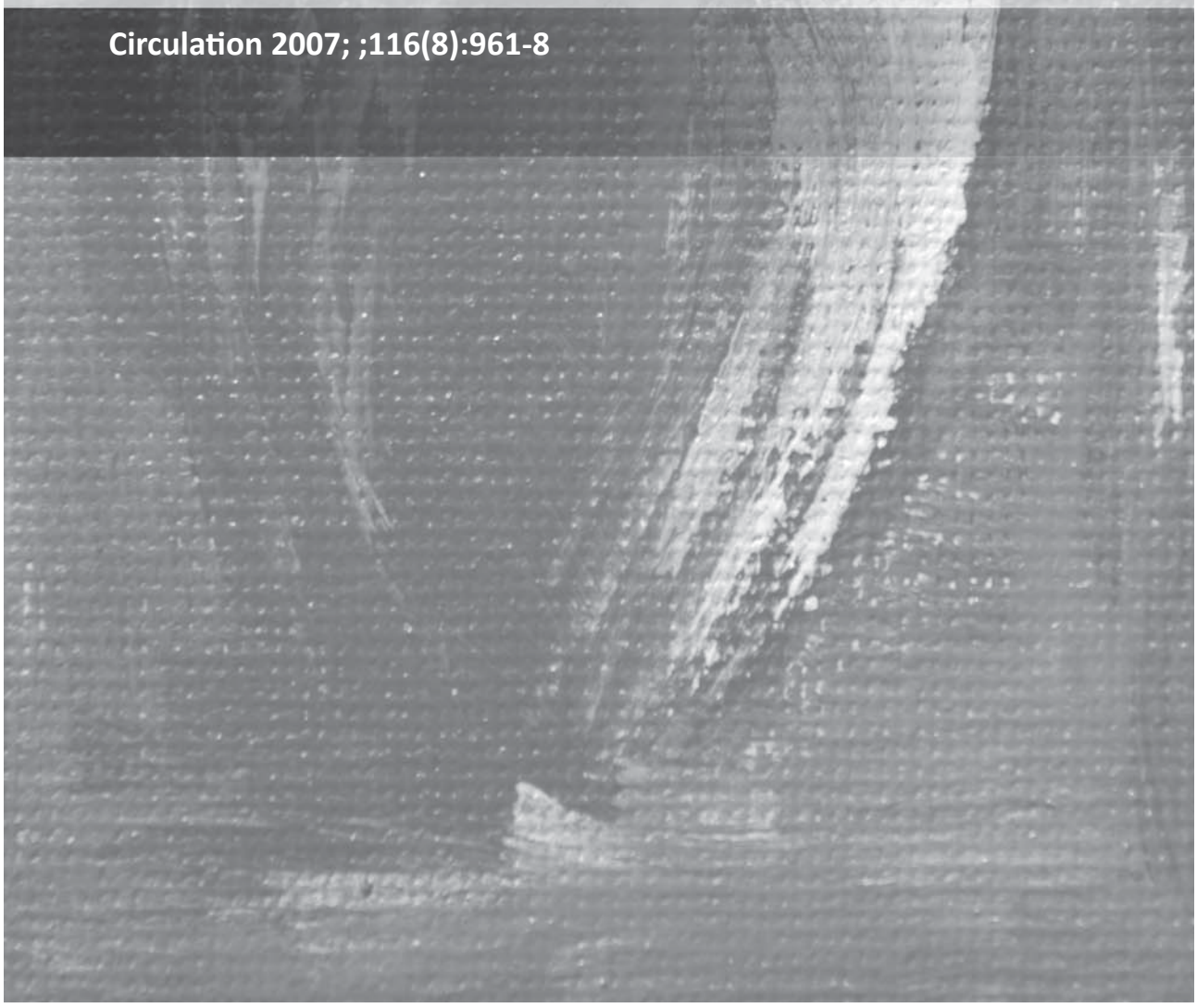

Drug-Eluting Stent Update 2007
Part II: Unsettled Issues

Joost Daemen, MD; Patrick W. Serruys, MD, PhD

Restenosis has been called the Achilles heel of coronary stenting and is caused by a combination of factors, including neointimal proliferation, elastic recoil, reorganization of thrombus, remodeling, and inflammation.[1] Long-term follow-up (>6 years) in patients with bare metal stents (BMS) shows that tissue proliferation reaches its peak at around 6 to 12 months and then regresses.[2] This pattern fits with the observed increase in revascularization rates up to 1 year, after which a plateau occurs. After drug-eluting stent (DES) implantation, Carter et al[3] showed a late catch-up of restenosis in sirolimus-eluting stents (SES) in porcine models. Although a 50% reduction of restenosis was observed at 30 days, restenosis rates for SES and BMS were equivalent at 6 months.[3] A similar catch-up phenomenon was observed after implantation of paclitaxel-eluting stents (PES) and tacrolimus-eluting stents in porcine models.[4,5] Conversely, in humans, there does not seem to be reason for concern about late catch-up for up to 4 years on both clinical and angiographic end points.[6–10] However, several long-term DES studies showed that, in contrast to BMS, the neointima continued to grow up to 2 years as assessed by intravascular ultrasound.[11] The discrepancy between porcine and clinical data is influenced by the temporal differences in arterial response in humans compared with animal models but also may be due to differences in species response to sirolimus and paclitaxel and physiological stimuli for neointimal formation.

Trading Restenosis for Thrombosis and Late Mortality?

The Problem of Restenosis

Restenosis has always been considered a benign and harmless entity. However, recent studies assessing the clinical presentation and long-term outcome of patients presenting with in-stent restenosis demonstrated worrying findings, leading some critics to ask whether restenosis had simply been traded for long-term issues like thrombosis and mortality.[12] At least 10% of all cases of BMS in-stent restenosis presented with a myocardial infarction (MI); 0.7% died.[13,14] Furthermore, long-term survival rates proved to be significantly lower in patients with binary restenosis.[15,16]

The Pros and Cons of DES Implantation

Since the clinical introduction of the first DES, the sirolimus-eluting Cypher (r) stent, in April 2002 in Europe, SES, PES, and many other new investigational agents like everolimus-, zotarolimus-, and tacrolimus-eluting stents have been tested extensively for their main purpose, namely their ability to reduce restenosis. Recent pooled data from the pivotal Cypher and TAXUS trials, evaluating the efficacy of both the SES and PES, proved that both DES are associated with a significantly lower rate of angiographic and clinical restenosis compared with BMS for up to 4 years in selected patients.[17]

Besides their superiority to BMS in reducing restenosis, DES also have been associated with several unintended consequences. First, DES proved to hamper the natural vascular healing process. A study of 48 matched DES-BMS postmortems (>30 days after stent implantation) revealed the following. First, re-endothelialization was observed in only 56% of the DES cases compared with 90% of the BMS cases, illustrated by significantly higher persistent fibrin depositions that reflect delayed healing caused by ongoing inflammation in the DES-treated lesions; and at least 61% of the DES cases showed signs of late stent thrombosis (ST) compared with only 8% of the BMS cases.[18] Although these results may not accurately represent the fate of patients who receive DES and survive, they do show that the natural healing process after DES implantation is not as optimal as originally hypothesized. Second, stent underexpansion (minimum stent area <5.0 mm^2), a factor linked to restenosis, proved to be significantly more frequent after DES implantation. Whereas stent underexpansion is observed in 20% of all restenotic BMS lesions, an incidence of 67% is reported in restenotic DES lesions.[19,20] These data were confirmed by a recent intravascular ultrasound study concluding that the angiographic restenosis rate was highest in lesions with stent area <5.5 mm^2 and stent length >40 mm.[21] In the BMS era, the theory of "the bigger, the better" was widely advertised and became an obsessive motto for the interventional cardiologist. Although a large final minimum lumen area was shown to be associated with lower repeated revascularization rates, the superior antirestenotic properties of DES groundlessly made optimal stent deployment less important. Nevertheless, this could be an explanation for the substantially higher rate of stent underexpansion in in-stent restenotic DES lesions.[22] Third, DES implantation was associated with a significant impairment in endothelial function, which in turn has been

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associated with a higher rate of late adverse cardiac events.[23–25] Fourth, 2 recent reports showed a significantly lower rate of neointimal coverage with DES (13.3% to 66%) than with BMS (90% to 100%), and subclinical thrombi tended to more common with DES ($P=0.09$).[18,26,27] It is exactly these issues that are hypothesized to cause higher rates of (late) ST in patients treated with DES.

Stent Thrombosis

ST has emerged as an important safety concern after stent implantation, although the rates have decreased from ≈20% after Wall stent implantation in the early 1990s to 0.2% to 1.8% after the implantation of current-generation BMS and DES.[28–36]

In an attempt to identify predictors of ST, several studies identified >15 patient- and procedure-related factors associated with early ST. Whereas in the early days the early pattern was hypothesized to be related mainly to technical aspects of stent implantation such as underexpansion and dissections, 2 recent large-scale registries showed that patient-related factors such as age, hypertension, smoking, renal failure, acute coronary syndrome at presentation, left ventricular function, and female gender also were independently associated with early ST.[37,38] Unfortunately, the lack of consistent data and the overall low number of events make it difficult to interpret these predictors. Conversely, the late form has been related to delayed endothelialization and a hypersensitivity reaction to the drug or polymer.[39–41] The most common predictors of late ST proved to be acute coronary syndrome at presentation, diabetes, and stent implantation of the left anterior descending coronary artery.[37,38] A worldwide controversy is currently ongoing as to whether (late) ST indeed occurs more frequently after DES implantation. Two meta-analyses showed early ST rates between 0.51% and 0.9% for patients treated with BMS.[29,42] Ong et al[43] published a series of 2512 unselected patients who underwent stenting. Early ST proved to be equal in patients treated with BMS, SES, and PES and occurred in 1% to 1.5% of all patients, depending on the definition. The concerns for late ST (>30 days) after DES implantation originate from a report of a patient in the European SIRolImUS-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions (E-SIRIUS) study, who developed late ST 18 months after SES implantation.[40] Because of the presence of polymer fragments surrounded by giant cells and eosinophils, the authors concluded that this might have been the cause of the thrombotic event rather than the drug itself, which is no longer present in the vessel wall after 60 days. Additionally, McFadden et al[44] reported 4 cases of late ST when antiplatelet therapy was interrupted after elective implantation of either an SES (n=2) or a PES (n=2).

For on-label use, pooled analyses of the randomized Cypher and TAXUS family trials demonstrated identical ST rates of ≈3.5% (using the new Academic Research Consortium definitions[45] that take not only angiographically proven ST but also MI in the target region and sudden unexplained death into consideration) in both selected BMS and DES patients up to 4 years.[46] However, a trend seems to arise toward a higher rate of late ST (between 30 and 365 days) in patients treated with BMS that is partially related to target lesion revascularization, reaching its peak at ≈6 months, which is compensated for by a higher rate of very late (>1 year) ST in the DES patients not related to repeated interventions. An additional interesting finding from the meta-analyses of the Cypher and TAXUS trials was the association between intervening target lesion revascularization and ST.[46] In the Cypher trials, 6 of 15 cases (40%) of definite or probable ST in the BMS group occurred after repeated target lesion intervention. Conversely, in the SES group, 13 of 13 (100%) of the ST was primary, without intervening target lesion revascularization. In the randomized TAXUS trials, a similar pattern was observed; 5 of 18 cases (28%) of definite or probable ST occurred after intervening target lesion revascularization in the BMS group compared with 21 of 22 cases (95%) of primary ST in the PES group. Remarkably, in pooled patient-level data of the ENDEAVOR-I, II, and III trials, although limited to 2 to 3 years of follow-up, the occurrence of very late ST was 3 times lower after zotarolimus-eluting stent implantation than after BMS implantation, and ST after repeated intervention occurred in only 1 patient in both the DES and BMS groups.[47]

Recently presented long-term follow-up data of 8146 patients treated with DES in 2 academic institutions showed that ST, observed in 152 patients, occurred at a median of 9 days and accrued at a steady rate of 0.6% per year between 30 days and 3 years of follow-up.[38] It is uncertain whether these rates exceed those of unselected patients treated with BMS after many years of follow-up. To settle this issue, extremely large-scale randomized observations comparing DES and BMS in all patients are needed. Unfortunately, the likelihood that in the present era these trials will actually be performed is low, and even if they were started, it would take at least another 3 to 4 years for valid conclusions about the long-term results to be drawn. For now, we need to rely on large-scale registries in which the BMS control groups often comprise lower-risk patients and lesions.

From ST to Hard Clinical End Points

Knowing that DES are able to reduce restenosis by ≈70%, one could subsequently expect a long-term benefit in survival.[48,49] Instead, concerns were raised about a higher rate of death and MI after DES implantation, and even cancer was hypothesized to occur more frequently in DES-treated patients.[50,51]

Frightened by these detrimental findings, stent manufacturers put complete data sets of randomized trials with long-term patient-level–based follow-up at the disposal of independent researchers and statisticians for further analyses. After several intense scrutinizing exercises, long-term death and MI rates appeared to be similar in pooled analyses of the pivotal Cypher and TAXUS trials, including relatively low-risk patients.[17,52]

In real-world registries in which the off-label DES use accounted for up to 60% of the population, the outcomes seem more at variance. Whereas the large DEScover and West Denmark registries and the 3-year follow-up of the

Rapamycin Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry showed equal survival rates between DES and BMS, a large-scale Swedish registry highlighted a significantly lower survival rate in the DES group compared with the BMS group at 2.4 years of follow-up.[7,53–55] Of note, the BMS control groups in the above-mentioned registries comprised significantly less complex patients because of either the sequential nature of the cohorts or substantial selection bias favoring the BMS control groups. It remains disputed whether comprehensive regression and propensity analyses are able to completely account for these differences.

It is to be expected that, in the long term, higher rates of very late ST after DES implantation will put our DES-treated patients at higher risk for death and MI. Although DES have been shown to be safe up to 4 years for on-label use, the off-label long-term safety has not yet been determined, given the controversial findings of large real-world registries and the lack of properly powered randomized controlled trials.

DES Use for Off-Label Indications

Whereas DES seem to be not only safe and effective but also preferable to BMS for on-label use, a lack of dedicated research makes off-label use debatable. This issue was reviewed at a recent panel meeting of the US Food and Drug Administration on ST to which key opinion leaders from the entire world were invited.

High-Risk Patient Subgroups

Two of the most widely discussed indications for DES use are diabetes mellitus and acute MI. Although diabetic patients make up ≈25% of our current population, the most safe and effective device for this high-risk subgroup remains disputed.[56] Patients with diabetes are known to have an accelerated and more aggressive form of atherosclerosis and tend to develop substantially higher rates of restenosis compared with nondiabetics.[57–59] The latter finding can be explained by the smaller vessel size, longer lesion length, greater plaque burden, and a possibly different-acting restenotic cascade compared with patients without diabetes.[60,61] To date, retrospective subset analyses in various randomized controlled trials and a select number of small single-center experiences reported that both SES and PES are effective in reducing restenosis and repeated revascularizations compared with BMS in diabetic patients for up to 1 year.[59,62–64] However, in a randomized trial by Dibra et al,[65] the extent of late loss and angiographic restenosis was greater in patients treated with PES than in patients with SES, although the difference in the clinical end points was not statistically significant.[65] Conversely, the Strategic Transcatheter Evaluation of New Therapies (STENT) registry compared the outcome of 1680 diabetic patients treated with either SES or PES and showed no significant difference in each of the clinical end points at 9 months.[66] These clinical findings were supported by recent results from a retrospective subgroup analysis of 702 diabetic patients from the RESEARCH and Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registry.[67,68] After propensity analysis, no significant differences in any of the clinical end points between SES and PES were noted after 2 years of follow-up. Finally, the Latin American Society of Interventional Cardiology (SOLACI) and the Taxus Express2 Stent versus Cypher Stent: What's Your Real-World Experience? (TC-WYRE) registry showed even lower target vessel revascularization rates in diabetic patients treated with PES compared with those treated with SES.[69,70]

In assessments of the efficacy of both DES in diabetic patients, the different mechanisms of action of both drugs and the theory behind insulin resistance deserve some attention. Paclitaxel acts differently than the "limus" family drugs, which all inhibit the mTOR (mammalian target of rapamycin) gene. mTOR is dependent on the PI3 kinase pathway, which is degraded in patients with non–insulin-dependent diabetes mellitus.[71] Whether these physiological differences will result in a significant long-term clinical difference between SES and PES remains to be determined.

A second high-risk subgroup in which the long-term safety and efficacy are not yet unanimously proven is the acute MI subset. A recent editorial incorporating a pooled analysis of the first retrospective subset analyses of MI patients treated with DES (mostly SES) concluded that the SES was safe and effective in reducing restenosis and repeated revascularizations in this high-risk subset.[72] However, the number of patients included in these preliminary reports was small, and the studies were underpowered to definitively prove a beneficial effect of DES. Recently, the randomized Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated With Balloon Angioplasty (TYPHOON) and randomized Sirolimus Stent Versus Bare Stent in Acute Myocardial Infarction (SESAMI) trial proved that SES were superior to BMS in reducing restenosis and repeated revascularization in patients presenting with acute MI.[73,74] As a result of the negative findings of the Paclitaxel-Eluting Stent Versus Conventional Stent in Myocardial Infarction With ST-Segment Elevation (PASSION) trial and the nonsignificantly different repeated revascularization rates in the Helsinki Area Acute Myocardial Infarction Treatment Reevaluation: Should the Patient Get a Drug-Eluting or a Normal Stent? (HAAMU-stent) study, it is currently unclear whether this also holds for PES.[75–77] We look forward to the results of the upcoming Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS AMI) trial, which is designed to prove the efficacy of the PES in acute MI patients.

Of note, all the above-mentioned studies showed similar safety profiles (expressed by hard clinical end points like death, MI, and ST) for both DES and BMS in MI patients. However, this evidence goes no further than 1 year. Considering that very late ST was significantly more frequent after DES implantation (11 of 2278 cases) than after BMS implantation (1 of 2267)[46] and knowing that acute MI proved to be among the strongest predictors of ST, we acknowledge that the long-term safety of DES in these patients remains debatable.[35,36,38,78]

Off-Label Indications

A substantial amount of randomized controlled trials proved the efficacy of DES for off-label indications like chronic total occlusions, in-stent restenosis, small vessels, and bypass grafts.[79–83] However, the primary end points of these trials were most often angiographic, and the follow-up is not reported beyond 1 year. Because of the limited number of patients in these trials, making them underpowered for assessing hard clinical end points, the long-term safety of DES for off-label indications needs to be determined on the basis of both pooled meta-analyses of these trials and real-world registries.

Duration of Antiplatelet Therapy

Currently, product labeling recommends 3 months of clopidogrel after SES implantation and 6 months after PES implantation, accompanied by lifelong administration of aspirin. Looking back on the rationale for these recommendations brings us to the First in Man (FIM) trial and the Randomized Study With the Velocity Balloon-Expandable SES in the Treatment of Patients With De Novo Native Coronary Artery Lesions (RAVEL) trial in which 2 months of ticlopidine or clopidogrel was mandated on the basis of the fact that the FIM was planned as a 60-day safety trial with concomitant ticlopidine use for 60 days. Although it would take another 2 years for the first concerns for late ST after DES implantation to be raised,[44] clopidogrel prescription was prolonged to 3 and 6 months in the pivotal SIRIUS and TAXUS-I trials, respectively. Unfortunately, the rationale for this prolongation remains unclear.

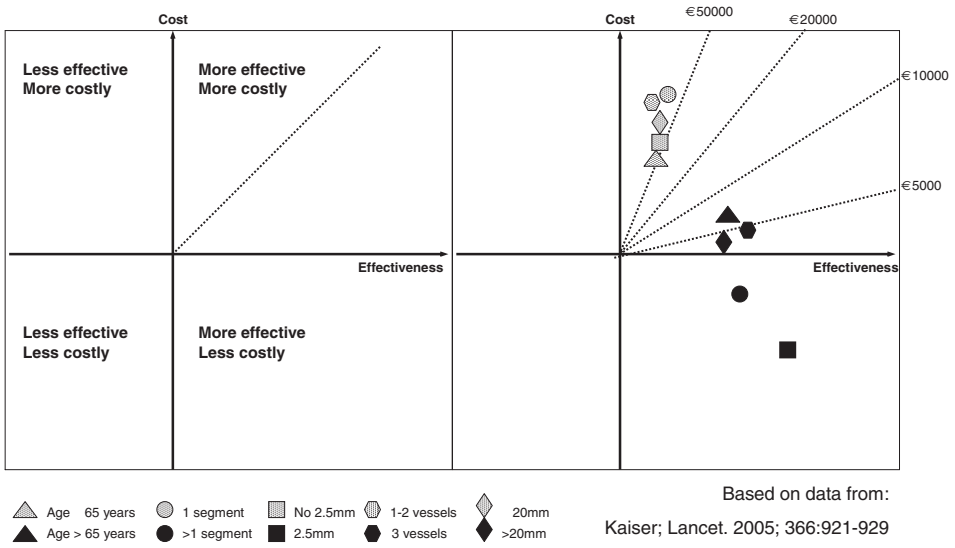
It has been 5 years since the introduction of the first DES, and the optimal duration of dual antiplatelet therapy remains to be determined. In dedicated trials in the BMS era, the benefit of clopidogrel therapy proved to be apparent mainly in the first 1 to 6 months after stent implantation. The randomized Clopidogrel in Unstable Angina to Prevent Recurrent Events (PCI-CURE) trial proved that long-term administration of clopidogrel was associated with a 31% reduction in cardiovascular death or MI ($P=0.002$) in patients presenting with a non–ST-segment elevation acute coronary syndrome.[84] However, as supported by the findings of the Clopidogrel for the Reduction of Events During Observation (CREDO) trial, which included only elective patients, the observed benefit was already achieved in the first month.[84,85] No significant difference in death or MI between the clopidogrel- and placebo-treated groups was noted between 1 and 6 months.[86] Given the lack of dedicated randomized trials in the DES era, we are forced to rely on indirect evidence indicating possibly severe consequences after the premature discontinuation of dual antiplatelet therapy.[32,34,35,87,88] Currently, the Food and Drug Administration and the updated American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions guidelines recommend at least 12 months of clopidogrel in patients at low risk for bleeding.[89,90] The currently available evidence supporting long-term clopidogrel use is controversial. On the one hand, 2 recent large-scale registries demonstrated that 25% to 50% of all late ST events occurred in patients who were still on dual antiplatelet therapy.[38,87] On the other hand, Eisenstein et al[91] recently demonstrated a significant higher 2-year survival in patients remaining on dual antiplatelet therapy at 6 and 12 months compared with those who stopped clopidogrel. Unfortunately, the study does not report on the antiplatelet use at the time the 662 censored events in the first 6 months (156 of 1501 in the DES group versus 506 of 3165 in the BMS group) occurred. Finally, in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial, which randomly assigned 15 603 patients with either clinically evident cardiovascular disease or multiple risk factors to receive clopidogrel (75 mg/d) plus low-dose aspirin (75 to 162 mg/d) or placebo plus low-dose aspirin and followed them up for a median of 28 months, clopidogrel plus aspirin was not significantly superior to aspirin alone, and additional harm such a significantly higher risk of bleeding could not be excluded.[92]

Cost-Effectiveness

Although both SES and PES proved to be highly effective in reducing restenosis and the need for reinterventions, their cost-effectiveness is still debated. The cost-effectiveness analyses for both RAVEL and SIRIUS showed that SES were relatively cost-effective for simple lesions.[93,94] Although the cost-effectiveness analyses of the RAVEL trial adjusted for the consequences of mandated angiographic follow-up, the results of economical analyses based on such trials should be interpreted with caution.

The Basel Stent Kosten Effektivitäts Trial (BASKET) analyzed the cost-effectiveness of both eluting stents combined compared with standard BMS in a real-world single-center setting.[95] Total costs at 6 months were higher with DES (mean, €10 544; SD, €6849) than with BMS (mean, €9639; SD, €(9067; $P<0.0001$). At 6 months, the lower reintervention rates did not compensate for the higher initial costs. The incremental cost-effectiveness ratio of DES compared with BMS to avoid 1 major event was €18 311, and costs per quality-adjusted life-year gained exceeded €50 000. Subgroup analyses showed that DES were more cost-effective for elderly patients and specific high-risk subgroups like patients with 3-vessel disease, longer lesions, and type B lesions (the Figure). However, several methodological issues with this trial merit discussion. First, the analysis was based on 6-month clinical outcome, whereas we know from the randomized TAXUS and SIRIUS family trials that the Kaplan-Meier curves for target lesion revascularization for these DES compared with BMS continue to diverge up to 12 months. This would lead to a serious underestimation of their cost-effectiveness. In the simple incremental cost-effectiveness ratio equation, which expresses cost-effectiveness as change in cost divided by change in effect, the difference in cost would be overestimated, whereas the difference in effect would be underestimated.

Second, the cost-effectiveness was based on the performance of "DES," in this case a combined population of both SES and PES patients. Blending the outcomes of both stents may affect the accuracy of the cost-effectiveness for each



Overview of efficacy and cost-effectiveness of DES (SES or PES) vs BMS in several subgroups. Gray symbols represent low-risk patients; black symbols, high-risk patients.

product. The 18-month cost-effectiveness results of BASKET are expected soon and should be much more informative.

As mentioned in BASKET, the possible cost-effectiveness of DES has to be driven by the ability to reduce the need for reinterventions because death and MI rates proved to be comparable. Ong et al[96] evaluated the cost-effectiveness of SES in the RESEARCH study and concluded that the SES was not cost-effective at 1 or 2 years of follow-up compared with BMS. However, Ong et al concluded that the incremental cost-effectiveness ratio per target vessel revascularization avoided was €29 373 at 1 year and €22 267 at 2 years in the total cohort. On the basis of these results, the calculated maximum cost-effective price after 1 year of follow-up is €1336 per SES for all-comers or €1023 to achieve cost neutrality. It is clear that longer-term follow-up is needed to determine the number of reinterventions that could be avoided to make DES cost-effective. It is worth noting that an inherent trap exists when the incremental cost-effectiveness equation is applied for all new medical technologies that do not, for example, apply to pharmaceuticals. The incremental cost-effectiveness ratio will be heavily influenced by the costs of both the new and old technology. The more successful the new technology is, the more rapidly and farther the price of the old technology that it is replacing is likely to fall. Thus, although initially cost-effective, the new technology may no longer be so 1 or 2 years later according to this equation.

Conclusions

So far, DES have been proved to be safe and effective with significantly lower rates of repeated revascularization. The trend toward a higher incidence of very late ST in patients treated with DES does not seem to affect the long-term hard clinical end points like death and MI, at least for on-label use and assuming compliance with the antiplatelet regimen. Whether this restricted 4-year safety profile can be extended to 5 or even 10 years and to higher-risk patients remains to be determined, given the lack of dedicated trials sufficiently powered for clinical safety end points like death and MI. It is evident that DES are associated with adverse side effects like endothelial dysfunction and a severely disturbed vascular healing process. Future research has to demonstrate if, how, and when this will affect long-term safety and efficacy.

Although adherence to 6 months of clopidogrel in DES-treated patients seems crucial in preventing stent thrombotic events, dedicated large-scale randomized trials are needed to settle the pros and cons of prolonged dual antiplatelet therapy.

Disclosures

None.

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KEY WORDS: stents ■ restenosis ■ thrombosis ■ myocardial infarction ■ diabetes mellitus

Chapter 4

Two-year clinical follow-up of the unrestricted use of the paclitaxel-eluting stent compared to the sirolimus-eluting stent as part of the Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) Registry

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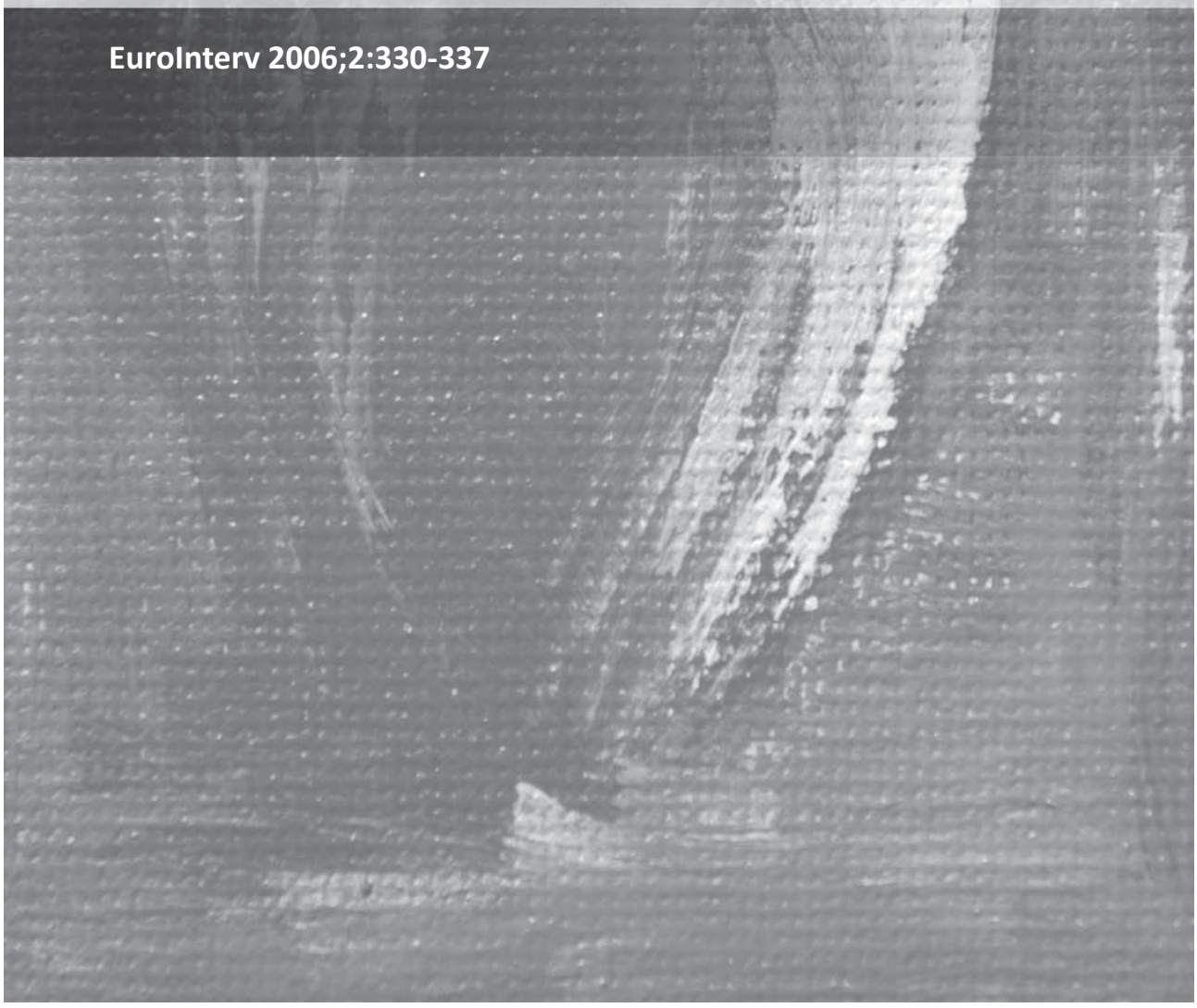

EuroIntervention

Two-year clinical follow-up of the unrestricted use of the paclitaxel-eluting stent compared to the sirolimus-eluting stent as part of the Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registry

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The authors have no conflicts of interest to declare.

KEYWORDS
Sirolimus, Paclitaxel, stent, T-SEARCH, two-year

Abstract

Aims: To investigate the medium term (2 year) clinical outcome of the use of the paclitaxel-eluting stent (PES) compared to the sirolimus-eluting stent (SES). To date, there are no direct comparative data on the efficacy of these stents over medium term follow-up. Furthermore, a possible late restenotic phenomenon has not been excluded.

Methods and results: The Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registry compared 576 consecutive "all-comer" patients, exclusively treated with PES, with 508 patients who received SES from the RESEARCH registry in the preceding period. Patients were enrolled irrespective of clinical or angiographic features. At 2 years, major adverse cardiac event (death, myocardial infarction or target vessel revascularisation) rates were comparable in the two groups: 15.4% in the SES group versus 18.9% in the PES group (HR 1.26, 95% CI 0.94-1.69, p=0.12). Correcting for differences in both groups resulted in an adjusted HR of 1.11 (95% CI 0.82-1.50, p=0.51, using significant univariate variables). Target vessel revascularisation was 8.0% in the SES group compared with 9.6% in the PES group (HR 1.23, 95% CI 0.81-1.86, p=0.33).

Conclusions: The unrestricted use of SES and PES was safe at two years of follow-up. No significant difference was found between the two devices in terms of death or MI, MACE, TVR or TLR. No late clinical restenotic phenomenon was observed.

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Abbreviations and acronyms

CI: Confidence interval

HR: Hazard Ratio

MACE: Major Adverse Cardiac Event

MI: myocardial infarction

RAVEL: Randomised study with the sirolimus-eluting BxVelocity balloon -expandable stent in the treatment of patients with *de novo* native coronary artery lesions.

RESEARCH: Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital

T-SEARCH: Taxus-Stent Evaluated at Rotterdam Cardiology Hospital

SES: sirolimus-eluting stent

PES: paclitaxel-eluting stent

TLR: target lesion revascularisation

TVR: Target vessel revascularisation

Introduction

Several years have elapsed since the commercial introduction of sirolimus and paclitaxel eluting stents and to date more than 3 million drug-eluting stents have been implanted worldwide.

Both stents, loaded with antiproliferative drugs, have shown to be highly effective in reducing restenosis in stenotic coronary arteries compared to bare metal stents[1-5]. Evidence was seen from the early days of DES with trials describing the effect of the Rapamycin covered SES in relatively simple lesions in the FIM trial[6,7] and the RAVEL trial[8]. Currently, randomised trials, such as the REALITY, TAXI, CORPAL, SIRTAX, ISAR Diabetes trial and BASKET trial, are comparing SES and PES in a wide variety of patient and lesion types[9-14]. Although a recent meta-analysis has demonstrated the efficacy of DES, and the superiority of SES to PES in reducing restenosis and target lesion revascularisation (TLR), the randomised REALITY trial did not show a difference in binary restenosis and neither in major adverse cardiac events (MACE) at 8 and 12 months between both devices[9,15]. Of note, no difference was seen in the rates of death and myocardial infarction after relatively short-term follow-up in both studies.

The purpose of the present study is to report the two-year clinical outcome of an unselected patient cohort compromising 1,084 consecutive patients treated with a sirolimus- or paclitaxel-eluting stent. The study was performed for two reasons: First, to evaluate the incidence of late adverse events – the importance of this issue can be demonstrated by a variety of complications that showed up after several years of clinical experience using multiple drug-eluting devices such as; stent thrombosis more than one year after implantation despite continuation of anti-platelet therapy[16], delayed neointimal growth[17], and a phenomenon of late restenosis in porcine models[18]. Secondly, to see whether both devices were still associated with a comparable outcome at 2 years[19].

Methods

Study design and patient population

The Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registry is a single-centre prospective registry with the aim of evaluating the safety and efficacy of the unrestricted use of PES (PES, TAXUS, Boston Scientific Corp., Natick, Massachusetts, USA) implantation in an unselected patient population typical of daily practice. Its design and methodology are similar to that of the RESEARCH registry[20] and follows the dynamic registry design described by Rothman and Greenland[21].

PES was granted *Conformité Européenne* (CE) approval on February 16, 2003 and replaced SES (SES, Cypher, Cordis corporation, Warren, NJ, USA) as the default strategy for every percutaneous coronary intervention (PCI) in our institution. Up to September 30, 2003, a total of 576 patients with *de novo* lesions were treated exclusively with PES and are included in the present report (PES group). In this period, 84% of all patients with *de novo* disease received a PES. Patients not treated purely with PES or patients included in other drug-eluting stent trials were excluded from the present report. This PES group was compared with a control group that comprised the active arm of the RESEARCH registry, including 508 patients with *de novo* disease treated solely with SES (SES group). Written informed consent was acquired for every patient included. Our study fulfilled the criteria of the declaration of Helsinki and was approved by the hospital ethics committee.

Procedures and post-intervention medications

All procedures were performed according to current standards, with the final interventional strategy (including direct stenting, postdilatation and the use of intravascular ultrasound) left to the operator's discretion[20]. Angiographic success was defined as residual stenosis ≤30% by visual analysis in the presence of Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow. All patients were pretreated with 300mg clopidogrel. For patients in the SES group post procedure clopidogrel (75 mg/day) was prescribed for at least 3 months. Several exceptions were made for patients treated for long lesions (stented segment >36 mm), chronic total occlusions, bifurcations and patients in whom more that 3 stents were used. These patients received at least 6 months clopidogrel. In the PES population clopidogrel (75 mg/day) was prescribed for at least 6 months according to the protocol of several randomised clinical trials[3,5]. Furthermore, all patients were advised to maintain life-long aspirin treatment (at least 80 mg/day).

End point definitions

Our primary endpoint was MACE at 2 years. MACE was defined as a composite of all cause death, non-fatal myocardial infarction (MI) or target vessel revascularisation (TVR). Secondary endpoints were target lesion revascularisation (TLR), defined as a treatment of a lesion in-stent or within 5 mm of the stent borders, and clinically driven repeat revascularisation, defined as any intervention motivated by a significant luminal stenosis (≥50% diameter stenosis) in the presence of anginal symptoms and/or proven myocardial ischaemia

on the target vessel territory by noninvasive testing. Myocardial infarction was diagnosed by a rise in creatine kinase-MB fraction (CK-MB) of three times the upper normal limit according to American Heart Association/American College of Cardiology guidelines[22,23]. Subacute angiographic stent thrombosis was defined as an angiographically documented complete occlusion (TIMI grade 0 or 1 flow) or a flow-limiting thrombus (TIMI grade 1 or 2 flow) in the first 30 days after a successful procedure. Late angiographic stent thrombosis was defined as late – occurring at least one month after DES implantation with acute symptoms; angiographic – stent thrombosis confirmed angiographically; stent thrombosis – defined as thrombosis with TIMI grade 0 or 1 flow or the presence of a flow limiting thrombus (TIMI flow 1 or 2)[24].

Two-year follow-up data

Long-term survival status was obtained by information provided by the municipal civil registry. Subsequently, questionnaires were sent to all living patients inquiring about new interventions (either surgical or percutaneous), myocardial infarction and medication usage. If patients had an MI or underwent a re-intervention in another hospital, discharge letters from the referring hospitals were requested and analysed for additional information. In cases of doubt, the local cardiologist or general practitioners were contacted. All information was prospectively collected in a dedicated database. We were not able to retrieve complete follow-up information on 30 patients, mostly due to emigration or due to an illegal status in the Netherlands. Finally, follow-up was available for 97% of the patients in both groups.

In both groups, follow-up coronary angiography was clinically driven by symptoms or signs suggestive of myocardial ischaemia or mandated by the operator at the end of the index procedure predominantly for complex procedures. In the PES group 18.4% underwent angiographic follow-up, as part of three specific complex subgroups: left main stenting, crush-bifurcation procedures, and patients who were part of a vulnerable plaque substudy. Of the SES patients, 36.0% underwent angiographic follow-up, as part of the following complex subgroups: bifurcation lesions, chronic total occlusions, very small vessels, left main stenting, long stent length (36 mm), and acute MI.

Statistical analysis

Continuous variables are presented as mean ±SD and were compared by Student's t-test. Categorical variables are presented as counts and percentages and compared by Fisher's exact test. All statistical tests are 2-tailed and a p-value <0.05 was considered significant. The cumulative incidence of adverse events was estimated according to the Kaplan-Meier method, and Cox proportional hazards models were used to assess differences between the two strategies. Curves were compared by log-rank test. Separate Cox proportional hazards models were performed to identify independent predictors of adverse events, using clinical, angiographic, and procedural variables contained in Tables 1 and 2. The Cox proportional hazards regression models were used to control for differences between groups, and the final results are presented as

Table 1. Baseline characteristics of patients treated with SES or PES

	SES Group (n=508)	PES Group (n=576)	P- value
Male,%	68	74	0.04
Age, years ±SD	61±11	62±11	0.4
Diabetes,%	18	18	0.8
Non-insulin dependent,%	12	13	0.5
Insulin-dependent,%	6	5	0.2
Hypertension,%	41	42	0.9
Hypercholesterolaemia,%	56	62	0.03
Current smoking,%	31	29	0.6
Previous myocardial infarction,%	30	45	0.13
Previous angioplasty,%	19	18	0.8
Previous coronary bypass surgery,%	9	6	0.05
Single-vessel disease,%	46	44	0.5
Multivessel disease,%	54	56	0.5
Clinical presentation			<0.001
Stable angina,%	45	45	
Unstable angina,%	37	27	
Acute myocardial infarction,%	18	28	
Cardiogenic shock,%*	10	13	

* Relative to patients with acute myocardial infarction.

Table 2. Angiographic and procedural characteristics of patients treated with SES or PES

	SES Group (n=508)	PES Group (n=576)	P- value
Treated Vessel			
Left anterior descending,%	59	55	0.3
Left circumflex,%	32	33	0.6
Right coronary,%	39	38	0.9
Left main coronary,%	3	4	0.3
Bypass graft,%	3	3	1.0
Lesion type*			
Type A or B1%	47	32	<0.001
Type B2 or C%	76	87	<0.001
Multivessel treatment,%	32	29	0.3
Glycoprotein IIb/IIIa inhibitor,%	19	28	0.002
Clopidogrel prescription, months ±SD		6±0	<0.05
Bifurcation stenting,%	16	16	0.9
Number of stented segments ±SD	2.0±1.0	1.7±0.9	<0.001
Number of stented vessels ± SD	1.3±0.6	1.3±0.6	0.8
Number of implanted stents ± SD	2.1±1.4	2.2±1.5	0.09
Total stented length per patient, mm ± SD	38.7±23.7	42.9±31.2	0.02
Nominal stent diameter ≤2.5 mm,%	36	35	0.7
Total stented length >33mm,%	45	48	0.5
Angiographic success of all lesions,%	97	97	0.9

* Percentage of patients with at least 1 lesion type within the category.

adjusted hazard ratios (HRs). Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored.

Results

Baseline and procedural characteristics

Both baseline and procedural characteristics are shown in Tables 1 and 2. In summary, patients were predominantly male and slightly more frequent in the PES group, PES patients had more myocardial infarctions (MIs) and cardiogenic shock as their presenting symptom and hypercholesterolaemia was more often present. Furthermore, PES patients had more complex lesions, received longer total stent lengths and glycoprotein IIb/IIIa inhibitors were administered more frequently (28% versus 19%; p=0.002). Furthermore, fewer PES patients had a history of previous coronary bypass surgery, and fewer segments per patients were stented, although the number of vessels treated per patient was identical. Other baseline and procedural characteristics were similar.

Two-year follow-up

The one-year results of our study have been published previously[19]. At two years of clinical follow-up there was no significant difference in mortality between the SES- and PES-groups, (5.8% versus 7.7% respectively, HR 1.35, 95% CI 0.84 - 2.16, p=0.21) (Figure 1a). No difference was found in the combined endpoint of death or MI in the SES- versus PES-group (9.8% versus 11.9%, HR 1.23, 95% CI 0.85-1.78, p=0.26) (Figure 1b). TLR and TVR rates were similar in both groups. Cumulative incidence of TLR was 6.8% versus 6.3% in the SES group versus the PES group respectively (HR 0.94, 95% CI 0.58-1.51, p=0.79) and TVR was 8.0% in the SES-group versus 9.6% in the PES-group (HR 1.23, 95% CI 0.81-1.86, p=0.33) (Figure 1c). Clinically driven TVR was performed in 7.2% of the SES group compared with 9.4% in the PES group (HR 1.34, 95% CI 0.87-2.06, p=0.18). The two-year cumulative incidence of combined MACE was 15.4% in the SES-population versus 18.9% in the PES-population (unadjusted HR 1.26, 95% CI 0.94-1.69, p=0.12) (Figure 1d). Late stent thrombosis at 2 years occurred in 0.3% of the PES group compared with 0.2% in the SES group. Total rate of stent thrombosis was 1.6% in the PES group versus 0.6% in the SES group (p=0.15).

Table 3. Events between one and two year of clinical follow-up, additional to one-year events

	SES Group (n=508)	PES Group (n=576)	P- value*
Death, n (%)	12 (2.4)	12 (2.1)	0.84
Myocardial infarction, n (%)	2 (0.4)	1 (0.2)	0.60
TLR, n (%)#	11 (2.2)	4 (0.7)	0.065
TVR (including TLR), n (%)‡	13 (2.6)	9 (1.6)	0.28
Non TVR, n (%)	13 (2.6)	5 (0.9)	0.03

target lesion revascularisation; ‡ target vessel revascularisation
* by Fisher exact test

Events between one and two years

In this period a total of 48 events occurred. Twelve patients died in the SES group, two died of a cardiac cause, 6 patients died of a non-cardiac cause, 2 patients died suddenly of unknown cause and of 2 patients the cause of death was unknown. Twelve patients died also in the pre-SES group, 5 of a cardiac cause, 3 patients died of non-cardiac causes and the cause of death of 4 patients was unknown. Three MI's occurred (two in the SES group versus one in the PES group). Furthermore, 13 patients received a TVR in the SES group versus 9 in the PES group, all of them were clinically driven. Eleven patients treated with SES underwent a target lesion revascularisation and only 4 out of the PES population (p=0.065). Additionally, 13 patients treated with SES and 5 with PES required a repeat intervention in a different vessel. One case of late-stent thrombosis was reported between one- and two-years.

Predictors of adverse events

In order to identify independent predictors of MACE at two years of follow-up, Cox regression analysis was performed for all baseline characteristics listed in Tables 1 and 2. The following variables were significant in predicting MACE at two years of follow-up: age > 65, female gender, diabetes mellitus, multivessel disease, left main stenting, bifurcation stenting, lesion type B2 or C and total stented length (per 10 mm increment) (Table 4). A second analysis was performed to determine independent predictors of TVR. Diabetes mellitus, lesion type B2 or C, bifurcation stenting and total stented length per 10 mm increment were found to be significant. Subanalyses were performed in several subgroups according to baseline and procedural characteristics (Figure 2). In patients of normal weight, defined as body mass index (BMI) ≤25, patients

Table 4. Independent predictors of MACE and TVR by COX separate regression analysis. Population tested, includes all patients#

Major Adverse Events*	HR	95% CI
Cardiogenic Shock	3.67	2.09-6.46
Left Main treatment	3.44	2.12-5.60
Lesion type B2 or C	2.96	1.72-5.10
Multivessel disease	1.92	1.40-2.62
Diabetes Mellitus	1.87	1.36-2.59
Female gender	1.64	1.22-2.20
Bifurcation stenting	1.62	1.15-2.30
Total stented length (per 10 increment)	1.13	1.07-1.21
Age	1.01	1.00-1.03
Target Vessel Revascularisation	**HR**	**95% CI**
Lesion type B2 or C	4.17	1.69-10.28
Bifurcation stenting	2.00	1.25-3.19
Diabetes	1.73	0.98-2.76
Total stented length (per 10mm increment)	1.18	1.08-1.28

* Including death, myocardial infarction and target vessel revascularisation
# Stent type was not an independent predictor when entered into the model

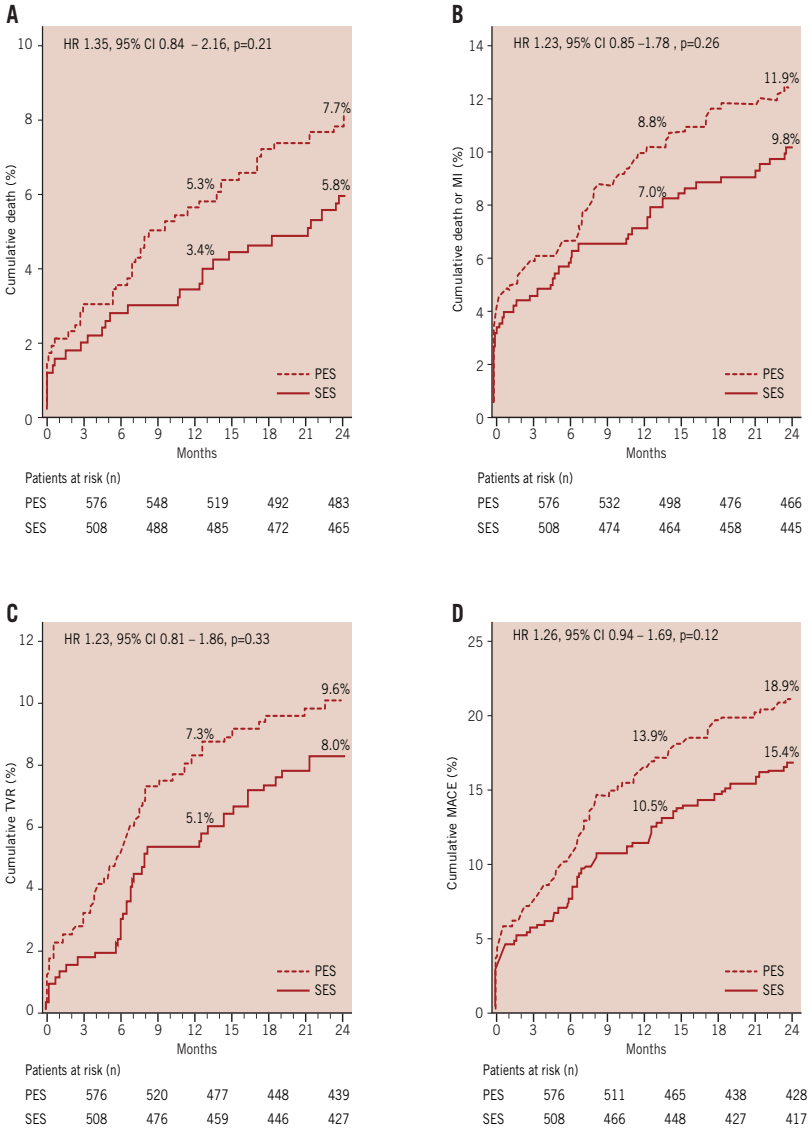

Figure 1. Two-year adverse events in patients treated with sirolimus- and paclitaxel-eluting stents (SES and PES). Cumulative risk of death (A); death or myocardial infarction (MI) (B); target vessel revascularisation (C); death, myocardial infarction or target vessel revascularisation (MACE) (D).

treated with SES had a significantly lower rate of TVR compared to the PES group (p=0.02). In all other subgroups no superiority was noticed between SES and PES.

Adjustment for differences between both groups

The Cox proportional hazards regression model was used to adjust the two groups by correcting for multiple potential confounders in the baseline and procedural characteristics. First, a model was built forcing stent type and all independent predictors listed in Table 4. All previously significant variables remained significant except for bifurcation treatment, age and total stented length. The adjusted HR for use of PES became even less significant, decreasing from HR 1.26 (95% CI 0.94-1.69, p=0.12) to HR 1.12 (95% CI 0.83-1.51, p=0.44), after controlling for the increased complexity in the PES group.

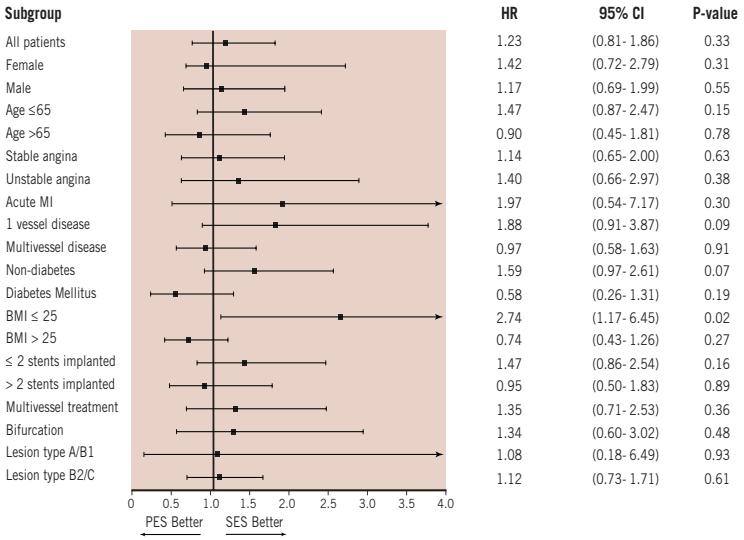

Figure 2. Hazard ratios (HR) of stent type at two-year follow-up for target vessel revascularisation in subgroups of patients according to baseline and procedural characteristics. MI=myocardial infarction.

A second model was then built forcing stent type and significant univariate variables (independent predictors plus number of stents), and the adjusted outcome of MACE at two year was similar between SES and PES (adjusted HR 1.11, 95% CI 0.82 to 1.50, p=0.51). Finally, stent type was also not a significant predictor of TVR when adjusted for lesion type, bifurcation stenting, diabetes and total stented length (adjusted HR 1.09, 95% CI 0.72-1.66, p=0.68).

Discussion

The present study reports on the 2-year clinical outcome of the use of SES and PES in a real world patient cohort and confirms that neither one of both devices is superior to the other in preventing MACE. Additionally, no differences were found in the occurrence of death and MI, TLR and TVR between both groups.

Death and MI occurred in a similar amount in both groups, which is in accordance with randomised trials[15]. Additionally, there was a trend towards a higher incidence of stent thrombosis in the PES group. It has to be mentioned that in the second year, 2 patients in the SES group and 3 patients in the PES group died of sudden death of unknown cause or of a fatal out-of-hospital cardiac arrest. It cannot be excluded these patients also suffered late thrombotic events. Whether the SES is superior to PES in terms of late luminal loss and the ability to reduce the need for re-interventions, is still a topic of debate. In terms of target lesion revascularisation, both the SIRTAX and ISAR-DESIRE showed TLR rates favouring SES[12,25]. However, the TAXI, REALITY, ISAR-DIABETES and CORPAL studies did not show a difference between both devices[9,10,13,26]. In terms of angiographic restenosis, both the SIRTAX and ISAR-DIABETES showed results favouring the SES. Although, it has to be mentioned that in the SIRTAX trial the incomplete angiographic follow-up may have resulted in an overestimation of the difference owing to attrition bias. However, the medium to long-term difference remains unknown. The present study reports the 2-year clinical follow-up of the use of the sirolimus- and paclitaxel- eluting stents in a real world patient cohort and confirms that neither one of the devices is superior to the other in preventing the need for revascularisations or the occurrence of overall MACE. The incidence of baseline characteristics with a predictive value towards a worse outcome was higher in the PES cohort and the lesions treated in the PES patients were more difficult overall. This is reflected in the adjusted MACE rate, in which the difference becomes even smaller. Additionally it has to be mentioned that between one and two years, the TLR rate is in favour of the paclitaxel-eluting stent (2.2% versus 0.69%; p=0.065).

When compared to the PES patients, a significantly higher amount of SES patients underwent angiographic follow-up. Of all patients with angiographic follow-up, only 6 (6.6%) underwent a TVR because of a significant (>50% stenosis) without "documented" anginal symptoms. Of note, 2 were because of severe proximal stenosis with large areas of myocardium at risk. Thereby, all TVRs performed in the second year were clinically driven. It is for this reason, that we did not choose clinically driven TVR as a primary endpoint.

An additional rebound phenomenon, as seen in porcine models and brachytherapy, does not seem to occur, at least after two years of follow-up. This latter is supported by the FIM study with 4 years of angiographic follow-up, which demonstrated the absence of a catch-up phenomenon of restenosis in a small patient population[7]. Although both sirolimus- and paclitaxel-eluting stents have been shown to reduce neointimal proliferation, their mechanisms of action are different. Both devices modify the healing process after stent injury, which is the most likely explanation for the reduction in

restenosis[27]. Nevertheless, both drugs interfere with a different part of the cell cycle and both stents have different polymer coatings and dissimilar drug-release kinetics[28,29]. The clinical implications in the differences between both devices still have to be determined.

Looking at the independent predictors of MACE (table 4), it can be concluded that patients treated for left main stenosis or complex lesions (type B2/C) had a significantly higher risk of adverse events at 2 years. Several trials, like the FREEDOM, COMBAT, SYNTAX and CARDIA trial, are currently ongoing to see whether these patients would benefit more from coronary artery bypass surgery[30,31].

In the subgroup analyses, we found that patients with a BMI ≤25 treated with SES had a superior outcome with respect to the need for TVR when compared to PES. A paradox in the relationship between BMI and late mortality after PCI with bare-metal stents has been previously described, however, repeat revascularisation rates were not shown to be affected by body mass[32]. Whether the "obesity paradox" will extend to repeat revascularisations in the DES-era and will be influenced by the type of DES needs further investigation.

We realize this is an observational, non-randomised cohort study and thus suffers from its design. For instance, the two sequential cohorts are separated by a 4-month interval, resulting in several differences in both baseline and procedural characteristics. In general, the PES population was more complex overall. More primary PCIs were performed, because of the implementation of a pre-hospital protocol that triaged more patients to primary PCI. More complex (Type B2/C) lesions were treated and more stents were implanted. This latter is likely due to the growing confidence in the superior properties of DES compared to BMS.

However, our study comprises an all-inclusive unrestricted patient population which is able to represent the daily clinical practice of a large catheterisation laboratory and thus may possess a greater generalisability than has been possible with randomised trials.

Conclusion

The medium term follow-up of the T-SEARCH registry shows that the unrestricted use of SES and PES was still safe at two years. No significant difference was found in the adjusted outcome of both devices in terms of death or MI, TLR, TVR or MACE. The inferior trend in crude outcome seen in PES was, in part, due to its higher-risk population. A trend towards less TLR in the PES group between one and 2 years was also observed. No late clinical restenotic phenomenon was seen in either group and stent thrombosis after one year occurred in only one patient.

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Chapter 5

Three-year clinical follow-up of the unrestricted use of the sirolimus-eluting stent compared to the use of a standard bare metal stent as part of the Rapamycin-Eluting-Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) Registry

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Three-Year Clinical Follow-Up of the Unrestricted Use of Sirolimus-Eluting Stents as Part of the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) Registry

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Sirolimus-eluting stents (SESs) have been shown to decrease restenosis compared with bare metal stents (BMSs). Currently, there are limited data on the long-term efficacy of these devices in a real-world patient population. Furthermore, the potential of a late restenotic phenomenon has not yet been excluded. From April to October 2002, 508 consecutive patients with de novo lesions exclusively treated with SESs were enrolled and compared with 450 patients treated with BMSs in the preceding 6 months (control group). Patients in the SES group more frequently had multivessel disease and type C lesions, received more stents, and had more bifurcation stenting. After 3 years, the cumulative incidence of major adverse cardiac events (comprising death, myocardial infarction, and target vessel revascularization) was significantly lower in the SES group compared with the pre-SES group (18.9% vs 24.7%, hazards ratio 0.73, 95% confidence interval 0.56 to 0.96, p = 0.026). The 3-year risk of target lesion revascularization was 7.5% in the SES group versus 12.6% in the pre-SES group (hazards ratio 0.57, 95% confidence interval 0.38 to 0.87, p = 0.01). In conclusion, the unrestricted use of SESs is safe and superior to the use of BMSs. The beneficial effects, reported after 1 and 2 years in reducing major adverse cardiac events, persisted with no evidence of a clinical late restenotic "catch-up" phenomenon. **(Am J Cardiol 2006;98:895–901)**

Sirolimus-eluting stents (SESs) have been shown to markedly decrease neointimal hyperplasia compared with bare metal stents (BMSs).[1–7] Although there was no significant change in neointimal thickness at 2 to 4 years of follow-up in the first-in-human trial,[8] other data have suggested a possible delayed healing response that might result in a late restenotic phenomenon. Examples of this phenomenon are a few reports of delayed neointimal growth, a local hypersensitivity reaction with late in-stent thrombosis, and some cases of stent fracture with local tissue proliferation.[9–12] Although a recent meta-analysis demonstrated the efficacy of drug-eluting stents in general in decreasing restenosis,[13] no difference was seen in rates of death and myocardial infarction after relatively short-term follow-up. This study presents the 3-year clinical outcome of the unrestricted use of the SES compared with a BMS in a real-world patient population that was treated for de novo lesions. Our objectives were to investigate whether the positive 2-year results were still present after 3 years and to describe the events that occurred between the second and third years.[14]

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Methods and Results

Methods of the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry have been previously reported.[15] Briefly, the RESEARCH is a single-center registry evaluating the safety and efficacy of SES implantation in patients treated in daily practice. On April 16, 2002, our institution commenced the use of SESs (Cypher, Cordis Corporation, Warren, New Jersey) as the default strategy for every percutaneous coronary intervention, with the aim of including a patient population representing the "real world." In the first 6 months of enrollment, 508 patients with de novo lesions were treated exclusively with SESs (SES group) and compared with a group of 450 consecutive patients treated with BMSs for de novo lesions in the preceding 6 months (pre-SES group) matched for stent diameter.[16] This protocol was approved by the hospital ethics committee and was in accordance with the Declaration of Helsinki. Written informed consent was obtained from every patient.

All procedures were performed according to current standard procedural guidelines, and their details have been previously reported.[17] Angiographic success was defined as residual stenosis <30% by visual analysis in the presence of Thrombolysis In Myocardial Infarction grade 3 flow. All patients were advised to maintain lifelong aspirin. At least 1-month of clopidogrel treatment (75 mg/day) was recommended for patients treated in the pre-SES phase. For patients treated with SESs, clopidogrel was prescribed for ≥3

Table 1
Baseline clinical characteristics

Variable	Pre-SES Group (n = 450)	SES Group (n = 508)	p Value
Men	72%	68%	0.4
Age (yrs), mean ± SD	61 ± 11	61 ± 11	0.7
Diabetes mellitus	15%	18%	0.3
Non–insulin-dependent mellitus	11%	12%	0.7
Insulin-dependent mellitus	4%	6%	0.2
Hypertension	48%	41%	0.2
Hypercholesterolemia*	55%	56%	1.0
Current smoking	34%	31%	0.3
Previous myocardial infarction	40%	30%	<0.01
Previous angioplasty	18%	19%	0.8
Previous coronary bypass surgery	8%	9%	0.5
Single-vessel disease	52%	46%	0.05
Multivessel disease	48%	54%	0.05
Clinical presentation	—	—	0.7
Stable angina pectoris	48%	45%	—
Unstable angina pectoris	35%	37%	—
Acute myocardial infarction	18%	18%	—
Cardiogenic shock†	12%	10%	0.7

* Defined as a fasting cholesterol level >5.5mmol/L or use of lipid-lowering therapy.
† Compared with patients with acute myocardial infarction.

Table 2
Angiographic and procedural characteristics

	Pre-SES Group (n = 450)	SES Group (n = 508)	p Value
Treated coronary vessel*			
Left anterior descending artery	59%	59%	0.8
Left circumflex artery	33%	32%	0.7
Right artery	34%	39%	0.2
Left main artery	2%	3%	0.6
Bypass graft	2%	3%	0.2
Lesion type			
A	20%	22%	0.4
B1	32%	31%	0.7
B2	50%	49%	0.8
C	30%	43%	<0.01
Glycoprotein IIb/IIIa inhibitor	33%	19%	<0.01
Clopidogrel prescription (mo)	2.9 ± 2.0	4.0 ± 2.0	<0.01
Bifurcation stenting	8%	16%	<0.01
No. of stented segments	1.8 ± 0.9	2.0 ± 1.0	<0.01
No. of implanted stents	1.9 ± 1.2	2.1 ± 1.4	<0.01
Individual stent length ≥33 mm	10%	35%	<0.01
Total stented length per patient (mm)	30.1 ± 19.6	38.7 ± 28.7	<0.01
Nominal stent diameter ≤2.5 mm	23%	36%	<0.01
Postdilatation with a balloon ≥0.5 mm larger	19%	55%	<0.01
Angiographic success of all lesions	97%	97%	1.0

Values are numbers (percentages) or means ± SDS.
* Expressed as percentage of patients with vessel type treated. Total exceeds 100%.

months, unless 1 of the following was present: multiple SES implantation (>3 stents), total stented length >36 mm, persistent total occlusion, and bifurcations. In these cases, clopidogrel was maintained for ≥6 months.

Our primary end point was major adverse clinical events (MACEs) at 3-year follow-up. MACEs were defined as a composite of all-cause death, nonfatal myocardial infarction, or target vessel revascularization. Target vessel revascularization was defined as a reintervention driven by any lesion located in the same coronary vessel. A secondary end point was target lesion revascularization, defined as treatment of a lesion in the stent or within 5 mm of the stent borders. Myocardial infarction was diagnosed by an increase in creatine kinase-MB fraction of 3 times the upper limit of normal, according to American Heart Association/American College of Cardiology guidelines.[18,19] Late stent thrombosis was defined as angiographically defined thrombosis with Thrombolysis In Myocardial Infarction grade 0 or 1 flow or the presence of a flow-limiting thrombus, occurring ≥1 month after drug-eluting stent implantation accompanied by acute symptoms.[20] Hypercholesterolemia was defined as a fasting serum cholesterol level >5.5 mmol/L or use of lipid-lowering therapy at the time of the procedure.

Patients were contacted at 6 months and at 1, 2, and 3 years. Follow-up will continue yearly until 5 years. Survival status was obtained through municipal civil registries. Health questionnaires inquiring about postdischarge repeat coronary interventions (surgical or percutaneous), myocardial infarction, and medication usage were subsequently sent to all living patients. Follow-up information was prospectively entered into a dedicated database. If a patient had a myocardial infarction or reintervention at another center, medical records or discharge letters were requested and systematically reviewed. Local cardiologists or general practitioners were also contacted as necessary. Follow-up was available for 97.5% of our patients at a mean time of 1,095 ± 265 days.

Continuous variables are presented as mean ± SD and were compared by Student's *t* test. Categorical variables are presented as counts and percentages and were compared by Fisher's exact test. The cumulative incidence of adverse events was estimated according to the Kaplan-Meier method, and curves were compared using log-rank test. Separate Cox regression analyses were performed to identify independent predictors of adverse events using clinical, angiographic, and procedural variables listed in Tables 1 and 2. Cox proportional hazards regression models were used to control for differences between groups and independent predictors of outcome. Final results are presented as adjusted hazard ratios. Patients lost to follow-up were considered at risk until the date of final contact, at which point they were censored.

Baseline and procedural characteristics have been previously described and are presented in Tables 1 and 2. Approximately 50% of patients in the 2 groups were admitted with acute coronary syndromes, and diabetes was present in 16%. Patients treated with SESs had significantly more multivessel disease, more type C lesions, more bifurcation stenting, more segments stented, and more stents used (p <0.01).

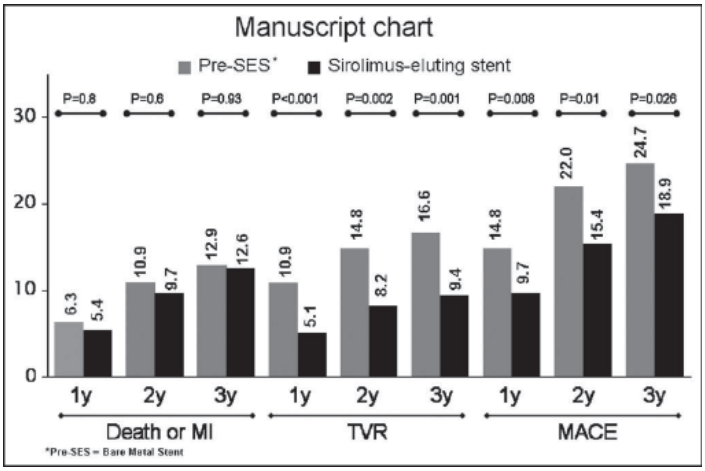

Figure 1. Cumulative incidence of adverse events at 1, 2, and 3 years in patients treated with SESs *(black bars)* and BMSs *(gray bars)*. MI = myocardial infarction; TVR = target vessel revascularization.

Further, in the SES group, long stents and stents with smaller diameters were more frequently used. Periprocedural administration of glycoprotein IIb/IIIa inhibitors was more frequent in the pre-SES phase (33% vs 19%; $p < 0.01$). The angiographic success rate was similar in the 2 groups.

The 1-, 2-, and 3-year results are shown in Figure 1. At 1 year, the cumulative risk of MACEs (a composite of death, myocardial infarction, or target vessel revascularization) was significantly decreased in the SES group (9.7% vs 14.8% in the pre-SES group, hazard ratio 0.62, 95% confidence interval 0.44 to 0.89, $p = 0.008$). This difference remained significant after 2 years, with an incidence of 15.4% in the SES group versus 22% in the pre-SES group (hazard ratio 0.68, 95% confidence interval 0.50 to 0.91, $p = 0.01$). The difference in outcomes between groups was mainly due to a decreased need for target vessel revascularization in the SES group. The cumulative incidence of death and death or myocardial infarction remained similar between groups after 1 and 2 years of follow-up.

At 3 years, there were no significant differences in cumulative mortality between the SES and pre-SES groups (8.7% vs 7.9%, hazard ratio 1.09, 95% confidence interval 0.70 to 1.71, $p = 0.69$; Figure 2). The combined end point of death or myocardial infarction was also similar at 12.9% in the SES group versus 12.6% in the pre-SES group (hazard ratio 1.02, 95% confidence interval 0.71 to 1.45, $p = 0.93$; Figure 2). The 3-year incidence of the combined end point of MACEs remained lower in the SES group compared with the pre-SES group (18.9% vs 24.7%, unadjusted hazard ratio 0.73, 95% confidence interval 0.56 to 0.96, $p = 0.026$; Figure 2) and was driven by a significantly lower incidence of target vessel revascularization in the SES group (9.4% vs 16.6% respectively, hazard ratio 0.54, 95% confidence interval 0.37 to 0.78, $p = 0.001$; Figure 2). Similarly, the difference in target lesion revascularization remained significantly lower at 7.5% in the SES group compared with 12.6% in the pre-SES group (hazard ratio 0.57, 95% confidence interval 0.38 to 0.87, $p = 0.01$).

Between 2 and 3 years, 31 events occurred (Table 3). Fourteen patients in the SES group died: 3 were classified as cardiac and 6 as noncardiac. Four patients died suddenly of unknown causes and in 1 case the cause of death was unknown. Seven patients in the pre-SES population died: 4 died of cardiac death and 3 died from an unknown cause. Three myocardial infarctions occurred in the SES group compared with 2 in the pre-SES group. Further, in the SES group, 6 target vessel revascularizations occurred compared with 7 in the pre-SES group. Target lesion revascularization occurred in 3 patients in the SES group versus 5 in the pre-SES group. Overall, MACE rates were 18 versus 12 in the SES and pre-SES groups, respectively, between 2 and 3 years of follow-up. In addition, 2 patients in the SES group versus 3 in the pre-SES group underwent revascularization in a different vessel. There was no significant difference between groups for any of these different event rates. Two cases of angiographically documented late stent thrombosis occurred in the SES group. The first patient, a 60-year-old woman, was admitted 36 months after a procedure with acute myocardial infarction. Clopidogrel was contraindicated because of gastrointestinal bleeding of unknown origin after the procedure. The second patient, a 71-year-old man, was admitted with cardiogenic shock 26 months after the procedure and died.

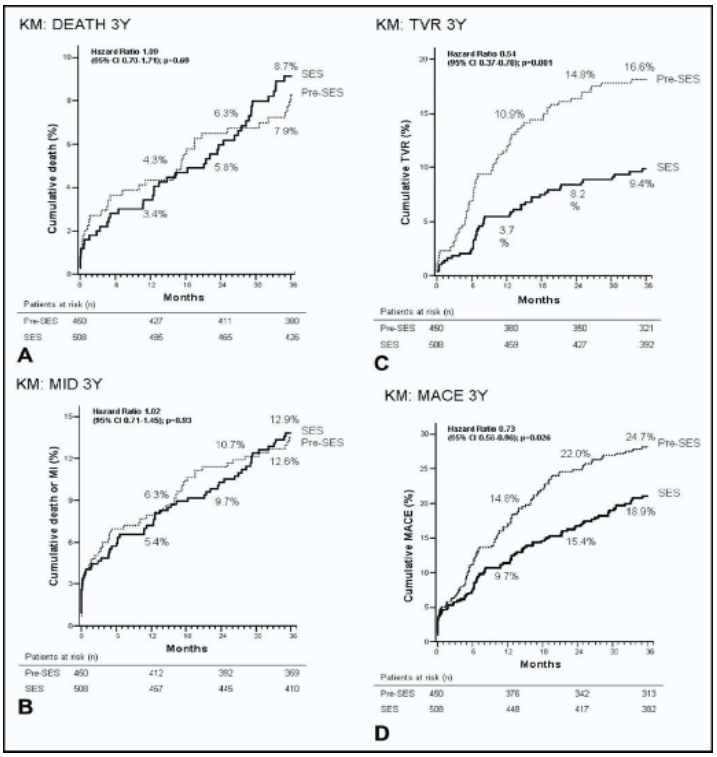

Figure 2. Three-year adverse events in patients treated with BMSs (pre-SES) and SESs: *(A)* cumulative risk of death, *(B)* death or myocardial infarction (MID), *(C)* target vessel revascularization, *(D)* death, myocardial infarction, or target vessel revascularization. CI = confidence interval; other abbreviations as in Figure 1.

To identify independent predictors of MACEs and target vessel revascularization at 3 years, Cox regression analyses were performed for all baseline and procedural characteristics listed in Tables 1 and 2 (Table 4). Age, diabetes, hypertension, previous angioplasty, multivessel disease, cardiogenic shock at presentation, lesion type B2 or C, treatment of the left main coronary artery, and total stented length (per 10-mm increment) were significant predictors of MACEs at 3 years. In addition, saphenous graft treatment and the use of SESs were protective. Further, diabetes, hypertension, previous percutaneous coronary intervention, acute coronary syndrome at presentation, lesion type B2 or C, and total stented length (per 10-mm increment) were significant predictors of target vessel revascularization, whereas acute coronary syndrome at entry and the use of SESs were protective.

When adjusted for these independent predictors of MACE and target vessel revascularization, the use of SESs remained significantly protective for MACEs (hazard ratio 0.61, 95% confidence interval 0.46 to 0.81, $p = 0.001$) and target vessel revascularization (hazard ratio 0.44, 95% confidence interval 0.30 to 0.65, $p < 0.001$) at 3 years of follow-up.

Discussion

Currently, there are no long-term results of the unrestricted use of SESs in a real-world patient population. The present report shows that SESs remain superior to BMSs in decreasing the need for reinterventions in the long term, even after adjustment for independent predictors of adverse events. At 3 years, the use of SESs resulted in a relative decrease of

Table 3
Events between two and three years of clinical follow-up

Variable	Pre-SES Group (n = 450)	SES Group (n = 508)	p Value
Death	7 (1.6%)	14 (2.8%)	0.27
Myocardial infarction	2 (0.4%)	3 (0.6%)	1.00
TLR	5 (1.1%)	3 (0.6%)	0.48
Target vessel revascularization (including TLR)	7 (1.8%)	6 (1.2%)	0.78
Nontarget vessel revascularization	3 (0.7%)	2 (0.4%)	0.67
MACEs	12 (2.7%)	18 (3.5%)	0.46

TLR = target lesion revascularization.

Table 4
Independent predictors of major adverse cardiac events and target vessel revascularization by Cox separate regression analysis

	HR	95% CI
MACEs		
Cardiogenic shock	3.61	1.91–6.82
Left main treatment	2.70	1.47–4.95
Diabetes mellitus	2.08	1.53–2.84
Lesion type B2 or C	1.74	1.22–2.47
Multivessel disease	1.63	1.23–2.16
Previous angioplasty	1.57	2.14–2.16
Hypertension	1.38	1.05–1.81
Total stented length (per 10-mm increment)	1.10	1.05–1.15
Age	1.02	1.00–1.03
Use of SESs	0.73	0.56–0.96
Saphenous graft treatment	0.41	0.23–0.74
Target vessel revascularization		
Diabetes mellitus	2.21	1.48–3.31
Lesion type B2 or C	1.69	1.06–2.69
Previous intervention	1.55	1.02–2.36
Hypertension	1.49	1.04–2.15
Total stented length (per 10-mm increment)	1.11	1.05–1.18
Acute coronary syndrome at presentation	0.60	0.41–0.86
Use of SESs	0.54	0.37–0.78

CI = confidence interval; HR = hazard ratio.

39% in MACEs, whereas target vessel revascularization was decreased by 56% compared with the use of BMSs. No difference was found between groups in terms of death and myocardial infarction. These findings are particularly noteworthy because patients treated with SESs generally had more complex disease than those treated with BMSs; however, they are in accordance with the findings of a large meta-analysis on drug-eluting stents and many other publications that showed no difference in long-term survival outcome, not even compared with medical therapy.[13,21,22]

Between 2 and 3 years of follow-up, relatively few nontarget vessel revascularizations occurred in the 2 groups (3 in the pre-SES group vs 2 in the SES group). Twenty-one patients died. Whether the 4 patients in the SES group who died suddenly of an unknown cause between 2 and 3 years died of stent thrombosis remains an important question. However, because of the low frequency of postmortems, a detailed analysis of the exact causes of death was not feasible. In terms of overall causes of death, our results concur with those of several trials, which reported an almost equal incidence of cardiac and noncardiac causes of death after ±2 years of follow-up in this type of population.[1–5]

Patients treated for left main stenosis or complex lesions (type B2/C) were independently associated with a worse MACE outcome at 3 years. Several trials, such as the Future Revascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease (FREEDOM), COMparison of Bypass Surgery and AngioplasTy Using Sirolimus-eluting Stent in Patients With Unprotected Left Main Coronary Artery Disease (COMBAT), Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX), and Coronary Artery Revascularisation in Diabetes (CARDIA) trials, are currently ongoing to investigate whether these patients would benefit more from coronary artery bypass surgery.[23,24]

Several post hoc subanalyses were performed and, although they concern relatively small numbers of patients, the results give an impression of the outcome of different patient groups treated with SES after 3 years of follow-up (Figure 3). In patients treated for acute coronary syndromes at entry, the use of SESs demonstrated a decrease of 70% in clinically driven target vessel revascularization ($p = 0.006$) at 1 year.[16] At 3 years, we found a risk decrease in target vessel revascularization of 38%, with only a trend toward a more favorable outcome with the use of SESs ($p = 0.1$; Figure 3). The same finding was observed in patients presenting with an acute myocardial infarction and patients treated for multivessel disease and bifurcation lesions. Further, the benefit of SESs was not statistically significant after 1 year or at 3 years in women and diabetic patients. Although limited to 1 year of follow-up, previous studies showed that diabetic patients treated with SESs had a better outcome than those treated in a conventional way.[25] This was a post hoc subgroup analysis with small numbers of patients, and the results justify larger, longer term, and more detailed studies with these subpopulations.

With MACE rates remaining constant between 1 and 3 years, no late clinical restenotic phenomenon was observed. It is clear that the long-term beneficial effects of SESs are mainly due to the marked decrease in restenosis rates in the first year. After 1 year, the Kaplan-Meier curves for target vessel revascularization and MACEs remain essentially parallel, but, more importantly, the beneficial results are sustained. These findings are in accordance with the 2-year angiographic follow-up data after SES implantation and with the recently published 3-year results of the Randomized study with the sirolimus-eluting Velocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions (RAVEL) trial.[6,26,27] The present study extends these observations to a population that is representative of 1 treated in a tertiary intervention center with the unrestricted use of SESs.

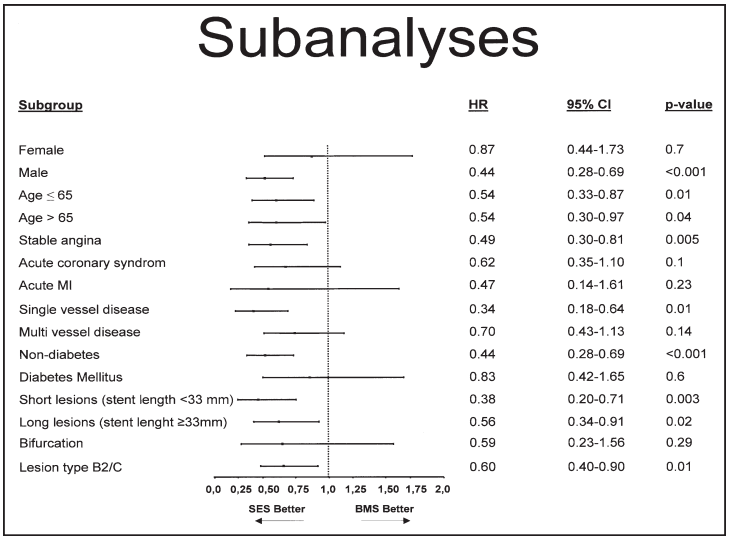

Figure 3. Hazard ratios (HRs) of stent type at 3-year follow-up for target vessel revascularization in subgroups of patients according to baseline and procedural characteristics. Other abbreviations as in Figure 2.

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Appendix

The following operators were involved in the procedures of the discussed patient population: Chourmouzios A. Arampatzis, MD; Eugene McFadden, MD, PhD; Pim J. de Feyter, MD, PhD; Willem J. van der Giessen, MD, PhD; Sjoerd H. Hofma, MD, PhD; Angela Hoye, MBChB, MRCP; Peter P.T. de Jaegere, MD, PhD; Evelyn Regar, MD, PhD; Patrick W. Serruys, MD, PhD; Georgios Sianos, MD, PhD; and Pieter C. Smits, MD, PhD.

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Chapter 6

Four-year clinical follow-up of the rapamycin-eluting stent evaluated at Rotterdam Cardiology Hospital registry

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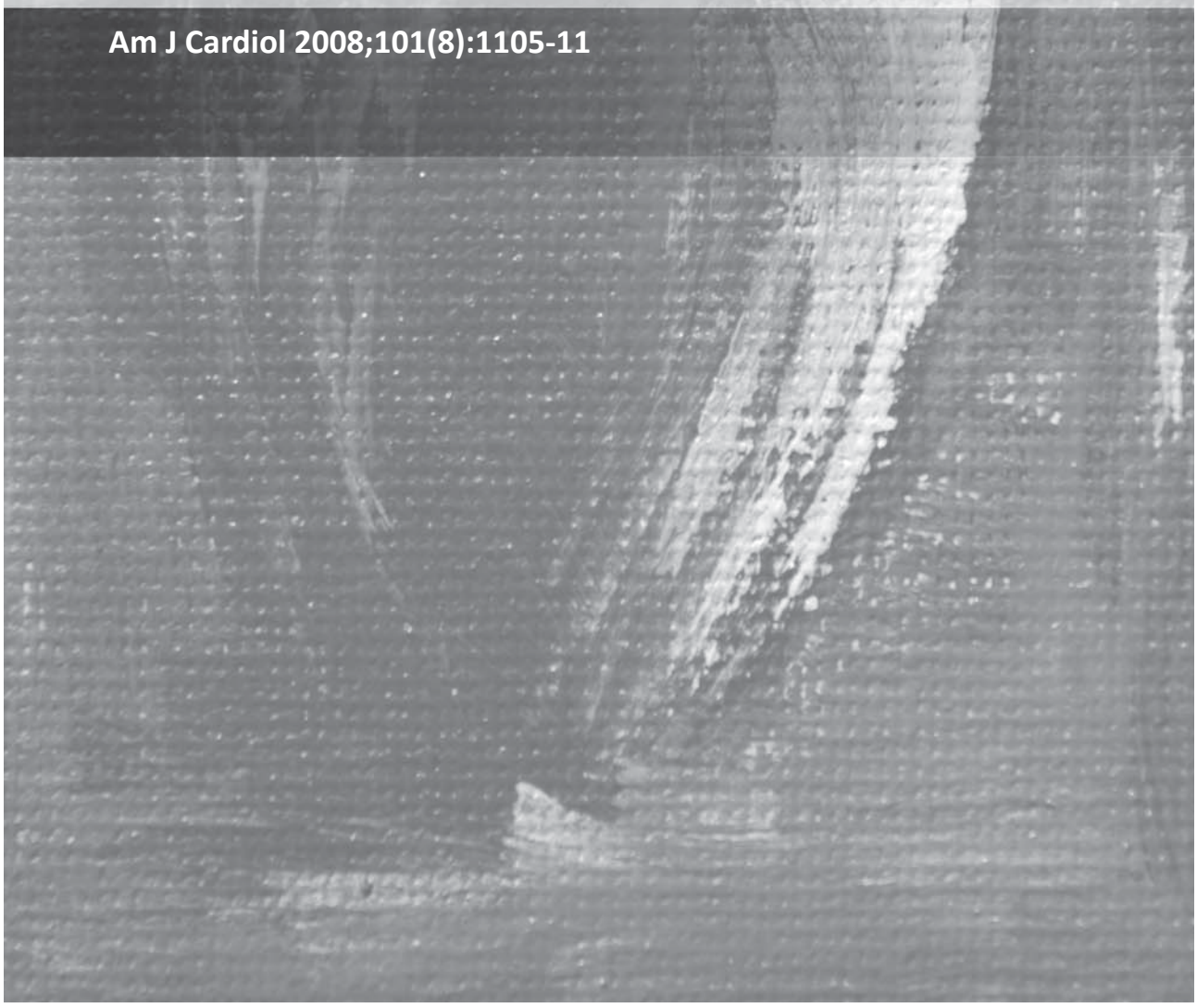

Four-Year Clinical Follow-Up of the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital Registry

Joost Daemen, MD, Neville Kukreja, MRCP[a], Piet-Hein van Twisk, MA, MBBS, MRCP, Yoshinobu Onuma, MD, Peter P.T. de Jaegere, MD, PhD, Ron van Domburg, PhD, and Patrick W. Serruys, MD, PhD*

Although the safety of drug-eluting stents has been under considerable scrutiny, limited real-world follow-up data extending up to 4 years are available. The randomized clinical trials carefully selected patients and are not reflective of everyday practice. From April to October 2002, 508 consecutive patients treated with sirolimus-eluting stents (SES) were enrolled. The control group consisted of 450 patients treated with bare-metal stents during the preceding 6 months. After 4 years of follow-up, the incidence of composite major adverse clinical events (all-cause death, myocardial infarction, or target vessel revascularization) was found to be significantly lower in the SES group (23.0% vs 28.7%, adjusted hazard ratio 0.66, 95% confidence interval 0.51 to 0.86), as were rates of target vessel revascularization (12.2% vs 17.8%, adjusted hazard ratio 0.57, 95% confidence interval 0.39 to 0.83). There were no differences in all-cause mortality (10.5% for SES vs 10.6% for bare-metal stents, p = 0.9) or in the rates of cardiac death (4.5% vs 6.9%, p = 0.1). Although there was no difference in overall stent thrombosis (2.3% vs 2.2%, p = 1.0), SES had a higher rate of very late stent thrombosis (1.4% vs 0%, p = 0.02), balanced by a lower rate of early stent thrombosis (0.4% vs 1.8%, p = 0.05). In conclusion, after 4 years, SES were found to remain safe and effective compared with bare-metal stents. Nevertheless, the higher rate of very late stent thrombosis remains a concern. Longer term follow-up will be required to determine the extent of this problem. **(Am J Cardiol 2008;101:1105–1111)**

Long-term analyses of randomized trials of drug-eluting stents (DES) show a persisting benefit of DES on restenosis and target lesion revascularization, whereas mortality rates with DES and bare-metal stents (BMS) are equivalent, despite concerns regarding late stent thrombosis.[1–5] Inevitably, these randomized trials have selective inclusion criteria, but in the real world, DES are often used beyond their labeled indications, for example, in bifurcation lesions, coronary artery bypass grafts, chronic total occlusions, long lesions requiring multiple overlapping stents, and acute myocardial infarction (MI).[6] Despite using sirolimus-eluting stents (SES) for "off-label" indications in a considerable number of cases, we have previously reported an ongoing benefit of SES after 3 years of follow-up in real-world consecutive patients.[7] Here, we present the clinical outcomes after 4 years.

Methods

The Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry has already been described.[8] On April 16, 2002, our institution commenced the use of SES (Cypher; Cordis Corporation, Miami Lakes, Florida) as the default strategy for every percutaneous coronary intervention. In the first 6 months of enrollment, 508 patients with de novo lesions were treated exclusively with SES (the SES group) and compared with a group of 450 consecutive patients treated with BMS for de novo lesions in the preceding 6 months (the pre-SES group), matched for stent diameter.[9] The protocol was approved by the hospital's ethics committee and is in accordance with the Declaration of Helsinki. Written informed consent was obtained from every patient.

All procedures were performed following current standard procedural guidelines as previously reported.[10] Angiographic success was defined as residual stenosis <30% by visual analysis in the presence of Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow. All patients were advised to maintain lifelong aspirin. At least 1 month of clopidogrel treatment (75 mg/day) was recommended for patients treated in the pre-SES phase. For patients treated with SES, clopidogrel was prescribed for ≥3 months, unless 1 of the following was present: multiple SES implantation (>3 stents), total stented length >36 mm, chronic total occlusion, or bifurcation treatment. In these patients, clopidogrel was maintained for ≥6 months.

The prespecified primary end point was major adverse clinical events (MACEs), defined as a composite of all-cause death, nonfatal MI, or target vessel revascularization (TVR).[8] MI was diagnosed by an increase in creatine kinase-MB fraction of 3 times the upper limit of normal, according to American Heart Association and American College of Cardiology guidelines.[11,12] Stent thrombosis was defined as angiographically documented thrombus with

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Table 1
Baseline characteristics

Variable	BMS (n = 450)	SES (n = 508)	p Value
Men	70.4%	67.9%	0.4
Age (yrs)	60.8 ± 11.0	61.1 ± 11.0	0.7
Body mass index (kg/m^2)	26.6 ± 3.6	27 ± 4	0.1
Previous MI	39.7%	30.2%	0.02
Previous coronary bypass surgery	8.0%	9.3%	0.5
Previous percutaneous intervention	18.0%	18.8%	0.8
Multivessel coronary disease	47.8%	54.2%	0.05
Hypercholesterolemia*	55.3%	55.3%	1.0
Hypertension‡	37.6%	41.3%	0.2
Family history of coronary disease	28.2%	32.5%	0.2
Current smoker	34.0%	30.7%	0.3
Diabetes mellitus	14.9%	17.7%	0.2
Clinical presentation			0.6
Stable angina pectoris	47.6%	44.7%	
Unstable angina pectoris	34.7%	37.2%	
Acute MI	17.8%	18.1%	
Cardiogenic shock†	11.3%	9.8%	0.7

Data are expressed as mean ± SD or percentages.
* Defined as fasting total cholesterol >5mmol/L (193 mg/dl) or the use of lipid-lowering therapy.
† Refers to patients with acute MIs.
‡ Defined as blood pressure >140/90 mm Hg or treatment for hypertension.

Table 2
Procedural characteristics

Variable	BMS (n = 450)	SES (n = 508)	p Value
Coronary vessel treated*			
Left anterior descending	59.3%	58.7%	0.8
Right	34.0%	38.6%	0.1
Left circumflex	33.1%	31.7%	0.6
Saphenous vein graft	2.0%	3.3%	0.2
Left main	2.2%	3.0%	0.5
ACC/AHA lesion type			
A	19.6%	21.9%	0.4
B1	31.8%	30.7%	0.7
B2	49.6%	48.6%	0.8
C	29.8%	42.5%	<0.01
Bifurcation	7.8%	15.7%	<0.01
Nominal stent length ≥33 mm	9.8%	35.0%	<0.01
No. of stents	1.8 ± 1.1	2.2 ± 1.4	<0.01
Total stent length (mm)	30.1 ± 19.6	38.8 ± 27.9	<0.01
Glycoprotein IIb/IIIa inhibitor used	33.3%	19.3%	<0.01
Average stent diameter (mm)	3.15 ± 0.31	2.85 ± 0.21	<0.01
Angiographic success	97.3%	97.2%	0.9
Clopidogrel duration (mo)	1 ± 0.1	4.2 ± 2	<0.01

Data are expressed as mean ± SD or percentages.
* Patients with each vessel type, hence total >100%.
ACC = American College of Cardiology; AHA = American Heart Association.

Table 3
Cumulative incidence of adverse events

Variable	BMS	SES	p Value
Death	48 (10.6%)	53 (10.5%)	0.9
MI	23 (5.2%)	21 (4.2%)	0.5
TVR	78 (17.8%)	60 (12.2%)	0.02
Composite MACEs	127 (28.7%)	115 (23.0%)	0.05
Stent thrombosis	10 (2.2%)	12 (2.3%)	1.0

TIMI grade 0 or 1 flow, accompanied by acute symptoms (consistent with the definition of definite stent thrombosis as recommended by the Academic Research Consortium).[13,14] The timing of stent thrombosis was categorized into early (<30 days after implantation), late (30 days to 1 year), or very late (>1 year).[14]

Follow-up survival data for all patients were obtained from municipal civil registries. The causes of death were classified according to the International Classification of Diseases and Related Health Problems, 10th Revision. A health questionnaire was subsequently sent to all living patients with specific inquiries on rehospitalization and MACEs. Because ours is the principal regional cardiac referral center, repeat procedures (percutaneous and surgical) are normally performed at our institution and recorded prospectively in our database. For patients who had adverse events at other centers, medical records or discharge summaries from the other institutions were systematically reviewed. General practitioners, referring cardiologists, and patients were contacted as necessary if further information was required.

Continuous variables were compared using Student's *t* test and are presented as mean ± SD. Categorical variables were compared using either Fisher's exact test or Pearson's chi-square test (both 2-sided) and are presented as counts and percentages. The cumulative incidence of adverse events was estimated according to the Kaplan-Meier method, and curves were compared using the log-rank test. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. Separate Cox regression analyses were performed to identify predictors of adverse events, using the clinical, angiographic, and procedural variables listed in Tables 1 and 2. Variables with a significance of $p < 0.05$ were entered into a Cox multivariate regression analysis; the final results are presented as adjusted hazard ratios (HRs) with 95% confidence intervals (CIs).

Results

Complete follow-up was available for 95.5% of patients. The baseline clinical characteristics of the 2 groups were similar except for a higher prevalence of multivessel disease in the SES group (54.2% vs 47.8%, $p = 0.05$) and a lower incidence of previous MI (30.2% vs 39.7%, $p = 0.02$). Full baseline and procedural details are listed in Tables 1 and 2. Overall, patients treated with SES underwent more complex treatment (more type C lesions, more bifurcations, more stents used, longer total stent length, and smaller average stent diameter). As previously reported, overall 38% of SES group underwent repeat coronary angiography in the first year, while none of the BMS group underwent a scheduled restudy.[9] After the first year, all cases of repeat angiography were clinically mandated.

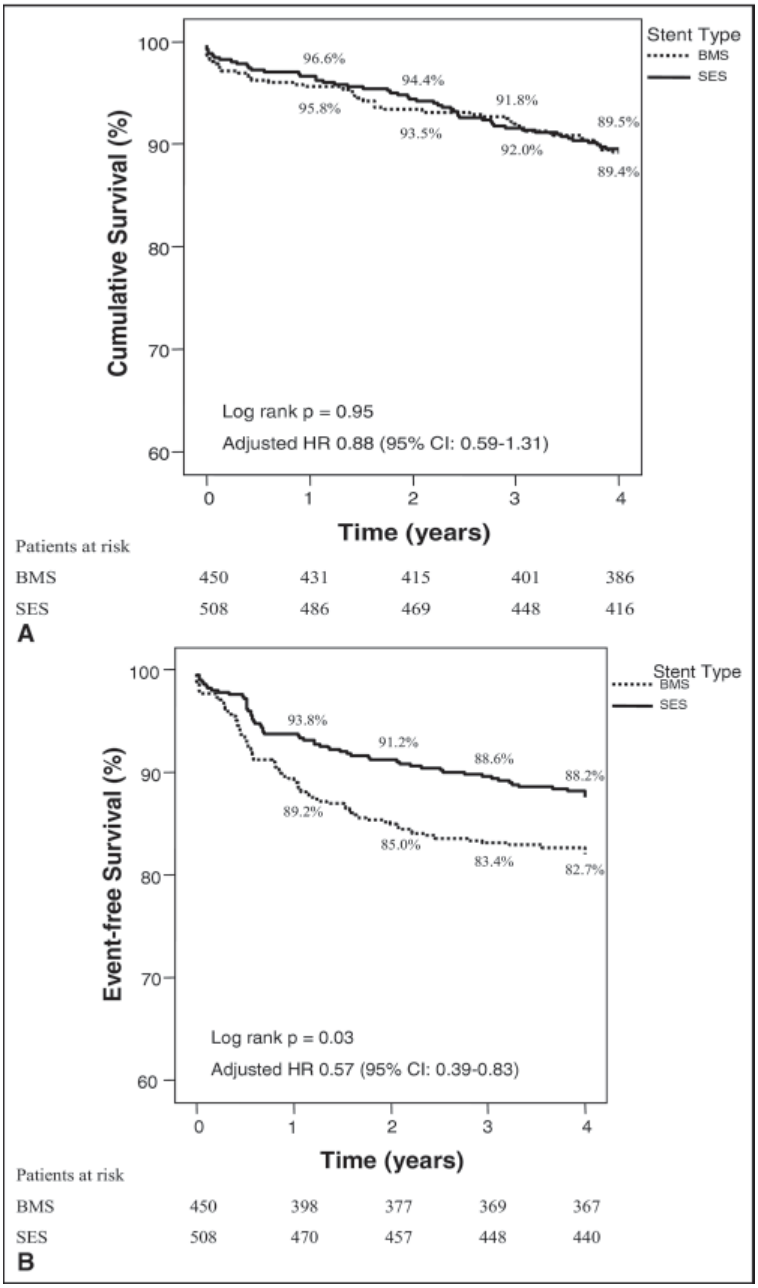

Figure 1. Kaplan-Meier survival curves for *(A)* freedom from death, *(B)* freedom from TVR, *(C)* freedom from composite MACEs (defined as or TVR), and *(D)* freedom from stent thrombosis.

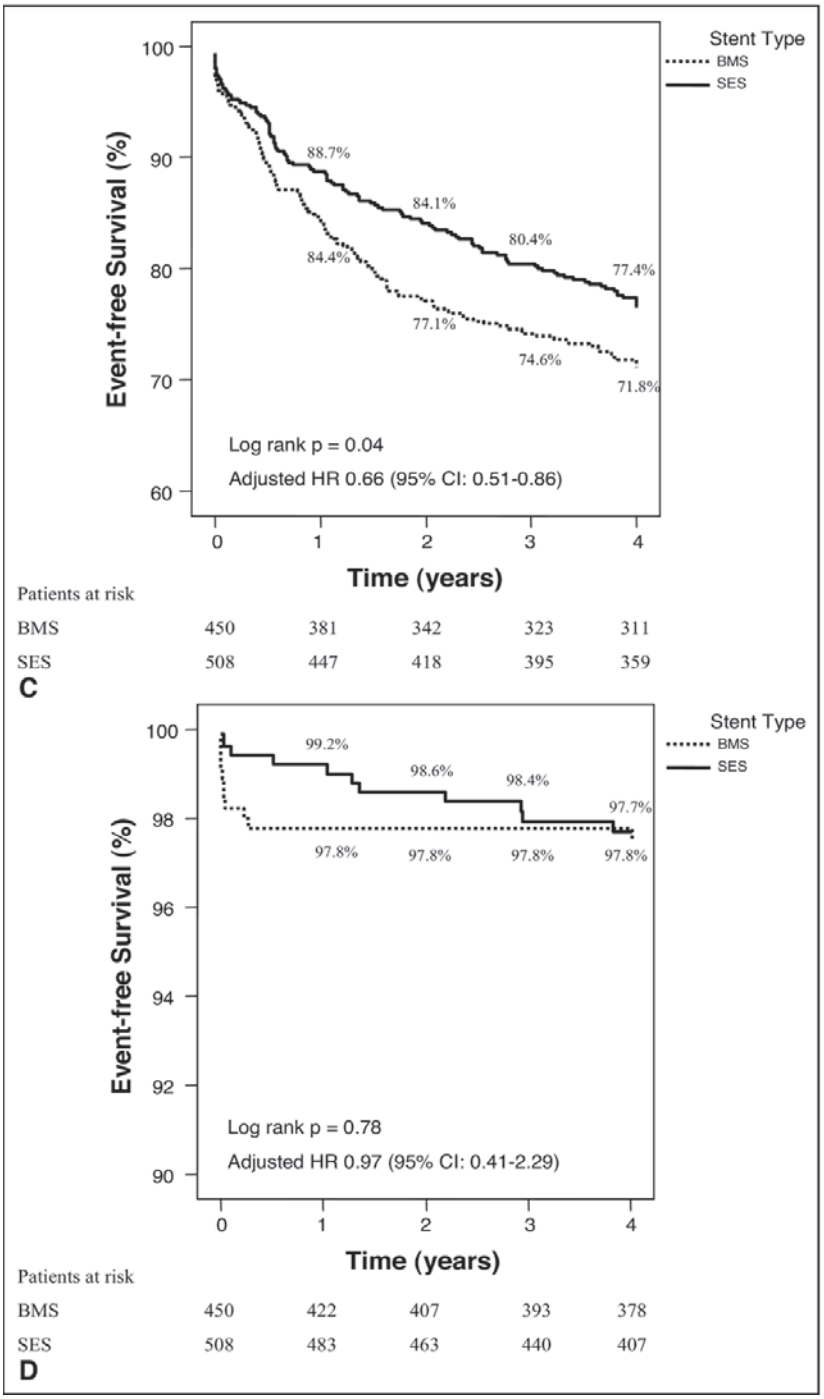

Figure 1. *(continued).*

Table 4
Events between 3 and 4 years of follow-up

Variable	BMS	SES	p Value
Death	11 (2.4%)	10 (2.0%)	0.66
MI	1 (0.2%)	2 (0.4%)	1.0
TVR	5 (1.1%)	10 (2.0%)	0.31
Composite MACEs	13 (2.9%)	19 (3.7%)	0.48
Stent thrombosis	0 (0%)	1 (0.1%)	1.0
Other revascularization	2 (0.4%)	4 (0.8%)	0.69

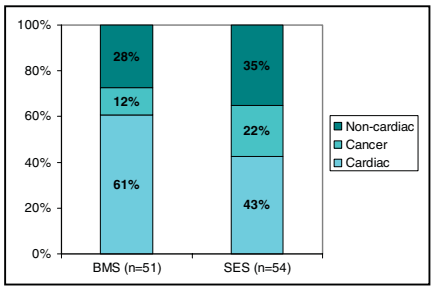

Figure 2. Causes of death expressed as percentages of all deaths in each group. There were no statistically significant differences for any of the categories.

Table 5
Timing of definite stent thrombosis

Variable	BMS	SES	p Value
Early	8 (1.8%)	2 (0.4%)	0.05
Acute	4 (0.9%)	1 (0.2%)	0.2
Subacute	4 (0.9%)	1 (0.2%)	0.2
Late	2 (0.4%)	2 (0.4%)	1.0
Very late	0 (0%)	7 (1.4%)	0.02
Total	10 (2.2%)	11 (2.2%)	1.0

Early stent thrombosis was defined as occurring within 30 days of the index procedure, acute stent thrombosis within 24 hours, subacute stent thrombosis from 24 hours to 30 days, late stent thrombosis from 30 days to 1 year, and very late stent thrombosis >1 year after the index procedure.

The clinical outcomes after 3 years of follow-up have already been reported.[7] The event rates after 4 years are listed in Table 3. The cumulative survival rates for death, TVR, overall MACEs, and stent thrombosis are displayed in Figure 1. As indicated in Table 4, there were no statistically significant differences in the occurrence of any clinical end point between 3 and 4 years of follow-up, although there was a trend toward a higher rate of TVR in the SES group. The cause of death was ascertained in all cases. Analysis of the causes of death showed no significant differences between the 2 groups during 4 years of follow-up, as demonstrated in Figure 2.

Further examination of patients with stent thrombosis revealed that despite no statistically significant difference in overall stent thrombosis rates between the 2 groups, the BMS group had a higher incidence of early stent thrombosis, whereas the SES group had a higher incidence of very late stent thrombosis, as listed in Table 5. The status of antiplatelet therapy at the time of stent thrombosis was available for 18 of the 21 patients. One BMS patient with early stent thrombosis and 1 DES patient with very late stent thrombosis had recently stopped clopidogrel (within 1 week). The details of antiplatelet therapy at the time of stent thrombosis are shown in Figure 3.

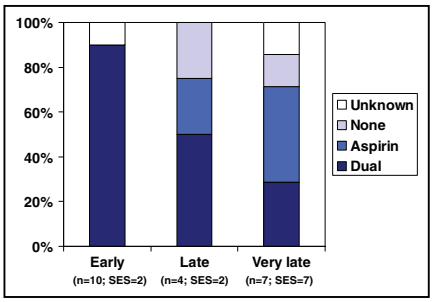

Figure 3. Antiplatelet therapy at the time of stent thrombosis.

Table 6
Independent predictors of target vessel revascularization and major adverse clinical events

Variable	HR	95% CI
TVR		
Diabetes mellitus	1.80	1.18–2.77
AHA/ACC lesion type B2 or C	1.78	1.08–2.95
Previous percutaneous intervention	1.62	1.06–2.46
Treatment with SES	0.57	0.39–0.83
Prespecified composite MACEs		
Cardiogenic shock	3.59	1.81–7.14
Left main treatment	1.98	1.06–3.73
Diabetes mellitus	1.81	1.34–2.43
Previous percutaneous intervention	1.52	1.12–2.05
Total stent length (per 10-mm increment)	1.11	1.00–1.23
Treatment with SES	0.66	0.51–0.86

Abbreviations as in Table 2.

The independent predictors of mortality were cardiogenic shock (HR 5.79, 95% CI 2.46 to 13.6), left main coronary artery treatment (HR 2.17, 95% CI 1.00 to 4.17), diabetes mellitus (HR 1.78, 95% CI 1.11 to 2.85), age (per 10-year increment HR 1.42, 95% CI 1.16 to 1.74), and angiographic success (HR 0.43, 95% CI 0.19 to 0.98). The only independent predictors of definite stent thrombosis were the presence of insulin-dependent diabetes (HR 3.87, 95% CI 1.13 to 13.3), acute MI at presentation (HR 2.58, 95% CI 1.03 to 6.44), and treatment of the left anterior descending artery (HR 0.33, 95% CI 0.11 to 0.99). The presence of diabetes was the only independent predictor of MI (HR 2.16, 95% CI 1.12 to 4.15). All independent predictors for TVR or composite MACEs are listed in Table 6. Treatment with SES did not predict

death (adjusted HR 0.88, 95% CI 0.59 to 1.31), MI (adjusted HR 0.67, 95% CI 0.36 to 1.23), or overall stent thrombosis (adjusted HR 0.97, 95% CI 0.41 to 2.29) but was protective against TVR (adjusted HR 0.57, 95% CI 0.39 to 0.83) and composite MACEs (adjusted HR 0.66, 95% CI 0.51 to 0.86).

Discussion

In this report, we have described long-term clinical outcomes after the use of SES in an all-comers, real-world registry. We have previously reported results after 1, 2, and 3 years of follow-up, all of which have demonstrated no difference in mortality but a continued benefit of SES with respect to TVR and overall MACEs.[7,9,15] To date, there appears to be no diminution of the protective effect of SES treatment with time; after 2 years, the HR for TVR was 0.53 (95% CI 0.36 to 0.79), and the HR for composite MACEs was 0.68 (95% CI 0.50 to 0.91), while after 4 years, these values were 0.57 (95% CI 0.39 to 0.83) and 0.66 (95% CI 0.51 to 0.86), respectively.[15] Thus, after 4 years, the beneficial treatment effect of SES on TVR and composite MACEs was maintained, with no evidence of any late "catch-up" effect of restenosis. Although 4-year follow-up data are available for the randomized trials of SES, our data provide the longest possible follow-up for more complex patients because we used SES as a default treatment strategy for all patients as soon as they became commercially available.

There have been several recent reports addressing the safety of DES, particularly with regard to mortality and stent thrombosis.[1–5,16] Two analyses examined 1,748 patients enrolled in the 4 main randomized SES trials (the Randomized Study With the Sirolimus-Eluting Velocity Balloon-Expandable Stent [RAVEL], Sirolimus-Eluting Stent in Coronary Lesions [SIRIUS], Canadian Sirolimus-Eluting Stent in Coronary Lesions [C-SIRIUS], and European Sirolimus-Eluting Stent in Coronary Lesions [E-SIRIUS]).[3,4] They found no significant differences in 4-year rates of mortality or stent thrombosis between SES and BMS. Another meta-analysis of 4,958 patients enrolled in randomized trials, including some complex patients such as those presenting with acute MI and those who underwent saphenous vein or chronic total occlusion treatment, also found no difference in the rate of death or stent thrombosis between SES and BMS patients after a maximum of 5 years of follow-up.[1] A recently reported network analysis of >18,000 patients enrolled in 38 randomized DES trials (including 6,771 patients treated with SES and 4,921 patients treated with BMS) also found no differences between SES and BMS with regard to mortality or stent thrombosis after up to 4 years of follow-up.[5] However, treatment with SES was protective against MI (HR 0.81, 95% CI 0.66 to 0.97).

The findings in this report are consistent with these recent meta-analyses: we also found no difference in mortality or stent thrombosis, although our overall mortality rates were higher than those reported in the meta-analyses of the randomized trials.[1,3,4] In our patients, we found no significant differences in mortality between the BMS and SES groups, although the SES patients underwent more complex treatment. Reassuringly, there was a trend toward a reduced rate of cardiac death with SES compared with BMS (4.5% vs 6.9%, $p = 0.1$).

Similarly, the rate of definite stent thrombosis (2.3% for SES vs 2.2% for BMS) was higher in our cohort than in a meta-analyses of the randomized trials (1.2% for SES vs 0.6% for BMS using the trial definitions for stent thrombosis and 1.5% for SES vs 1.7% for BMS using the Academic Research Consortium definitions for definite and probable stent thrombosis).[16] An analysis of >8,000 patients treated with DES (paclitaxel-eluting stents and SES) demonstrated an overall stent thrombosis rate of 2.9% after 3 years, with an ongoing incidence of late stent thrombosis of 0.6% per year.[2] Among the 3,875 patients treated with SES, the stent thrombosis rate was 2.7% after 4 years of follow-up.[17] In the present cohort, the early stent thrombosis rate was lower in the DES group, despite the DES patients' receiving glycoprotein IIb/IIIa antagonists less frequently and having undergone treatment of smaller vessels and longer lesions. Although early stent thrombosis is associated with suboptimal angiographic and intravascular ultrasound findings,[18] the pathophysiologic mechanisms of late stent thrombosis are quite different (related to delayed healing and incomplete endothelialization[19,20]); late stent thrombosis was more common in our DES cohort, although there were no significant differences in overall stent thrombosis. Most patients with stent thrombosis were on some form of antiplatelet therapy at the time of the event, but our patient numbers were too small to draw any conclusions from this. It remains unclear whether prolonged dual-antiplatelet therapy would have prevented these adverse events.

Data are available from several large registries from across the globe, all of which demonstrate decreased mortality with DES compared with BMS.[21–25] The Swedish Coronary Angiography and Angioplasty Registry (SCAAR) initially reported on 19,771 patients and found that after 3 years, treatment with DES was associated with a 32% increase in mortality.[26] However, subsequent data from SCAAR conformed to those found by the other registries, namely, that DES are associated with improved survival (although not reaching statistical significance in all).[23,27]

Although these registries included much larger numbers of patients, they tended to investigate patients treated at institutions at which DES and BMS were used concomitantly, raising the possibility of selection bias. Furthermore, only approximately 1/3 of these patients were treated with DES, and the maximum published follow-up data are for 3 years. As such, the mortality rates in our 2 patient groups were higher than in the other registries, whose outcomes data reflect the randomized trials more closely.

Our study also highlights the particular risk endured by diabetic patients: diabetes was an independent predictor of all clinical events, serving a reminder that these patients need aggressive risk factor and lifestyle management. Furthermore, treatment of the left main stem was associated with an increased 4-year risk for overall MACEs and death, suggesting that coronary artery bypass surgery should remain the preferred strategy for such patients. Ongoing randomized multicenter studies will shed further light on this issue.

In conclusion, after 4 years, therefore, it appears that the

safety of SES is maintained in real-world patients. Mortality rates for the BMS and SES groups were higher than those reported in the randomized trials; presumably, this reflects the higher risk and more complex nature of our series of consecutive all-comers as opposed to carefully selected randomized trial patients.

The major weakness of this study is that it was a single-center registry using a historically lower risk BMS control group. Furthermore, the patient numbers may have been too small to detect small differences in mortality.

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Chapter 7

Treatment of coronary artery disease of dialysis patients with sirolimus-eluting stents: 1-year clinical follow-up of a consecutive series of cases

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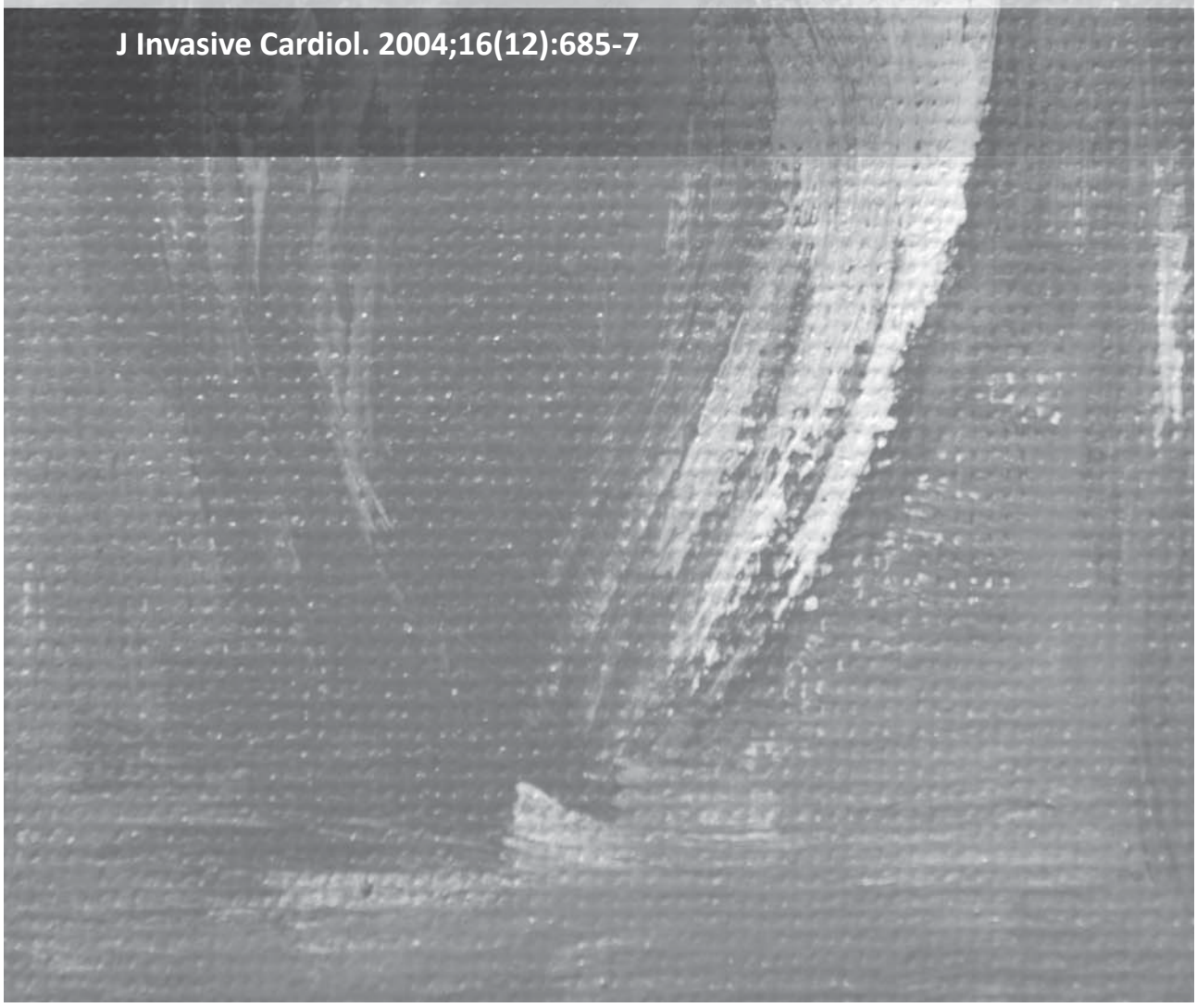

Treatment of Coronary Artery Disease of Dialysis Patients With Sirolimus-eluting Stents: 1-year Clinical Follow-up of a Consecutive Series of Cases

Joost Daemen, MD, Pedro Lemos, MD, Jiro Aoki, MD, Chourmouzios Arampatzis, MD, Angela Hoye, MD, Eugene McFadden, MD, Patrick Serruys, MD

ABSTRACT: From April 16, 2002 to October 16, 2002, 10consecutive patients with coronary disease on chronic dialysis were treated with sirolimus-eluting stents. Diabetes was present in 30% and half of the patients had multivessel coronary disease. On average, patients had been on dialysis for 5 years prior to the procedure (range: 2–15 years). Five patients were on hemodialysis and 5 patients were on peritoneal dialysis. Overall, 18 lesions were treated with 1.9 ± 1.1 sirolimus-eluting stents per patient. At a mean follow-up of 403 days, there were no cases of death, myocardial infarction, or target lesion revascularization.

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Key words: renal failure, dialysis, coronary disease, stent, restenosis, drug-eluting stent

In this preliminary series, sirolimus-eluting stent implantation appeared safe and effective for the treatment of dialysis patients with coronary artery disease. Dialysis patients are well known to be a high-risk population for cardiovascular morbidity and mortality, especially due to coronary atherosclerotic disease. However, the management of coronary disease in patients with end-stage renal failure is often problematic due to the presence of multiple co-morbidities and frequent limitations to drug prescription.[1] Moreover, these patients have been reported to be at a higher risk for short- and long-term complications after invasive treatment compared to non-dialysis patients.[2,3]

The overall impact of invasive coronary treatment in dialysis patients is an ongoing debate. In a recent report, coronary bypass surgery was associated with superior outcomes compared to conventional stenting, with in-stent restenosis being suggested as a possible contributor to the impaired outcomes after percutaneous treatment.[4]

Sirolimus-eluting stents (SES) have been recently shown in randomized studies to markedly decrease neointimal growth and in-stent restenosis in comparison with conventional stents.[5-7] However, all clinical trials conducted to date excluded patients with decreased renal function, and therefore the impact of SES implantation in patients with renal failure is currently unknown. The present study aimed to report on the 1-year clinical outcomes of a consecutive series of patients on chronic dialysis treated with SES.

Since April 2002, SES (Cypher; Johnson & Johnson-Cordis unit, Cordis Europa NV, Roden, the Netherlands) have been routinely utilized as the device of choice for all patients treated with percutaneous coronary intervention in our institution.[8] During the first 6 months of this policy, SES implantation was performed in ten consecutive patients on chronic dialysis, who comprise the present study population. All patients on either chronic haemodialysis or peritoneal dialysis at the time of the procedure were included.

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Methods

Percutaneous interventions were performed utilizing standard techniques, with the final strategy entirely left at the discretion of the operator aiming to achieve a residual stenosis < 30% by visual analysis with TIMI 3 antegrade flow. All patients were advised to maintain lifelong aspirin and clopidogrel was prescribed for at least 3 months.

Patients were prospectively evaluated during follow-up for the occurrence of death, non-fatal myocardial infarction, or target lesion revascularisation (TLD). Myocardial infarction was diagnosed by a rise in the creatine kinase level to more than twice the upper normal limit with an increased creatine kinase-MB. TLD was defined as a repeat intervention (surgical or percutaneous) to treat a luminal stenosis within the stent or in the 5-mm distal or proximal segments adjacent to the stent. This protocol was approved by the local ethics committee and is in accordance with the Declaration of Helsinki. Written, informed consent was obtained from every patient.

Clinical, procedural, and follow-up characteristics of the 10 patients included in the present report were detailed in Table 1. Mean age was 55 years, and 5 patients (50%) were male. Diabetes was present in 3 patients (30%) and most were hypertensives (70%). Half of the patients had multivessel coronary disease. On average, patients were on dialysis for 5 years prior to the procedure (range: 2–15 years). Five patients were on hemodialysis and 5 patients were on peritoneal dialysis. Two patients had had kidney transplantation prior to the procedure. Patient 5 underwent kidney transplantation 12 years ago and lost his transplant 1 year after the transplantation, while patient 6 underwent kidney transplantation twice, 24 and 18 years ago, but lost the last graft 14 years ago.

Overall, 18 lesions (range 1–4 lesions per patient) were treated with 1.9 ± 1.1 SES per case (range 1–4), and an average stented length of 38 ± 26 mm per patient (range 8–87 mm). The left anterior descending artery was stented in 5 patients (50%) and the left main coronary in one patient. All treated lesions were *de novo* lesions and moderate to severe coronary

Table 1. Baseline, procedural, and follow-up characteristics of 10 dialysis patients treated with sirolimus-eluting stents

Patient no.	1	2	3	4	5	6	7	8	9	10
Age, years	54	62	52	59	48	57	46	41	82	44
Male sex	0	+	0	+	0	+	+	0	+	0
Risk factors										
Diabetes mellitus	0	0	0	0	+	0	0	+	0	+
Systemic hypertension	+	0	+	0	+	+	0	+	+	+
Hypercholesterolemia	+	+	+	0	+	+	0	0	0	+
Current smoking	0	0	0	0	0	0	+	0	0	0
Previous coronary surgery	0	0	0	0	0	0	0	0	+	0
Previous angioplasty	0	0	0	0	0	0	0	0	0	0
Previous myocardial infarction	0	+	0	0	0	0	0	0	0	0
Previous renal transplantation	0	0	0	0	+	+	0	0	0	0
Dialysis										
Duration at procedure, years	4	5	3.5	4	15	5	0.5	3	6	2
Route	perit	perit	Hemod	hemod	hemod	perit	perit	perit	hemod	hemod
Clinical presentation	SAP	UAP	SI	SI	AP	UAP	SI	AUP	AP	UAP
Coronary vessel disease	1	2	2	1	3	1	1	2	2	1
Vessels treated	RCA	RCA, LAD	LAD, LCx	RCA	RCA, LM	RCA	RCA	LAD, LCx	RCA, LAD	LAD
Number of SES implanted	1	3	2	1	4	1	1	3	2	1
Total stented length, mm	8	59	66	18	87	18	18	49	41	18
Clinical Follow-up										
Duration, days	445	463	388	446	374	368	393	392	380	379
Renal transplantation during follow-up	at 8 mo.	at 5 mo.	0	at 6 mo.	0	0	at 3 mo.	0	0	0
Death	0	0	0	0	0	0	0	0	0	0
Myocardial infarction	0	0	0	0	0	0	0	0	0	0
Target lesion revascularization	0	0	0	0	0	0	0	0	0	0

hemod = hemodialysis; LAD = left anterior descending; LCx = left circumflex artery; LMC = left main coronary; perit = peritoneal; RCA = right coronary artery; SAP = stable angina pectoris; SES = sirolimus-eluting stents; SI = silent ischemia; UAP = unstable angina pectoris.

angiographic calcification was observed in 4 patients (40%). Glycoprotein IIbIIIa inhibitors were not utilized in any patient (Table 1).

Complete clinical follow-up was available for all patients at an average of 403 days (range: 338–463). There were no cases of death, myocardial infarction, or target lesion revascularization. One patient (patient 4), was admitted with unstable angina 8 months after the procedure. Coronary angiogram showed widely patent SES but severe lesion progression in other vessel segments. The patient was referred to surgical treatment. Another patient (patient 5) underwent balloon dilatation in a side branch at 6 months, with no evidence of restenosis at the previously stented site. Four of our patients underwent kidney transplantation during follow-up, at 8 months (patient 1), 5 months (patient 2), 6 months (patient 4), and 3 months post-procedure (patient 7) (Table 1).

Results

In the present study, SES implantation for patients on dialysis appeared to be safe and associated with an extremely low incidence of adverse events at 1-year follow-up, with no cases of repeat intervention due to restenosis.

Table 2. Previous studies with end stagerenal disease patients treated with percutaneous coronary intervention.

Author	Year	Follow-Up (months)	No.	Death	Repeat revascularization	MACE
Hang[16]	2000	14	31	65%	NA	NA
Kahn[9]	1990	20	17	41%	67%	NA
Ahmed[10]	1994	12	21	33%	NA	NA
Rinehart[11]	1995	24	24	49%	NA	NA
Marso[13]	1996	24	23	63%	52%	NA
Herzog[15]	1999	24	6887	47%	NA	NA
Herzog[8*]	2002	42	4280	71%	NA	NA
Hase[21*]	2001	12	23	5%	13%	28%
Malanuk[20*]	2001	18	10	30%	0%	30%
Simsir[14]	1998	18	19	31%	NA	40%
Le Feuvre[17*]	2000	12	27	15%	33%	41%
Agirbasli[18]	2000	12	122	23%	16%	44%
Azar[19*]	2000	9	34	18%	39%	50%
Le Feuvre[22]	2003	48	112	27%	44%	51%
Koyanagi[12]	1996	5	20	10%	75%	82%
RESEARCH	2003	12	10	0	20%	20%

**Numbers shown to patients treated with stent implantation. NA = not available; MACE = death, myocardial infarction, or any repeat revascularization.*

Discussion

Our favourable results clearly contrasts with the previously reported high rate of late complications following angioplasty in dialysis patients, as shown in Table 2.[2,4,9–22] Although the present study did not include an angiographic re-evaluation, the uneventful late clinical outcomes observed were consistent with a marked reduction in the incidence of restenosis, as seen in non-dialysis patients.[5–7]

Coronary surgery has been associated with better clinical outcomes than percutaneous intervention in patients on chronic dialysis.[4] However, the impact of restenosis as a contributor to the worse outcomes after angioplasty is still to be clarified.[4] Five out of ten patients in the present series had undergone multivessel SES implantation. In all of these patients, the interventional treatment included stenting of lesions located in the left anterior descending artery or left main coronary, an anatomical scenario typically referred to surgical treatment. Whether SES constitutes an effective therapeutic option for dialysis patients with multivessel disease will have to be determined in further studies incorporating larger number of patients.

The SES decrease restenosis by locally delivering the antiproliferative drug, which eventually inhibits neointimal formation and prevents late lumen renarrowing. The interaction between the local administration of sirolimus and the systemic immunosuppression therapy in patients undergoing renal transplantation is currently unclear. In our series, renal transplantation was performed in 4 patients during the follow-up period. None of these patients presented any clinical complication that could be associated with increased drug toxicity. However, importantly, in all cases the transplantation was performed at least 3 months after the coronary procedure and, based on the known drug kinetics of SES, most of the drug should have been released by 1 month after the implantation.

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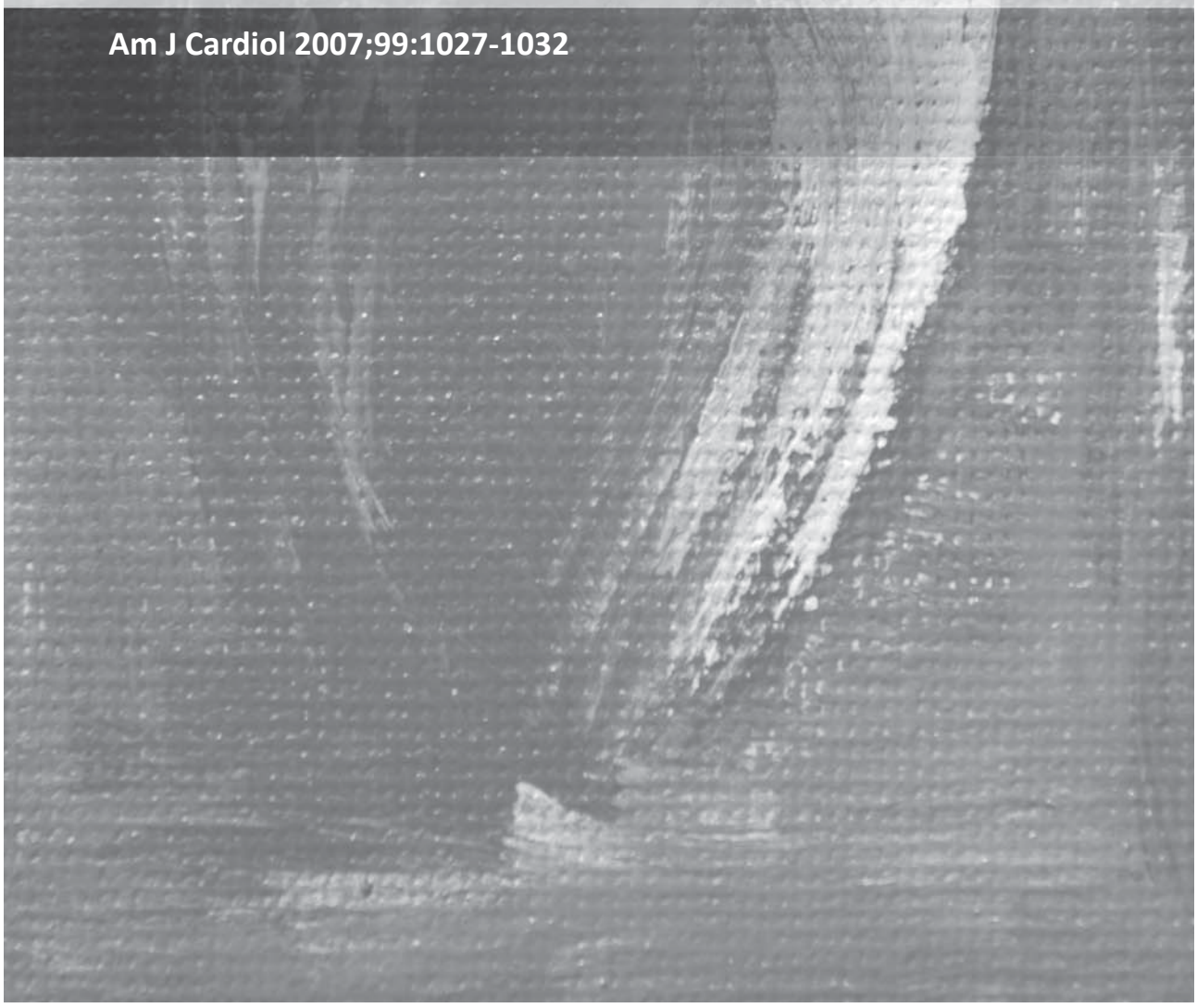
Chapter 8

Comparison of three-year clinical outcome of sirolimus and paclitaxel-eluting stents versus bare metal stents in patients with ST-segment elevation myocardial infarction (from the RESEARCH and T-SEARCH Registries)

Daemen J, Tanimoto S, García-García HM, Kukreja N, van de Sande M, Sianos G, de Jaegere PT, van Domburg RT, Serruys PW

Am J Cardiol 2007;99:1027-1032



Comparison of Three-Year Clinical Outcome of *Sirolimus*- and *Paclitaxel*-Eluting Stents Versus Bare Metal Stents in Patients With ST-Segment Elevation Myocardial Infarction (from the RESEARCH and T-SEARCH Registries)

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Sirolimus-eluting stents (SESs) recently proved to be superior to bare metal stents (BMSs) in decreasing the need for repeat revascularization in patients with ST-segment elevation myocardial infarction (STEMI) at 1 year. Whether this also holds for paclitaxel-eluting stents (PESs) is currently unclear and the long-term relatively efficacy of the 2 drug-eluting stents is currently unknown. We investigated the 3-year efficacy of SESs and PESs versus BMSs in patients with STEMI. Primary angioplasty was performed in a consecutive group of 505 patients (BMSs in 183, SESs in 186, PESs in 136). At 3 years, the cumulative mortality rate was comparable in the 3 groups: 13.3% in the BMS group, 11.5% in the SES group, and 12.4% in the PES group (nonsignificant for all). The rate of target vessel revascularization (TVR) was 12.0% in the BMS group compared with 8.0% and 7.7% in the SES and PES groups, respectively ($p = 0.12$ for BMS vs SES, 0.30 for BMS vs PES, 0.62 for SES vs PES). The cumulative incidence of death, MI, or TVR was 25.5% in the BMS group compared with 17.9% and 20.6% in the SES and PES groups, respectively ($p = 0.06$ for BMS vs SES, 0.32 for BMS vs PES, 0.45 for SES vs PES). Angiographic stent thrombosis occurred in 2.4% of all patients (BMS 1.6%, SES 2.7%, PES 2.9%). In conclusion, in this relatively small consecutive patient cohort, the use of SESs and PESs was no longer associated with significantly lower rates of TVR and major adverse cardiace events in patients with STEMI after 3 years of follow-up. A high frequency of stent thrombosis was observed in the 2 drug-eluting stent groups. **(Am J Cardiol 2007;99:1027–1032)**

Primary percutaneous coronary intervention, with or without stenting, has been shown to result in superior long-term outcome compared with thrombolytic therapy in patients with acute myocardial infarction (MI).[1] Recently, several studies have reported that sirolimus-eluting stents (SESs) and paclitaxel-eluting stents (PESs) are more effective in decreasing restenosis and the frequency of repeat interventions than are bare metal stents (BMSs), which rapidly resulted in an unrestricted use of drug-eluting stents also in patients with ST-segment elevation MI (STEMI).[2–4] Shortly after the introduction of SESs in 2002 the first studies appeared, hypothesizing that the therapeutic range of SESs could be extended to use in patients presenting with MI. Compared with BMSs, SESs were associated with less restenosis and target vessel revascularization (TVR) up until 1 year of follow-up.[3,5] Currently it is unclear whether this also holds for PESs.[4,6] To date, there are no data on the long-term outcome of the use of SESs and PESs in patients with STEMI, a growing high-risk subgroup that is becoming a substantial recipient of the total number of percutaneous coronary interventions in many centers all over the world. For that reason, we evaluated the 3-year clinical outcomes of a series of consecutive patients with STEMI treated with BMSs, SESs, or PESs as part of a primary percutaneous coronary intervention strategy.

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Methods

On April 16, 2002, our institution commenced the use of SESs (Cypher, Cordis Corp., Warren, New Jersey) as the default strategy for every percutaneous coronary intervention, with the aim of including a patient population representing the "real world."[7] Up until January 2003, 186 consecutive patients were treated with primary angioplasty using exclusively SESs for STEMI. In February 2003 the PES replaced the SES as the device of choice for all percutaneous coronary interventions. Until September 2003, 136 primary percutaneous coronary interventions were performed using exclusively PESs for STEMI. A control group of 183 consecutive patients with STEMI treated with BMSs immediately before April 2002 was retrospectively selected. Of note, the 2 study groups were part of the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital

Table 1
Baseline and procedural characteristics of patients treated with bare metal, sirolimus, or paclitaxel-eluting stents

Variable	BMS Group (n = 183)	SES Group (n = 186)	PES Group (n = 136)	p Value
Men	79%	75%	84%	0.2
Age (yrs)	57 ± 12	60 ± 12	59 ± 12	0.1
Diabetes mellitus	12%	12%	6%	0.1
Hypercholesterolemia*	34%	37%	46%	0.1
Hypertension	26%	27%	24%	0.8
Current smoker	48%	47%	42%	0.5
Previous MI	24%	14%	11%	0.006
Previous coronary angioplasty	9%	7%	6%	0.6
Previous coronary bypass grafting	3%	2%	2%	0.6
No. of coronary arteries narrowed >50%				0.6
1	48%	55%	52%	
2	29%	27%	29%	
3	24%	18%	19%	
Cardiogenic shock	10%	13%	12%	0.6
Time from symptom onset to angioplasty (h)	3.5 ± 3.8	3.3 ± 2.1	3.2 ± 2.4	0.8
Infarct-related coronary vessel				0.7
Left anterior descending	57%	53%	52%	
Left circumflex	10%	8%	9%	
Right coronary	30%	37%	36%	
Left main	1%	2%	2%	
Bypass graft	2%	—	2%	
TIMI flow at baseline				0.8
Grade 0/1	73%	73%	78%	
Grade 2	15%	17%	11%	
Grade 3	13%	10%	10%	
TIMI flow after angioplasty				0.6
Grade 0/1	4%	2%	2%	
Grade 2	17%	15%	12%	
Grade 3	79%	83%	86%	
Bifurcation lesion	4.4%	9.1%	9.6%	0.13
No. of implanted stents	1.7 ± 1.0	1.9 ± 1.2	1.8 ± 1.1	0.1
Total stented length (mm)	30.3 ± 20	34.7 ± 24	35.9 ± 23	0.055
Clopidogrel prescription (mo)	2.3 ± 1.6	4.2 ± 2.0	5.7 ± 1.0	<0.001
Glycoprotein IIb/IIIa inhibitor	56%	37%	55%	<0.001
Peak creatinine kinase (U/L)	3,957 ± 5,135	3,126 ± 3,126	2,875 ± 2,713	0.1
Peak creatinine kinase-MB (IU/L)	319 ± 230	296 ± 255	320 ± 306	0.7

Values are percentages of patients or means ± SDs.
* Defined as a fasting total serum cholesterol level >5.5 mmol/L (210 mg/dl) or use of lipid-lowering therapy.
TIMI = Thrombolysis In Myocardial Infarction.

(RESEARCH) and Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registries, respectively. All patients were enrolled in the analysis including patients in cardiogenic shock (defined as systolic blood pressure persistently <90 mm Hg or the need for inotropic support or intra-aortic balloon pump implantation to maintain a blood pressure >90 mm Hg with evidence of organ end failure and increased left ventricular filling pressures). Patients who underwent rescue percutaneous coronary intervention after failed thrombolysis or who had previous brachytherapy were not included in this study. This protocol was approved by the hospital ethics committee and is in accordance with the Declaration of Helsinki. Written informed consent was obtained from every patient.

All procedures were performed according to current standard procedural guidelines and their details have been reported previously.[8,9] Baseline and postprocedural flows were evaluated offline according to the Thrombolysis In Myocardial Infarction criteria by cardiologists blinded to stent group and clinical outcomes. All patients were advised to maintain lifelong aspirin. At least 1 month of clopidogrel treatment (75 mg/day) was recommended for patients treated in the BMS group. In the 2 drug-eluting stents groups, clopidogrel was prescribed for ≥3 months unless multiple SES implantation (>3 stents), total stented length >36 mm, persistent total occlusion, or bifurcations was present. In these cases clopidogrel was prescribed for ≥6 months.

Patients were prospectively followed for the occurrence of major adverse cardiac events (defined as a composite of all-cause death, nonfatal MI, or TVR). Reinfarction was diagnosed by recurrent symptoms and/or new electrocardiographic changes in association with increases in creatine kinase and creatine kinase myoglobin levels of >1.5 times the previous value, if within 48 hours, or >3 times the upper normal limit, if 48 hours after the index infarction.[10,11] TVR was defined as a reintervention driven by any lesion located in the same coronary artery. A secondary end point was

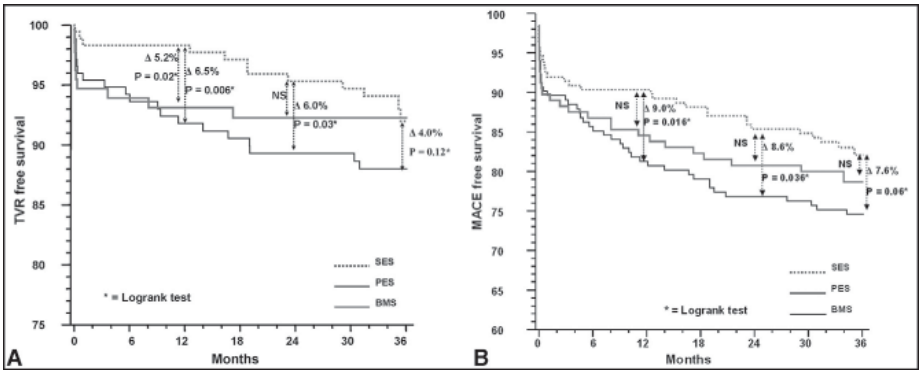

Figure 1. Kaplan-Meier survival curves of *(A)* TVR and *(B)* combined cumulative incidence of major adverse cardiac events (MACE; death, MI, and TVR). Δ = change.

Table 2
Major adverse cardiac events at one year and two and three years

Variable	BMS Group (n = 183)	SES Group (n = 186)	PES Group (n = 136)	p Value
Events in first year				
All-cause mortality	17 (9.3%)	15 (8.1%)	11 (8.1%)	0.89
MI	6 (3.3%)	2 (1.1%)	6 (4.4%)	0.17
TVR (all)	14 (7.7%)	3 (1.6%)	9 (6.6%)	0.021
Stent thrombosis	3 (1.6%)	1 (0.5%)	4 (2.9%)	0.22
Hierarchical MACEs	34 (18.6%)	18 (9.7%)	21 (15.4%)	0.048
Events in second year				
All-cause mortality	5 (2.7%)	4 (2.2%)	3 (2.2%)	0.92
MI	—	1 (0.5%)	—	0.42
TVR (all)	4 (2.2%)	5 (2.7%)	1 (0.7%)	0.45
Stent thrombosis	—	1 (0.5%)	—	0.423
Hierarchical MACEs	8 (4.4%)	9 (4.8%)	4 (2.9%)	0.69
Events in third year				
All-cause mortality	2 (1.1%)	2 (1.1%)	2 (1.5%)	0.94
MI	—	3 (1.6%)	—	0.075
TVR (all)	2 (1.1%)	4 (2.2%)	—	0.21
Stent thrombosis	—	3 (1.6%)	—	0.075
Hierarchical MACEs	4 (2.2%)	6 (3.2%)	2 (1.5%)	0.76

MACEs = major adverse cardiac events.

target lesion revascularization, defined as treatment of a lesion in stent or within 5 mm of the stent borders. Subacute stent thrombosis was defined as an angiographically documented complete occlusion (Thrombolysis In Myocardial Infarction grade 0 or 1 flow) or a flow-limiting thrombus (Thrombolysis In Myocardial Infarction grade 1 or 2 flow) in the first 30 days after a successful procedure. Late stent thrombosis was defined as angiographically defined thrombosis with Thrombolysis In Myocardial Infarction grade 0 or 1 flow or the presence of a flow limiting thrombus occurring ≥1 month after drug-eluting stent implantation accompanied by acute symptoms.[12]

Three-year survival status was obtained through municipal civil registries. Health questionnaires were subsequently sent to all living patients and inquired about post-discharge repeat coronary interventions (surgical or percutaneous) and MI. If a patient had an MI or a reintervention at another center, medical records or discharge letters were requested and systematically reviewed. Local cardiologists or general practitioners were contacted if necessary. Follow-up was available for 98% of patients with BMSs, 98% of patients with SESs, and 97% of patients with PESs.

Continuous variables are presented as mean ± SD. Categorical variables are expressed as percentages. Comparisons across the 3 groups were performed by the F test from an analysis of variance for continues variables and Pearson chi-square test for categorical variables. The cumulative incidence of adverse events was estimated according to the Kaplan-Meier method. Patients were censored at 1, 2, and 3

Table 3
Major adverse cardiac events up to three years

Variable	BMS Group (n = 183)	SES Group (n = 186)	PES Group (n = 136)	Relative Risk (95% CI)		
				SES vs BMS	PES vs BMS	PES vs SES
Mortality at 1 yr	9.4%	8.1%	8.1%	0.81 (0.36–1.81)	1.01 (0.66–1.53)	1.24 (0.52–2.95)
Mortality at 3 yrs	13.3%	11.5%	12.4%	0.78 (0.41–1.51)	1.08 (0.77–1.52)	1.62 (0.80–3.27)
Nonfatal MI at 1 yr	3.5%	1.2%	4.7%	0.30 (0.06–1.53)	1.11 (0.62–1.99)	5.40 (1.07–27.6)
Nonfatal MI at 3 yrs	3.5%	4.0%	4.7%	0.95 (0.30–2.98)	1.11 (0.62–1.99)	2.03 (0.63–6.51)
TVR at 1 yr	8.2%	1.7%	6.9%	0.23 (0.06–0.85)	1.11 (0.72–1.72)	10.45 (1.76–62.2)
TVR at 3 yrs	12.0%	8.0%	7.7%	0.65 (0.30–1.37)	0.98 (0.66–1.46)	1.69 (0.70–4.07)
MACEs (death, MI, and TVR) at 1 yr	18.7%	9.7%	15.5%	0.57 (0.32–1.03)	0.99 (0.75–1.31)	1.49 (0.79–2.82)
MACEs (death, MI, and TVR) at 3 yrs	25.5%	17.9%	20.6%	0.77 (0.48–1.23)	0.97 (0.76–1.24)	1.17 (0.69–1.97)

CI = confidence interval; other abbreviation as in Table 2.

years to report the cumulative incidence of major adverse cardiac events and TVR in the 2 Kaplan-Meier curves. Overall incidences were tested using log-rank test. Cox proportional hazards regression analyses were performed to correct for independent predictors of adverse events and differences across groups. Independent predictors were determined for each end point in the 3 compared groups (SES vs BMS, SES vs PES, PES vs BMS) by using all univariate significant ($p < 0.1$) baseline and procedural characteristics listed in Table 1. Independent predictors of outcome were forced into the model, together with stent type used. The final results are presented as adjusted hazard ratios. Patients lost to follow-up were considered at risk until the date of final contact, when they were censored.

Results

Clinical baseline characteristics were comparable among groups, with the exception of previous MI, which was more frequent in the BMS group (24%) than in the SES and PES groups (14% and 11%, respectively, $p = 0.006$; Table 1). There were few differences in procedural characteristics among groups: Glycoprotein IIb/IIIa inhibitor use was higher in the BMS (56%) and PES (55%) groups than in the SES group (37%, $p < 0.001$), and as defined by the study protocol clopidogrel prescription was longer in the 2 drug-eluting stent groups than in the BMS group.

Thirty-day and 1-year outcome have been reported previously.[8,9] At 3 years, the cumulative mortality rate was comparable in the 3 groups (13.3% in the BMS group, 11.5% in the SES group, and 12.4% in the PES group; log-rank $p = 0.63$ for BMS vs SES, 0.78 for BMS vs PES, 0.86 for SES vs PES). Cause of death was cardiac in 62%, unknown in 18%, and noncardiac in 20% of patients. In the BMS group 3.5% developed a new MI compared with 4.0% in the SES group and 4.7% in the PES group (log-rank $p = 0.99$ for BMS vs SES, 0.62 for BMS vs PES, 0.52 for SES vs PES). Target lesion revascularization was performed in 8.4% of patients in the BMS group compared with 6.2% in the SES group and 6.1% in the PES group (log-rank $p = 0.27$ for BMS vs SES, 0.56 for BMS vs PES, 0.58 for SES vs PES). There was a trend toward a higher incidence of TVR in the BMS group (12.0%) compared with the SES (8.0%) and PES (7.7%) groups (Figure 1). The combined cumulative incidence of major adverse cardiac events was 25.5% in the BMS group compared with 17.9% in the SES group and 20.6% in the PES group (Figure 1). Events occurring in the second and third years of follow-up are presented in Table 2.

At 3 years, 12 patients (2.4%) presented with angiographically documented stent thrombosis. Three patients (1.6%) in the BMS group developed stent thrombosis compared with 5 (2.7%) in the SES group and 4 (2.9%) in the PES group ($p = 0.72$ for SES vs BMS, 0.46 for PES vs BMS). Stent thrombosis occurred relatively soon after the index percutaneous coronary intervention at a mean of 8.7 days (range 6 to 11) and 3.5 days (range 0 to 6) in the BMS and PES groups, respectively. In contrast, in the SES group stent thrombosis occurred much later, at a mean of 685 days (range 18 to 1,074). Three of 4 patients with stent thrombosis after 1 year were on single antiplatelet therapy with aspirin and 1 stopped using aspirin 2 days before the event. Two patients presented with unstable angina and 2 with MI. One patient in the PES group had 3 recurrent thrombotic events at 4, 8, and 11 days after the procedure and died during the third event of a subsequent MI despite being on dual antiplatelet therapy. Although beyond the scope of the present analysis, it is worth mentioning that 1 patient in the PES group developed stent thrombosis at 1,100 days after the procedure, 2 days after stopping dual antiplatelet therapy, because of an elective surgical procedure. All cases of stent thrombosis were treated using balloon angioplasty with 100% glycoprotein IIb/IIIa use and additional stents were used in 4 cases.

In Cox multivariate analysis performed in the total population, bifurcation treatment (in which 2 stents were used in 92% of patients) proved to be the strongest predictor of stent thrombosis (hazard ratio 7.84, 95% confidence interval 2.12 to 29.03) followed by female gender, which had a cardioprotective effect (hazard ratio 0.17, 95% confidence interval 0.05 to 0.58). Cox multivariate regression models were also used to correct for differences and independent predictors of adverse events between each pair of groups (SES vs BMS, PES vs BMS, and PES vs SES; Table 3). After adjustment, no significant differences were seen in the 3 comparisons in any clinical end point (death, nonfatal MI, TVR, and major adverse cardiac events).

Discussion

The main findings of the present analysis of 505 consecutive patients presenting with STEMI are (1) the superiority of

SESs in decreasing TVR compared with BMSs and PESs at 1 year was no longer present at 3 years, (2) PESs were not superior to BMS in decreasing the incidence of adverse cardiac events at 1, 2, and 3 years of follow-up, and (3) stent thrombosis in this high-risk subgroup occurred with an overall incidence of 2.4% at a mean of 289 days after the procedure (median 10 days, interquartile range 4.5 to 757) and did not differ significantly across the 3 groups.

Previous (non)randomized studies have reported that the use of the 2 types of drug-eluting stent result in similar rates of death and MI compared with BMSs.[13,14] A recent meta-analysis of randomized trials comparing SESs with PESs also showed no significant difference in these end points.[15] The results of the present study concur with those of the previously mentioned studies and are supported by a recent meta-analysis of the results of SES implantation in patients with acute MI.[5]

The success of drug-eluting stents is primarily driven by their capability to decrease restenosis and the need for repeat interventions, but the currently available long-term follow-up is based on randomized studies, which excluded patients with STEMI.[14] At 1 year, we observed a relative decrease of 80% in the risk for TVR with the use of SESs compared with BMSs ($p = 0.006$). However, at 2 and 3 years, the relative decreases were 59% ($p = 0.003$) and 44% ($p = 0.12$), respectively. PESs showed no significant benefit in decreasing TVR compared with BMSs at 1 years or 2 or 3 years. These 1-year results concur with those of the Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty (TYPHOON) trial, which randomized >700 patients and showed that SESs were superior to BMSs in patients presenting with acute MI.[3] With regard to PESs, the randomized Paclitaxel-Eluting Stent versus Conventional Stent in Myocardial Infarction with ST-Segment Elevation (PASSION) trial confirmed our findings that PESs were not superior to BMSs in each clinical end point at 1 year of follow-up.[4] The favorable results of the SESs in the TYPHOON trial might have been influenced by the high TVR rate in the BMS control arm and the angiographic follow-up in a considerable number of patients.

The loss of the superiority of SESs compared with BMS after 1 year of follow-up might be partly explained by the occurrence of late stent thrombosis, which occurred in 4 patients (2.1%) in the SES group in the third year of follow-up compared with a 0% incidence in the BMS group. These 4 cases of late stent thrombosis comprised 50% of the total number of TVRs performed in the third year of follow-up and accounted for 100% of all MIs occurring between the first and third year. The increased incidence in very late stent thrombosis in the SES group is in accordance with a recent report by Togni et al,[16] which showed a trend toward a higher incidence of very late stent thrombosis in patients treated with SESs. Although stenting in the setting of MI proved to be a consistent predictor of stent thrombosis, current reports about the occurrence of stent thrombosis after 1 year and especially after 2 years are still scarce.[17–19]

The total incidence of stent thrombosis in this high-risk patient population was 2.4% and was, although mostly due to the longer follow-up, higher than that in previous reports in which stent thrombosis rates were 1.0% to 1.7%.[12,20,21] The incidence of stent thrombosis in the BMS group in the present study was 1.6% and in is agreement with that in previous reports.[22] Stent thrombosis occurred in 2.9% of patients in the PES group, all within the first week after the index percutaneous coronary intervention. No late stent thrombosis was observed from 1 year to 3 years. This latter observation does not concur with a previous study, which reported late stent thrombosis rates of ~0.8% in patients treated with PESs.[23] However, the occurrence and rate of early stent thrombosis in the PES group was comparable to that in the BMS group, occurring mainly within the first 2 weeks after stent implantation.[24] It is unknown whether the late deaths of unknown cause were due to stent thrombosis.

Dual antiplatelet therapy was not able to prevent the 10 early thrombotic events. Whether it would have prevented the late cases of stent thrombosis remains unclear. Thus, the relative efficacy of dual antiplatelet therapy remains unknown, even when taking into account the increased costs, higher bleeding risk, and possibility of aspirin and/or clopidogrel resistance.[25–28]

A limitation of the present study is that the results are based on a nonrandomized patient population without completely identical groups. An example of this is glycoprotein IIb/IIIa prescription, which was lower in the SES group. However, its use did not prove to be protective against adverse events and short- and long-term outcomes in the present study, which is in accordance with the current literature.[29] Further, the results are based on a relatively small patient cohort and therefore may have lack of power. Nevertheless, the present study is the first in the world to complete longer-term follow-up of this high-risk patient subset because Europe was the first to grant Conformité Européenne mark approval for the 2 types of drug-eluting stent, whereas approval by the US Food and Drug Administration was granted >1 year later.

The recently published 1-year results of the randomized, controlled PASSION and TYPHOON trials showed dis-similar outcomes with respect to the different drug-eluting stents used.[3,4] However, until they are able to present longer-term follow-ups, the present single-center prospective registry, which aims to represent a real-world patient population, shows that the "unrestricted" use of SESs and PESs might not be justified in patients presenting with STEMI when taking into account the long-term adverse events.

Appendix

The following operators were involved in the procedures of the discussed patient population: Chourmouzios A. Arampatzis, MD, Eugene McFadden, MD, PhD, Pim J. de Feyter, MD, PhD, Willem J. van der Giessen, MD, PhD, Sjoerd H. Hofma, MD, PhD, Angela Hoye, MBChB, MRCP, Peter P.T. de Jaegere, MD, PhD, Patrick W. Serruys, MD, PhD, Evelyn Regar, MD, PhD, Georgios Sianos, MD, PhD, and Pieter C. Smits, MD, PhD.

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Chapter 9

The long-term value of Sirolimus- and Paclitaxel-Eluting Stents as Compared to Bare Metal Stents in Patients with Diabetes Mellitus

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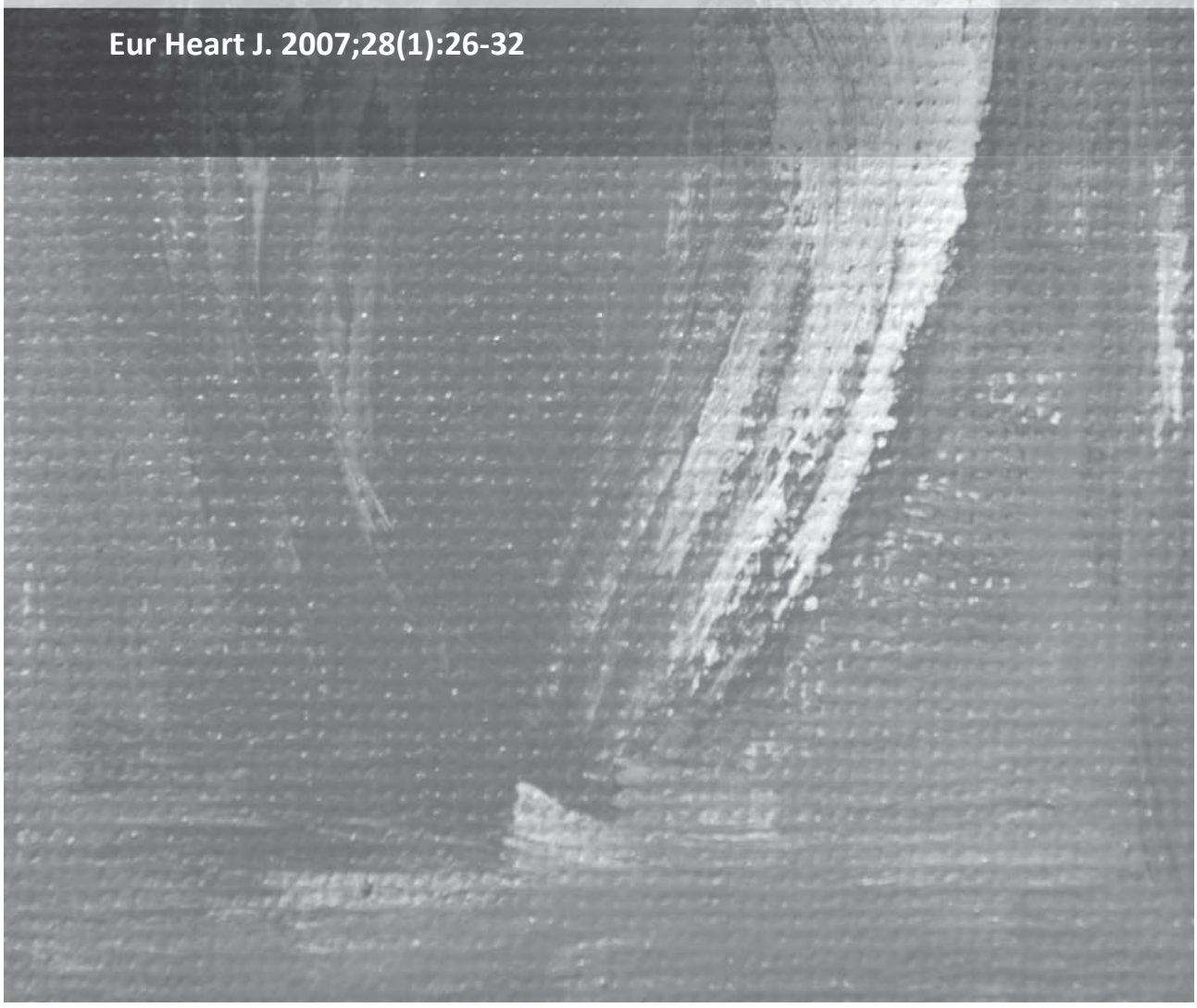

The long-term value of sirolimus- and paclitaxel-eluting stents over bare metal stents in patients with diabetes mellitus

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Aims To investigate the outcome of a real world diabetic patient cohort treated with bare metal stents (BMS), sirolimus-, or paclitaxel-eluting stents (SES and PES, respectively). Due to the different mechanisms of action of both drugs it is currently unknown which device is the best option to treat these high-risk patients.

Methods and results The study compares the 2-year clinical outcome of 708 consecutive diabetic patients (25% insulin treated) treated with either a BMS ($n = 252$), a SES ($n = 206$), or a PES ($n = 250$), as part of the RESEARCH and T-SEARCH registries. Target vessel revascularization was 19.5% in the BMS group, vs. 15.3% in the SES group and 9.7% in the PES group. PES (21.2%), but not SES (28.9%), were superior to BMS (29.7%) in reducing major adverse cardiac events. After propensity analyses, none of the differences remained significant. The incidence of stent thrombosis (ST) was high in both DES groups.

Conclusion There was a trend towards a more favourable outcome associated with the use of PES over BMS. There was no significant difference between SES and PES in each of the clinical endpoints, and neither in the NIDDM patients, which are hypothesized to be better-off with PES.

Introduction

Patients with diabetes mellitus (DM) are known to have a higher incidence of mortality and cardiovascular disease compared with non-diabetic patients.[1] Major reasons are the more diffuse and accelerated form of atherosclerosis, accompanied by longer lesion lengths, smaller vessel size, and greater plaque burden.[2–5] Insulin-requiring diabetics are, especially, more susceptible to adverse cardiac events.[6]

Several trials that pre-date the drug-eluting stent (DES) era showed that the event-free survival was significantly higher in patients treated with coronary artery bypass surgery over percutaneous coronary intervention (PCI) with balloon angioplasty or bare metal stents (BMS), mainly due to the high restenosis rates, inability to fully revascularize multiple ischaemic areas, and the rapid progression of atherosclerosis.[7–11] To date, both sirolimus- and paclitaxel-eluting stents (SES and PES) proved to be more effective in reducing restenosis and target vessel revascularization (TVR) in diabetic patients when compared with BMS up until 1 year of follow-up in several retrospective subset analysis of randomized controlled trials and small single-centre experiences.[12–16] Whether besides these benefits, the long-term hard clinical endpoints as mortality and myocardial infarction (MI) remain comparable between both groups remains questionable.[17,18].

Of interest is that patients with type II diabetes exhibit a breakdown in the PI3-kinase insulin signal transduction pathway, the pathway in which mammalian target of rapamycin (mTOR) is involved.[19] It can be hypothesized that in this situation, inhibiting protein synthesis by blocking mTOR with rapamycin may be less effective. Paclitaxel conversely, inhibits signalling downstream, independent of insulin resistance. Whether this hypothesis can be translated into clinical practice remains puzzling and is currently illustrated by various studies focusing on differences between SES and PES in selected patients up to 1 year of follow-up.[20–22] Our goal is to present the 2-year clinical outcome of 708 consecutive diabetic patients treated with a BMS, SES, or a PES.

Methods

Study design and patient population

In April 2002, our institution began to use SES (Cypher®; Cordis Corporation, Warren, NJ, USA) as a default strategy for all patients undergoing PCI. In February 2003, the PES (Taxus, Boston Scientific Corp., Natick, MA, USA) replaced the SES as the default treatment.

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From April 2002 to February 2003, 206 consecutive patients were treated exclusively with SES. From February 2003 to April 2004, 250 consecutive DM patients received a PES. A group of 252 consecutive diabetic patients treated with BMS immediately before April 2002 were retrospectively selected as a control group. The present diabetic population ($n = 708$) comprises 20% of the patients treated within the framework of the consecutive and similarly designed RESEARCH and T-SEARCH registries, which are described elsewhere.[23,24] Patients were eligible for inclusion if they were undergoing pharmacological treatment with either insulin or hypoglycaemic agents at the time of the index procedure and patients with transient hyperglycaemia were not included in the present analysis.

The protocol was approved by the hospital Ethics Committee and is in accordance with the Declaration of Helsinki. Written informed consent was obtained from every patient.

Procedures and post-intervention medications

All procedures were performed according to standard clinical guidelines.[24] Angiographic success was defined as a residual stenosis $\leq$30% by visual analysis in the presence of Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow. All patients were pretreated with 300 mg of clopidogrel. At least 1-month of clopidogrel treatment (75 mg/day) was recommended for patients treated in the BMS phase. Patients who received a PES were prescribed $\geq$6 months of clopidogrel (75 mg/day), and those who received an SES were prescribed clopidogrel for $\geq$3 or 6 months depending on the complexity of the procedure.[25] All patients were advised to maintain aspirin ($\geq$80 mg/day) lifelong.

Endpoint definitions and clinical follow-up

DM was defined by the presence of therapy: patients taking solely oral medication were classified as non-insulin dependent diabetes mellitus (NIDDM) and those on insulin therapy as insulin-dependent diabetes mellitus (IDDM).

The primary endpoint was the occurrence of major cardiac events, defined as a hierarchical composite of all-cause death, non-fatal MI, or TVR. MI was diagnosed by an increase in creatine kinase-MB fraction of greater than three times the normal upper limit.[26] Target lesion revascularization (TLR) was defined as a repeat intervention (surgical or percutaneous) to control a luminal stenosis within the stent or in the 5-mm proximal or distal segments adjacent to the stent. TVR was defined as a re-intervention of a lesion in the same epicardial vessel. Subacute angiographic stent thrombosis was defined as an angiographically documented complete occlusion (TIMI grade 0 or 1 flow) or a flow-limiting thrombus (TIMI grade 1 or 2 flow) in the first 30 days after a successful procedure. Late-stent thrombosis was defined as angiographically defined thrombosis (TIMI grade 0 or 1 flow or the presence of a flow-limiting thrombus) occurring at least 1 month after DES implantation accompanied by acute symptoms.[27] Creatinine clearance was used as the measure of renal function with the baseline creatinine clearance calculated from most recent preprocedural creatinine value according to the formula proposed by Cockcroft and Gault.[28] Hypercholesterolaemia was defined as a fasting serum cholesterol level $>$5.5 mmol/L or use of lipid-lowering therapy at the time of the procedure.[29]

Two-year follow-up data

Survival data for all patients were obtained from municipal civil registries. A health questionnaire was subsequently sent to all living patients with specific questions on re-hospitalization and major adverse cardiac events. Patients treated with BMS or SES were contacted at 6 months, 1 year, and 2 years post-procedure, whereas patients treated with PES were contacted at 1 and 2 year(s) post-procedure. All repeat interventions and re-hospitalizations were prospectively collected during follow-up and entered into a dedicated database. When needed, referring physicians and institutions were contacted for additional information. Finally, follow-up was available for 98% of the patients in both DES groups and for 97% in the BMS group.

Statistical analysis

Continuous variables are presented as mean $\pm$ SD. Categorical variables are expressed as counts and percentages. Comparisons among the three groups were performed by the *F*-test from an analysis of variance for continues variables and Pearson's χ^2 test for categorical variables. The cumulative incidence of adverse events was estimated according to the Kaplan–Meier method and the log-rank test was used to evaluate differences between groups. Cox proportional hazards regression analysis was performed to correct for independent predictors of adverse events. Independent predictors, using all the baseline and procedural characteristics listed in *Tables 1* and *2*, were determined for each of the endpoints in the three compared groups (SES vs. BMS; SES vs. PES; PES vs. BMS). Independent predictors of outcome ($P < 0.1$), were forced into the model, together with the stent-type (=crude hazard ratios) and the assumptions of the proportional hazards model were tested using Omnibus tests of model coefficients. In order to avoid chance predictors, all predictors were carefully evaluated and none of them was in contrast to previously known risk factors. Control of potential confounders was attempted by constructing a propensity score using logistic regression.[30] The propensity score was the probability that a patient would receive either a BMS, an SES, or a PES, and was computed using an extensive, non-parsimonious, logistic regression model including the following variables: age, gender, clinical presentation, previous PCI, previous MI, previous coronary artery bypass surgery, multivessel disease, hypertension, dyslipidaemia, family history of coronary artery disease, smoking, diabetes, creatinine clearance, body mass index (BMI), glycoprotein IIb/IIIa inhibitor use, bifurcation treatment, vessel treated (RCA, LAD, LCX, LM, bypass graft), lesion type, chronic total occlusion, average stent diameter, number of stents, and total stented length. The selection of the variables was made so as to get the best discriminating model as assessed by the *C*-statistics. Covariate interactions and higher-order terms for the continuous variables proved unnecessary for the balance of baseline characteristics across quintiles. In the PES vs. BMS comparison, the propensity score became significant in the model for which we deleted the first quintile. In the PES vs. SES comparison, we deleted the fifth quintile. The resulting propensity score was then included in the Cox proportional hazards model as a continuous variable. The final results are presented as adjusted HRs. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. In all cases, $P < 0.05$ was considered significant. Statistical analysis were performed with SPSS 12.0.2 for Windows (SPSS Inc., Chicago IL, USA).

Results

Baseline and procedural characteristics

Baseline, angiographic, and procedural characteristics are included in *Tables 1* and *2*. There were more patients requiring insulin treatment in both DES groups: 31% (SES), 28% (PES), than in the BMS group (18%), $P < 0.002$. Both hypertension and hypercholesterolaemia increased over time and so was the presence of multivessel disease and the duration of clopidogrel prescription. The complexity of the procedures also increased over time, reflected by the treatment of type C lesions, incidence of multivessel treatment, number of stented vessels, number of implanted stents, total stented length, average stent diameter, and treatment of chronic total occlusions.

Table 1 Baseline clinical characteristics

	Bare ($n = 252$)	SES ($n = 206$)	PES ($n = 250$)	*P*-value
Male, *n* (%)	162 (64)	136 (66)	82 (67)	0.78
Age (years ± SD)	62.7 ± 10	62.0 ± 10	63.8 ± 11	0.2
NIDDM, *n* (%)	208 (82)	142 (69)	180 (72)	0.002
IDDM, *n* (%)	44 (18)	64 (31)	70 (28)	0.002
Hypertension, *n* (%)	135 (54)	142 (69)	176 (70)	<0.001
Hypercholesterolaemia, *n* (%)	150 (60)	145 (70)	207 (83)	<0.001
Current smoking, *n* (%)	55 (22)	41 (20)	47 (19)	0.69
Previous myocardial infarction, *n* (%)	92 (37)	74 (36)	102 (41)	0.49
Previous angioplasty, *n* (%)	69 (27)	65 (32)	67 (27)	0.49
Previous coronary bypass surgery, *n* (%)	40 (16)	21 (10)	40 (16)	0.14
Multivessel disease, *n* (%)	151 (60)	139 (67)	177 (71)	0.03
Clinical presentation				
Stable angina, *n* (%)	125 (50)	100 (49)	116 (47)	0.77
Unstable angina, *n* (%)	99 (39)	73 (35)	93 (37)	0.70
Acute myocardial infarction, *n* (%)	28 (11)	33 (16)	41 (16)	0.18
Creatinine clearance (mL/min)	107.6 ± 72.4	96.2 ± 35.2	89.5 ± 40.0	0.02
BMI (kg/m^2)	29.5 ± 6	29.0 ± 5	29.1 ± 11	0.76

Table 2 Angiographic and procedural characteristics

	Bare ($n = 252$)	SES ($n = 206$)	PES ($n = 250$)	*P*-value
Treated coronary vessel[a]				
Left anterior descending, *n* (%)	145 (58)	126 (61)	135 (54)	0.31
Left circumflex, *n* (%)	83 (33)	74 (36)	87 (35)	0.79
RCA, *n* (%)	88 (35)	82 (40)	160 (64)	<0.001
LM coronary, *n* (%)	14 (6)	13 (6)	12 (5)	0.78
Bypass graft, *n* (%)	19 (7.5)	6 (3)	23 (9)	0.024
Lesion type [b]				
Type A, *n* (%)	41 (16)	42 (20)	22 (9)	0.002
Type B1, *n* (%)	82 (32)	76 (37)	56 (22)	0.002
Type B2, *n* (%)	122 (48)	107 (52)	125 (50)	0.75
Type C, *n* (%)	100 (40)	86 (42)	132 (53)	0.007
Number of coronary vessels treated, *n* (%)				<0.001
1	166 (66)	124 (60)	137 (55)	
2	71 (28)	68 (33)	63 (25)	
3	15 (6)	14 (7)	50 (20)	
Multivessel treatment, *n* (%)	85 (34)	82 (40)	114 (46)	0.025
Bifurcation stenting, *n* (%)	20 (8)	38 (18)	30 (12)	0.003
No. of stented vessels	1.4 ± 0.6	1.5 ± 0.6	1.7 ± 0.8	<0.001
Number of implanted stents ± SD	1.9 ± 1.2	2.3 ± 1.4	2.3 ± 1.4	<0.001
Total stented length per patient (mm ± SD)	30.5 ± 22.4	44.1 ± 29.2	48.8 ± 32.9	<0.001
Average stent diameter (mm ± SD)	3.27 ± 0.49	2.82 ± 0.25	2.91 ± 0.37	<0.001
Nominal stent diameter ≤2.5 mm, *n* (%)	21 (8.4)	31 (15.1)	52 (20.6)	0.001
Chronic total occlusion (>3 months), *n* (%)	14 (6)	20 (10)	54 (22)	<0.001
Glycoprotein IIb/IIIa inhibitor, *n* (%)	80 (32)	41 (20)	64 (26)	0.02
Clopidogrel prescription (months) ± SD	3.17 ± 3.23	4.68 ± 2.73	6.32 ± 2.58	<0.001
Angiographic success of all lesions, *n* (%)	244 (97)	190 (92)	235 (94)	0.1

Values are means ± SD or percentages.
[a]Expressed as percentage of patients with vessel type treated. Total exceeds 100%.
[b]Expressed as percentage of patients with lesion type. Total exceeds 100%.

Two-year follow-up

Two-year cumulative incidence of mortality was comparable among the three groups: 9.8% in the BMS group vs. 13.3% and 11.5% in the SES and PES groups, respectively (*Figure 1A*). However, a significantly higher number of patients in the SES group died in the second year: 12 (5.8%) when compared with only three (1.2%) in the PES group ($P = 0.007$). Eight patients (3,2%) died in the second year in the BMS group. MI was more frequent in the BMS (7.7%) and SES (5.1%) groups when compared with the PES group (3.4%) ($P = 0.048$ PES vs. BMS). The cumulative incidence of the combined endpoint of death and MI occurred in 15.4% of

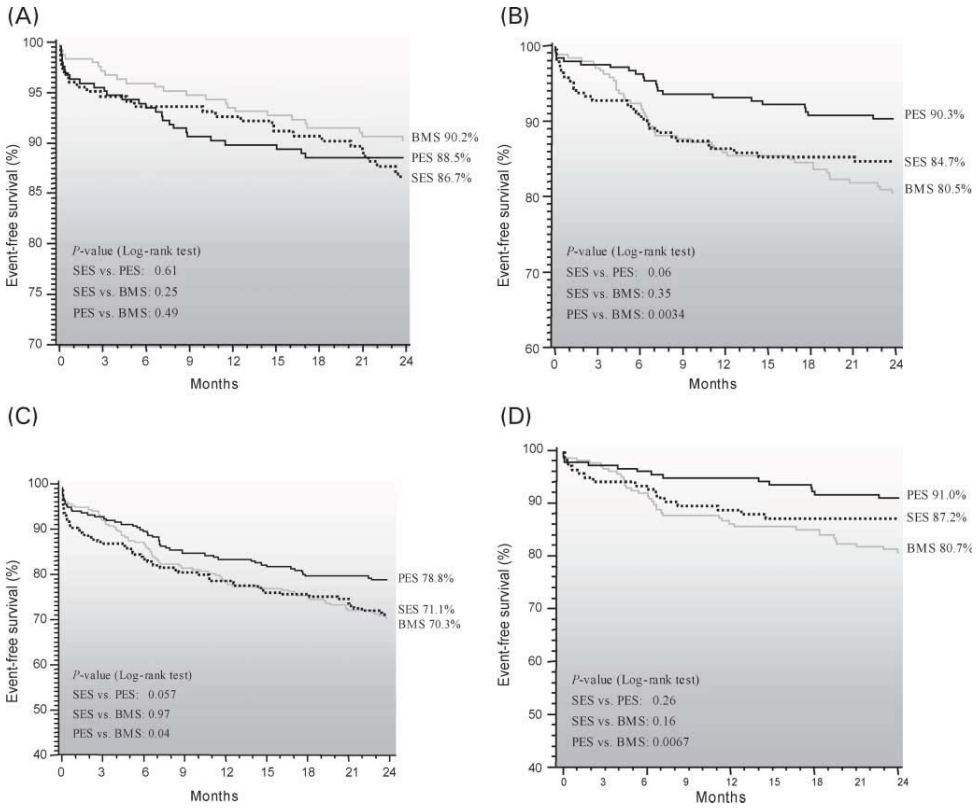

Figure 1 Two-year cumulative incidence of mortality (*A*), TVR (*B*), major adverse cardiac events (*C*), and TVR in NIDDM (*D*), in patients treated with BMS, SES, or PES, respectively.

the BMS patients, vs. 18.2% and 14.7% of the SES and PES patients, respectively ($P = 0.33$ SES vs. PES). TLR was performed in a remarkably low percentage of PES patients (5.3%) when compared with the BMS (15.6%) and SES (13.2%) patients ($P = 0.0037$ SES vs. PES; $P = 0.0004$ PES vs. BMS). Also, TVR was significantly lower in the PES group (9.7%) when compared with the BMS group (19.5%) ($P = 0.0034$). The cumulative incidence of TVR in the SES group was 15.3% and was neither inferior to PES ($P = 0.06$) nor superior to BMS ($P = 0.97$) (*Figure 1B*). The composite endpoint of MACE was found in 29.7% of the BMS patients, almost comparable with the SES group, in which a 28.9% incidence of MACE was found. MACE rates in the PES group (21.2%) were significantly lower when compared with the BMS group (29.7%), $P = 0.04$ (*Figure 1C*). Of interest was the high incidence of ST, which occurred in 4.4% of the SES patients (3.4% early ST) compared with 2.4% in the PES group (2.0% early ST) and only 0.8% in the BMS group (0.8% early ST) (*P*-values: SES vs. BMS, 0.015; PES vs. BMS, 0.18; SES vs. PES, 0.29). Of the total 17 patients with ST, two died, seven presented with an MI, and 12 patients were still on dual-antiplatelet therapy at the time of the event.

When patients were classified with respect to the use of insulin, the cumulative incidence of mortality was significantly higher in IDDM patients (16.7%) compared with the NIDDM patients (9.6%); ($P = 0.013$). TVR was performed in a comparable number of IDDM patients (17.1%) as in NIDDM patients (14.1%); ($P = 0.36$). Comparing TVR rates in the NIDDM patients (*Figure 1D*), the outcomes remained comparable to those of the overall population, showing no significant superiority of PES to SES.

Cox multivariable regression models were used to correct for differences and independent predictors of adverse events between each pair of groups (SES vs. BMS; PES vs. BMS; and PES vs. SES) (*Table 3*). After correcting for independent predictors of adverse events, the use of PES remained significantly superior to BMS in terms of TVR at both 1 (HR 0.66; 95% CI 0.49–0.89) and 2 years (HR 0.69; 95% CI 0.53–0.89), and MACE at 2 years (HR 0.75; 95% CI 0.60–0.94). The use of SES was neither significantly superior

Table 3 Multivariable predictors of major adverse cardiac events at 2 years (Cox proportional hazards model)

	BMS ($n = 252$)	SES ($n = 206$)	PES ($n = 250$)	SES vs. BMS, relative risk (95% CI)	PES vs. BMS, relative risk (95% CI)	PES vs. SES, relative risk (95% CI)
Mortality at 1 year (%)[a]	6.5	7.3	10.2	0.59 (0.23–1.5)]	0.95 (0.61–1.47)	1.72 (0.75–4.00)
Including propensity score				0.65 (0.20–2.14)	1.31 (0.64–2.69)	1.89 (0.69–5.21)
Mortality at 2 years (%)[a]	9.8	13.3	11.5	1.32 (0.76–2.29)	0.89 (0.61–1.31)	0.93 (0.48–1.82)
Including propensity score				1.55 (0.77–3.14)	1.08 (0.58–1.99)	2.31 (0.81–6.58)
Death or non-fatal MI at 1 year (%)[a]	10.9	12.2	12.6	1.04 (0.60–1.78)	0.85 (0.61–1.20)	1.24 (0.66–2.34)
Including propensity score				1.13 (0.58–2.19)	0.92 (0.57–1.51)	1.53 (0.70–3.39)
Death or non-fatal MI at 2 years (%)[a]	15.4	18.2	14.7	1.01 (0.62–1.63)	0.80 (0.59–1.08)	0.78 (0.50–1.24)
Including propensity score				1.20 (0.66–2.19)	0.90 (0.64–1.26)	0.89 (0.44–1.80)
TVR at 1 year (%)[a]	14.1	13.6	6.9	0.99 (0.59–1.65)	0.66 (0.49–0.89)	0.57 (0.29–1.14)
Including propensity score				0.98 (0.52–1.83)	0.69 (0.46–1.03)	0.66 (0.26–1.67)
TVR at 2 years (%)[a]	19.5	15.3	9.7	0.77 (0.48–1.24)	0.69 (0.53–0.89)	0.73 (0.40–1.35)
Including propensity score				0.83 (0.47–1.47)	0.73 (0.51–1.05)	0.65 (0.29–1.47)
MACE (Death, MI, and TVR) at 1 year (%)[a]	21.5	21.4	16.7	0.95 (0.64–1.42)	0.82 (0.65–1.02)	0.75 (0.49–1.15)
Including propensity score				0.97 (0.60–1.58)	0.77 (0.58–1.03)	0.55 (0.32–0.95)
MACE (Death, MI, and TVR) at 2 years (%)[a]	29.7	28.9	21.2	0.99 (0.70–1.40)	0.75 (0.60–0.94)	0.70 (0.49–1.02)
Including propensity score				1.11 (0.72–1.70)	0.77 (0.55–1.07)	0.68 (0.36–1.30)

[a]Crude HRs without propensity scores.

to BMS nor significantly inferior to PES. Of interest was that when the propensity score was added to the models, none of the comparisons remained significant although a trend remained towards a better outcome with PES when compared with both BMS and SES.

Discussion

The present study, comprising a series of 708 consecutive diabetic patients, showed that in contrast to the SES-treated patients, the crude relative risk for both TVR and MACE was significantly lower in the PES group over the BMS group, at 2 years of clinical follow-up. However, after propensity analyses, these differences did not remain significant. Although hypothesized, PES was not superior to SES in the NIDDM subset in reducing TVR or MACE. When compared with IDDM, NIDDM was associated with a better long-term survival.

The 2-year event-free survival rate in this diabetic subset was 24.8%, irrespective of the stent type used, and was substantially lower than reported in DES trials including a general population.[31–33] This latter confirms again the detrimental effect of DM on the prognosis following PCI, despite the use of DES in the majority of our patients.[34]

Both SES and PES have been shown to be superior to BMS in patients with DM up until 1 year of follow-up.[15,16] In a randomized trial by Dibra *et al.*, there was no significant difference between both devices in any of the clinical endpoints at 9 months of follow-up, despite the superiority of SES in reducing late lumen loss and binary restenosis.[20] A meta-analyses of randomized trials comparing either SES or PES to BMS showed that when the diabetic subsets were pooled, the use of SES was associated with a 65% reduction in in-stent restenosis compared with PES, albeit there was again no significant difference between both SES and PES in reducing TVR and MACE.[35] Because of its clinical approach, the present report is not completely comparable to these previous studies with angiographic primary endpoints, which show that inconsistencies between clinical and angiographic endpoints are far from being resolved. Nevertheless, our results are in line with other registries. The STENT registry, including 1680 diabetic patients, confirmed the comparable results achieved with both devices at 9 months of follow-up and the SOLACI registry showed even lower TVR rates in diabetics treated with PES, compared to those treated with SES.[21,36]

Stent thrombosis in both DES arms was high (SES: 4.4%, PES: 2.4%) when compared with the BMS patients (0.8%). Studies focusing on the incidence of ST following treatment with DES in a general population, reported ST rates of 1.0–1.6% and depicted diabetes as an independent predictor of ST.[27,37] The present report emphasizes the need for longer-term follow-up and confirms that ST, mainly in the DES-treated patients, continues to occur after 6–12 months of follow-up.[38] As 78% of the patients with ST were still on dual-antiplatelet therapy, lifelong prescription of clopidogrel, additionally associated with higher bleeding risks, higher costs, and a potential of clopidogrel resistance, does not seem warranted.[39–41] Nevertheless, we feel that these numbers should encourage researchers to continue to follow their patients and not to stop their follow-up when the initial ($\leq$1 year) results look promising.

Of interest are the mechanisms of action of both drugs. Sirolimus is a natural macrocyclic lactone that is capable of inhibiting the mTOR and blocking the cell-cycle during the transition from G1 to S phase.[42] mTOR is dependent of the PI3-kinase pathway, which is hypothesized to be degraded in insulin-resistant diabetics.[19] This latter suggests SES to be less effective in diabetic patients (comprising $\sim$70% NIDDM). Paclitaxel on the other hand stabilizes microtubules, which are known to be responsible for cell division, and acts completely independent of the PI3-kinase pathway. This hypothesis is partly supported by the results of the present study. We observed an almost identical occurrence of MACE in the SES and BMS groups, providing some evidence for the non-superiority of SES in diabetics. Although many would refer to previously published studies, which did prove this superiority, one has to realize that these studies

included only highly selected patients not reflecting daily clinical practice. Not only patients presenting with acute coronary syndrome, chronic total occlusions, and (un)protected left main (LM) stenosis, but also the typical diabetics with diffuse disease in multiple vessels, requiring extensive revascularization were often excluded.[12,14,15] In this study, these high-risk patients comprised ~60% of the present population. Although we were not able to show a superiority of PES over SES, there were two interesting findings. First, MACE rates were significantly higher in the SES group when compared with the PES group at 1 year (propensity analysis), which is in agreement with NIDDM arm, the large-scale STENT registry.[43] Secondly, there was a significantly higher mortality rate during the second year in the SES group. Although this difference could be due to ST, focusing on the combined endpoint of death and MI revealed comparable rates in all three groups, especially when correcting for independent predictors. Moreover, it has to be commented that the overall mortality rate (11.4%) in the present population was higher than reported in previous trials and is most likely related to the high complexity of the present population. Excluding patients presenting with multivessel disease, LM lesions and presentation with acute myocardial infarction resulted in a 2-year mortality rate of only 7.6%.

The present study suffers from the inherent limitations of a non-randomized trial. The compared groups were not completely identical, which was mainly due to the relatively large inclusion period in which the complexity of the procedures increased. In order to partly compensate for the differences in baseline characteristics, with an increasing risk over time, we performed a multivariable analysis and a propensity analysis. Thereby, the TLR rate might be less accurate in predicting clinical restenosis compared with a non-diabetic population, since diabetic patients are known to have a significantly greater incidence of silent ischaemia than non-diabetics and the lack of an angiographic follow-up.[44] Finally, ST related only to angiographically document ST, using a definition consistent with previous reports on ST either after DES or BMS implantation. This latter may have led to an underestimation of the actual incidence of ST, particularly, in patients suffering from sudden cardiac death or silent stent occlusion.

Nevertheless, this report focuses on the 2-year 'clinical' outcome of the unrestricted use of BMS, SES, and PES in diabetic patients in a 'real world' setting and demonstrates the importance of longer-term follow-up. More larger scale and randomized trials are needed to elucidate the best treatment for patients with DM and the possible superiority of one DES compared to another, also taking into account the long-term adverse events like ST.

Conclusion

Although there was a trend towards lower MACE rates in the PES group at 2 years of clinical follow-up, the superiority of both SES and PES over BMS in diabetic patients remains questionable. There was no significant difference between SES and PES in the NIDDM patients, who are hypothesized to be better-off with PES, and ST was more frequent in both DES groups.

Conflict of interest: none declared.

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Chapter 10

Three-year outcome with sirolimus- and paclitaxel-eluting stents and bare metal stents for diabetic patients with de-novo coronary artery stenosis

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Submitted for publication

Three-year Outcome with Sirolimus- and Paclitaxel-eluting Stents and Bare Metal Stents for Diabetic Patients with de-novo Coronary Artery Stenoses

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on behalf of the interventional cardiologists of the Thoraxcenter (2000-5).

Submitted for publication

Aims: To clarify long-term clinical outcomes after percutaneous coronary intervention with bare-metal stents (BMS) or drug-eluting stents in diabetic patients Methods and Results: This study reports 3-year outcomes of 885 consecutive diabetic patients with *de-novo* coronary lesions exclusively treated with either BMS (n=295), sirolimus-eluting stent (SES; n=139) or paclitaxel-eluting stent (PES; n=451). All-cause mortality was comparable among three groups (BMS 15.9%; SES 13.9%; PES 14.9%). Target vessel revascularization (TVR) was lower percentage of PES (11.2%) than BMS group (22.5%) (P = 0.001) but was comparable between SES (16.9%) and BMS group (P=0.25). After multivariate adjustment, risks of TVR and MACE (all-cause mortality, any myocardial infarction or TVR) in PES were lower than in BMS (Hazard ratio [HR] 0.50 [95%CI: 0.33-0.75] for TVR, HR 0.65 [95%CI: 0.48-0.87] for MACE), but these risks in SES were comparable with BMS (HR 0.75 [95%CI: 0.46-1.24] for TVR, HR 0.77 [95%CI: 0.52-1.13] for MACE). Conclusions: PES was associated with a lower risk of TVR and MACE at 3 years in comparison with BMS, while the relative benefit of SES appears less convincing.

INTRODUCTION

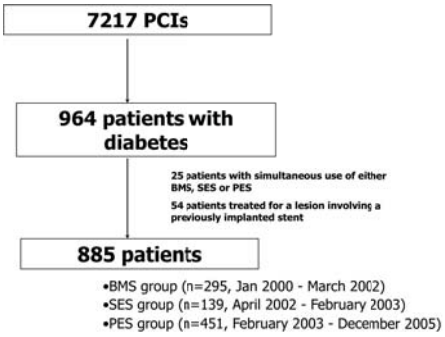
Patients with diabetes mellitus represent up to 25% of all patients undergoing percutaneous coronary intervention (PCI) (1, 2). Revascularization in diabetic patients is particularly challenging as they have significantly worse clinical outcomes compared to nondiabetic patients after bare-metal stent (BMS) implantation (3-6), mainly due to high restenosis rates, inability to fully revascularize multiple ischemic areas and the rapid progression of atherosclerosis (7-9). Sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) were shown to markedly reduce the incidence of restenosis and repeat revascularization in patients with diabetes when compared with BMS up until 2 years of follow-up in several retrospective registry subset analyses (10-14). However, whether long-term hard clinical endpoints such as mortality remain comparable between DES and BMS is still controversial in diabetics (15-17). A meta-analysis of 4 randomized trials comparing SES and BMS found increased mortality with SES in the diabetic subgroup(18), while a analysis from 5 randomized trials of PES versus BMS demonstrated no difference in the 4-year mortality rates (16). Also the relative efficacy of SES and PES in diabetic patients remains unclear. Several registries comparing SES and PES in diabetic patients revealed no difference in outcome regarding restenosis and revascularization procedures (12, 19,20), while data from randomized trials demonstrated a favorable effect of SES in reduction of angiographic restenosis and repeat revascularization up to 2 years.(21, 22) Since long-term comparisons between BMS and different DES in diabetic patients are still limited especially in real-world settings, we undertook this study to assess the impact of diabetes on three-year outcome in patients undergoing PCI with BMS, SES and PES implantation.

Methods

Study design and patient population

Between January 1, 2000 and December 31, 2005, a total of 7,217 PCI procedures in 6129 patients were performed in our institution using BMS, SES or PES. Initially, all patients were treated with BMS, but on 16th April 2002, our institution adopted the use of SES (Cypher; Cordis, Warren, NJ) as the default strategy for all coronary interventions, as part of RESEARCH registry (23). On 16th February 2003, SES was replaced by PES (TAXUS™ Express2™, Boston Scientific, Natick, MA) as the default stent, as part of the T-SEARCH registry(24). In this study, patients were eligible for inclusion if they were undergoing pharmacological treatment with either insulin or hypoglycemic agents at the time of the index procedure; patients with transient hyperglycemia were not included in the present analysis. The exclusion criteria were the implantation of more than one different stent type during the index procedure or PCI for a lesion of in-stent restenosis. For patients undergoing multiple procedures, the first procedure at our institution was recorded as the index

Figure 1.Flowchart showing patient recruitment



procedure: all subsequent procedures were counted as repeat interventions. Patients initially in one of the sequential cohorts (BMS, SES or PES group) were maintained for analytical purposes throughout the follow-up period in their original cohort, even if a repeat revascularization was performed using a different type of stent. For example, a repeat revascularization of BMS patient with DES is counted as an event, but the patient remained as "BMS" patient and was not included in the DES cohort despite the fact that the instent restenosis was treated with DES. In total, 1165 procedures (BMS group: n=383, SES group: n=206, PES group: n=576) were performed in diabetic patients. Since 201 procedures were counted as repeat procedure in the same patients during the period, 964 patients were initially enrolled (Figure1). After excluding 79 patients (25 patients receiving more than one type of stent, 54 treated with in-stent restenosis), 885 diabetics were included in the current study (BMS group: n=295, SES group: n=139, PES group: n=451).

Procedures and medications

All procedures were performed according to standard clinical guidelines at the time(25). Angiographic success was defined as a residual stenosis ≤30% by visual analysis in the presence of Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow. All patients were pretreated with 300 mg of clopidogrel. At least one-month of clopidogrel treatment (75mg/day) was recommended for patients treated with BMS. Clopidogrel was prescribed for ≥3 or 6 months for patients with SES depending of the complexity of the procedure, for ≥6 months for patients treated with PES. Life-long aspirin therapy is recommended in all patients.

Endpoint definitions and clinical follow-up

Diabetes was defined by the presence of anti-diabetic therapy. Patients taking only oral medication were classified as non-insulin dependent diabetes mellitus (NIDDM) and those on insulin therapy were classified as insulin dependent diabetes mellitus (IDDM). The primary endpoint was major adverse clinical endpoints (MACE, defined as all-cause death, any myocardial infarction irrespective of vascular territory or target vessel revascularization). Secondary endpoints included all-cause mortality, any myocardial infarction (MI), target vessel revascularization (TVR), target lesion revascularization (TLR), definite stent thrombosis, and the composites of all-cause death or any MI. MI was diagnosed by a rise of creatine kinase-MB greater than 3 times the normal upper limit (26). TVR was defined as a repeat revascularization of a lesion in the same epicardial vessel treated in the index procedure (27). TLR was defined as a repeat intervention in the stent or in the 5 mm proximal or distal segments to the stent. Hypercholesterolemia was defined as a fasting serum cholesterol level > 5.5 mmol/l or use of lipid-lowering therapy at the time of the procedure. The creatinine values before the procedure were used to calculate baseline creatinine clearance according to the formula proposed by Cockcroft and Gault: creatinine clearance (ml/min)=(140 - age) x weight (kg) / 72 x serum creatinine (mg/dl) (x 0.85 for women).(28) Renal impairment was arbitrarily defined as a creatinine clearance below 70 ml/min (29). Stent thrombosis was defined as angiographically defined thrombosis with TIMI grade 0 or 1 flow or the presence of a flow limiting thrombus, accompanied by acute symptoms, irrespective of whether there had been an intervening reintervention. (30) The timing of stent thrombosis was categorized as early (within 30 days after implantation), late (between 30 days and 1 year) or very late (more than 1 year). (31)

Follow-up data

Survival data for all patients were obtained from municipal civil registries on a yearly basis. A questionnaire was subsequently sent to all living patients with specific questions on re-hospitalization and major adverse cardiac events. As the principal regional cardiac referral center, most repeat revascularization either percutaneous or surgical are normally performed at our institution and recorded prospectively in our database. For patients who suffered an adverse event at another center, medical records or discharge letters from the other institutions were systematically reviewed. General practitioners and referring physicians were contacted for additional information if necessary.

Table 1. Patient and procedural characteristics

	BMS (n=295)	SES (n=139)	PES (n=451)	p values
Patient characteristics				
Age, years	63.3±10.7	61.9±10.7	63.9±10.7	0.18
male, n(%)	191(64.7)	88(63.3)	298(66.1)	0.82
Clinical presentation				
Stable angina	122(41.4)	62(44.6)	208(46.1)	0.44
Unstable angina	122(41.4)	54(38.8)	147(32.6)	0.04
Myocardial infarction	51(17.3)	22(15.8)	96(21.3)	0.23
Cardiogenic shock	1(0.3)	5(3.6)	3(0.7)	0.004
Insulin dependent DM	27(9.2)	44(31.7)	104(23.1)	<0.001
Non-insulin dependent DM	268(90.8)	95(68.3)	347(76.9)	<0.001
Hypertension	151(51.2)	102(73.4)	322(71.4)	<0.001
Hypercholesterolemia	156(52.9)	97(69.8)	344(76.3)	<0.001
Family history	60(20.3)	37(26.6)	149(33.0)	0.001
Current smoking	65(22.0)	31(22.3)	90(20.0)	0.73
Previous PCI	48(16.3)	8(5.8)	52(11.5)	0.006
Previous CABG	54(18.3)	12(8.6)	61(13.5)	0.021
Previous MI	105(35.6)	50(36.0)	145(32.2)	0.53
Renal impairment	3（1.0）	8（5.8）	19（4.2）	0.015
Multivessel disease	186(63.1)	94(67.6)	279(61.9)	0.47
Procedural characteristics				
*Treated Vessels**				
LAD	162（54.9）	90（64.7）	232（51.4）	0.022
LCx	103（34.9）	51（36.7）	149（33.0）	0.69
RCA	115(39.0)	54(38.8)	176(39)	0.99
LM	15（5.1）	7（5.0）	30（6.7）	0.61
Bypass	30（10.2）	3（2.2）	28（6.2）	0.006
Bifurcation	11（3.7）	16（11.5）	53（11.8）	0.001
Chronic total occlusion	30(9.4)	9(6.0)	47(10.0)	0.33
Lesion type†				
Type B2	139（47.1）	73（52.5）	196（43.5）	0.16
Type C	120（40.7）	60（43.2）	189（41.9）	0.88
Multivessel treatment	111（37.6）	58（41.7）	147（32.6）	0.1
No. of implanted stents	1.93±1.27	2.45±1.47	2.35±1.51	<0.001
Total stented length per patient, mm	30.5±21.4	47.3±31.29	47.7±33.9	<0.001
Average stent diameter, mm	3.22±0.53	2.82±0.22	2.92±0.59	<0.001
Glycoprotein IIb/IIIa	104（35.3）	29（20.9）	81（18.0）	<0.001
Recommended duration of clopidogrel prescription, months	2.38±2.69	4.51±1.85	6.47±2.67	<0.001
Angiographic success of all lesions	278（94.2）	128（92.8）	401（94.1）	0.81

Values are n(%) or mean±standard deviation; * expressed as percentage of patients with each vessel type, hence total > 100%; † expressed as percentage of patients with each lesion type, hence total > 100%; BMS = bare-metal stent, SES = Sirolimus-eluting stent, PES = Paclitaxel-eluting stent, DM = diabetes mellitus, PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft, MI = myocardial infarction, LAD = left anterior descending

artery, RCA = right coronary artery, LCx = left circumflex artery, LM = left main

Statistical analysis

Continuous variables are presented as mean ± standard deviation, whereas categorical variables are expressed as percentages. Comparisons among the 3 groups were performed by F-test from an analysis of variance for continuous variables and Pearson's Chi-Square test for categorical variables. All statistical tests were 2-tailed and p value of <0.05 was considered as statistically significant. The incidence of events over time was studied with the use of the Kaplan-Meier method, whilst log-rank tests were applied to evaluate differences between the treatment groups. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. To elucidate the treatment effect of each stent type, separate Cox regression models were built to adjust multiple potential confounders in the baseline and procedural characteristics for each paired treatment comparison

Table 2. Adjusted Hazard ratios for all clinical endpoints

	Hazard Ratio SES vs. BMS (95% confidence interval)	Hazard Ratio PES vs. SES (95% confidence interval)	Hazard Ratio PES vs. BMS (95% confidence interval)
All-cause death	0.67(0.37-1.22)	1.13(0.64-2.02)	0.93(0.61-1.44)
propensity score adjusted	0.57(0.25-1.29)	1.30(0.63-2.69)	1.08(0.61-1.90)
Myocardial infarction	0.39(0.15-1.05)	1.10(0.46-2.60)	0.65(0.33-1.28)
propensity score adjusted	0.33(0.09-1.19)	0.96(0.34-2.70)	0.66(0.28-1.52)
All-cause death or Myocardial infarction	0.76(0.46-1.26)	1.03(0.64-1.65)	0.86(0.59-1.26)
propensity score adjusted	0.54(0.27-1.08)	1.16(0.65-2.10)	1.01(0.61-1.67)
Target lesion revascularization	0.50(0.27-0.92)	0.69(0.36-1.33)	0.37(0.23-0.60)
propensity score adjusted	0.46(0.20-1.05)	0.57(0.27-1.21)	0.34(0.19-0.62)
Target vessel revascularization	0.75(0.46-1.24)	0.68(0.40-1.16)	0.50(0.33-0.75)
propensity score adjusted	0.65(0.32-1.31)	0.53(0.29-0.99)	0.40(0.24-0.67)
MACE (all-cause death or myocardial infarction or target vessel revascularization)	0.77(0.52-1.13)	0.81(0.55-1.19)	0.65(0.48-0.87)
propensity score adjusted	0.62(0.36-1.06)	0.83(0.52-1.31)	0.63(0.43-0.92)
Stent Thrombosis	2.99(0.95-9.42)	0.56(0.21-1.50)	1.39(0.47-4.19)
propensity score adjusted	1.67(0.32-8.81)	0.41(0.13-1.32)	1.64(0.44-6.19)

BMS = bare-metal stent, SES = Sirolimus-eluting stent, PES = Paclitaxel-eluting stent, MACE = Major Adverse Cardiac Events

(SES vs. BMS, PES vs. BMS and SES vs. PES). In these analyses, stent type was forced into forward stepwise models using the variables in Tables 1 with entry and stay criteria of 0.05 and 0.10, respectively. The results are presented as adjusted hazard ratios (HR) with 95% confidence intervals (CI). For additional adjustment, a propensity score for the predicted probability of receipt of a drug-eluting stent in each patient was estimated with the use of a logistic-regression model fit with variables in table 1(32). The resulting propensity scores and stent type were then forced into separate forward stepwise Cox multivariate regression models using the variables in Table 1. Separate Cox multivariate regression models with all variables in Table 1 and stent type were used to identify independent predictors of clinical endpoints: forward stepwise regression was performed with entry and stay criteria of 0.05 and 0.10, respectively. Statistical analysis was performed with SPSS 12 for windows (SPSS Inc., Chicago IL, USA).

Results

Baseline and procedural characteristics

Both baseline and procedural characteristics are depicted in Table 1. There were more patients requiring insulin treatment in both DES groups (SES: 31.7%, PES: 23.1% and BMS: 9.2%, P<0.001). A history of previous revascularization was less frequent in SES patients than in other 2 groups. More complex lesions were treated in both DES groups than in the BMS group, which was reflected by a higher incidence of bifurcation lesions, increased number of implanted stents, higher total stented length, and lower average stent diameter.

Clinical outcomes

Clinical follow-up was available in 850 patients (96.0%) with a median duration of follow-up of 1243 days (IQR: 805-1699). Cumulative incidences of clinical endpoints up to 3 year are presented in Figure 2. The all-cause mortality rate was comparable among the three groups: 15.9% in the BMS group vs. 13.9% and 14.9% in the SES and PES groups, respectively (Figure 2A). Also the cumulative incidence of all-cause death or any MI was similar in three groups (Figure 2B). TVR was observed in a significantly lower percentage of PES patients (11.2%) when compared with the BMS (22.5%) (log-rank p = 0.001) (Figure 2C). This trend was observed in the comparison between PES (11.2%) and SES (16.9%), but did not reach statistical significance (log-rank p=0.06). The composite endpoint of MACE was found in 35.4% of the BMS patients as compared with 30.8% in the SES group (log-rank p=0.42) (Figure 2D). MACE rates in the PES group (26.0%) were significantly lower when compared with the BMS group (35.4%) (log-rank p=0.01). The rate of stent thrombosis was higher in SES patients with 5.2% (2.9% early) compared with 2.7% in the PES group (1.1% early) and 1.8% in the BMS group (1.1% early), however, these differences did not reach statistical significance (BMS vs. SES: log-rank p=0.051, BMS vs. PES: log-rank p=0.10, SES vs. PES: log-rank p=0.10) (Figure 2E). In the NIDDM subpopulation, the TVR rate was lower in the DES groups than BMS group, although it was not statistically different between SES and PES group (Figure 2F). Despite small numbers, the cumulative survival curve for the IDDM subpopulation (Figure 2G) revealed that SES was associated with a significantly

Table 3. Independent predictors of each clinical endpoint at 3 years

	Adjusted HR	95%CI	P value
Mortality			
Procedural success	0.43	0.24-0.77	0.005
RCA	0.58	0.37-0.89	0.012
Stable angina	0.58	0.39-0.87	0.009
Age#	1.05	1.03-1.07	<0.001
Type B2	1.54	1.01-2.34	0.04
Type C	1.79	1.17-2.75	0.008
Multivessel disease	2.79	1.62-4.83	<0.001
Renal Impairment	3.42	1.63-7.18	0.001
Myocardial Infarction			
Total stented length†	1.01	1.01-1.02	0.025
LAD	2.17	1.12-4.22	0.022
Previous CABG	2.25	1.09-4.64	0.028
Target vessel revascularization			
PES use	0.54	0.37-0.80	0.002
Left main	2.37	1.27-4.40	0.007
Target lesion revascularization			
Number of stent*	1.28	1.11-1.46	<0.001
BMS use	2.47	1.61-3.79	<0.001
Death or Myocardial Infarction			
Procedural success	0.46	0.27-0.78	0.004
Stable angina	0.60	0.42-0.85	0.004
RCA	0.65	0.46-0.94	0.02
Age#	1.04	1.02-1.05	<0.001
Number of stents*	1.16	1.03-1.31	0.014
Multivessel disease	2.13	1.38-3.29	0.001
Renal impairment	2.41	1.17-4.98	0.02
Death or MI or TVR			
Stable angina	0.71	0.54-0.93	0.012
Age#	1.02	1.01-1.03	0.002
Multivessel disease	1.62	1.20-2.18	0.002
Left main	2.08	1.29-3.35	0.003
Renal impairment	2.13	1.09-4.16	0.027
Definite stent thrombosis			
Type B2	0.32	0.12-0.84	0.02
Number of stents*	1.30	1.01-1.68	0.04
LAD	7.69	1.78-33.22	0.006

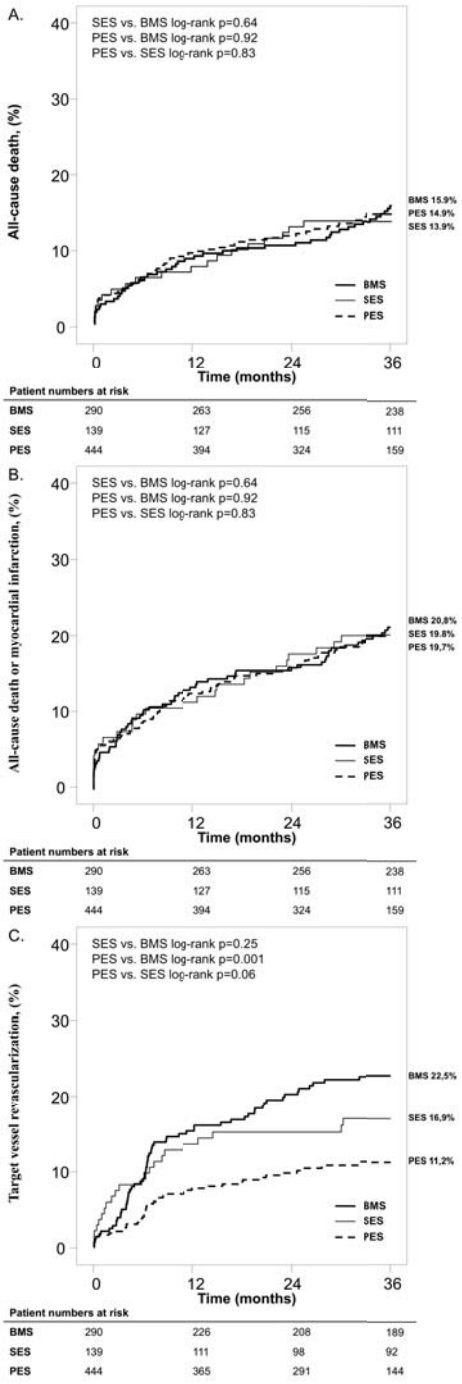
BMS = bare-metal stent, PES = Paclitaxel-eluting stent, PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting, LAD = left anterior descending artery, RCA = right coronary artery, MI = myocardial infarction, TVR = target vessel revascularization; # = per each extra year; * = per each extra stent; † = per each extra mm

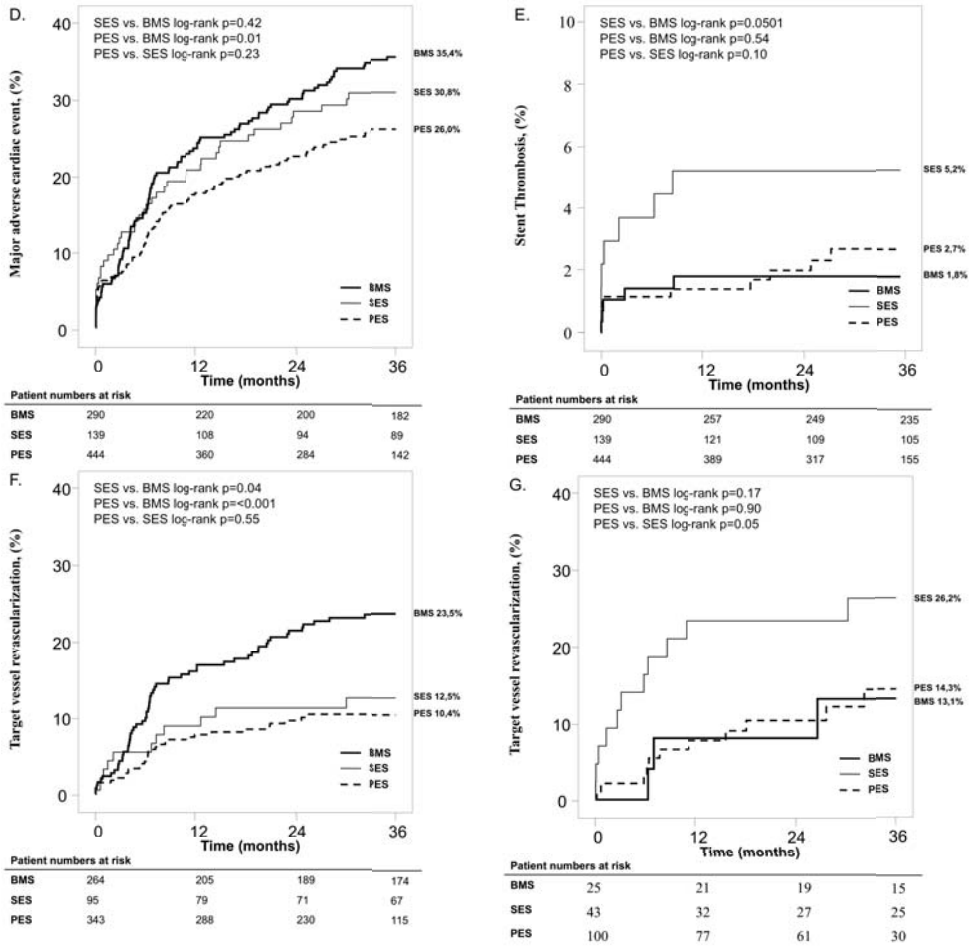
higher TVR rate than the other 2 groups (BMS 13.1%, SES 26.2% and PES 14.3%).

Multivariate analyses

Cox multivariable regression models were used to correct for differences of baseline characteristics in

Figure 2.





Kaplan Meier curves for cumulative for all-cause mortality (A), a composite endpoint of all-cause death or myocardial infarction (B), target vessel revascularization (C), major adverse cardiac events (D) and definite stent thrombosis (E). Figure 2F and 2G represents cumulative Kaplan-Meier curves for target vessel revascularization in non-insulin dependent diabetes mellitus and insulin dependent diabetes mellitus subpopulation, respectively.

comparisons between each stent type (SES vs. BMS; PES vs. SES; and PES vs. BMS, Table 2). Repeat revascularization rates (both TVR and TLR) as well as MACE rates were significantly lower in the PES group than in the BMS group. The SES group had a lower rate of TLR than the BMS cohort (HR 0.50, 95%CI 0.33-0.75). When the propensity score was added to the models, the lower hazard rate of TLR, TVR or MACE in the PES cohort in comparison with BMS cohort remained significant, while the lower rate of TLR in SES group became non-significant. In addition, the TVR rate in the PES group became significantly lower than the SES group.

Multivariate predictors of clinical endpoints are shown in Table 3. Use of PES was an independent predictor of a lower risk of target vessel revascularization (adjusted HR 0.54, 95% CI 0.37-0.80), while use of BMS was an independent predictor of a higher risk of TLR (adjusted HR 2.47 1.61-3.79, p<0.001). For the other outcomes, stent type was not detected as an independent predictor. Independent predictors of MACE were age (adjusted HR 1.02 [per each year-old], 95% CI 1.01-1.03, p=0.002), multivessel disease (adjusted HR 1.62, 95% CI 1.20-2.18, p=0.002), left main lesion (adjusted HR 2.08, 95% CI 1.29-3.35, p=0.003), renal impairment (adjusted HR 2.13, 95%CI 1.09-4.16, p=0.027) and

presentation with stable angina (adjusted HR 0.71, 95% CI 0.54-0.93, p=0.012).

Discussion

The current study demonstrates that at 3 years, the relative risk for TVR and MACE was significantly lower in the PES group than the BMS group, whereas SES failed to show a significant reduction of any clinical endpoint in comparison with BMS. For hard clinical endpoints such as all-cause death or any myocardial infarction, no significant differences were observed between the 3 groups. Both SES and PES have been shown to be more effective in reducing angiographic restenosis and clinical revascularization as compared with BMS. A meta-analysis of 1520 diabetic patients enrolled in 8 trials(10) confirmed the beneficial effects of DES on neointimal suppression (mean late lumen loss with SES 0.12mm, mean late lumen loss with PES 0.34 mm compared to 0.93mm with BMS), which translated into a marked decrease in in-stent restenosis (Risk ratio [RR] of DES vs BMS: 0.14, p<0.001) and TLR (RR: 0.34, p<0.001) at 6-9 month follow-up. In a post hoc analysis using patient data from four randomized, multicentre, controlled clinical trials (TAXUS II, IV, V, and VI) including 685 diabetic patients, Dawkins et al. reported decreased TLR rates in the PES group relative to BMS controls by 59% (p=0.0001) among diabetic patients treated with oral medications, and by 66% (p=0.006) among those treated with insulin(33).

The DIABETES trial, randomizing 160 diabetic patients to either SES or BMS demonstrated this favourable ability of SES over BMS to reduce the rate of TLR up to 2 years (SES 7.7% vs BMS 35%, p<0.001). An analysis of 559 diabetic patients in the REgistro Regionale Angiop Lastiche Emilia-Romagna (REAL) registry also demonstrated no difference in mortality and significantly lower TVR (11.6% vs. 15.0%; HR0.66 [95% CI, 0.46 to 0.96]) in the DES group at 2 years. In our current study, PES have been shown to be superior to BMS in patients with DM at 3 years in reducing TLR and TVR, while the possible benefit of SES regarding either TLR or TVR could not be demonstrated.

Whether there is a difference between the two DES types in their ability to reduce restenosis and revascularization events in diabetics is still unclear. In a randomized trial directly comparing PES and SES in the diabetic population (21), there was no difference between both devices in any of the clinical endpoints at 9 months of follow-up, despite the superiority of SES in reducing late lumen loss and binary restenosis. Another meta-analysis of 10 randomized trials comparing either SES or PES to BMS showed that the use of SES was associated with a 65% reduction in in-stent restenosis compared with PES when the diabetic subsets were pooled, although there was no difference between both SES and PES in reducing TVR and MACE. (34) In our current analysis, after propensity score adjustment, the TVR rate was lower with PES than SES. Although our present report is not absolutely comparable to these previous studies with angiographic primary endpoints, our results are still in line with other registry data such as TC WYRE showing lower 12-month TVR rates in PES group (SES 8.5% vs. PES 2.8%, p=0.004) (35).

It is noteworthy that the superiority of PES over SES might result from the different mechanisms of action in terms of inhibition of neointimal proliferation. Type 2 diabetics exhibit a breakdown in the PI3-kinase insulin signal transduction pathway, in which the mammalian target of rapamycin (mTOR) is involved. Rapamycin (sirolimus), a natural macrocyclic lactone, inhibits mTOR thereby blocking the cell-cycle during the transition from G1 to S phase: inhibiting protein synthesis by blocking mTOR with rapamycin may be less effective in type 2 diabetics (comprising ~70% NIDDM) (36). On the other hand, paclitaxel might exert the same potency in diabetics as in non-diabetics by inhibiting a formation of microtubulus, independent of insulin resistance (36). However, despite this hypothesis, the subanalysis of NIDDM patients (figure 2F) showed no difference between PES and SES in terms of TVR, while SES was associated with a higher TVR rate compared to PES in the IDDM population (figure 2G). The efficacy of different type of DES in the IDDM population should be a target for future investigation.

Our data suggests a comparable safety of drug-eluting stents compared with BMS in terms of all-cause mortality at 3 years. Although this is compatible with other registry data up to 2 years (37), data from randomized trials showed conflicting results. Spaulding et al. demonstrated higher 4-year mortality in the SES group than in BMS group (12.2% vs. 4.4%, p=0.004) in a pooled analysis of 428 diabetic patients from 4 randomized trials comparing SES with BMS(15). In contrast to this meta-analysis, Kirtane et al. demonstrated no difference in the 4-year mortality rates (8.4% vs. 10.3%, respectively, p=0.61) using 827 patient-level data from 5 randomized trials of PES versus BMS (16). More recently, using data of 3,853 diabetics from 35 randomized trials, Stettler et al. suggested that inconsistency in all-cause mortality appeared to be related to the duration of dual anti-platelet therapy (38). In a collaborative network analysis by the same group including 38 randomized trials of higher risk patients (17) with 3,870 diabetics, no differences in mortality were demonstrated when comparing SES, PES and BMS (SES vs. BMS: HR 1.24, 95% CI 0.74–1.87, p=0.29; PES vs. BMS: HR 1.16, 95% CI 0.78–1.84, p=0.55; SES vs. PES: HR 1.06, 95% CI 0.76–1.59, p=0.78). To further establish the safety of

DES use in the diabetic population, longer-term follow-up is necessary for patients from all-comer registries.

Late stent thrombosis is a major concern after DES implantation. Studies focusing on the incidence of stent thrombosis following treatment with DES in a general population, reported stent thrombosis rates of 1.0–1.6% and depicted diabetes as an independent predictor of stent thromobosis(39).

In the present study, stent thrombosis in both DES cohorts was high (SES 5.2% and PES 2.7%) when compared with the BMS cohort (1.8%). The Kaplan-Meier curve (Figure 2E) confirmed the occurrence of very late stent thrombosis (more than 12 months after stent implantation) in the PES group. This emphasizes the necessity of longer follow-up data from larger populations and the potential impact of stent thrombosis on repeat revascularization rates.

In this study, we employed a patient-based analysis method by including only one index procedure for each patient, while previous publications from our group used a per-procedural analysis(12, 19). Although we extended the patients cohort, the number of patients in the SES group is therefore smaller (n=135) than previous reports (n=206) (12, 19). Despite this discrepancy in methodology, the overall results were similar to the 2-year results reported(12).

Limitations

The current study suffers from the inherent limitations of a non-randomized trial. There were significant differences between the cohorts in terms of baseline demographics. To compensate for these differences, we have performed adjustments employing multivariate analysis with a propensity score, although we cannot adjust hidden confounding factors and other sources of bias typical of observational studies. Nevertheless, these unselected patients represent real-world practice, whereas patients enrolled in clinical trials are carefully selected. We only investigated angiographically documented stent thrombosis, using a definition consistent with previous reports on stent thrombosis either after DES or BMS implantation. This latter may have led to an underestimation of the actual incidence of stent thrombosis, particularly, in patients suffering from sudden cardiac death or silent stent occlusion.

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Conflict of interest:

none declared

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Chapter 11

Multi-lesion culotte and crush bifurcation stenting with sirolimus-eluting stents: long-term angiographic outcome

Daemen J, Lemos PA, Serruys PW

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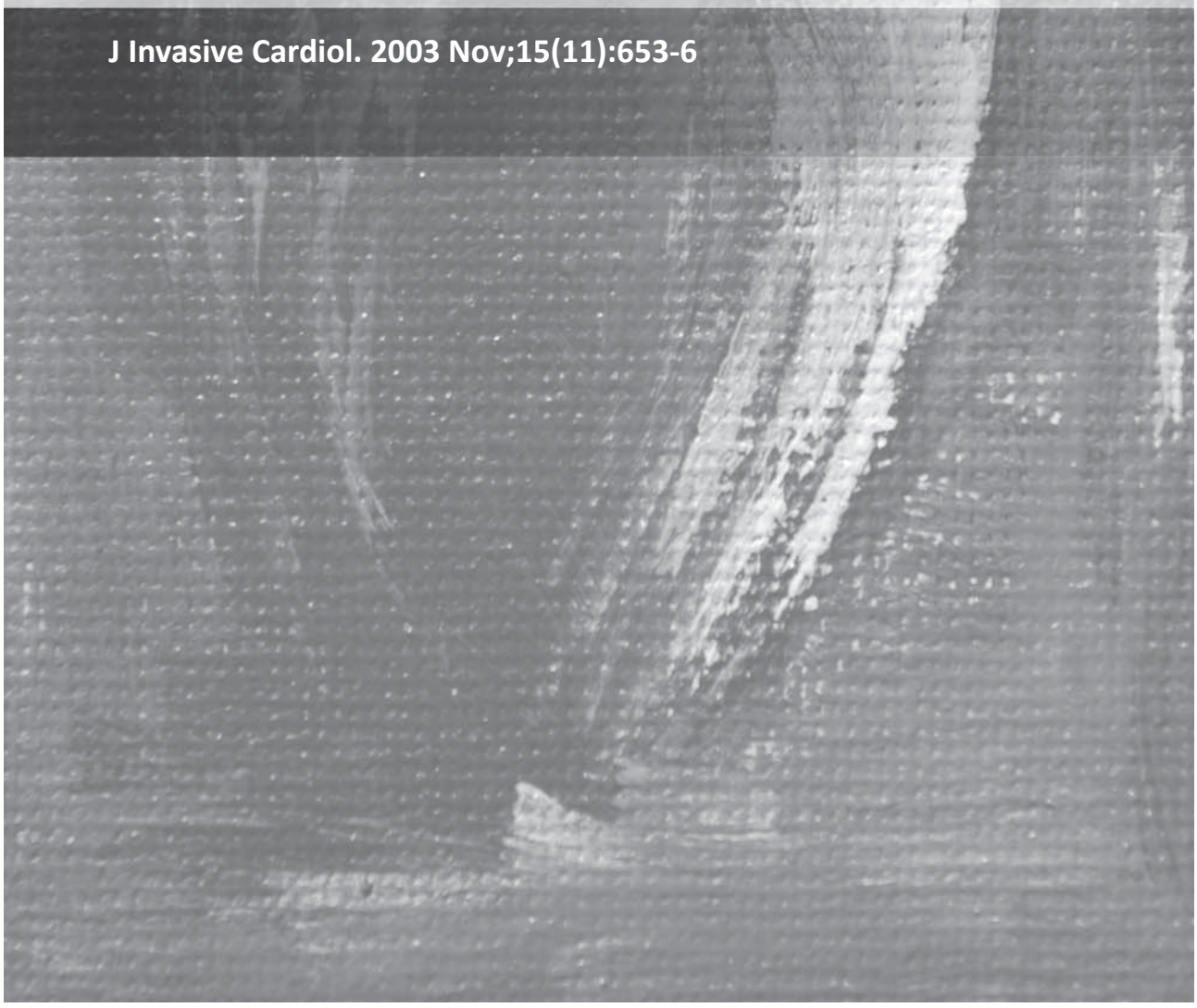

Multi-Lesion "Culotte" and "Crush" Bifurcation Stenting with Sirolimus-Eluting Stents: Long-Term Angiographic Outcome

Joost Daemen, Pedro A. Lemos, MD, Patrick W. Serruys, MD, PhD

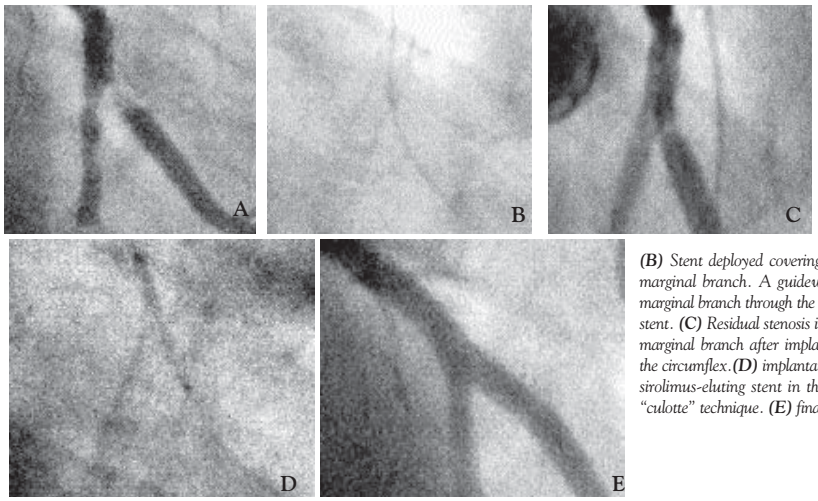

Figure 1. ***(A)*** *Left coronary angiogram (caudal right anterior oblique projection) showing diffuse disease with distal occlusion of the left circumflex artery and severe ostial stenosis in first obtuse marginal branch.* ***(B)*** *Stent deployed covering the origin of the first marginal branch. A guidewire was placed in the marginal branch through the struts of the circumflex stent.* ***(C)*** *Residual stenosis in the ostium of the first marginal branch after implantation of the stent in the circumflex.* ***(D)*** *implantation of a 3.0 X 18 mm sirolimus-eluting stent in the LCx-OM using the "culotte" technique.* ***(E)*** *final angiographic result.*

Case Report. A 63-year-old man, an ex-smoker with a history of hypertension and previous myocardial infarction, was admitted with stable angina (Canadian Cardiovascular Society Class 1) for elective percutaneous coronary intervention. Pre-procedure coronary angiogram revealed diffuse disease in the proximal and mid segments of the left circumflex artery (LCx) that was totally occluded in its distal portion (Fig. 1A). The first obtuse marginal branch (OM) presented a severe ostial stenosis (Fig. 1A). Also, the left anterior descending artery (LAD) presented a long stenosis in its mid portion, involving the origin of the first and second diagonal branches (Fig. 2A). The right coronary artery (RCA) showed mild irregularities without any localized significant stenosis.

The left coronary was cannulated with a 7 French (Fr) Vista Brite Amplatz Left guiding catheter (Johnson & Johnson, Cordis Corporation, Miami Lakes, Florida). The ostial lesion in first OM was crossed with a PT Graphix Intermediate 0.014″ guidewire. Another PT Graphix Intermediate 0.014″ guidewire was inserted in the LCx, but the total occlusion in its distal segment could only be partially recannalized. A 2.5 x 18 mm sirolimus-eluting Cypher stent (Cordis Corp.) was deployed (14 atm) in a stenotic lesion in the LCx just proximal to the site of the vessel occlusion in an attempt to facilitate further measures to recannalize the vessel; the stent was deployed covering the origin of the first marginal branch (Fig. 1B). A 3.0 X 18 mm sirolimus-eluting Cypher stent (Johnson & Johnson, Cordis Corp.) was then implanted in the LCx-OM using the "culotte" technique (20 atm) (Figs. 1C and 1D). A residual stenosis in the proximal LCx was treated with an additional 3.0 x 18 mm sirolimus-eluting Cypher stent overlapping the distal stent (20 atm). Further attempts to recannalize the distal LCx were unsuccessful. The final result is depicted in Figure 1E.

Two PT Graphix Intermediate 0.014″ guidewires were inserted in the LAD and second diagonal branch. A "crush" stent implantation was performed: a 2.25 x 8 mm sirolimus-eluting stent and a 3 x 33 mm sirolimus-eluting stent (Cypher) were concomitantly positioned in the second diagonal and mid LAD, respectively (Figure 2B). The 2.25 x 8 mm sirolimus-eluting stent was deployed (12 atm) with its proximal portion partially placed through the LAD (Figure 2B). Importantly, the LAD-diagonal stent was implanted while the undeployed 3 x 33 mm sirolimus-eluting-stent was already positioned in the LAD in the site of its future implantation (covering the origin of the diagonal branch) (Fig. 2B). Subsequently, the balloon-catheter was retrieved from the diagonal branch and the LAD stent was deployed (22 atm) (Fig. 2B). After implantation of the LAD stent, a residual stenosis was noted in the proximal stent edge together with ostial compromise of the first diagonal branch, possibly due to plaque shiftening towards its origin (Fig. 2C). Additional "crush" stenting was performed to treat the LAD-first diagonal bifurcation (Fig. 2D). Following the same strategy as describe above, a 2.25 x 8 mm

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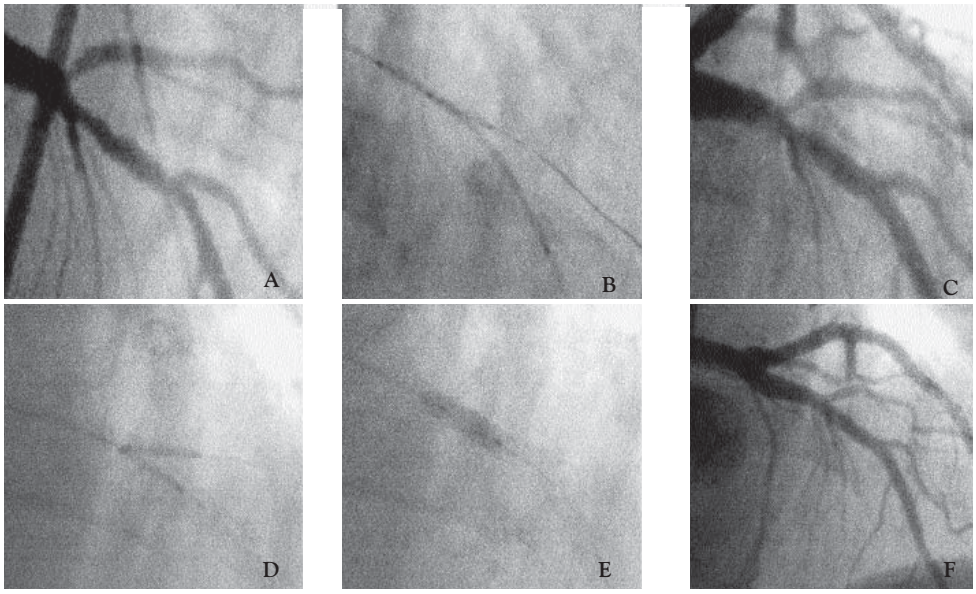

Figure 2. ***(A)*** *Left anterior descending artery (cranial right anterior oblique projection) presenting a long stenosis in its mid portion, involving the origin of the first and second diagonal branches.* ***(B)*** *"Crush" stenting: a 2.25 X 8 mm sirolimus-eluting stent and a 3 X 33 mm sirolimus-eluting Cypher stent (Johnson & Johnson, Cordis Corporation) concomitantly positioned in the second diagonal and mid LAD, respectively. Note that the proximal portion of the stent placed in the diagonal is protruding into the LAD.* ***(C)*** *Residual stenosis noted in the proximal LAD together with ostial compromise of the first diagonal branch after implantation of the distal stent in the LAD.* ***(D)*** *"Crush" stenting in the LAD-first diagonal bifurcation: a 2.25 X 8 mm sirolimus-eluting Cypher stent (Johnson & Johnson, Cordis Corporation) in first diagonal branch is positioned with its proximal portion partially located though the LAD. An undeployed 3 X 8 mm sirolimus eluting-stent was concomitantly positioned in the LAD along the diagonal ostium.* ***(E)*** *A 3 x 8 mm SES deployed at a small gap between the two LAD SES. The radiopaque stents implanted in the 2 previously treated bifurcations are noted.* ***(F)*** *Final angiographic result of the treatment of the LAD with a TIMI 3 grade flow and minimal residual stenosis in all treated lesions.*

sirolimus-eluting Cypher stent was implanted in the first diagonal (12 atm) with its proximal portion partially deployed in the LAD (Fig. 2D) while an undeployed 3 x 8 mm sirolimus eluting-stent was already placed in the LAD (along the diagonal ostium) (Fig. 2D). The LAD stent was then deployed (20 atm) covering the ostium of the first diagonal branch (Fig. 2D). A small gap between the two LAD stents was noted and a 3 x 8 mm sirolimus-eluting Cypher stent was implanted (20 atm) to accomplish complete lesion coverage (Fig. 2E). Final high-pressure post-dilatation (22 atm) was performed in the mid LAD (Maverick balloon 3.0 x 9 mm, Boston Scientific, Natick, Massachusetts). Care was taken to inflate the balloon inside the stented area in order to avoid vessel injury in the non-stented edges. Excellent final angiographic result was achieved with TIMI 3 grade flow and minimal residual stenosis in all treated lesions (Fig. 2F).

The patient was included in the Rapamycin Eluting-Stent Evaluated At Rotterdam Cardiology Hospitals (RESEARCH) registry and agreed to undergo late angiographic follow-up.[1] After 208 days, the patient remained asymptomatic and a stress test was negative. No adverse events had occurred. At coronary angiography, the RCA was unchanged. All stents were widely patent with no angiographic evidence of stenosis (Figs. 3A and 3B).

References

1. Lemos PA, Lee C, Degertekin M, et al. Early outcome after sirolimus-eluting stent implantation in patients with acute coronary syndromes. Insights from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. *J Am Coll Cardiol* 2003;41:2093–2099.

How Would you Manage this Case?

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The approach to this 60-year-old man with stable angina after a MI (presumably in the region of the posterolateral marginal branch of the left circumflex coronary artery) selected by the authors shows virtuosity and fantasy in the use of coronary stents. It can be condoned as exclusively drug-eluting stents (DES) with a low restenosis potential used. Also, the excellent long-term result proves the strategy right. The costs, however, are of concern and a far less expensive simple approach as described below would also have had a good chance of good long-term patency of all important branches.

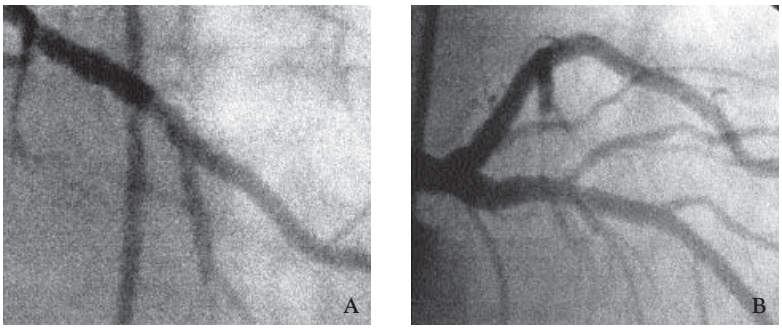

Figure 3. (A) *Angiographic follow-up of the LCx-OM ostial lesions. No restenosis has occurred.* **(B)** *Excellent result after 6 months angiographic follow-up of the LAD.*

Working exclusively with 5 Fr coronary catheters (often inserted without an introducer thereby keeping the puncture hole smaller than that of a 4 Fr introducer), kissing balloon techniques are out of the question. The same holds true for "crush" stenting. I would have used a left Amplatz II catheter exactly like the authors, but 2 Fr smaller. I would then have first tried to recanalize the posterolateral marginal branch of the LCx. The authors failed on that, so would have I presumably. This would have reduced the bifurcation lesion in the LCx to a single vessel lesion, which I would have dilated with a 3 mm balloon and stented with a DES if the result had not been pleasing. Given the initial lesion, this would have been the case with a 60% probability.

I would have used the LAD approach second, because you want a virgin coronary guidewire and balloon catheter to tackle a chronic occlusion and you also want the potential benefit of reversed collaterals from an initially recanalized LCx if problems arise in the LAD. I would have dilated the segment of the LAD encompassing the 2 involved diagonal branches. With a probability of about 30%, I would have found a need to stent the entire segment again using a DES. After this, I would have turned my attention to the 2 diagonal branches. I would have first tried to cross them with the wire and 3 mm balloon used for all dilatations so far. if they looked significantly stenosed. Only if a take-off stenosis of more than 50% of these diagonal branches had persisted, I would have tried to stent one or both take-offs with a short 2.5 mm stent, again using drug-eluting stents. The likelihood of this need can be guessed at 30% each. After such diagonal stenting, almost unvariably the 3 mm balloon would have had to be reinserted into the LAD for a final dilatation of this main axis, still using the same guidewire.

In a follow-up angiogram, the chances of the LAD or the only important branch of the LCx to be restenosed would have been the same as with the technique described by the authors. The risk of a restenosis in one or both of the diagonal branches is projected at about 50%, if they had not been stented, and about 20% if they had been stented. The risk of an abrupt closure of an important vessel with the frugal approach should not have been increased (it might even have been decreased), as stents harbor overall an equal or even higher risk for acute or subacute closure than balloon angioplasty with an acceptably looking result. My tab at the end of the day would have shown one coronary guidewire, one 3.0 mm balloon, and 1–3 DES, rather than 2 coronary guidewires, two balloons, and about 7 or 8 (I lost count) DES. The thriftiness would have carried a risk of about 30% to wind up with one or two take-off restenoses of diagonal branches, unlikely to be clinically apparent. The other risks would have been the same as with the authors approach.

The 5 Fr catheter without an introducer could have been pulled at the end, requiring only a 10–15 minute manual compression, rather than a closure device or a mechanical compression device, usually used in conjunction with a 7 Fr guiding catheter inserted through an introducer (about 8.5 Fr outer diameter). I failed to mention the reduced amount of x-ray and contrast medium used, and the shorter occupation of the catheterization laboratory with the simple approach (perhaps even if you include the remote possibility of a redilatation later).

Chapter 12

Two-Year clinical outcome after coronary stenting of very small vessels using 2.25mm sirolimus- and paclitaxel-eluting stents: Insight into the RESEARCH and T-SEARCH registries

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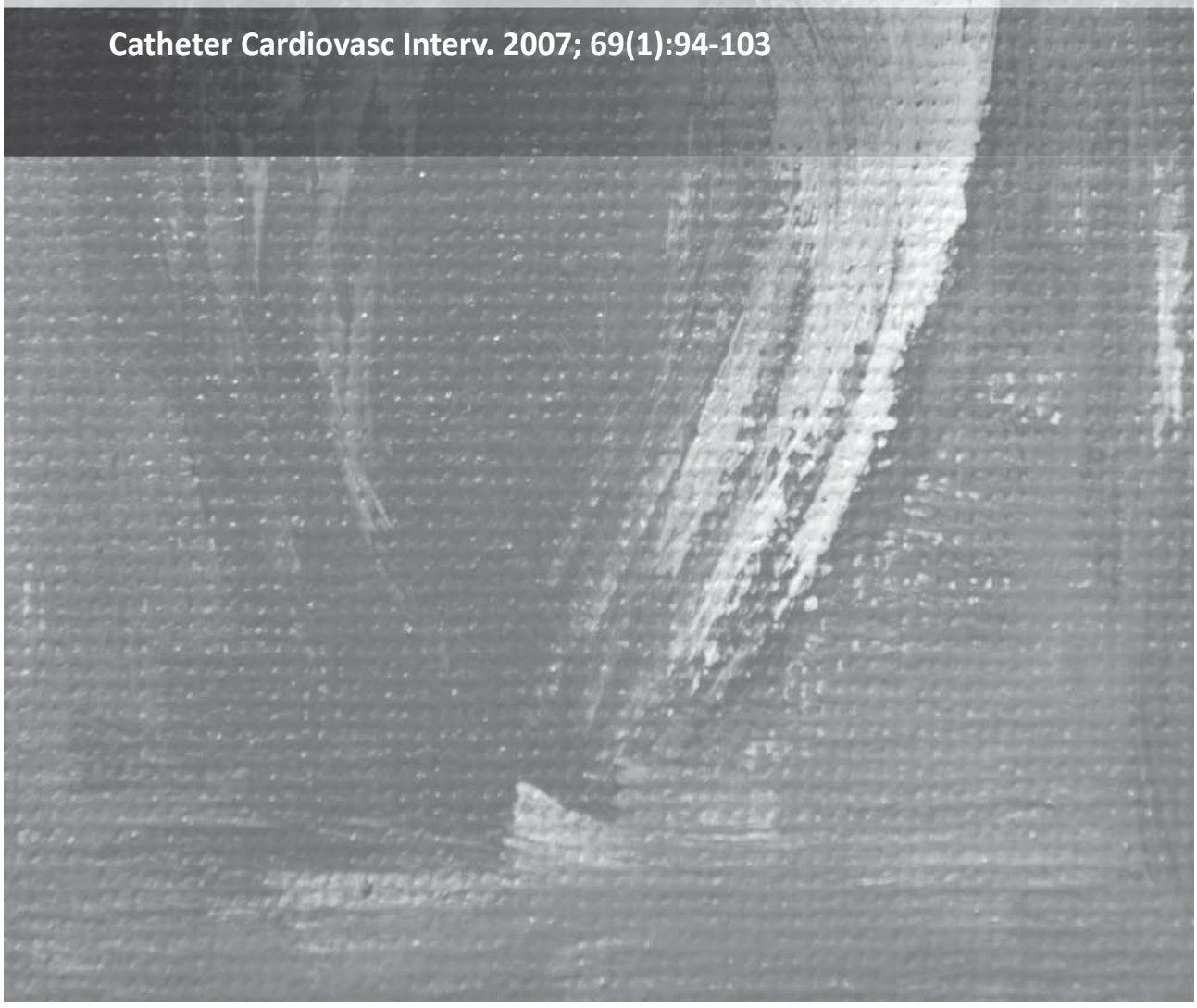

Two-Year Clinical Outcome After Coronary Stenting of Small Vessels Using 2.25-mm Sirolimus- and Paclitaxel-Eluting Stents: Insight Into the RESEARCH and T-SEARCH Registries

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Objectives: To evaluate long-term outcomes after drug-eluting stents (DES) implantation in small coronary vessels. Background: Sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) have been reported to improve both the angiographic and clinical outcomes compared with bare metal stents even in 'real world' settings. Currently, no data is available on long-term outcomes after DES implantation in small vessels. Methods: Since April 2002, our institution has implanted DES, either SES or PES, as a default strategy in all patients irrespective of their clinical presentation. Between October 2002 and September 2003, 197 consecutive patients were enrolled: 107 consecutive patients received at least one 2.25-mm SES (SES group) and 90 consecutive patients received at least one 2.25-mm PES (PES group). Results: The two cohorts presented with high-risk characteristics. At 2 years, the cumulative incidence of major adverse cardiac events (MACE) in the SES group was significantly lower than that in the PES group (10.3% vs. 23.3%, *P* = 0.02). There were two subacute angiographic stent thromboses in the PES group and none in the SES group. By multivariate analysis, PES utilization (HR 2.37, 95% CI 1.07–5.26), presentation with acute coronary syndromes (ACS) (HR 3.34, 95% CI 1.44–7.70) and multi-vessel disease (MVD) (HR 3.91, 95% CI 1.27–12.0) were identified as independent predictors of MACE. Conclusions: In an unselected population treated for small vessel disease, SES were associated with significantly better 2-year clinical outcomes than PES. The use of PES and the presentation with ACS and MVD were identified as independent predictors of MACE.

Key words: coronary artery disease; drug-eluting stents; sirolimus; paclitaxel

INTRODUCTION

Percutaneous coronary intervention (PCI) is a major treatment strategy for patients with ischemic heart disease, and currently coronary stents are widely used [1]. Bare metal stents (BMS) reduce coronary restenosis and significantly improve the angiographic and clinical outcomes in vessels with a reference diameter (RD) more than 3 mm by their ability to prevent both early elastic recoil and late vascular remodeling, as compared to balloon angioplasty [2–4]. On the other hand, several randomized trials have failed to show an advantage of BMS over balloon angioplasty in vessels with a RD less than 3 mm [5,6]. Therefore, whether stent implantation in small vessels improves outcomes compared to balloon angioplasty alone still remains controversial. At present, however, PCI in small vessels of less than 3 mm accounts for almost 50% of all revascularization procedures and leads to a higher incidence of restenosis and adverse cardiac events [7].

In the last 3–4 years, drug-eluting stents (DES), either sirolimus-eluting stents (SES) or paclitaxel-eluting stents (PES), have revolutionized the interventional cardiology practice by reducing restenosis and the need for repeat revascularizations as compared to BMS. Several multicenter randomized trials have evaluated the efficacy of DES for the treatment of vessels with a RD

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less than 3 mm and shown a significant reduction in both restenosis and clinical events [8–11]. More recently, several trials comparing SES with PES were performed [12–17]. The general conclusion from a meta-analysis of these trials is that SES are significantly better at reducing neointimal hyperplasia and confer an advantage over PES in terms of clinical outcomes [18]. However, there is limited information on the relative safety and efficacy of SES compared to PES in patients with small vessel disease [19,20].

Some recent studies have also cautioned that either SES or PES could increase thrombotic complications compared to BMS, especially late stent thrombosis [21,22], due to decreased endothelial function [23], delayed vascular healing [24], and/or hypersensitivity reactions to the polymer coating of the DES and the drug itself [25,26]. Although BMS implantation in small vessels had been previously cited as a risk factor for stent thrombosis [27], improved techniques of optimal stent deployment and dual antiplatelet regimens appear to have largely resolved this problem so that the risk of stent thrombosis in small vessel stenting now seems to be similar to that in larger vessel stenting [28]. But, DES implantation in small vessels may increase the risk of stent thrombosis because of their features as mentioned earlier. Therefore, long-term follow-up as well as short- and medium-term follow-up are needed to determine whether DES implantation is safe in the subset of patients with small vessel disease.

To the best of our knowledge, there is currently no available publication comparing the long-term efficacy of SES and PES for the treatment of small coronary arteries. The present study, which is derived from our previous study population [19], is conducted to compare clinical outcomes in terms of safety and efficacy at 2 years after implantation of 2.25-mm diameter SES and PES.

MATERIALS AND METHODS

Study Design and Patient Population

Since April 2002, SES (Cypher®; Cordis Corporation, Warren, NJ) have been implanted as the default strategy for every PCI in our institution as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry [29]. This strategy continued until February 2003, when PES (Taxus™; Boston Scientific Corporation, Galway, Ireland) implantation became the default strategy for all patients with coronary artery disease as part of the Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registry [30]. The methods and design of both studies have been described previously [29,30]. Both trials evaluated the safety and efficacy of SES and PES implantation for patients treated in daily practice. All patients were included irrespective of their clinical presentation and lesion characteristics.

Between October 2002 and September 2003, a total of 197 consecutive patients were enrolled: 107 patients received at least one 2.25-mm diameter SES (SES group) and 90 patients received at least one 2.25-mm diameter PES (PES group). The study protocol was approved by the institutional ethics committee, and all patients provided written informed consent.

Procedures and Postinterventional Medications

All procedures were performed in accordance with standard techniques. The interventional strategy and use of glycoprotein IIb/IIIa inhibitors were left entirely to the discretion of the operator. All patients were advised to take aspirin lifelong (at least 80 mg/day). A loading dose of 300 mg clopidogrel was given before the intervention. Postprocedural clopidogrel treatment (75 mg/day) differed between the two groups. For patients treated with SES, clopidogrel was prescribed for at least 3 months, unless one of the following was present (in which case clopidogrel was maintained for at least 6 months): multiple SES implantation ($\geq$3 stents), total stent length $\geq$36 mm, chronic total occlusion, and bifurcations. Patients treated with PES were prescribed at least 6 months of clopidogrel in accordance with the product labeling and instructions for use, based on existing data from randomized, controlled trials [31]. The methodology of quantitative coronary angiography (QCA) evaluation has been described previously [19].

Definition and Follow-Up

Patients were prospectively followed-up for the incidence of major adverse cardiac events (MACE), which included all-cause mortality, nonfatal myocardial infarction, and target lesion revascularization (TLR) or target vascular revascularization (TVR). Myocardial infarction (MI) was diagnosed by a rise in the creatine kinase-MB fraction (CK-MB) of more than three times the upper limit of normal, according to the American Heart Association/American College of Cardiology guidelines [32]. TLR was defined as a repeat intervention (surgical or percutaneous) to treat a luminal stenosis within the stent or in the 5-mm distal or proximal segments adjacent to the stent. TVR was defined as a reintervention driven by any lesions located in the same treated epicardial vessel. Stent thrombosis was defined as angiographically documented complete occlusion (TIMI flow grade 0 or 1) or flow-limiting thrombus (TIMI flow grade 1 or 2) in previously successfully treated artery. Information about the in-hospital outcomes was derived from our institutional electronic clinical database and by review of the hospital

TABLE I. Baseline Characteristics

	SES ($n = 107$)	PES ($n = 90$)	P value
Age (years ± SD)	61.3 ± 11.1	62.9 ± 12.4	0.34
Male, *n* (%)	75 (70.1)	59 (65.6)	0.54
Diabetes mellitus, *n* (%)	20 (18.7)	20 (22.2)	0.6
Type I, *n* (%)	6 (5.6)	6 (6.7)	0.77
Type II, *n* (%)	14 (13.1)	14 (15.6)	0.68
Hypertension, *n* (%)	47 (43.9)	44 (48.9)	0.57
Hypercholesterolemia, *n* (%)	72 (67.3)	55 (61.1)	0.38
Family history, *n* (%)	35 (32.7)	48 (53.3)	0.004
Current smoking, *n* (%)	20 (18.7)	28 (31.3)	0.047
Previous myocardial infarction, *n* (%)	35 (32.7)	40 (44.4)	0.11
Previous angioplasty, *n* (%)	28 (26.2)	25 (27.8)	0.87
Previous coronary bypass surgery, *n* (%)	9 (8.4)	6 (6.7)	0.79
Vessel disease			0.91[a]
1-vessel disease, *n* (%)	33 (30.8)	24 (26.7)	
2-vessel disease, *n* (%)	42 (39.3)	44 (48.9)	
3-vessel disease, *n* (%)	32 (29.9)	22 (24.4)	
Multivessel disease, *n* (%)	74 (69.2)	66 (73.3)	0.53
Clinical presentation			0.86[a]
Stable angina, *n* (%)	61 (57.0)	52 (57.8)	
Unstable angina, *n* (%)	33 (30.8)	28 (31.1)	
Acute myocardial infarction, *n* (%)	13 (12.1)	10 (11.1)	
Acute coronary syndrome, *n* (%)	46 (43.0)	38 (42.2)	1.00
Left ventricular ejection fraction (%)	50.4 ± 9.70	51.2 ± 9.50	0.61
Number of implanted stents/patients ± SD	1.40 ± 0.69	1.31 ± 0.57	0.32
Total stent length/patient (mm ± SD)	23.4 ± 14.5	21.6 ± 11.1	0.35
Number of lesions/patient ± SD	1.50 ± 0.71	1.63 ± 0.77	0.19
Glycoprotein IIb/IIIa use, *n* (%)	33 (30.8)	30 (33.3)	0.76

[a]Across all groups.

records of those discharged to referring hospitals. Postdischarge survival status was obtained from the municipal civil registries. Health questionnaires were subsequently sent to all living patients, inquiring about postdischarge repeat coronary interventions (either surgical or percutaneous) and the occurrence of MI. All repeat interventions and rehospitalizations were prospectively collected during follow-up. Referring physicians and institutions were contacted for additional information if required.

Statistical Analysis

Continuous variables were presented as mean ± SD and were compared by means of the Student's unpaired t test. Categorical variables were presented as counts and percentages and compared by means of the χ^2 test or Fisher's exact test. The cumulative incidence of adverse events was estimated according to the Kaplan–Meier method and compared by the log rank test. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. Multivariate analyses were performed to identify independent predictors of adverse events, using all clinical, angiographic, and procedural variables included in Tables I and II. Cox proportional hazards survival models were used to assess risk reduction of adverse events. The hazard ratio (HR) and its 95% confidence intervals (CI) were computed for outcome measures. A P value of <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Table I shows baseline characteristics of the study population. No significant differences were observed between both groups apart from a higher prevalence of smoking and family history of coronary artery disease in the PES group. A large number of patients with previous history of MI (38.1%), multi-vessel disease (MVD) (71.1%), and acute coronary syndromes (ACS) (42.6%) were enrolled. The number of implanted stents and total stent length per patient were similar in both groups.

Baseline Angiographic and Procedural Characteristics

Baseline angiographic and procedural data are displayed in Table II. There were 127 lesions in the SES group and 97 lesions in the PES group. A larger stent, in addition to 2.25-mm stent, was deployed in 76.6 and 85.6% of SES and PES patients ($P = 0.11$). The reasons for stenting with a 2.25-mm device were reported in detail in a previous paper [19]. A high

TABLE II. Angiographic and Procedural Characteristics

	SES ($n = 127$)	PES ($n = 97$)	P value
Treated vessel			
Right coronary artery, *n* (%)	20 (15.7)	9 (9.3)	0.17
Left anterior descending, *n* (%)	29 (22.8)	25 (25.8)	0.64
Diagonal, *n* (%)	31 (24.4)	18 (18.6)	0.33
Left circumflex, *n* (%)	35 (27.6)	25 (25.8)	0.88
Obtuse or intermediate marginal, *n* (%)	12 (9.4)	18 (18.6)	0.07
Bypass graft, *n* (%)	0 (0)	2 (2.1)	0.19
ACC/AHA modified lesion classification			
Type A or B1, *n* (%)	58 (45.7)	38 (39.2)	0.34
Type B2 or C, *n* (%)	69 (54.3)	59 (60.8)	0.34
Calcification (moderate/severe), *n* (%)	15 (11.8)	7 (7.2)	0.37
Thrombus, *n* (%)	10 (7.9)	8 (8.2)	1.00
Ostial, *n* (%)	36 (28.3)	15 (15.5)	0.025
Bifurcation, *n* (%)	32 (25.2)	24 (25.3)	1.00
Total occlusion, *n* (%)	33 (26.0)	22 (22.7)	0.64
TIMI grade 3 flow post procedure, *n* (%)	122 (96.0)	95 (97.9)	0.70
Number of stent/lesion ± SD	1.17 ± 0.42	1.21 ± 0.48	0.58
Total stent length/lesion (mm ± SD)	19.8 ± 10.9	19.8 ± 9.5	0.99
Direct stenting, *n* (% ± SD)	65 (51.2)	58 (60.4)	0.22
Postdilatation, *n* (% ± SD)	30 (23.6)	18 (18.6)	0.41
Max. pressure (atm ± SD)	16.0 ± 3.3	14.9 ± 3.0	0.046
Quantitative coronary angiography analysis			
Pre			
Reference diameter (mm ± SD)	1.86 ± 0.37	1.95 ± 0.38	0.15
Minimal lesion diameter (mm ± SD)	0.47 ± 0.38	0.57 + 0.38	0.06
Diameter stenosis (% ± SD)	74.8 ± 20.1	70.3 ± 19.3	0.10
Lesion length (mm ± SD)	13.0 ± 8.5	16.4 ± 10.4	0.02
Post			
Minimal lesion diameter (mm ± SD)	1.73 ± 0.31	1.82 ± 0.36	0.06
Diameter stenosis (% ± SD)	12.3 ± 10.0	14.0 ± 9.80	0.19

ACC, American College of Cardiology; AHD, American Heart Association; TIMI, Thrombolysis In Myocardial Infarction.

prevalence of bifurcation lesions was observed in the entire cohort (25.0%). The prevalence of target lesions located at an ostium was significantly higher in the SES group than in the PES group (28.3% vs. 15.5%, $P = 0.025$). The mean maximal pressure at stent deployment was significantly higher in the SES group (16.0 ± 3.3 atm vs. 14.9 ± 3.0 atm in the PES group, $P = 0.046$). The number of implanted stents and total stent length per lesion were comparable between the two groups. By QCA analysis, the minimal lesion diameter both pre- and post-PCI was smaller in the SES group (0.47 ± 0.38 mm and 1.73 ± 0.31 mm vs. 0.57 ± 0.38 mm and 1.82 ± 0.36 mm in the PES group; $P = 0.06$ and 0.06, respectively), whereas lesion length was significantly longer in the PES group than in the SES group (16.4 ± 10.4 mm vs. 13.0 ± 8.5 mm; $P = 0.02$).

Clinical Outcome

Two-year follow-up data were obtained for 105 patients (98.1%) in the SES group and 89 patients (98.9%) in the PES group. MACE was analyzed at 1 month (30 days), 1 year (365 days), and 2 years (730 days) (Table III).

One-Month (30 Days) and One-Year (365 Days) Follow-Up

The 1-month and 1-year clinical outcomes have been previously reported [19]. Briefly, three patients died in the first month (2 PES and 1 SES); all these patients presented with MVD and ACS on their admission and died of cardiac cause. There were two episodes of angiographically documented subacute thrombosis in the PES group (2.2%) and none in the SES group ($P = 0.21$). These two patients who presented with stent thrombosis were alive at 2-year follow-up.

At 1 year, one patient (0.9%) died in the SES group, and four patients (4.3%) died in the PES group ($P = 0.18$): their causes of death were cardiac. The incidence of TLR, TVR, and TVR-MACE was more frequent in the PES group, but it did not reach statistical significance (11.1, 12.2, and 18.9% vs. 6.5, 7.5, and 9.3% in the SES group; $P = 0.31$, 0.33, and 0.06, respectively). TLR-MACE rate was significantly lower

TABLE III. Major Adverse Cardiac Events

	Events	SES ($n = 107$)	PES ($n = 92$)	P value[a]
30 days	Death, *n* (%)	1 (0.9)	2 (2.2)	0.59
	MI, *n* (%)	3 (2.8)	6 (6.7)	0.31
	TLR, *n* (%)	3 (2.8)	5 (5.6)	0.47
	TVR, *n* (%)	3 (2.8)	5 (5.6)	0.47
	Death or MI, *n* (%)	4 (3.7)	7 (7.8)	0.35
	TLR MACE, *n* (%)	5 (4.7)	11 (12.2)	0.07
	TVR MACE, *n* (%)	5 (4.7)	11 (12.2)	0.07
	Stent thrombosis[b]	0 (0)	2 (2.2)	0.21
365 days	Death, *n* (%)	1 (0.9)	4 (4.3)	0.18
	MI, *n* (%)	3 (2.8)	7 (7.8)	0.19
	TLR, *n* (%)	7 (6.5)	10 (11.1)	0.31
	TVR, *n* (%)	8 (7.5)	11 (12.2)	0.33
	Death or MI, *n* (%)	4 (3.7)	9 (10.0)	0.09
	TLR MACE, *n* (%)	9 (8.4)	17 (18.9)	0.04
	TVR MACE, *n* (%)	10 (9.3)	17 (18.9)	0.06
	Stent thrombosis[b]	0 (0)	2 (2.2)	0.21
730 days	Death, *n* (%)	2 (1.9)	7 (7.6)	0.08
	MI, *n* (%)	3 (2.8)	7 (7.6)	0.19
	TLR, *n* (%)	7 (6.5)	11 (12.2)	0.22
	TVR, *n* (%)	8 (7.5)	12 (13.3)	0.24
	Death or MI, *n* (%)	5 (4.7)	12 (13.3)	0.04
	TLR MACE, *n* (%)	10 (9.3)	21 (23.3)	0.01
	TVR MACE, *n* (%)	11 (10.3)	21 (23.3)	0.02
	Stent thrombosis[b]	0 (0)	2 (2.2)	0.21
366–730 days	Death, *n* (%)	1 (0.9)	3 (3.3)	0.33
	MI, *n* (%)	0 (0)	0 (0)	
	TLR, *n* (%)	0 (0)	1 (1.1)	0.46
	TVR, *n* (%)	0 (0)	1 (1.1)	0.46
	Death or MI, *n* (%)	1 (0.9)	3 (3.3)	0.33
	TLR MACE, *n* (%)	1 (0.9)	4 (4.3)	0.18
	TVR MACE, *n* (%)	1 (0.9)	4 (4.3)	0.18
	Stent thrombosis[b]	0 (0)	0 (0)	

MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization; MACE, major adverse cardiac events.
[a]By Fisher's exact test or the χ^2-test.
[b]Angiographically documented stent thrombosis.

in the SES group (8.4% vs. 18.9% in the PES group; $P = 0.04$). Angiographic late stent thrombosis, which was defined as occurring 30 days after stent implantation, was not seen during the first year.

Two-Year (730 Days) Follow-Up

At 2 years, there were two deaths (1.9%) in the SES group and seven deaths (7.6%) in the PES group ($P = 0.08$). The combined endpoint of death and MI was significantly different between the two groups (4.7% in the SES group and 13.3% in the PES group; $P = 0.04$). An event-free survival rate of this composite endpoint is shown in Fig. 1 (log rank $P = 0.031$, by Kaplan–Meier estimate). The prevalence of TLR and TVR was lower in the SES group compared to the PES group, but did not achieve statistical significance ($P = 0.22$ and 0.24, respectively). The 2-year incidence of TVR-MACE was significantly higher in the PES group (23.3% vs. 10.3% in the SES group; $P = 0.02$), with a MACE-free survival rate of 76.6 and 89.7% in patients treated with PES and SES, respectively (log rank $P = 0.012$, by Kaplan–Meier estimate) (Fig. 2).

Events From One (365 Days) to Two Years (730 Days)

Between 1 and 2 years, five events occurred. There was one death in the SES group and three deaths in the PES group ($P = 0.33$); noncardiac death was observed in one patient in the SES group, the causes of death in the PES group were one cardiac and two unknown. No patient in either group experienced MI or late angiographic stent thrombosis during this period. Including TLR, there was only one additional TVR in the PES group and none in the SES group ($P = 0.46$).

Multivariate Predictors of Outcomes

Cox regression analysis was performed to identify independent predictors of MACE and the composite endpoint of death and MI at 2 years (Table IV). PES utilization (HR 2.37, 95% CI 1.07–5.26; $P = 0.03$), the presentation with ACS (HR 3.34, 95% CI 1.44–7.70; $P = 0.005$) and MVD (HR 3.91, 95% CI 1.27–12.0; $P = 0.017$) were found to be significant independent predictors of the 2-year MACE rate. Significant predictors of the 2-year composite endpoint of death or MI included PES utilization (HR 4.48, 95% CI 1.19–16.79; $P = 0.03$), the presentation with ACS (HR 4.46, 95% CI 1.14–17.46; $P = 0.03$) and diabetes mellitus (HR 5.54, 95% CI 1.65–18.62; $P = 0.006$). Hypercholesterolemia was found to be a protective factor for the 2-year composite endpoint of death or MI (HR 0.16, 95% CI 0.04–0.59; $P = 0.006$).

DISCUSSION

The main findings of this study were (1) SES implantation significantly reduced the incidence of MACE at 2 years as compared to PES implantation, (2) the use of PES and the presence of ACS and MVD were independent factors of 2-year MACE, and (3) the efficacy of the SES was maintained up to 2 years in a very challenging real world population.

Study Population

It is noteworthy that the overall population included in this study had a markedly increased risk of adverse outcomes. We included clinical and procedural subsets commonly excluded from most studies such as patients with acute MI, totally occluded vessels, left ventricular

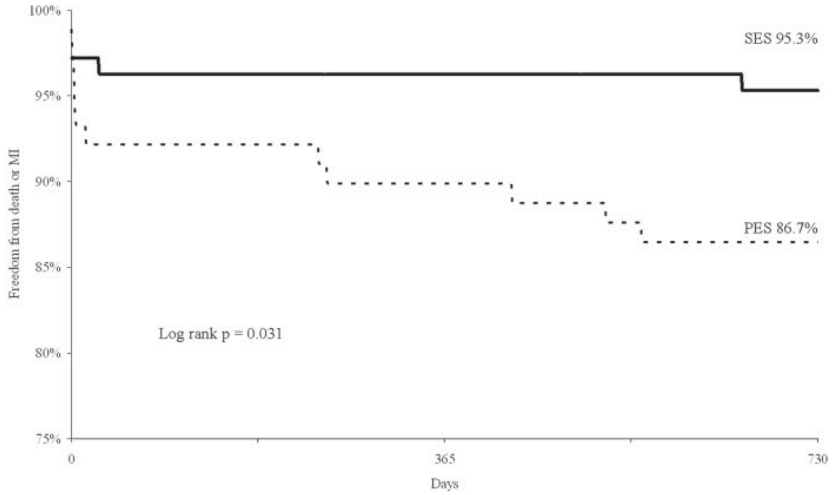

Fig. 1. Survival free of the composite of death or myocardial infarction of patients treated with sirolimus-eluting stents (SES) versus paclitaxel-eluting stents (PES) by Kaplan–Meier estimate up to 2 years.

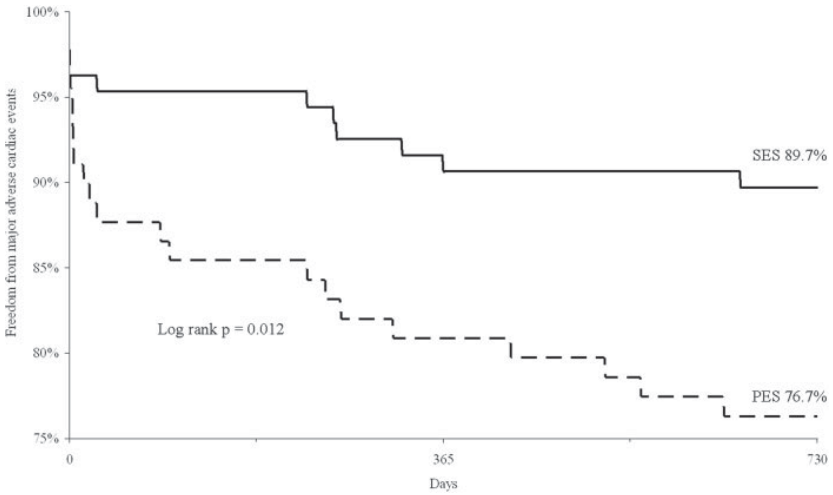

Fig. 2. Survival free of major adverse cardiac events (MACE) of patients treated with sirolimus-eluting stents (SES) versus paclitaxel-eluting stents (PES) by Kaplan–Meier estimate up to 2 years.

dysfunction, and thrombotic and calcified lesions. Indeed, there was a marked high prevalence of patients with MVD (71.1%), ACS (42.6%), and chronic total occlusion (24.4%) in the present study. In addition, mean RD of the target vessels was particularly small (1.90 ± 3.8 mm).

TABLE IV. Independent Predictors of MACE and the Composite Endpoint of Death or MI at 2-Year Follow-Up

	MACE at 2 years		Death or MI at 2 years	
	HR	*P* value	HR	*P* value
PES utilization	2.37 (1.07–5.26)[a]	0.03	4.48 (1.19–16.79)	0.03
Acute coronary syndrome	3.34 (1.44–7.70)	0.005	4.46 (1.14–17.46)	0.03
Multivessel disease	3.91 (1.27–12.0)	0.02	2.32 (0.46–11.74)	0.31
Diabetes mellitus	1.56 (0.66–3.68)	0.31	5.54 (1.65–18.62)	0.006
Hypercholesterolemia	0.55 (0.25–1.19)	0.13	0.16 (0.04–0.590)	0.006

MACE, major adverse cardiac events; MI, myocardial infarction; PES, paclitaxel-eluting stents; HR, hazard ratio; CI, confidence intervals.
[a]Values in parentheses are 95% CI.

TABLE V. Published Papers on Drug-Eluting Stent Implantation in Patients With Very Small Vessels

	Study											
	SES-SMART [35]			TAXUS V subanalysis [36]			ISAR-SMART 3 [20]			The present study		
Trial design	Randomized trial			Randomized trial			Randomized trial			Nonrandomized		
Clinical follow-up (month)	8			9			12			24		
Angiographic follow-up	8			9			6–8			NA		
Stent	SES	BMS	*P* value	PES	BMS	*P* value	SES	PES	*P* value	SES	PES	*P* value
No. of patients, *n*	129	128		108	95		198	204		107	92	
Reference diameter (mm)	2.22	2.17	0.15	2.07	2.10	0.46	2.44	2.40	0.34	1.86	1.95	0.15
Lesion length (mm)	13.0	10.7	<0.01	16.6	16.4	0.91	12.9	11.7	0.12	13.0	16.4	0.02
In-stent restenosis (%)	4.9	49.1	<0.01	24.7	44.7	<0.01	8.0	14.9	0.04	NA	NA	NA
TLR (%)	7.0	21.1	<0.01	10.4	21.5	0.03	6.6	14.7	0.008	6.5	12.2	0.22
MACE (%)	9.3	31.3	<0.01	18.9	26.9	0.23	NA	NA	NA	10.3	23.3	0.02
Stent thrombosis (%)	0.8	3.1	0.21	1.0	1.1	>0.99	NA	NA	NA	0.0	2.2	0.21

TLR, target lesion revascularization; MACE, major adverse cardiac events; SES, sirolimus-eluting stents; PES, paclitaxel-eluting stents; BMS, bare metal stents; NA, not available.

Clinical Results

Small vessel size is known to be an independent predictive factor of restenosis after PCI [33]. It remains controversial whether BMS placement in small vessels less than 3 mm in diameter is actually superior to balloon angioplasty. The latest meta-analysis on small vessel stenting reported that rates of restenosis and MACE in patients treated with BMS were 27.8 and 17.6%, respectively [34]. This high restenosis rate is due to the fact that absolute late lumen loss after stenting in small vessels is similar to that in large vessels so that even a small volume of neointimal hyperplasia induce a diameter stenosis more than 50% in small vessels more easily than in large vessels [28]. The high incidence of angiographic restenosis could lead to high MACE rates in this clinical setting.

The advent of DES, which markedly inhibited neointimal hyperplasia and reduced restenosis, created the expectation of reducing restenosis substantially in patients with small vessels. Indeed, several randomized studies have demonstrated that both DES resulted in remarkably low angiographic restenosis rates (~0–6%) and revascularization rates (~3–4%) as compared to BMS for the treatment of vessels with a RD of less than 3 mm [8–11]. But in some trials, which focused on DES implantation in small vessels (mean RD less that 2.5 mm), the incidence of cardiac events was relatively high and differed between SES and PES utilization (Table V). The SES-SMART trial [35], which enrolled patients with small vessels (mean RD was 2.2 mm), showed that the incidence of TLR and MACE in the SES arm was 7.0 and 9.3%, respectively. The subanalysis of TAXUS V trial [36], in which patients treated with 2.25-mm diameter PES were included and mean RD was 2.08 mm, indicated that the TLR and MACE rates were 10.4 and 18.9%, respectively. The most important conclusion of the subanalysis of TAXUS V was that there was no significant difference between the MACE rates in the PES and BMS arms despite considerably lower rates of angiographic restenosis and TLR in the PES arm when compared with the BMS arm. The ISAR-SMART 3 study [20] was a head-to-head comparative trial (SES vs. PES) for patients with small vessel disease (mean RD was about 2.4 mm), and reported that SES was more effective in reducing restenosis and TLR when compared with PES (8.0 and 6.6% in the SES group vs. 14.9 and 14.7% in the PES group; $P = 0.04$ and 0.008, respectively). Interestingly, our clinical results

in the two arms at 1 year were comparable to these three trials, though the mean RD of the entire cohort was smaller (mean RD 1.90 mm) and the present populations were at higher risk of clinical events as mentioned above. In addition, our results, like those in the ISAR-SMART 3 trial, also indicated that the SES tended to have a lower 1-year TLR rate as compared to the PES (6.5% vs. 11.1%; $P = 0.31$). Moreover, by multivariate analysis, the use of SES rather than PES was found to be an independent protective factor for the prevention of MACE at 2 years in the present study.

Considering these results, it can be said that the SES is likely to be more effective than the PES in this clinical setting. This propensity was verified by the results of recent large head-to-head, randomized controlled trials [13–15,17,18], which indicated that SES was significantly better at reducing neointimal hyperplasia and had a slight advantage in clinical outcomes when compared with PES. Different drug-release kinetics and mechanisms of inhibiting neointimal hyperplasia between SES and PES presumably accounts for the observed difference in their performance. However, it is difficult to directly compare previous trials with the present study because the inclusion criteria and endpoints of each study were different. In addition, the number of enrolled patients in each study was too small and underpowered to definitely assess the effect of DES on the rate of TVR or MACE in this patient population. Moreover, it is worth emphasizing that to date the ISAR-SMART 3 trial is the only randomized controlled prospective study comparing the efficacy of SES with that of PES in patients with small vessels. Further investigations are needed to identify which DES is more effective than the other in this particular clinical setting.

Safety Concerns of DES Implantation in Small Vessels

After DES were approved, these devices were implanted in a large number of patients with coronary artery disease and many trials indicated the use of them to be feasible and safe. Recently, however, certain potential issues with their use have been raised. One of the problems was delayed restenosis, which was usually called a "late catch-up phenomenon" and noticed as a complication following brachytherapy. This concern has been fueled by findings in the porcine model [37,38]. In humans, continued hyperplastic growth of neointima during the follow-up period was noted in some trials in which serial intravascular ultrasound analyses were performed [39–41]. The precise reason for this observation is still unclear. Delayed neointimal hyperplasia could cause a high incidence of TLR and MACE with long-term follow-up. The present study showed only one patient treated with PES presented with TLR in the second year of follow-up. This result might suggest an absence of the late catch-up phenomenon within these small vessels. All we can mention with certainty in the present study is that the efficacy of DES, especially SES, was maintained up to 2 years.

Late stent thrombosis is another topical issue following DES deployment. Our result demonstrated that in the entire cohort the overall angiographic stent thrombosis rate was 1.0% and no late stent thromboses were seen. This incidence rate seems acceptable. However, it should be mentioned that not all patients suffering from stent thrombosis underwent coronary angiography. Indeed, as indicated in the results section, three patients in our study who died suddenly during the first month after stent implantation were suspected of having subacute stent thrombosis but they could not be confirmed as having stent thrombosis in the absence of coronary angiography. To assess this rare and unexpected late complication precisely, a much larger sample size and long-term follow-up are needed. Nevertheless, this study provides some reassurance about this safety concern for both DES in the small vessel subsets.

Independent Factors of Late Cardiac Events

Besides the use of PES, the presence of ACS and MVD were also independent predictive factors of 2-year TVR-MACE. These factors are well known to be predictors of restenosis and late cardiac adverse events. The patients receiving small vessel stenting, who presented with ACS and MVD on admission, should be attended and followed-up carefully. ACS as well as diabetes mellitus, in addition to the use of PES, were also significant predictive factors for the composite endpoint of death or MI. To prevent the onset of ACS, detecting vulnerable patients early is very important. It is imperative that intensive glucose control physically and pharmaceutically is implemented to reduce late cardiac events. Curiously, in our multivariate analysis, the presence of hypercholesterolemia was a protective factor for the composite endpoint of death or MI. This result is not easy to explain.

Study Limitation

This study presents several limitations related to its small sample size, nonrandomized nature, and lack of a true control group. The fact that a large percentage of the population enrolled in the present study were simultaneously treated with larger stent size DES (more than 2.25 mm) might have influenced the accuracy of our result. Another potential limitation is that

each group was treated in different time periods. This might lead to some bias in terms of patient selection and affect procedural characteristics, as treatment strategy has evolved over time. However, it should be noted that this study enrolled consecutive patients treated in daily practice: we enrolled all comers and had no exclusion criteria. To definitively address the efficacy and safety of each DES in patients with small coronary arteries, larger head-to-head randomized trials are needed.

CONCLUSIONS

In an unselected population treated for small vessel disease, SES was associated with significantly better 2-years clinical outcomes, especially MACE, when compared with PES. The use of PES and the presence of MVD and ACS were independent predictors of 2-year MACE. The efficacy and safety of SES utilization was maintained up to 2 years.

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Chapter 13

Three-year clinical outcomes after coronary stenting of chronic total occlusion using sirolimus-eluting stents: insights from the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital-(RESEARCH) registry

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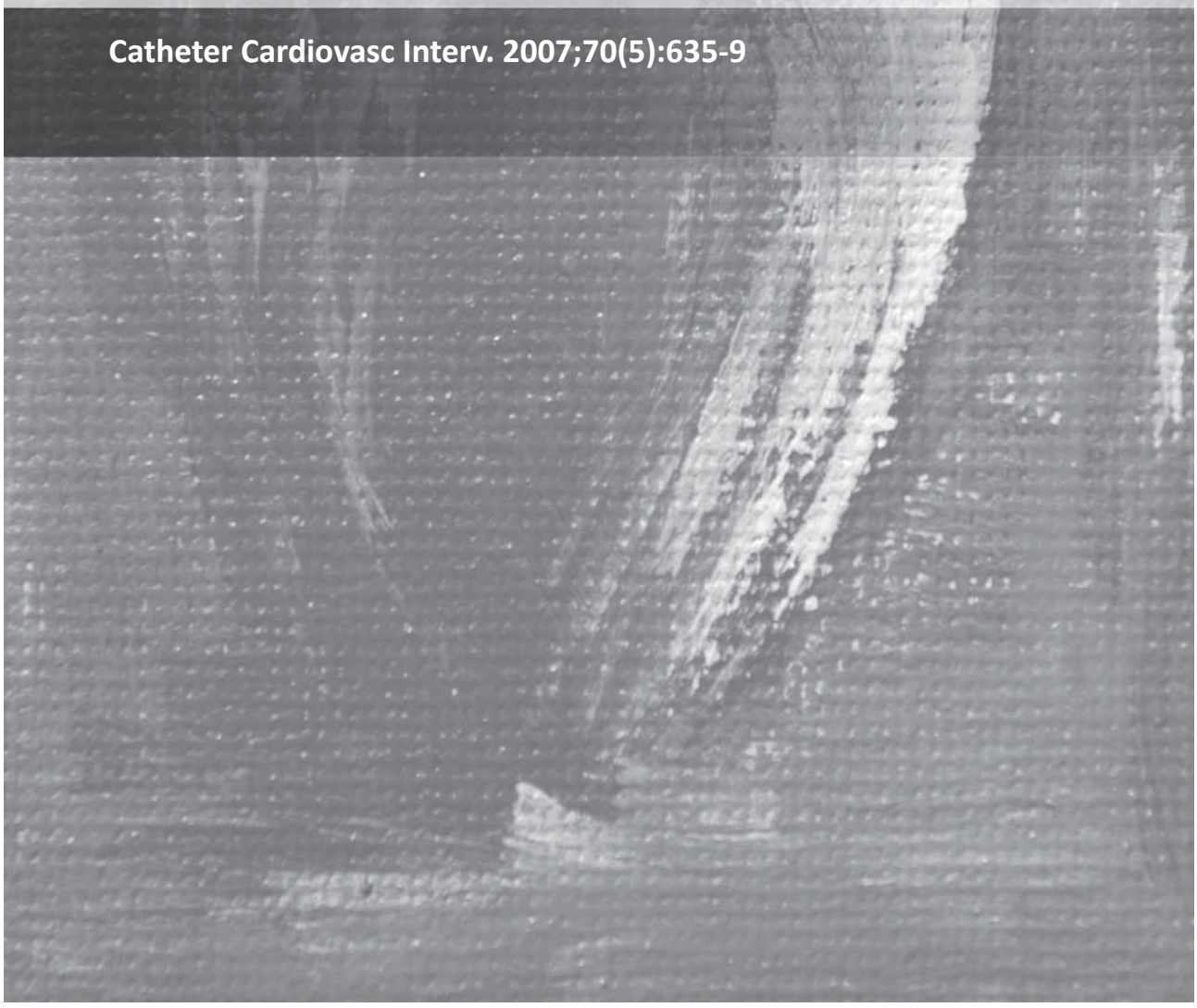

Three-Year Clinical Outcomes After Coronary Stenting of Chronic Total Occlusion Using Sirolimus-Eluting Stents: Insights From the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital—(RESEARCH) Registry

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Background: We previously reported that the 1-year survival-free from target lesion revascularization was 97.4% in patients with chronic total occlusion (CTO) treated with sirolimus-eluting stents (SES). There are currently no long-term results of the efficacy of SES in this subset of lesions. We assessed the 3-year clinical outcomes of 147 patients with CTO treated with either SES or bare metal stents (BMS). Methods and Results: A total of 147 (BMS = 71, SES = 76) patients were included. Four patients died in the BMS group while five patients died in the SES group, *P* = 0.8; two myocardial infarctions occurred in both groups, *P* = 0.9; and target vessel revascularization was performed in nine patients in the BMS and seven in the SES group, *P* = 0.5. The cumulative event-free survival of MACE was 81.7% in BMS group and 84.2% in SES group, *P* = 0.7. Two patients of the SES group had a coronary aneurism at 3-year angiographic follow-up. Conclusions: The use of SES was no longer associated with significantly lower rates of target vessel revascularization and major adverse cardiac events in patients with CTOs after 3 years of follow-up compared with BMSs.

Key words: drug-eluting stents; angiography; coronary; total occlusions; percutaneous coronary intervention; restenosis

INTRODUCTION

Drug-eluting stents (DES) are superior in terms of clinical outcomes and restenosis rate to bare-metal stents (BMS) in every angiographic and patient subset [1–3]. In particular, in patients with chronic total occlusion (CTO) DES have shown a significant decrease in need for repeat revascularization and restenosis rate [4–7], although this subset remains still in the DES era a predictor of restenosis [8]. Our group has previously reported the 6-month angiographic and clinical outcomes of sirolimus-eluting stent (SES) in patients with CTOs [9]. In this study, we showed a marked reduction in restenosis rate and major adverse cardiac events (MACE) compared with BMS. This observation was confirmed in the PRISON II study [10], a prospective, randomized trial that included a total of 200 patients treated either with a SES or BMS with both clinical and angiographical follow-up at 6 months. However, among the interventionalists, the clinical and angiographic long-term follow-up of the DES is still a major concern, especially in high-risk populations. We therefore investigated the 3-year clinical and angiographic follow-up of patients with CTO in a consecutive series of 147 patients, with comparison between the bare metal stents and SESs.

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MATERIALS AND METHODS

From April 2002 to February 2003, 76 patients with CTOs were treated solely with SES. In this period SES (Cypher®; Cordis Corporation, Warren, NJ) was the device of first choice for every PCI performed in our institution as part of the rapamycin eluting stent evaluated at rotterdam cardiology hospital (RESEARCH) registry, a prospective single center study set-up with the aim of evaluating the safety and efficacy of SES in a "real world" scenario, following the dynamic registry design described by Rothman and coworkers [11,12]. Except for contraindications to clopidogrel treatment, no exclusion criteria were made. All consecutive patients treated successfully were enrolled irrespective of clinical presentation and CTO lesion characteristics. Those patients treated with SES implantation were compared with all those treated for a CTO in the preceding 1 year with bare metal stents (BMS), identified from the departments' dedicated database. The same operators utilizing standard techniques treated all groups; the only difference being the type of stent.

This protocol was approved by the hospital ethics committee and is in accordance with the principles of Good Clinical Practice for Trials of Medicinal Products in the European Community and the Declaration of Helsinki. Written informed consent was obtained from every patient.

CTO Definition

CTO was defined as a complete occlusion on angiography with no antegrade filling of the distal vessel other than via collaterals. All the occlusions in a native vessel with at least 3-month duration based on the clinical history or a previous coronary angiogram were included [9].

Angiographic Analysis

Quantitative coronary analysis in those patients with angiographic follow-up was performed as previously described [9]. Briefly, three segments were analyzed: (1) stent segment; (2) the 5 mm proximal to the stent; and (3) the 5 mm distal to the stent. The target lesion comprised the in-stent plus the proximal and distal edge segments. Binary restenosis was considered as $>50\%$ diameter stenosis within the target lesion.

All patients were pretreated with 300 mg of clopidogrel, which was then prescribed at a dose of 75 mg/day for 6 months. All patients were advised to maintain aspirin ($\geq$80 mg/day) lifelong.

Our primary endpoints were the 3-year incidence of MACE, a compound endpoint of all-cause mortality, nonfatal myocardial infarction and target-vessel revascularization, in both groups. Secondary endpoints were target vessel revascularization (TVR) and myocardial infarction (MI). MI was defined by a rise in creatine kinase-MB fraction (CK-MB) of three times the upper limit of normal, according to American Heart Association/American College of Cardiology guidelines [13]. TVR was defined as a percutaneous reintervention or coronary artery bypass grafting (CABG) of a lesion in the same epicardial vessel. Subacute angiographic stent thrombosis was defined as an angiographically documented complete occlusion (TIMI grade 0 or 1 flow) or a flow-limiting thrombus (TIMI grade 1 or 2 flow) in the first 30 days after a successful procedure. Late stent thrombosis was defined as angiographically defined thrombosis with (TIMI grade 0 or 1 flow or the presence of a flow limiting thrombus), occurring at least 1 month after DES implantation accompanied by acute symptoms. Angiographic follow-up was performed in a subset of 30 patients in the SES group.

Three-Year Follow-Up Data

Patients were followed-up prospectively and evaluated for MACE-free survival of using both municipal civil registries and health questionnaires inquiring about postdischarge repeat coronary interventions (either surgical or percutaneous) and MI. Since our hospital is a tertiary referral center for our region, with a catchment area of $\sim$1.3 million people, most of the repeat interventions were performed at our institution. Follow-up information was prospectively entered into a dedicated database. If a patient had an MI or a reintervention at another center, medical records or discharge letters were requested and systematically reviewed. Local cardiologists or general practitioners were also contacted as necessary. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored.

Statistical Analysis

Continuous variables are presented as mean $\pm$ SD and were compared by the Student's t test. Categorical variables are presented as counts and percentages and compared by Fisher's exact test. The cumulative incidence of adverse events was estimated according to the Kaplan–Meier method and curves were compared using the log-rank test. Separate Cox regression analyses were performed to identify independent predictors of adverse events. Preselected variables were: age, gender, hypertension, diabetes, renal impairment, previous intervention, old MI, smoking, treatment of the left main coronary artery, and previous CABG. The final results are presented as adjusted hazard ratios (HRs).

TABLE I. Baseline Patient Characteristics

	BMS $n = 71$	SES $n = 76$	P value
Mean age (years)	60.9 ± 10.5	61.1 ± 10.6	0.9
Male sex (%)	76.7	65.8	0.1
Current smoker (%)	27.4	18.4	0.2
Diabetes mellitus (%)	5.5	14.5	0.07
Hypertension (%)	35.6	42.1	0.3
Hypercholesterolemia (%)	57.5	67.1	0.3
Previous myocardial infarction (%)	50.7	51.3	0.8
Previous CABG (%)	0	3.9	0.2
Glycoprotein IIb/IIIa inhibitor usage (%)	21.9	18.4	0.8
Target vessel			0.1
LAD (%)	27.5	46.1	
LCX (%)	27.5	19.7	
RCA (%)	44.9	36.8	
Mean number of stents	1.9 ± 0.8	2.2 ± 1.2	0.9
Mean diameter of the stent (mm)	3.1 ± 0.58	2.8 ± 0.3	<0.001
Mean length of stent (mm)	21.7 ± 6.3	22.5 ± 6.1	0.5

SES: sirolimus-eluting stents, PES: paclitaxel-eluting stents, CABG: coronary artery bypass grafting, PCI: percutaneous coronary intervention, LAD: left anterior descending artery, LCX: circumflex artery, RCA: right coronary artery.

RESULTS

Baseline and Procedural Characteristics

A total of 71 and 76 patients were included in the BMS group and in the SES group, respectively. There were no significant differences between the groups with respect to baseline patient characteristics (Table I). In the BMS group 76.1% and in the SES group 65.8% were male ($P = 0.1$) and the mean age was 60.9 ± 10.5 and 61.1 ± 10.6 years, respectively ($P = 0.9$). Although not statistically significant, in the SES group the number of diabetic patients and patients treated in the LAD were higher. Glycoprotein IIb/IIIa inhibitor use was low in both the BMS group (21.9%) and SES group (18.4%) ($P = 0.08$); as defined by protocol, clopidogrel prescription was longer in SES group (6 months) as compared with the BMS group (1 month).

Three-Year Clinical Follow-Up

Both 6-month and 1-year outcomes have been reported previously [9,14]. At 3 years, follow-up was available in 87.3% of the patients in the BMS group and in 96% of the SES group. Four patients died in the BMS group, two of unknown cause, one of noncardiac cause, and one of cardiac death; while five patients died in the SES group, $P = 0.8$; in this group, three deaths were of cardiac cause, one patient died of cancer, and the cause of one patient was unknown.

TABLE II. Clinical Events at Three-Year Follow-Up

	BMS, $n = 71$	SES, $n = 76$	P value
Death, n(%)	4(5.6)	5(6.6)	0.8
MI, n(%)	2(2.8)	2(2.6)	0.9
TLR, n(%)	8(11.3)	6(7.9)	0.5
TVR, n(%)	9(12.7)	7(9.2)	0.5
TLR/Death, n(%)	12(16.9)	11(14.5)	0.7
TVR/Death, n(%)	13(18.3)	12(15.8)	0.7
MI/Death, n(%)	4(5.7)	6(8.1)	0.6
MACE, n(%)	13(18.3)	12(15.8)	0.7

MI, myocardial infarction; TLR, target lesion revascularization; MACE, major adverse cardiac events.

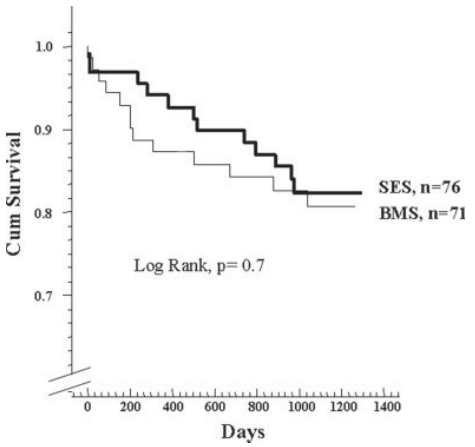

Fig. 1. Three-year cumulative incidence of major adverse cardiovascular events.

Two MI's occured in both groups, $P = 0.9$; and TVR was performed in nine patients in the BMS and seven in the SES group, $P = 0.5$. The cumulative survival-free of MACE was 81.7% in BMS group and 84.2% in SES group, $P = 0.7$ (Table II and Fig. 1). No cases of late stent thrombosis were identified in these two groups.

In the multivariate analysis the only variable that was an independent predictor of MACE was age, HR 1.04 (95%CI, 1.01, 1.07).

Three-Year Angiographic Follow-Up

Thirty patients underwent angiography at 3-year; the in-stent minimum lumen diameter was 1.9 ± 0.6 mm, the in-stent diameter stenosis was 30.5%, and the late loss 0.35 ± 0.50; four patients had binary restenosis; out of this four, two CTOs were found to be reoccluded (Fig. 2). One of these patients with reocclusion

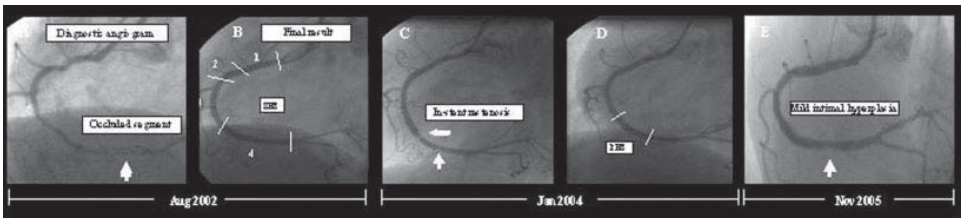

Fig. 2. A patient with a chronic total occlusion in the distal right coronary artery (panel A) was treated with four sirolimus stent (SES), in panel B the final result. Seventeen months later the patient underwent coronary angiogram due to stable angina and focal stent restenosis was seen in the gap between SES 3 and 4 (panel C). In addition, mild intimal hyperplasia was observed in the body of the SES number 4. Patient was treated with a PES (panel D). In the three-year angiographic follow-up an increase was seen in the intimal hyperplasia (panel E).

was treated due to the presence of symptoms, while the other patient was left untreated due to the absence of symptoms and it is awaiting noninvasive ischemia testing. Two patients had a coronary aneurism.

DISCUSSION

This report describes the 3-year clinical and angiographic follow-up of patients with CTO treated with either BMS or sirolimus stents.

There have been some publications comparing BMS vs. DES treatment for CTOs with 6-month follow-up [7,9,15], and recently the first randomized trial in the DES era that included exclusively CTO patients was published [10]; pooling these studies despite the different nature of data (e.g. registries vs. randomized trial), the analysis showed a decrease in TVR and MACE with DES, OR 0.25 (95%CI, 0.16, 0.40) and OR 0.36 (95%CI, 0.24, 0.53), respectively. Three 1-year follow-up studies have been published [5,6,14], (all registries), which also showed a sustained benefit of DES in terms of TVR and MACE, OR 0.1 (95%CI, 0.05, 0.20) and OR 0.17 (95%CI, 0.07, 0.43), respectively. Clinical reports including up to 1-year clinical follow-up, neither individually or globally, showed a decrease in terms of all cause death or MI.

Although due to the study design some baseline characteristics are different between the two groups such the presence of diabetes, treatment of the LAD (no statistically significant), and diameter of the stent, in the 6-month [9] and 1-year [14] reports in patients treated with SES a marked reduction in restenosis rate and MACE was observed compared with BMS. In turn, this 3-year follow-up report showed no difference whatsoever in any of the MACE components. This is in agreement with other two long-term follow-up substudies of the RESEARCH registry, patients with diabetes mellitus and acute MI [16]. The former report compared the 2-year clinical outcome of 708 consecutive diabetic patients treated with either a BMS (n = 252), a SES (n = 206), or a PES (n = 250). TVR rates were 19.5% in the BMS group, vs. 15.3% in the SES group and 9.7% in the PES group. PES (21.2%) but not SES (28.9%), were superior to BMS (29.7%) in reducing MACEs. However, after propensity analyses, none of the differences remained significant. The second report where primary angioplasty was performed in a consecutive group of 505 patients (BMS, n = 183; SES, n = 186; PES, n = 136), showed that the cumulative incidence of death or MI was comparable in the three groups: 16.6% in the BMS group, 14.6% in the SES group, and 16.9% in the PES group. At 3 years, TVR was 12.0% in the BMS group, compared with 8.0 and 7.7% in the SES and PES groups, respectively. The cumulative incidence of death, MI or TVR was 25.5% in the BMS group compared with 17.9 and 21.4% in the SES and PES groups, respectively. In light of these results, it seems that a late clinical restenotic phenomenon is observed in specific subsets of patients, and that the beneficial effects in restenosis rates of DES observed in the first year might drop over the time.

The present study has all the intrinsic limitations of a registry. Although in our center only in a limited period of time all comers were treated with sirolimus eluting stent and the number of CTO patients treated was relatively small, all consecutively treated CTO patients were included in this registry. A word of caution in interpreting the present findings as confirmative must be given, since the sample size is small. However, so far, in this subset of patients, this is the only registry with clinical and angiographic long-term follow-up.

CONCLUSIONS

Despite clinical benefit after 1 year, the use of sirolimus stent was no longer associated with significantly lower rates of TVR and MACEs in patients with

CTOs after 3 years of follow-up compared with bare metal stents.

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Chapter 14

Two-year outcome of the use of paclitaxel-eluting stents in aorto-ostial lesions

Tsuchida K, Daemen J, Tanimoto S, García-García HM, Kukreja N, Vaina S, Ong AT, Sianos G, de Jaegere PP, van Domburg RT, Serruys PW

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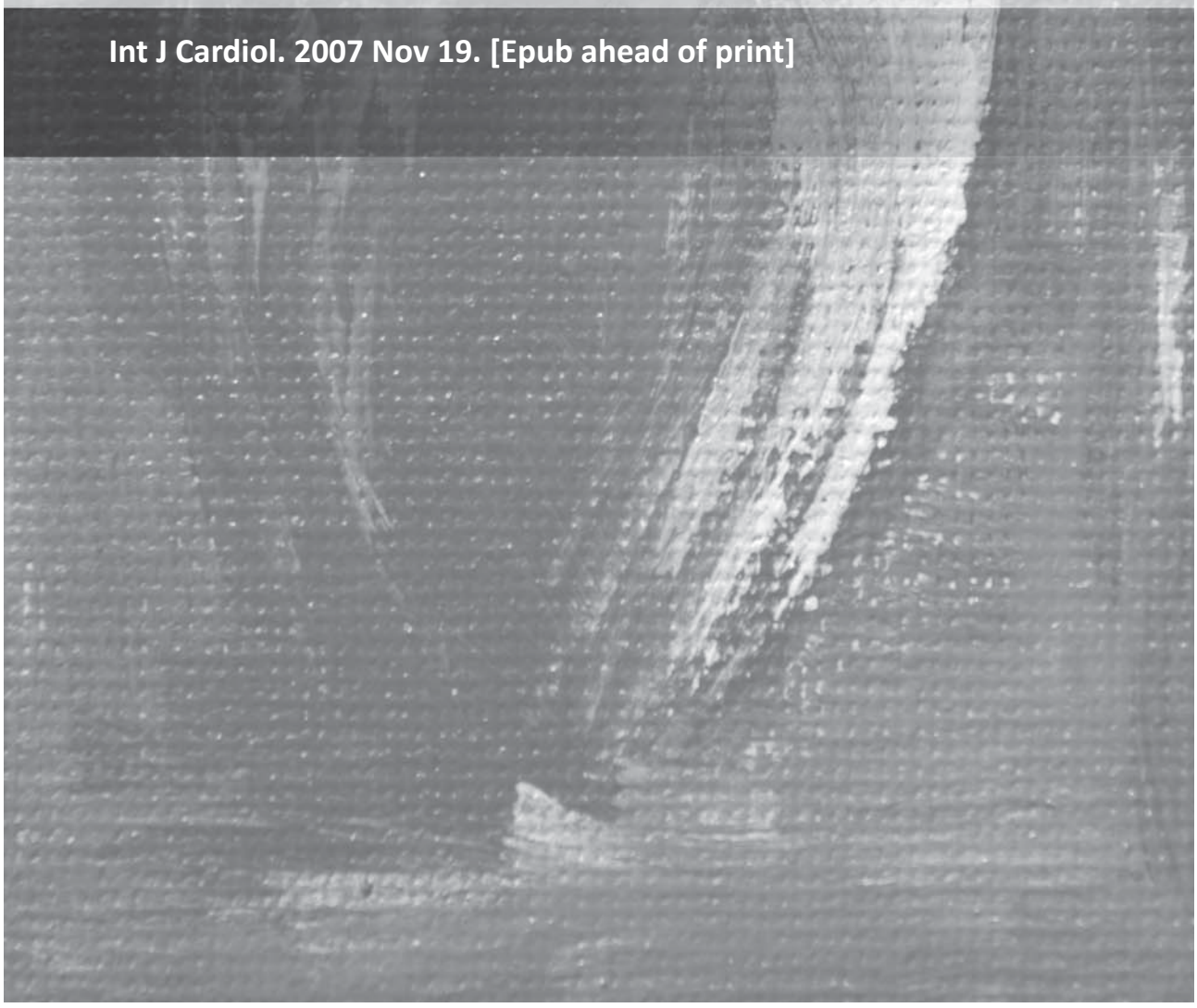

Two-year outcome of the use of paclitaxel-eluting stents in aorto-ostial lesions

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Abstract

Background: Percutaneous treatment of stenoses involving aorto-ostial lesions is technically demanding and has been associated with lower procedural success and poorer clinical and angiographic outcomes when compared with non-ostial lesions. This study evaluated the immediate and long-term (2-year) outcome of aorto-ostial stenoses treated with paclitaxel-eluting stents (PES).
Methods: From February 2003 to December 2004, a total of 76 consecutive patients with 76 lesions underwent percutaneous intervention with PES for aorto-ostial lesions (right coronary artery, 37; left main, 26; saphenous vein graft, 13). All patients were clinically followed for the occurrence of major adverse cardiac events (MACE), defined as cardiac death, non-fatal myocardial infarction (MI), target lesion revascularization (TLR) or target vessel revascularization (TVR).
Results: All stents (1.7/lesion) were successfully deployed. Three lesions (3.9%) were pre-treated with debulking devices. Thirty-seven lesions (48.7%) were post-dilated with non-compliant balloons (balloon/artery ratio, 1.2). Stents were positioned protruding into the aortic lumen in 29 lesions (38.2%). Cumulative 2-year event-free survival was 68.4%. There was one angiographically-proven stent thrombosis occurring 427 days after TLR for restenosis after the index procedure. The restenosis rate at 7 months (median) was 20.0% and in-stent late lumen loss was 0.48 mm in 40 patients with angiographic follow-up.
Conclusions: Utilization of PES in this complex lesion subset is feasible and associated with favorable angiographic results at 7 months. However, the gradual increase in later events up to 2 years suggests that aorto-ostial disease remains problematic even in the era of drug-eluting stents.

Keywords: Aorto-ostial lesion; Paclitaxel-eluting stent; Percutaneous coronary intervention; Aorto-ostial lesion; Paclitaxel-eluting stent

1. Introduction

Percutaneous treatment of stenoses involving aorto-ostial lesion is a technically demanding procedure for interventionalists and has been associated with lower procedural success, and poorer clinical and angiographic outcomes when compared with treatment of non-ostial lesion [1,2]. The extremely sclerotic and calcified nature of this lesion site [3–5] has contributed to suboptimal immediate and long-term results after balloon angioplasty as a stand-alone strategy [6]. Debulking strategies with directional coronary atherectomy (DCA) or rotational atherectomy (rotablator) were assumed to alter outcomes for this particular lesion subset, but their efficacies have not been determined. To counter the ostial elasticity resulting in high restenosis rates (enhanced recoil), stent implantation is a reasonable strategy for lesion scaffolding, and bare metal stents have resulted

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in better outcomes than conventional balloon angioplasty [7–9]. However, in addition to acute and chronic stent recoil, excessive neointimal growth after stenting in this location has been documented [10]. Although drug-eluting stents (DES) have shown even better clinical and angiographic results than bare metal stents, data on the efficacy of DES for ostial lesions are still limited, mostly due to the exclusion of these high risk lesions in the majority of the published randomized trials [11–14]. Percutaneous treatment with sirolimus-eluting stent (SES) for aorto-ostial lesions has already been reported to improve short-term clinical and angiographic outcomes [15]. Polymer-based paclicaxel-eluting stent (PES, TAXUS™ Express2™, Boston Scientific Corp., Natick, MA) is another FDA-approved drug-eluting stent that has been shown to reduce clinical events in simpler lesions [13]. To date, few reports are available on the treatment of ostial stenoses using PES. In addition, little is known about the long-term results of percutaneous treatment of aorto-ostial lesions using DES. This study was made to evaluate both the 7-month angiographic and 2-year clinical outcomes of the use of PES for aorto-ostial narrowings.

2. Methods

From February 2003 to December 2004, a total of 93 consecutive patients underwent percutaneous intervention for 93 aorto-ostial lesions in our institution. All the eligible lesions were primary culprit lesions for each patient and therefore stenting due to dissection, extended stenting from non-ostial lesions, or spasm induced by catheter tip were excluded. Seventeen patients were excluded from this study because of deployment of SES (Cypher™, Cordis/Johnson & Johnson, Warren, NJ) in 7, bare metal stents in 5, angioplasty without stenting in 2, unsuccessful guidewire crossing in 2 (chronic total occlusions), and PES with a different type of platform (Infinium™, Sahajanand Medical Technologies Pvt. Ltd., Gujarat, India) in 1. Thus, the study population consisted of 76 consecutive patients treated with TAXUS™ Express2™ stents. The study population is a constitutive part of Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registry of which the design and goals have been described previously [16]. An aorto-ostial lesions were defined as being located less than 3 mm (as measured by quantitative angiographic analysis) of the orifice of the right coronary artery, left main coronary artery, or saphenous venous graft when visualized in an angiographic projection without foreshortening [6]. The study protocol was approved by the local ethics committee and is in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

2.1. Medications and interventional procedures

Elective patients were all pre-treated with aspirin and clopidogrel. A loading dose of 300 mg of clopidogrel was adopted in emergency cases. Post-interventional prescription of antiplatelet was life-long aspirin and 6-month clopidogrel with daily dose of 75 mg. PESs were available in diameters of 2.25, 2.5, 2.75, 3.0 and 3.5 mm. Usage of debulking devices (DCA or rotablator), distal protection devices and administration of glycoprotein IIb/IIIa inhibitors was left to the discretion of each physician. Slight stent protrusion into the aortic lumen was determined in the least foreshortened angiographic projection. Angiographic success was defined as residual diameter stenosis $<30\%$ in the presence of Thrombolysis in Myocardial Infarction (TIMI) flow grade 3.

2.2. Clinical follow-up and definitions

Adverse events were assessed at 30 days, 1 and 2 years. The primary endpoint was the occurrence of major adverse cardiac events (MACE), defined as a composite of cardiac death, non-fatal myocardial infarction (MI), target lesion revascularization (TLR), and target vessel revascularization (TVR). All deaths were regarded as those of cardiac origin unless a noncardiac origin was proven either clinically or by autopsy. Non-fatal MI was defined as the occurrence of an elevated creatine kinase-MB fraction (CK-MB) >3 times the upper limit of normal [16]. TLR was defined as either surgical or percutaneous reintervention driven by significant ($\geq 50\%$) luminal narrowing either within the stent or the borders 5 mm proximal and distal to the stent that was undertaken in the presence of either anginal symptoms or objective evidence of ischemia. TVR was defined as reintervention in the treated vessel outside the target lesion. Stent thrombosis was defined as angiographically-documented complete occlusion (TIMI flow grade 0 or 1) or flow-limiting thrombus (TIMI flow grade 1 or 2) in a previously treated artery. Stent thrombosis was categorized according to its timing relative to the index procedure as early (within 30 days) or late (>30 days) thrombosis.

All patients were clinically followed for the occurrence of MACE. Information about in-hospital outcomes was obtained from an electronic clinical database maintained at our institution and by review of patients' records. Post-discharge survival status was examined from the Municipal Civil Registries. Occurrence of MI or revascularization at follow-up was collected by consulting our institutional electronic patient database and by contacting referring physicians and institutions.

2.3. Quantitative angiographic analysis

Quantitative angiographic analysis was performed using the computer-based validated QCA system (CAAS II, Pie Medical Imaging, Maastricht, the Netherlands). Quantitative measurements included the diameter of the reference vessel, the minimal luminal diameter, percentage (%) diameter stenosis, and late luminal loss (the difference between the minimal luminal diameter after the procedure and the minimal luminal diameter at follow-up). Binary restenosis was defined as a stenosis of at least 50% of the minimal

Table 1
Baseline clinical and angiographic characteristics ($n=76$)

Age, years	66.0±10.9
Male gender, *n* (%)	51 (67.1)
Smoking:	
current, *n* (%)	15 (19.7)
Former, *n* (%)	14 (18.4)
Diabetes:	
type I, *n* (%)	13 (17.1)
Type II, *n* (%)	4 (5.3)
Hypertension, *n* (%)	31 (40.8)
Hypercholesterolemia, *n* (%)	44 (57.9)
Renal insufficiency, *n* (%)	9 (11.9)
Family history, *n* (%)	28 (36.8)
Prior myocardial infarction, *n* (%)	26 (34.2)
Previous intervention, *n* (%)	18 (23.7)
Previous bypass surgery, *n* (%)	17 (22.4)
Multivessel disease, *n* (%)	55 (72.4)
Stable angina pectoris, *n* (%)	31 (42.1)
Unstable angina pectoris, *n* (%)	32 (42.1)
Acute myocardial infarction, *n* (%)	13 (15.8)
Cardiogenic shock, *n* (%)	4 (5.3)

luminal diameter in the target lesion at angiographic follow-up. In most cases, reference vessel diameter was obtained only from a point distal to the lesion. Angiographic patterns of restenosis were also determined [17].

2.4. Statistical analysis

Values in the text and tables are presented as mean±SD, or frequency (percentage) for descriptive purposes. The cumulative incidence of adverse events was estimated according to the Kaplan–Meier analysis. Statistical analyses were performed with SPSS 12.0.1 for Windows (SPSS Inc., Chicago, IL). A p value <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

Baseline patient, lesion, and procedural characteristics are shown in Tables 1 and 2. Multivessel disease was observed in 72.4% of the patients. More than half of the cases underwent index PCI for an acute coronary syndrome (unstable angina, 42.1%; acute myocardial infarction, 15.8%). There was no documentation of non-atherosclerotic etiologies associated with aorto-ostial disease such as syphilitic cardiovascular disease, Takayasu's arteritis, etc. [18].

The seventy-six target vessels in the present study consisted of 37 right coronary arteries, 26 left main coronary arteries, and 13 venous grafts. These lesions included seven restenotic lesions following bare metal stent implantation (9.2%). Moderate to severe calcification was documented in 19 lesions, presence of thrombus in 13, restenosis of bare metal stent in 7, chronic total occlusion (an occlusion period more than 3 months) in 1.

3.2. Procedural results

Target lesions were treated using 1.69±0.97 stents (total stent length per lesion, 32.11±26.58 mm) that were post-dilated using balloons 3.6±0.44 mm diameter (mean balloon–artery ratio, 1.24). Lesion modification by debulking devices or cutting balloon was made in 7 patients. Stent placement with slight protrusion of the proximal edge into the ascending aorta was performed in 38.2% of the cases. Two patients were complicated by aorto-coronary dissection involving in the sinus of Valsalva, which regressed conservatively over a short period. Thirty-five patients (46.1%) underwent concomitant treatment of non-ostial lesions either in the same or different vessels.

3.3. Clinical outcome up to 2 years

Thirty-day, one-year as well as 2-year outcomes in terms of clinical events are reported in Table 3.

Table 2
Baseline lesion and procedural characteristics ($n=76$)

Lesion characteristics	
Lesion location	
Right coronary artery, *n* (%)	37 (48.7)
Left main coronary artery, *n* (%)	26 (34.2)
Venous graft, *n* (%)	13 (17.1)
In-stent restenosis of bare metal stent, *n* (%)	7 (9.2)
Chronic total occlusion, *n* (%)	1 (1.3)
Thrombus-containing lesion, *n* (%)	13 (17.1)
Moderate to severe calcification, *n* (%)	19 (25.0)
Eccentric lesion, *n* (%)	24 (31.6)
TIMI flow grade ≤2:	
Baseline, *n* (%)	18 (23.7)
After procedure, *n* (%)	3 (3.9)
Procedural characteristics	
Number of stents/lesion, *n*	1.69±0.97
Total stent length/lesion, mm	32.11±26.58
Maximal balloon size, mm	3.64±0.44
Balloon/artery ratio	1.24±0.23
Maximal inflation pressure, atm	20.18±2.65
Debulking, *n* (%)	3 (3.9)
Cutting balloon, *n* (%)	4 (5.3)
Direct stenting, *n* (%)	33 (43.4)
Post-dilatation, *n* (%)	37 (48.7)
Use of glycoprotein IIb/IIIa inhibitors, *n* (%)	10 (13.2)
Distal protection device, *n* (%)	12 (15.8)
Intra-aortic balloon pump, *n* (%)	4 (5.3)
Left ventricular assist device (LVAD), *n* (%)[a]	1 (1.3)
Periprocedural stent thrombosis, *n* (%)	0 (0.0)
Stent protrusion, *n* (%)	29 (38.2)
Aorto-coronary dissection after procedure, *n* (%)	2 (2.6)
Concomitantly treated lesion, *n* (%)	35 (46.1)
Angiographic success, *n* (%)	73 (96.1)

[a] The Impella LVAD Recover LP 2.5 (Impella Cardiotechnik, Aachen, Germany).

Table 3
Major adverse cardiac events

30-day outcome	
Death	6 (7.9)
Non-fatal myocardial infarction	4 (5.3)
Target vessel revascularization	0
Target lesion revascularization	0
MACE	10 (13.2)
Stent thrombosis*	1 (1.3)
1-year outcome	
Death	6 (7.9)
Non-fatal myocardial infarction	4 (5.3)
Target vessel revascularization	8 (10.5)
Target lesion revascularization	3 (3.9)
MACE	18 (23.7)
Stent thrombosis*	1 (1.3)
2-year outcome	
Death	9 (11.8)
Non-fatal myocardial infarction	6 (7.9)
Target vessel revascularization	11 (14.5)
Target lesion revascularization	3 (3.9)
MACE	24 (31.6)
Stent thrombosis†	3 (3.9)

*Subacute stent thrombosis in a concomitantly-treated non-ostial target vessel (left anterior descending) 21 days after the index PCI; †One is subacute thrombosis in a non-ostial target vessel (left anterior descending) 2 days after stenting and the other is late thrombosis in the right coronary ostial lesion 427 days after TLR. MACE = major adverse cardiac events.

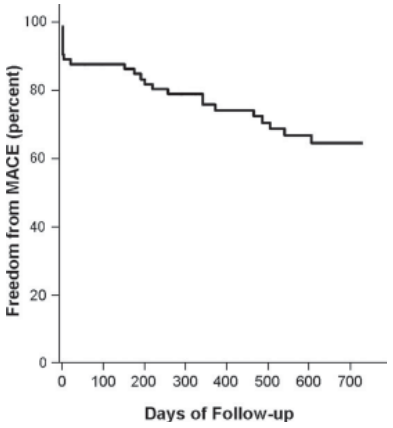

Fig. 1. Kaplan–Meier event-free survival at 2 years for major adverse cardiac events (MACE).

3.3.1. 30-day outcome

In the first month, 6 patients died, four of whom exhibited fatal MI resulting in refractory cardiogenic shock as a baseline clinical presentation, although stents were successfully deployed in each of the target lesions (1 right and 3 left main coronary arteries). One patient with stable angina underwent elective stenting for ostial left main disease, but died due to a rapid hemodynamic collapse resulting from compromised blood flow to the jailed left circumflex artery. One patient died 21 days after concomitant stenting in 2 target lesions (ostial right coronary artery and left anterior descending artery). This case was strongly suspected of having early stent thrombosis either in the territory of the right coronary artery or left anterior descending artery as the cause of sudden death, which was not angiographically-documented.

Out of the 4 MIs, 3 were MIs during the index procedures and the other was a subacute stent thrombosis in a concomitantly-treated different vessel (left anterior descending artery) 21 days after the index procedure. There were no cases of TLR or TVR in the first 30 days.

3.3.2. 1-year outcome

Neither further death nor MI was documented after 30 days up to 1 year. TVR was required in 8 patients (TLR, 3/8), all of which were treated percutaneously.

3.3.3. 2-year outcome

There was a gradual increase in MACE throughout 2 years (Fig. 1). There were 3 more deaths identified between 1 and 2 years. One patient who died 465 days after stenting was strongly suspected of having late stent thrombosis in the territory of the right coronary artery as the cause of sudden

Table 4
Quantitative coronary angiography ($n=76$)

Baseline	
Reference vessel diameter, mm	3.04±0.56
Minimum luminal diameter, mm	0.92±0.51
Diameter stenosis, %	69±16
Lesion length, mm	14.24±15.06
Post procedure	
Reference vessel diameter, mm	3.30±0.51
Minimum luminal diameter, mm	2.73±0.52
Diameter stenosis, %	17±9
Follow-up (n=40) at 7 months[a]	
Reference vessel diameter, mm	3.26±0.54
Minimum luminal diameter, mm	2.23±0.94
Diameter stenosis, %	34±26
In-stent late lumen loss, mm	0.48±0.88
Restenosis, *n* (%)[b]	8 (20%)
Focal — articulation	1
Focal — margin	1
Focal — body	2
Diffuse — intrastent	1
Diffuse — proliferative	1
Diffuse — total occlusion	2

[a]Median of follow-up period.
[b]Restenosis patterns were adopted from the classification by Mehran et al. (Ref. [17]).

death, though this was not angiographically confirmed. Additional 3 clinically-driven TVRs were performed. The 2-year cumulative incidence of MACE was 31.6%. There were two additional stent thromboses (early and late) identified. One occurred 2 days after stenting a non-ostial lesion (left anterior descending) and the other was a late thrombosis 427 days after the index PCI for the right coronary ostial lesion.

3.4. Angiographic results

Quantitative coronary angiographic analysis is summarized in Table 4. The mean reference vessel diameter was 3.04 mm. Angiographic follow-up data were obtained in 40 patients (52.6%) at the median timing of 7 months after the index stenting. Binary in-stent restenosis rate was 20.0% (8/40). Focal patterns of restenosis were found in 50% (4/8). In-stent late lumen loss of PES in this lesion subset was 0.48 mm.

4. Discussion

The present study provides the 7-month angiographic and 2 year clinical outcomes of PES in aorto-ostial lesions in a larger consecutive population than that of earlier studies [1,9,15,19]. The results of the present study suggest the following two main findings: 1) PES utilization is a feasible treatment option in this complex lesion setting by keeping the restenosis rate to 20.0% and thereby TLR rate to 5.3%; 2) The long-term efficacy of PES, however, in overall clinical outcome still remains to be determined due to the subsequent increase in later events.

Aorto-ostial disease can be a critical cause of fatal myocardial infarction or sudden cardiac death due to the relatively large myocardial territory exposed to risk [3]. Lesions in this location are distinctive from branch ostial lesions because of their specific histopathological characteristics such as highly increased fibrous cellularity, calcification and sclerosis [3–5]. Reflecting this lesion background, Tsunoda et al. reported that excessive neointimal growth and chronic stent recoil might be two important etiologic factors for stent restenosis at this particular location [10]. With regards to the former factor, stents coated with antiproliferative agents are reasonable devices of choice and PES demonstrated successful reduction of neointimal growth after stenting (late loss, 0.48 mm),. To overcome another potential factor for restenosis, the combination of debulking and DES may be a particularly optimal approach. Plaque modification prior to stent implantation has been initially embraced as a preferred treatment strategy for this lesion subset [4]. However, since the role of debulking in the era of DES has not been clarified, we performed adjunctive debulking in only 3 patients. Instead of using atherectomy devices, we aggressively post-dilated by adopting a relatively large-sized non-compliant balloon (balloon–artery ratio, 1.24) in order to achieve a satisfactory angiographic result. Because of the delayed healing response of injured vessel wall after implantation of DES [20], it might be speculated that the relatively high mechanical injury resulting from atherectomy further delayed healing process following DES placement. Furthermore, atherectomy of aorto-ostial lesions is technically demanding because of the need to pull the guiding catheter from the coronary ostium while leaving the atherectomy catheter in position for debulking. Additionally, when performing DCA or rotablation for aorto-ostial lesions, great care should be taken to avoid excision of guiding catheter material [21,22].

Slight stent protrusion into the aorta is usually associated with a benign clinical course. However, unapposed protruding stent struts may theoretically promote platelet activation, thrombosis, and/or distal embolization. In addition, protruding stent struts may not only pose an inability to easily re-engage the ostium with either diagnostic or guiding catheters, but also can complicate future interventional as well as surgical procedures [23–26]. We encountered only one angiographically-documented stent thrombosis related to the target vessel and stent protrusion was not implicated in this case. Of the 2 possible stent thrombosis cases, stent placement with slight protrusion was performed in one (465 days after stenting) and not in the other (21 days after stenting). The 2 cases with very late stent thrombosis occurring beyond 1 year suggest that current US Food and Drug Administration-approved indications for 6-month clopidogrel use following TAXUS implantation may not be sufficient to prevent late stent thrombosis. Eisenstein et al. showed that longer-term clopidogrel use may be associated with more favorable clinical outcome for patients receiving DES [27]. However, the small number of patients evaluated in this analysis do not allow for any definitive statement with respect to the safety profile of this stenting technique. So far, it appears that positioning of PES with protrusion of only a short segment of stent into the aorta might instead contribute to lower restenosis by adequately covering the lesion.

Despite the low incidence of TLR at 2 years, the limited role of PES on overall long-term outcome was also indicated because of the gradual increase in TVR rate. Obstruction at the origin of a coronary artery is most often associated with more generalized coronary atherosclerosis and the presence of multivessel coronary artery disease (72.4%). It may be helpful for long-term favorable outcome to prevent and adequately detect the progression of other non-ostial lesions that are not significant at time of treatment of ostial lesions in the same vessel. Long-term evaluation of non-ostial lesions in the target vessels should be considered.

4.1. Study limitations

There were several limitations in this study. First, this was a single-center's experience with implantation of PES in aorto-ostial stenoses. Second, no control group was used to compare the long-term efficacy of PES with other devices. In this regard, direct comparison between PES and bare stent/

SES would have been interesting to address whether a different drug and different stent platform might influence the incidence of restenosis. Third, the rate of follow-up angiography was limited to 52.6% of 76 patients. Finally, since each treatment strategy was not prespecified, the results may reflect our bias toward our treatment technique. However, this study more likely represents "real-life" practice of PES utilization.

5. Conclusions

In conclusion, our findings suggest that PES in aorto-ostial lesions is safe and feasible in light of the low incidence of restenosis at 7 months. However, the increase in later events, especially the TVR rate, may attrite the long-term benefit of PES in patients with this complex lesion subset.

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Chapter 15

Four-year safety and efficacy of the unrestricted use of sirolimus- and paclitaxel-eluting stents in coronary artery bypass grafts

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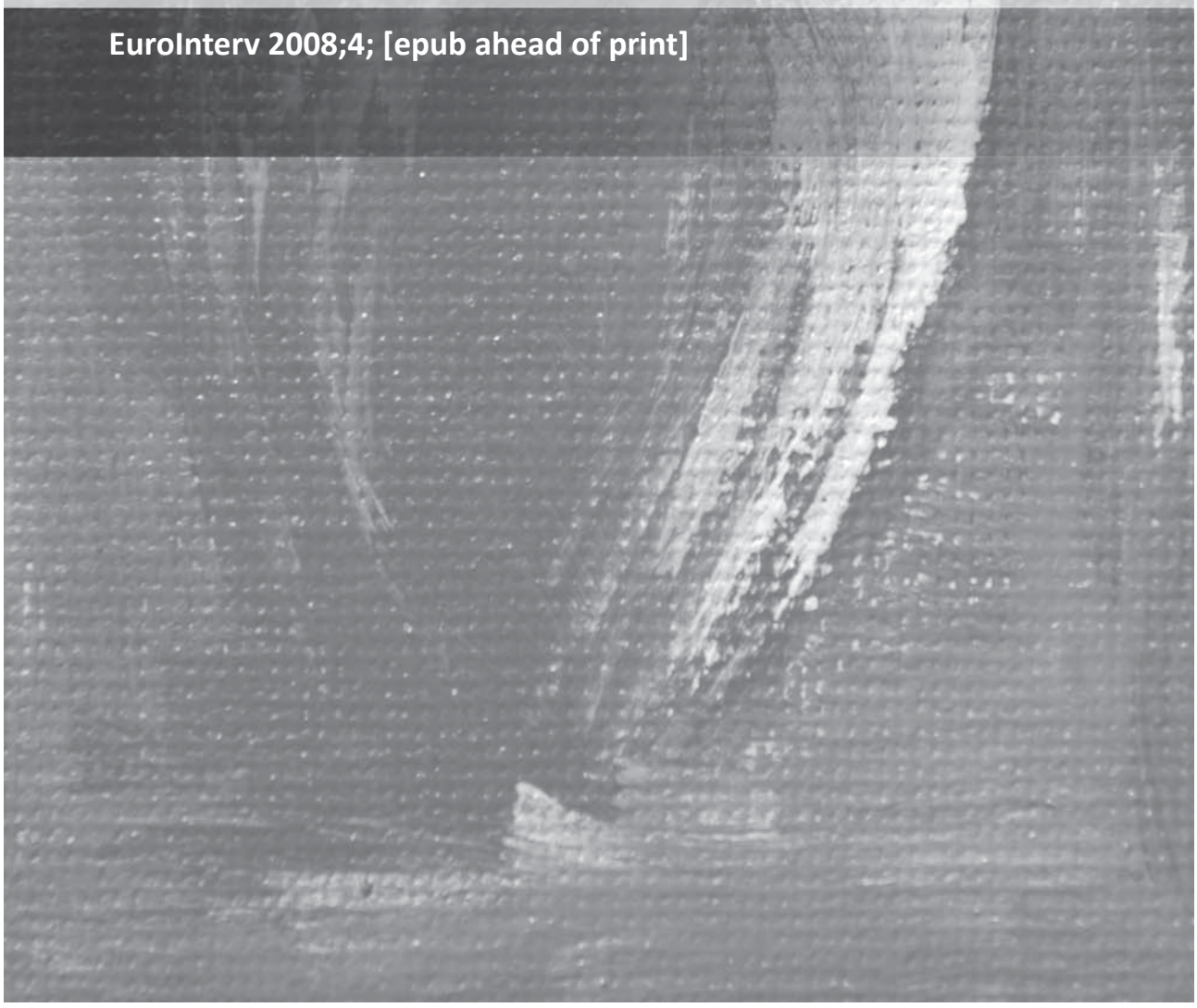

Four-year safety and efficacy of the unrestricted use of sirolimus- and paclitaxel-eluting stents in coronary artery bypass grafts

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The authors have no conflicts of interest to declare.

KEYWORDS
Bypass graft, drug-eluting stent, bare-metal stent, long-term safety

Abstract

Objectives: Recently, concerns were raised about the relative long-term safety and efficacy of drug-eluting stents (DES) in saphenous vein bypass grafts (SVG). Our objective was to assess the 4-year relative safety and efficacy of the unrestricted use of drug-eluting stents (DES) as compared to bare metal stents (BMS) in saphenous vein bypass grafts (SVG).

Methods: Between April 16, 2002 and December 2005 a total of 122 consecutive patients were treated with either sirolimus- or paclitaxel-eluting stents for saphenous vein graft disease. These patients were compared with 128 consecutive patients treated with BMS in the immediate preceding period (January 1, 2000 to April 2002).

Results: At 4-years the cumulative survival rate in the DES group was 77.5% versus 73.0% in the BMS group (adjusted HR 1.09; 95% CI 0.63-1.90, Logrank p=0.65). The cumulative survival free of major adverse cardiac events (MACE: death, myocardial infarction and target vessel revascularisation) was 61.5% vs. 46.8% in the DES and BMS groups respectively (adjusted HR 0.77, 95% CI; 0.51-1.16) due to a higher event free survival of clinically driven target vessel revascularisation in the DES group as compared to the BMS group (81.6% vs. 69.0%; adjusted HR 0.53; 95% CI 0.27-1.05).

Conclusions: In the present study, the use of DES for SVG PCI was associated a similar safety profile and there was a trend towards lower rates of TVR and MACE at four years as compared to BMS.

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Introduction

Saphenous vein grafts are the commonest conduit in coronary artery bypass graft surgery (CABG).[1] However, the lifespan of saphenous vein grafts (SVG) proved to be limited – at 10 years, 50% of such grafts contain at least one significant stenosis with a total occlusion rate of up to 40%.[2,3]

Currently the use of drug eluting stents (DES) for off-label indications is frequent (up to 60 % in our centre) and PCI has surpassed CABG as the treatment of first choice for treating coronary artery bypass graft disease.[4,5] Still, event-free survival after stent implantation remains low due to restenosis at the lesion site.[6-8] The use of DES in SVG lesions has led to a decrease in restenosis and the need for repeat revascularisation at one year as compared to bare metal stents (BMS).[9-11]

Currently there is still scarce evidence about the long-term safety and efficacy of DES when used in coronary artery bypass grafts. The recently published 32-months follow-up of the Delayed Reduction of Restenosis In Saphenous Vein Grafts With Cypher Sirolimus-Eluting Stent (RRISC) trial showed a catch-up in the repeat revascularisation rates in patients treated with sirolimus-eluting stents (SES).[12] Moreover, the authors reported a significant increase in late mortality in patients treated with SES as compared to those treated with bare metal stents (BMS).[12]

The current study was performed to assess the long-term outcome of a consecutive series of patients treated with BMS, sirolimus- or paclitaxel-eluting stents (SES and PES respectively) for lesions in venous bypass grafts.

Methods

Patient selection

Between January 1, 2000 and December 31, 2005 a total of 387 percutaneous interventions were performed in our institution using BMS, SES or PES in coronary bypass-graft lesions (arterial or venous bypass grafts) (Figure 1). A total of 62 procedures were excluded due to treatment restricted to balloon angioplasty (n=35) or the use of (previous) brachytherapy (n=27). Two patients received a Symbiot™ Covered Stent and were also excluded. Out of 323 procedures selected, 298 involved the treatment of saphenous vein grafts and in 25 procedures arterial grafts were treated. From January 2000 until April 16th 2002, 144 PCI procedures in a venous bypass-graft were performed using exclusively BMS, from April 16, until December, 2005, 154 procedures were performed using either sirolimus-eluting stents (Cypher®, Cordis Corp., Johnson & Johnson, Warren, NJ, USA) or using paclitaxel-eluting stents (TAXUS™ Express2™ or Liberté™, Boston Scientific, Natick, MA, USA).

Patients initially enrolled in one of the sequential cohorts (BMS or DES) were maintained for analytical purposes throughout the follow-up period in their original cohort, even if a repeat intervention was performed using a different type of stent at a later stage. Finally, 250 patients fulfilled these criteria.

This study was approved by the local ethics committee and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

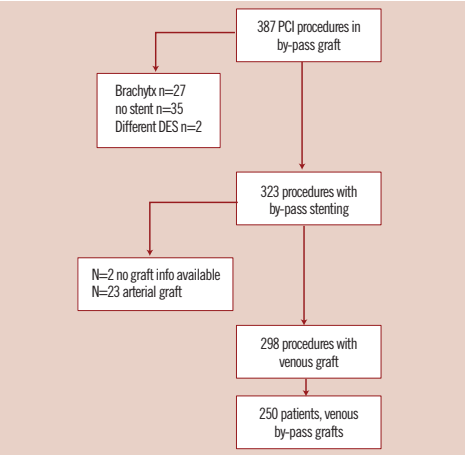

Figure 1. Inclusion flow chart of study population.

Procedural and baseline definitions

All procedures were performed following previously defined current standard procedural guidelines.[13] The use of distal embolisation protection devices and periprocedural glycoprotein IIb/IIIa inhibitors were left to the operator's discretion. Finally, the use of distal protection devices was low (4.7% in the BMS group vs. 1.6% in the DES group; p=0.28).

Patients were prescribed aspirin plus clopidogrel 75 mg/day (after a loading dose of 300 mg) before or during baseline coronary interventions. Patients treated with bare metal stents received at least one month of clopidogrel (median, three months, IQR: 2-6 months). Patients treated with DES received at least three months of clopidogrel (median, six months, IQR: 6-6 months). All patients were advised to remain on aspirin indefinitely.

Hypertension was defined as a blood pressure ≥ 140 systolic or ≥ 90 mm Hg diastolic or based on the current use of antihypertensive treatment. Dyslipidaemia was classified as a total serum cholesterol level of ≥ 6.2 mmol/l or the use of lipid lowering drugs. Diabetes was defined as treatment with either oral hypoglycaemic agent, insulin or through diet. Complete procedural success was defined by the achievement of <50% diameter stenosis (visual assessment) and Thrombolysis in Myocardial Infarction (TIMI) grade flow 3 in all lesions intended to treat. Clinical success was defined as procedural success without death or re-infarction during the index hospitalisation.

Endpoint definitions and clinical follow-up

Our primary endpoint was MACE (major adverse cardiac events; defined as a composite of all-cause death, myocardial infarction [MI] and target vessel revascularisation [TVR]) at 4-years. Secondary endpoints included the itemised outcomes all-cause

death, MI and TVR at 4-years. MI was defined as creatinine kinase-MB enzyme elevation ≥ 3 times the upper limit of normal. TVR was defined as a clinically driven (presence of clinical symptoms and/or signs of ischaemia) repeat revascularisation procedure (either percutaneous or surgical) of the index graft. Stent thrombosis (ST) was defined as angiographically defined thrombosis with TIMI grade 0 or 1 flow or the presence of a flow limiting thrombus, accompanied by acute symptoms, resembling the ARC definite criteria.[14,15]
Survival status was obtained from municipal registries. Cause of death was acquired via the central bureau of statistics, The Hague, The Netherlands and classified according to the international Classification of Diseases and Related Health Problems, 10th revision (ICD-10).[16] Questionnaires inquiring about patients current health status, and medication use were subsequently sent to all living patients. Events (MI, TVR) that occurred outside our institution were verified by contacting the peripheral hospital. Finally, follow-up was available for 98.4% of the BMS patients and 95.9% of the DES patients.

Statistical analysis

Summary statistics for all continuous variables are presented as medians together with the interquartile range (IQR). Categorical data are summarised as frequencies and percentages. Continuous variables were compared using the Mann-Whitney U test. Categorical variables were tested for significance using the Chi-square or Fisher's exact test. Survival and event-free survival analysis were presented using Kaplan-Meier survival curves and tested for difference using the log-rank test. Cox proportional hazards regression models were used to control for differences between groups and independent predictors of outcome. First, all baseline, clinical and procedural variables were put in a univariate cox proportional hazards regression model for the different endpoints. Second, all significant predictors of outcome ($p<0.1$) were forced into a second model along with stent type (BMS or DES) and tested for significance. Final results are reported as adjusted Hazard ratios (HR) with their respective 95% confidence intervals (CI). All statistical tests were two-tailed. A value of $p < 0.05$ (unless reported otherwise) was used for all tests to indicate statistical significance. All statistical analyses were performed using SPSS version 12 (SPSS Inc., Chicago, Illinois).

Results

Baseline and procedural characteristics are presented in Tables 1 and 2 respectively. Baseline characteristics were similar between the two groups, except for a significantly higher incidence of family history of coronary artery disease and dyslipidaemia in the DES group as compared to the BMS group. Procedural characteristics differed in terms of a smaller average stent diameter and a longer total stented length in the DES group. The use of glycoprotein IIb/IIIa inhibitors decreased over time, from 41% in the BMS group to 21% in the DES group, p=0.001). At 4-years, the cumulative survival free of MACE was 61.5% versus 46.8% in the DES and BMS groups respectively (adjusted HR 0.77, 95% CI; 0.51-1.16). [Figure 2, Table 3] A total of 57 patients died (23 in the DES group and 34 in the BMS group). The cause of death was cardiac in 15/23

Table 1. Baseline characteristics.

	Bare metal stent group n=128	Drug-eluting stent group n=122	P-value
Age (years)			
median	69.3	68.3	0.19
IQR	62.4-77.2	62.4-74.7	
Male gender	80% (102/128)	84% (103/122)	0.33
BMI			0.15
Median	25.8	26.5	
IQR	23.9-28.1	24.5-29.0	
Diabetes mellitus	21% (27/128)	31% (38/122)	0.07
Dyslipidaemia	45% (57/128)	66% (81/122)	0.001
Hypertension	43% (55/128)	49% (60/122)	0.33
Family history of CAD	17% (22/128)	28% (34/122)	0.043
Current smoker	16% (21/128)	8% (10/122)	0.049
Renal impairment	2% (2/128)	5% (6/122)	0.13
Previous MI	46% (59/128)	50% (61/122)	0.23
Previous PCI	27% (34/128)	30% (36/122)	0.77
Enrolment diagnosis			0.37
Stable angina	33% (42/128)	41% (50/121)	
Unstable angina	53% (68/128)	50% (60/121)	
Acute MI	14% (18/128)	8% (10/121)	
Shock	0% (0/128)	1% (1/121)	

Table 2. Lesion and procedural characteristics.

	Bare metal stent group n=128	Drug-eluting stent group n=122	P-value
Revascularisation territory			
LAD	49% (49/127)	33% (37/111)	0.40
LCX	53% (67/127)	49% (54/111)	0.53
RCA	31% (39/127)	34% (38/111)	0.56
Native vessels treated			
LAD	10.9% (14/128)	13.1 (16/122)	0.70
LCX	10.2% (13/128)	12.3% (15/122)	0.43
RCA	12.5% (16/128)	18% (22/122)	0.38
LM	2.3% (3/128)	1.6% (2/122)	1.00
In stent restenosis	8% (10/128)	8% (10/122)	0.91
Lesion type			
A	9% (11/128)	10% (12/122)	0.73
B1	27% (34/128)	25% (30/122)	0.72
B2	37% (47/128)	40% (49/122)	0.58
C	49% (63/128)	59% (72/122)	0.12
Clinical success	97% (124/128)	98% (117/122)	0.46
Number of lesions successfully treated			0.97
Median	1.00	1.00	
IQR	1.0-2.0	1.0-2.0	
Number of treated grafts			0.92
Median	1.0	1.0	
IQR	1.0-1.0	1.0-1.0	
Number of stents per lesion			0.21
Median	2.00	2.00	
IQR	1.0-2.0	1.0-3.0	
Total stent length, mm			0.02
Median	31.9	32.0	
IQR	18.0-40.3	18.0-58.5	
Average stent diameter, mm			<0.001
Median	3.5	3.1	
IQR	3.3-4.0	3.0-3.5	
Distal protection device used	4.7% (6/128)	1.6% (2/120)	0.28
Glycoprotein IIb/IIIa inhibitors	41% (53/128)	21% (26/122)	0.001

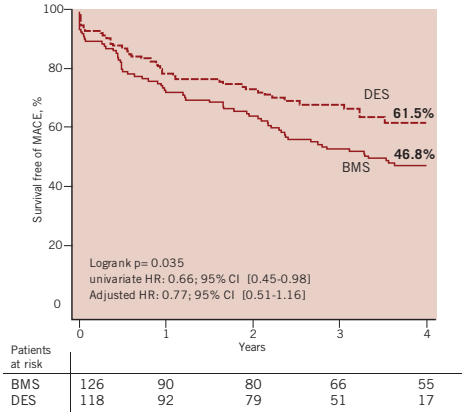

Figure 2. Kaplan Meier event free survival of major adverse cardiac events (MACE, the primary combined endpoints of all-cause mortality, myocardial infarction, and clinically driven target vessel revascularisation). DES stands for drug-eluting stent, BMS for bare metal stent.

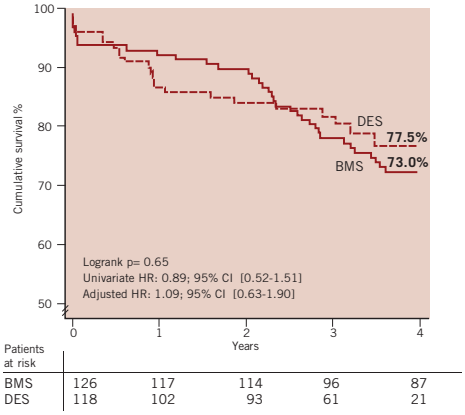

Figure 3. Kaplan Meier event free survival. DES stands for drug-eluting stent, BMS for bare metal stent, TVR for target vessel revascularisation, MI for myocardial infarction and MACE for major adverse cardiac events.

(65.2%) in the DES patients and 22/34 (64.7%) in the BMS patients. the cumulative survival rate in the DES group was 77.5% versus 73.0% in the BMS group (p=0.65). When adjusting for independent predictors the HR for death in the DES group was 1.09; 95% CI 0.63-1.90). [Figure 3, Table 3] The cumulative event free survival for the combined endpoint death/MI was 70.6 % in the DES group vs. 65.8% in the BMS group (adjusted HR 1.11 95% CI; 0.68-1.81).

Cumulative survival free of clinically driven TVR was higher in the DES group as compared to the BMS group (81.6% vs. 69.0% respectively; adjusted HR 0.53; 95% CI 0.27 - 1.05). [Figure 4, Table 3] A total of five (4.0%) patients treated with BMS suffered from stent thrombosis occurring at a median of 176 days (IQR 134-731) versus only 1 (0.8%) in the DES group occurring at 606 days.

Table 3. Event rates: total, in hospital and after 4 years.

Total population (n=250)	Crude event rates		Kaplan Meier estimates		Hazard rate [95% confidence interval]
Variables	BMS (128 patients)	DES (122 patients)	BMS (128 patients)	DES (122 patients)	
In Hospital events					
Total death	2.3% (3/128)	1.6% (2/122)	2.4%	1.7%	
Cardiac death	2.3% (3/128)	1.6% (2/122)	2.4%	1.7%	
Non-cardiac death	0.0% (0/128)	0.0% (0/122)	–	–	–
Myocardial infarction	3.1% (4/128)	2.6% (3/122)	3.2%	2.5%	
Target vessel revascularisation	1.6% (2/128)	0.0% (0/122)	1.6%	–	–
Major adverse cardiac events	7.0% (9/128)	4.1% (5/122)	7.1%	4.2%	
Events at 4 years					
Death	26.6% (34/128)	18.9% (23/122)	27.0%	22.5%	1.09; 95% CI 0.63-1.90*
Cardiac	17.2% (22/128)	9.0% (15/122)	18.6%	15.1%	1.02; 95% CI 0.52-1.04*
Non-cardiac	9.4% (12/128)	6.6% (8/122)	10.4%	8.6%	1.27; 95% CI 0.50-3.17*
Total myocardial infarction	10.2% (13/128)	5.7% (7/122)	11.1%	7.6%	0.71; 95% CI 0.27-1.82**
Target vessel revascularisation	28.1% (36/128)	13.9% (17/122)	31.0%	18.4%	0.53; 95% CI 0.27-1.05***
Major adverse cardiac events	52.3% (67/128)	33.6% (41/122)	53.2%	38.5%	0.77; 95% CI 0.51-1.16¶

* Adjusted for, diabetes, revascularisation territory LAD, indication acute coronary syndrome, positive family history of coronary artery disease and age
** Adjusted for, hypercholesterolaemia, revascularisation territory LAD
*** Adjusted for, hypertension, average stent diameter, number of treated grafts, number of stents, total stented length, diabetes, age and sex
¶ Adjusted for revascularisation territory LAD, gender, hypercholesterolemia, and indication acute coronary syndrome.

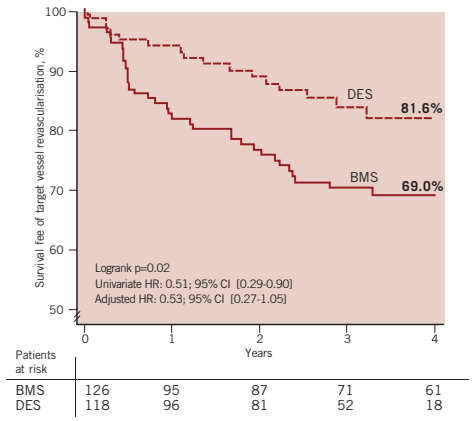

Figure 4. Kaplan Meier event free survival of clinically driven target vessel revascularisation. DES stands for drug-eluting stent, BMS for bare metal stent, TVR for target vessel revascularisation.

Discussion

The present study demonstrates that the use of DES in SVG remains safe and effective as compared to BMS up to four years of follow-up, illustrated by similar survival rates and a trend towards significantly lower rates of TVR in patients treated with DES. At four years, the use of DES tended to result in lower MACE rates, mainly caused by lower repeat revascularisation rates in the first year in patients treated with DES – even though definite conclusions cannot be drawn, this is a risk reduction comparable to that observed in both the general PCI population and in SVG stenting.[9,11,17-19]

The 32-months results of the randomised Delayed RRISC trial showed a catch-up in the repeat revascularisation rates in patients treated with SES along with a significant increase in late-mortality as compared to BMS.[12] Unfortunately, the sample size of the latter study was calculated based on in-stent late loss, which explains the sample size of only 75 patients and the highly selected patient population. Patients presenting with MI, with impaired renal function, distal graft lesions, chronic total occlusions were excluded, along with those presenting with aorto-ostial or calcified lesions making the results difficult to apply in real-world clinical practice. Yet, it was difficult to question these findings given the lack of long-term data regarding the safety of DES in SVG and the presence of previously raised concerns about a catch-up in the reintervention rates in diabetics and patients presenting with ST-segment elevation myocardial infarction treated with DES.[20,21] Thus far, individual patient level data meta-analyses of the pivotal randomised Cypher and TAXUS trials were not able to address this issue given the lack of high-risk patients and larger (network) meta-analyses simply precluded subgroup analyses due to the lack of the individual patient data.[17,18,22,23] To date, large-scale registries have not yet reported on the long-term outcome in this specific patient subset.[24,25]

The present study included a total of 250 real world consecutive patients treated for SVG disease of which the vast majority did not undergo routine angiographic follow-up. At four years, both all-cause and cardiac survival were identical between the BMS and DES group and there was no sign of a catch-up in TVR rates following DES use. The importance of detailed analyses of high-risk subgroups can be demonstrated by several recent studies suggesting that DES perform best in high-risk patients, like those presenting with small vessels, long-lesions, diabetes and SVG.[24,26] Thus far, the overall benefit of DES has been widely adopted, but concerns regarding their long-term safety[17,25,27] prompted investigators to further scrutinise their data for cost-effectiveness and heterogeneity of the treatment effect. While thus far, the safety concerns seem to be unfounded, a proper patient selection might become of crucial importance given the unfavourable cost-effectiveness profile of the DES.[26]

The steep drop in the TVR-free survival in the BMS group forced us to scrutinise the indications leading to the re-interventions occurring between 100 and 260 days. Only clinically driven cases of TVR were taken account into the present analysis. Out of the 14 TVR procedures occurring at six months in the BMS group, only two were due to angiographic follow-up and were not counted in the present analysis. Out of the remaining 12 patients who underwent a repeat intervention within this time frame, eight presented with unstable angina, three with stent thrombosis and one patient presented with stable angina and had a positive stress test.

Although patients treated with DES received clopidogrel for a longer period of time, the prescribed duration of clopidogrel did not seem to impact on any of the endpoints, even when adjusting for independent predictors.

The present study has several limitations. Firstly, although the DES and BMS groups in the present study were reasonably well matched in terms of baseline and procedural characteristics, it remains uncertain whether the use of extensive regression analyses was able to fully correct for the dissimilarities between the groups. Nevertheless, the overall risk profile was greater in the DES group. Large-scale randomised trials are needed to prove the long-term benefit advantage of DES over BMS in SVG. Secondly, the drug-eluting stent cohort contained both patients treated with SES and PES. However, no heterogeneity in the treatment effect was found regarding the use of either SES or PES.

Conclusions

In the present real world patient cohort, the use of DES for SVG lesions appeared safe and effective after 4-years of clinical follow-up. At 4-years, the use of DES tended to results in lower MACE rates as compared to BMS, due to similar survival rates and a trend towards lower rates of TVR.

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Chapter 16

Are drug-eluting stents associated with a higher rate of late thrombosis than bare metal stents? Late stent thrombosis: a nuisance in both bare metal and drug-eluting stents

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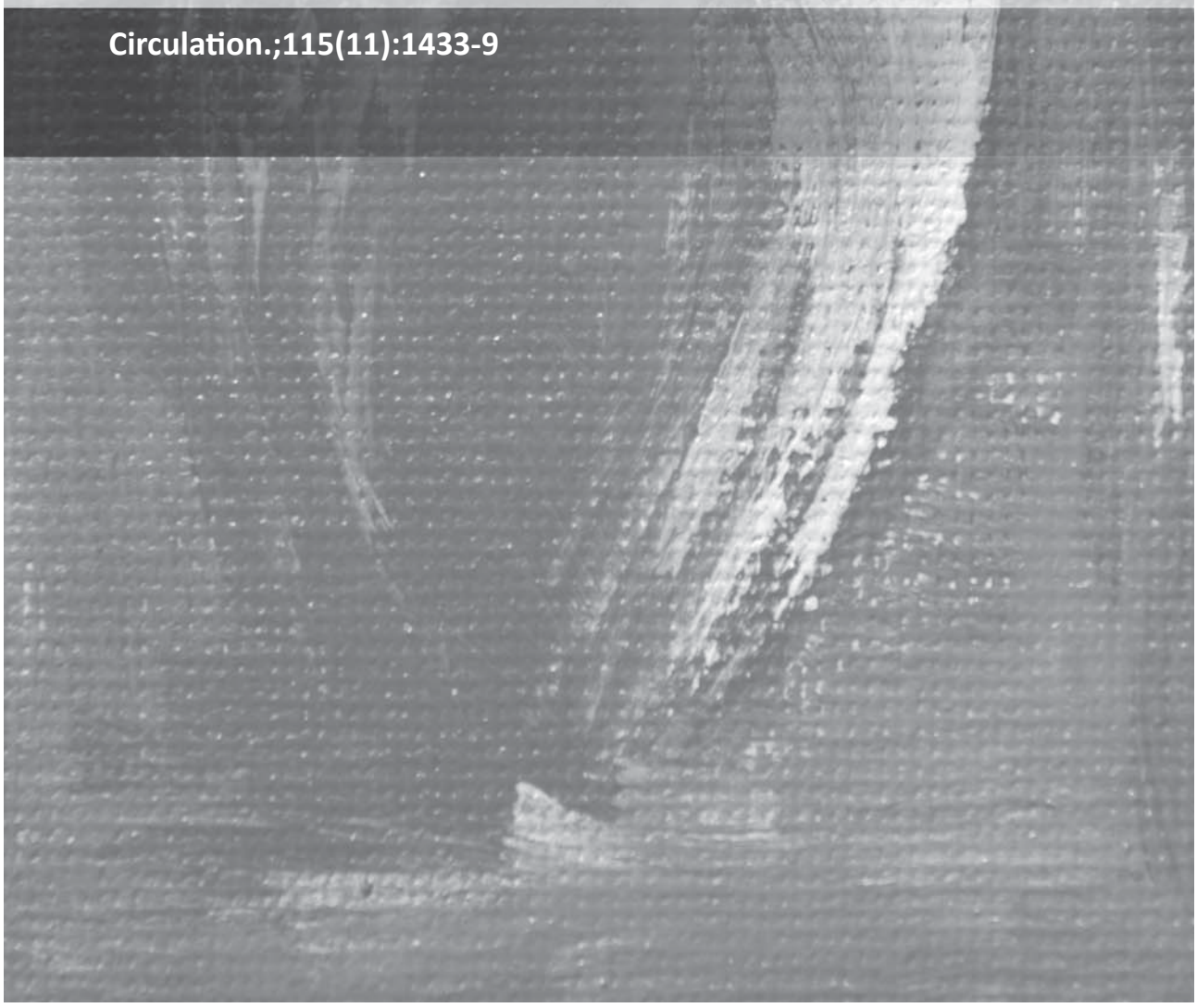

Are drug-eluting stents associated with a higher rate of late thrombosis than bare metal stents?

Late Stent Thrombosis

A Nuisance in Both Bare Metal and Drug-Eluting Stents

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Late stent thrombosis (ST) is for us an old foe that we have tracked repeatedly throughout the history of interventional cardiology. In 1991, we made headlines by publishing in the *New England Journal of Medicine* a rate of early and late ST of 20% among the first 151 patients having received a wall stent.[1] A few years later, when some believed that they had discovered the universal panacea for restenosis (vascular brachytherapy), we were the first to report in the literature 6 cases of late ST in 100 patients having undergone brachytherapy after stent implantation.[2] At that time, this seminal observation triggered a wave of observations; the cases of late ST after brachytherapy accrued month after month until the pioneer in the field, Ron Waksman, courageously admitted in an editorial that we were "sitting on a time bomb."[3] Five years later (2004), in the beginning of the drug-eluting stent (DES) era, we reported, together with Waksman's group, the first 4 cases of late ST.[4] In the following 2 years, the incidence of late ST, scrutinized by alerted clinicians, was publicized in reports that included >25 000 patients treated with DES; the incidence ranged from 0.2% in a postmarketing surveillance trial to 1.8% in a small series of multivessel stenting.[5–10] Around this period, we realized that Bern and Rotterdam had somewhat diverging incidences of late ST, 0.4% and 0.9%, and we joined efforts to retrospectively assess the rate of late ST over a period of 4 years. A steady rate of 0.6% per year was detected without abatement over a follow-up period of 3 years.[11] What makes the experience of these 2 groups unique is that both tertiary institutions embraced the technology of eluting stents at the time of their commercial introduction and decided to treat all comers with this new promising therapeutic approach. Of 8146 patients, we saw 61 patients coming back to our catheterization laboratory with symptoms and angiographic signs of late ST. Of these 61 patients, 3 died in hospital from late ST, and 44 sustained a myocardial infarction (MI). At the 6-month follow-up, an additional 2 patients had died and 2 sustained a reinfarction. In summary, 5 of 8146 patients died as a result of this dreadful complication of ST. These numbers were largely confirmed by the 3 years of follow-up of the Arterial Revascularization Therapies Study Part II, showing a similar annual increase of definite ST of 1.7%, 0.6%, and 0.4% at 1, 2 ,and 3 years, respectively, in a population with a majority of 3-vessel treatment and with an average stented length of 73 mm. By reporting these figures, we are not trying to minimize the phenomenon, and we recognize that we are describing only the tip of the iceberg by disregarding fatal MI and unexplained death as clinical surrogates of ST, but we do not believe that 0.6% per year could, by any means, be compared with the 6% late ST seen after vascular brachytherapy. In other words, we are not facing a new "vascular brachytherapy syndrome."

Response by Camenzind et al p 1439

After this introduction on the history of ST, we will analyze more judiciously the contentions by Camenzind et al

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that DES increase deaths, as headlined by the European Society and World Congress of Cardiology (ESC) newsletter at the congress in Barcelona 2006.[12]

Are There Physiopathological Reasons to Have Late ST?

Camenzind and coauthors referred to the classic triad of Virchow (altered blood constituents, flow pattern, and endothelial lining). This is without a doubt appealing to the readers, but let us analyze critically their arguments and the validity of their analogical comparison when they equate a stenotic lesion covered by a DES to an atherothrombotic phenomenon in the general circulation.

Their first argument suggests that implantation of DES with concomitant but transient administration of dual platelet therapy would generate at the time of the discontinuation a thrombogenic milieu. Using common sense, we have to point out that ≈99% of the patients worldwide discontinue their thienopyridine medication without experiencing ST within days. We were the first to link the interruption of aspirin with ST in DES.[4] In that respect, the relationship between platelet therapy and thrombosis is not unique to DES. In a study reporting on 1236 patients hospitalized for acute coronary syndrome, those who stopped aspirin presented significantly more often with ST-segment elevation acute coronary syndrome. Twenty percent of these cases involved a bare metal stent (BMS) thrombosis on an average of 15.5 months.[13] In fact, interruption of aspirin is a risk factor for every patient with atherosclerosis.[14] "Noncompliance or withdrawal of aspirin treatment has ominous prognostic implications in subjects with or at moderate-to-high risk for coronary artery disease. Aspirin discontinuation in such patients should be advocated only when bleeding risk clearly overwhelms that of atherothrombotic events." These are the conclusions of a recently published meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50 279 patients at risk for coronary artery disease.[14] Similarly, clopidogrel withdrawal is associated with proinflammatory and prothrombotic effects in patients with diabetes mellitus and coronary artery disease.[15] The concern in trials has not been the discontinuation of the antiplatelet therapy but its premature discontinuation, and this concept of premature discontinuation has to be critically discussed.

It is relevant to note that the patients included in the FIM (First in Man) and the RAVEL (Randomized Study with the Sirolimus-Coated Bx Velocity Balloon Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions) trials were prescribed 2 months of ticlopidine or clopidogrel. The rationale for the 2-month prescription is that initially (July 1999, trial discussion at the headquarters of Cordis) the First in Man trial was planned as a 60-day safety trial with concomitant use of 60 days of ticlopidine. Later, the protocol was converted into a 4- and 6-month study with quantitative coronary angiography and intravascular ultrasound.

After completion of the European pivotal trial, the American pivotal trial, SIRIUS (Sirolimus-Eluting Stent in De Novo Native Coronary Lesions), was initiated, and for reasons unknown to the authors, the prescription of clopidogrel was prolonged to 3 months, although no thrombotic issue was observed in the RAVEL trial in the first 5 years of follow-up. The decision to prescribe 6 months of clopidogrel in the TAXUS-I trial (and in the subsequent trials) was not discussed in the original report. In other words, the duration of prescription of clopidogrel does not seem to be validated by scientific arguments; consequently, the concept of premature discontinuation is arbitrary as well. So far, there is no evidence-based medicine that prolonged dual-antiplatelet therapy could reduce late ST in DES-treated patients. Of note, one quarter of our patients with late or very late ST were on dual-antiplatelet therapy.[11] The only evidence of a preventive effect of dual-antiplatelet therapy on late ST stems from the experience with brachytherapy in which prolongation of dual-antiplatelet therapy was effective in preventing late ST, although a rebound phenomenon in ST was observed after cessation of clopidogrel. At 15 months, the incidence of thrombotic occlusion was 15.9% in the Washington Radiation for In-Stent Restenosis Trial plus 6 months of clopidogrel (WRIST-PLUS) versus 13.5% in WRIST.[12,16,17]

The postmortem findings in patients with a DES constitute dramatic and compelling evidence that stented arteries show, in a limited number of patients, impaired reendothelialization with uncovered stent struts as a consequence. However, the eminent pathologist Dr Renu Virmani is the first to admit that in postmortem studies there is no common denominator and that the number of patients treated with DES in whom "uncovered stent struts" do not lead to ST is unknown but undoubtedly very large. Still today, the relative impact of the stent platform with a variety of strut thicknesses, polymers, and drugs on ST remains unclear. In her most recent presentation, Dr Virmani demonstrated a complete endothelialization of the struts with cells exhibiting cd31 (antigen surface marker of good endothelial functionality) at 14 days in rabbit iliac arteries stented with a DES eluting everolimus, a sirolimus analog with a sole and minimal alteration of the molecular structure of sirolimus in the binding domain, without any chemical modification of the mTOR binding domain. With such a subtle difference between sirolimus and everolimus, it becomes unclear whether we have to blame the drug, the polymer, or even the platform for the difference in reendothelialization.[18]

We are aware that DES may induce complex interactions between shear stress and inhibition of neointimal growth, resulting in a peculiar rheological profile that we described early on in *Circulation*,[19] and we have attempted to differentiate delayed neointimal growth (delayed restenosis) from adaptive shear stress–induced growth, which is a long-term physiological process.[20,21]

But before discussing in more detail the impact of vessel wall remodeling on late ST, we should clarify that late

acquired malapposition and stent underexpansion are 2 different entities with different possible consequences. In the early days of BMS, Colombo et al[22] convinced the world that incorrect deployment and incomplete apposition of stents were major contributors to subacute ST. This older generation of interventional cardiologists was painstakingly educated to postdilate the stent to avoid this incomplete deployment. Today, the lesson of the past seems to have been forgotten by a new generation of interventional cardiologists who rely too much on the antirestenotic properties of DES and do not care enough for correct mechanical deployment of the "metallic endoprosthesis." In an extensive and retrospective analysis of BMS patients treated in the previous decade, stent underexpansion (minimum stent area <5.0 mm^2) was present in 20% of all restenotic lesions.[23] In a comparable but smaller analysis of DES-treated patients, stent underexpansion (using the same definition) was observed in at least 67% of all cases.[24]

Incorrect deployment with early thrombosis in (non) eluting stents will remain an actuality.[25] Although late acquired malapposition also is observed with BMS, this phenomenon has been documented more frequently in patients with DES.[26] The question remains whether late acquired malapposition has an unfavorable prognosis with respect to late ST. Hoffman et al have compiled the intravascular ultrasound studies performed in the randomized trials (RAVEL, SIRIUS and E-SIRIUS) (personal communication). Intravascular ultrasound was available in 325 patients and the incidence of incomplete stent apposition at 6 months was 25% in the SES group versus 8.3% in the BMS group. The authors were unable to demonstrate any prognostic impact of incomplete stent apposition on death (2.2% with incomplete stent apposition versus 5.2% without incomplete stent apposition) and major adverse cardiac events (8.9% with incomplete stent apposition versus 12.6% without incomplete stent apposition) in patients treated with sirolimus-eluting stents. Late ST was observed in only 1 of 45 patients with incomplete stent apposition at a 6- to 8-month follow-up. Considering the fact that the era of trials comparing BMS and DES is coming to an end, such a comparison between DES and BMS on that topic might not be obtainable in the future.

The ESC Firestorm

At the ESC Barcelona 2006, some of us were caught off guard by a plenary session combining 3 critical presentations by Edoardo Camenzind, Salim Yousouf, and Alain Nordmann. After having pooled the published data from the 4 pivotal randomized controlled trials assessing the safety and efficacy of the Cypher stent (RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS), Camenzind and colleagues disclosed a rate of total death and Q-wave MI of 6.3% in the Cypher group versus 3.9% in the control group, with a value of $P=0.03$. It did not take too long for the lay media to report with sensationalism that DES were increasing the incidence of death and Q-wave MI by 66%. However, what was overlooked is that this meta-analysis was derived from data published in the literature at different time points of follow-up. Camenzind took 2 hard clinical end points, total death and Q-wave MI, and disregarded the non–Q-wave MI incidences, which were substantially lower in the Cypher group, did not fit with the general contention, and would have ruined the statistical foundation (a probability value would not have been reached with a composite of Q- and non–Q-wave MI). The TAXUS results of the perennial competitor Boston Scientific were not questioned because a meta-analysis derived from the randomized TAXUS family trial data in the literature did not show an alarming incidence of death and Q-wave MI.

In contrast to these data, we had access to the patient-level–based data for all 4 trials (RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS) with a complete follow-up of 4 years.[26a] These data had been transferred to 2 independent academic statisticians for verification. Previously, the data management had been performed by 2 independent central research organizations located in Rotterdam and Harvard. In these trials, the clinical events had been adjudicated by independent clinical event committees, whereas the incidence of ST had been readjudicated by the Harvard Central Research Institute according to new definitions of ST (Table 1). The definitions were formulated before the ESC congress by a consortium of interventional cardiologists from both sides of the Atlantic, representatives of the Food and Drug Administration, academic central research organizations (Harvard Central Research Institute, Duke Clinical Research Institute, Cardiovascular Research Foundation, and Cardialysis), and representatives from major stent manufacturers. Two meetings held in Washington in March 2006 and in Dublin in June 2006 aimed to reach a consensus on the new standard and to promote consistency for reporting to guarantee the transparency of the data. In the past, inappropriate comparisons and conclusions were based on various definitions with the potential to bias results by choosing definitions most favorable to those conducting analyses. In contrast to the data presented by Camenzind and colleagues, the actual rate of total death and all MI at 4 years was 11.4% in the Cypher group and 10.1% in the control group, with a value of $P=0.4$. Not being "*P* valuists," we recognized that the Kaplan-Meier curves were nevertheless slightly diverging over time. Although not completely correct from a methodological point of view, Camenzind's report at the ESC became a wakeup call for everybody (the device industry, principal investigators, clinical research organizations, The European Agency for the Evaluation of Medical Products, and the US Food and Drug Administration).

Puzzled by these observations, we started looking for heterogeneity of the treatment effect and discovered that the slight excess in mortality in the total population was due exclusively to the diabetic population. In the 428 diabetic patients enrolled in the 4 pivotal randomized trials, the 3-year survival was 96% in the BMS control group and 87.8% in the

TABLE 1. Academic Research Consortium Definitions of Stent Thrombosis

Timing
Acute stent thrombosis: 0–24 h after stent implantation
Subacute stent thrombosis: >24 h–30 d after stent implantation
Late ST*: >30 d–1 y after stent implantation
Very late ST*: >1 y after stent implantation
Three categories of evidence in defining stent thrombosis
Definite stent thrombosis
Angiographic confirmation of stent thrombosis
TIMI flow grade 0 with occlusion originating in the stent or in the segment 5 mm proximal or distal to the stent region in the presence of a thrombus*
TIMI flow grade 1, 2, or 3 originating in the stent or in the segment 5 mm proximal or distal to the stent region in the presence of a thrombus* and at least one of the following criteria has been fulfilled within a 48-h time window: new onset of ischemic symptoms at rest (typical chest pain with duration >20 min), new ischemic ECG changes suggestive of acute ischemia, or typical rise and fall in cardiac biomarkers (refer to definition non–procedure-related MI
Confirmation of stent thrombosis
Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved after thrombectomy
Probable stent thrombosis
Considered to have occurred after intracoronary stenting in the following cases: any unexplained death within the first 30 d and, regardless of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause
Possible ST
Clinical definition of possible ST is considered to have occurred with any unexplained death from 30 d after intracoronary stenting until end of trial follow-up

TIMI indicates Thrombolysis In Myocardial Infarction.
*Including primary and secondary late ST; secondary late ST is an ST after a target segment revascularization.

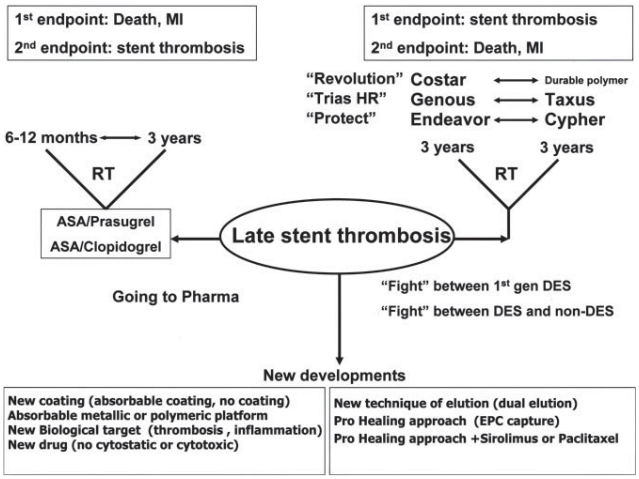
Cypher group, with a value of $P=002$. Because the nondiabetic Kaplan-Meier curves were nicely superimposed, our first reflex was to analyze the incidence of ST in these diabetic patients as a specific cause of mortality. The rate of definite or probable ST was 1.0% (2 of 195 patients) in the Cypher group versus 2.1% (5 of 233) in the control group. However, there was an imbalance between the Cypher (5.6%, 10 of 195) and control (1.7%, 4 of 233) groups in possible ST defined as any unexplained death from 30 days after the procedure. This intense scrutinizing exercise in comparing the death rate in these 428 diabetic patients boiled down to a difference of 6 unexplained deaths in the Cypher group and an excess of 3 cases of definite or probable ST in the control group, whereas the 3 categories of ST were very well balanced in the total population (Table 2).

However, a chronological analysis of the occurrence of these thromboses revealed some subtle differences in timing. In the DES group, the incidence of very late (n=23) primary ST (not a sequela of reintervention) was prominent, and the occurrence of ST after target lesion revascularization was not observed mainly because of the very low incidence of target lesion revascularization in the DES group. In the BMS group,

TABLE 2. Academic Research Consortium Definitions of ST in a Pooled Meta-Analysis of the Randomized RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS Trials

	Crude Event Rates, %		
Variables	Sirolimus-Eluting Stent (N=878 patients)	BMS (N=870 patients)	*P*
Any thrombosis by Academic Research Consortium definitions, % (n/N)	3.4 (30/878)	3.2 (28/870)	0.89
Acute ST (within 24 h)	0.0 (0/878)	0.0 (0/870)	...
Subacute ST (between 1 and 30 d)	0.5 (4/878)	0.3 (3/870)	1.00
Late ST (between 30 d and 1 y)	0.3 (3/878)	1.3 (11/870)	0.034
Very late ST (after 1 y)	2.6 (23/878)	1.6 (14/870)	0.18
Definite ST	1.1 (10/878)	0.8 (7/870)	0.63
Probable ST	0.3 (3/878)	0.9 (8/870)	0.14
Possible ST	1.9 (17/878)	1.5 (13/870)	0.58

Total population: n=1748.



Future directions of clinical trials. RT indicates randomized trials; ASA, acetylsalicylic acid; EPC, endothelial progenitor cell; and gen, generation.

9 late and 6 very late ST events were documented, of which 10 occurred after reintervention. These incidences of late ST in BMS are not uncommon and have been previously documented in the literature in >9000 patients, with rates of late ST (>30 days) ranging from 0.4% and 0.8%.[27–29]

These numbers emphasize the fact that restenosis with BMS is not just a nuisance but has potentially severe consequences. In 2006, Chen and colleagues[30] reported on the clinical presentation of 1186 consecutive episodes of in-stent restenosis in patients treated with BMS. Whereas 26.4% of the patients required hospitalization for unstable angina, an additional 9.5% presented with MI, and 0.7% died. Nayak et al[31] reported a similar 10% incidence of MI resulting from in-stent restenosis, and an additional 12% presented with a 2-fold increase in troponin. Additionally, 2 recent studies proved a close correlation between the extent of restenosis and late mortality.[32,33] In other words, by preventing 100 restenoses per 1000 patients (clinical restenosis reduced from ≈20% to 10%), DES could prevent 10 restenosis-related MIs (9.5% of 100 prevented restenosis), and we could surmise that a reduction of 10 per 1000 cases of restenosis-related MIs would be sufficient to offset an increase of 5 per 1000 in very late ST–related MIs, leading to similar late death and MI rates for DES and the BMS control.

How Do We Interpret the Data in Light of the Academic Research Consortium Definitions?

We have 3 options: there is a new problem, and the use of DES results in more (very) late thrombosis than BMS; there is no new problem, and the rate of (very) late ST after DES is similar to that of BMS; and there is a problem, and early and (very) late ST should be abolished. In the near future, we may consider 3 strategies (the Figure).

1. Pharmacological and long-term randomized trials will test the antithrombotic properties of current or novel dual-antiplatelet therapy in trials with death and MI as their primary end points and ST as their secondary end point.

2. Certain current active and passive coated stents claim to have lower rates of ST and will be compared in dedicated randomized trials with long-term follow-up with as a sole primary end point difference in ST with as secondary end point death and MI (eg, REVOLUTION, PROTECT [Prospective Reinfarction Outcomes in Thrombolytic Era Cardizem CD Trial], and TRIAS).

3. The current technology is viewed as imperfect, and the deficiencies should be amended by introducing more biocompatible absorbable coatings and new drugs with biological targets other than smooth muscle cell duplication (eg, thrombotic and inflammatory mechanisms) using dual elution of drugs or a prohealing approach such as the capture of endothelial progenitor cells with or without drug elution.

It is clear that abolishing neointimal hyperplasia is no longer the ultimate goal. Development of more biocompatible and bioabsorbable stents facilitating adequate endothelialization is expected in the near future.

Conclusions

Late ST exists in both DES and BMS. In an all-comer population, angiographic ST in DES seems to occur at a steady rate of 0.4% to 0.6% per year. Clinicians, regulators, and the device industry now realize that clinical surrogates for ST (death and MI) have to be incorporated into the long-term follow-up of the patient to capture late and very late ST patients who do not reach the catheterization laboratory to have their thrombosis angiographically confirmed. Fortunately, a first consensus on these angiographic and

clinical end-point definitions has been reached under the umbrella of the Academic Research Consortium. Retrospective analysis of ST, applying the Academic Research Consortium definitions in randomized controlled trials, does not disclose a different rate of late ST between BMS and DES up to 4 years. However, the chronology and circumstances of occurrence seem quite different. In DES, late ST occurs later than in BMS and seems to appear as primary thrombosis, whereas in BMS, a certain number of late thromboses are related to repeat interventions of the target lesion. Dedicated research is warranted to further elucidate the role of endothelial dysfunction, malapposition, and prolonged antiplatelet therapy. Currently, the second generation of DES is attempting to resolve the issues discovered so far with the first generation of DES.

Disclosures

None.

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Chapter 17

Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study

Daemen J, Wenaweser P, Tsuchida K, Abrecht L, Vaina S, Morger C, Kukreja N, Jüni P, Sianos G, Hellige G, van Domburg RT, Hess OM, Boersma E, Meier B, Windecker S, Serruys PW

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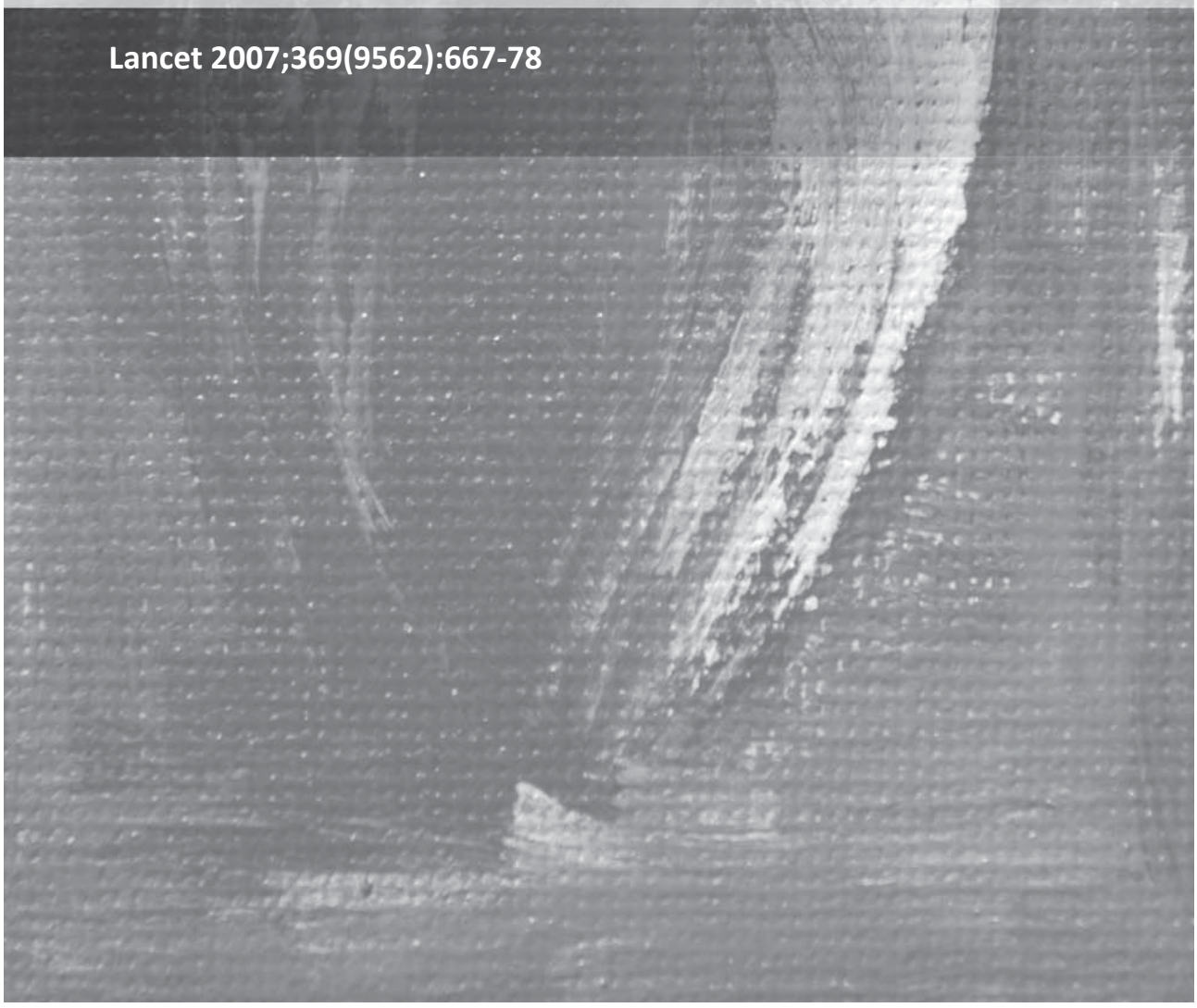

Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study

Joost Daemen, Peter Wenaweser, Keiichi Tsuchida, Linda Abrecht, Sophia Vaina, Cyrill Morger, Neville Kukreja, Peter Jüni, Georgios Sianos, Gerrit Hellige, Ron T van Domburg, Otto M Hess, Eric Boersma, Bernhard Meier, Stephan Windecker, Patrick W Serruys

Summary

Background **Stent thrombosis is a safety concern associated with use of drug-eluting stents. Little is known about occurrence of stent thrombosis more than 1 year after implantation of such stents.**

Methods **Between April, 2002, and Dec, 2005, 8146 patients underwent percutaneous coronary intervention with sirolimus-eluting stents (SES; n=3823) or paclitaxel-eluting stents (PES; n=4323) at two academic hospitals. We assessed data from this group to ascertain the incidence, time course, and correlates of stent thrombosis, and the differences between early (0–30 days) and late (>30 days) stent thrombosis and between SES and PES.**

Findings **Angiographically documented stent thrombosis occurred in 152 patients (incidence density 1·3 per 100 person-years; cumulative incidence at 3 years 2·9%). Early stent thrombosis was noted in 91 (60%) patients, and late stent thrombosis in 61 (40%) patients. Late stent thrombosis occurred steadily at a constant rate of 0·6% per year up to 3 years after stent implantation. Incidence of early stent thrombosis was similar for SES (1·1%) and PES (1·3%), but late stent thrombosis was more frequent with PES (1·8%) than with SES (1·4%; p=0·031). At the time of stent thrombosis, dual antiplatelet therapy was being taken by 87% (early) and 23% (late) of patients (p<0·0001). Independent predictors of overall stent thrombosis were acute coronary syndrome at presentation (hazard ratio 2·28, 95% CI 1·29–4·03) and diabetes (2·03, 1·07–3·83).**

Interpretation **Late stent thrombosis was encountered steadily with no evidence of diminution up to 3 years of follow-up. Early and late stent thrombosis were observed with SES and with PES. Acute coronary syndrome at presentation and diabetes were independent predictors of stent thrombosis.**

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Introduction

Drug-eluting stents significantly reduce rates of restenosis and target lesion revascularisation compared with bare metal stent. Since the publication of pivotal randomised trials on the two DES approved by the US Food and Drug Administration (polymer-based sirolimus-eluting stents [SES] and polymer-based paclitaxel-eluting stents [PES]),[1–4] these devices have been widely used in the percutaneous treatment of coronary artery disease worldwide.[5–8] However, several pre-clinical and clinical safety concerns[9–15] related to the use of drug-eluting stents have been expressed since then. One of the most important issues raised is stent thrombosis, a catastrophic, albeit infrequent, complication that results in abrupt coronary artery closure, which can lead to myocardial infarction or sudden cardiac death. This problem is not restricted to drug-eluting stents, and its incidence does not seem to exceed that seen with bare metal stents up to 1 year of follow-up.[16–22] However, case reports and observational studies have noted that some patients develop stent thrombosis unusually late after implantation of drug-eluting stents.[23–25]

To date, no large-scale study has focused on late stent thrombosis later than 1 year after drug-eluting stent implantation. Although variables such as acute coronary syndromes, bifurcation stenting, diabetes, discontinuation of antiplatelet therapy, renal failure, and stent length seem to be consistently associated with overall stent thrombosis,[19,26–28] predictors specific for late stent thrombosis have not yet been identified. We therefore assessed all angiographically documented stent thrombosis following unrestricted use of SES and PES in routine clinical practice at two academic referral hospitals between April, 2002, and December, 2005. The purposes of this investigation were to: estimate the incidence and time course of stent thrombosis with drug-eluting stents in routine clinical practice; identify predictors of stent thrombosis; identify differences between early and late stent thrombosis; and assess differences between SES and PES.

Methods

Study group and design

Between April 16, 2002, and Dec 31, 2005, a total of 8146 consecutive patients underwent percutaneous coronary intervention with SES or PES at two academic referral hospitals in the Netherlands and Switzerland. 3823 patients were treated with SES (Cypher, Cordis Corporation, Johnson and Johnson, Warren, NJ, USA) and 4323 patients with PES (TAXUS, Express2, or Liberté, Boston Scientific, Natick, MA, USA). In the Dutch

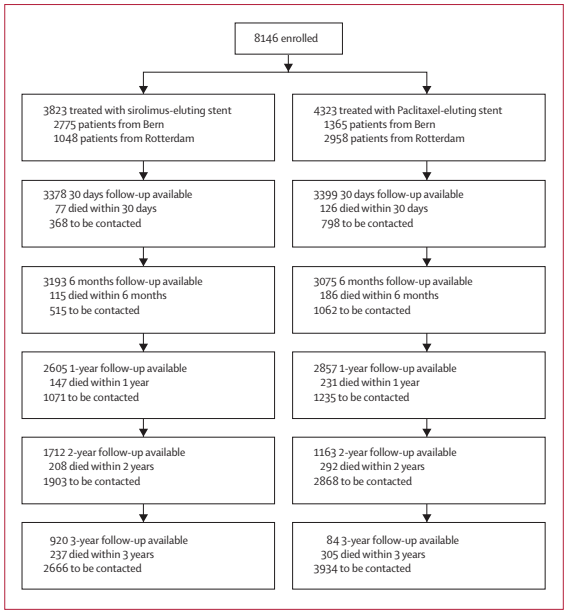

Figure 1: **Study profile**

institution, SES have been used as a default strategy for PCI as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry[7] since April, 2002. From the first quarter of 2003, PES became commercially available and replaced SES as default device for such procedures, as part of the Taxus Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registry.[5] In the Swiss institution, SES have been used since April, 2002, and PES since March, 2003. Between April, 2003, and May, 2004, a randomised trial was done to compare the devices.[6] Between June, 2004, and March, 2005, the use of SES and PES was alternated on a daily basis. Since April, 2005, the use of PES has been abandoned and SES have been used as the default device. Patients treated with both types of stents (SES and PES) in one lesion, and lesions previously treated with brachytherapy, were excluded from the study population. The study was designed during a conference between the Bern and Rotterdam investigators. Baseline clinical and angiographic variables, procedural characteristics, and endpoints of interest were identified, and a template with all variables of interest for this study was supplied to the two study sites. Data from both sites were then entered into a database, held at the Thoraxcenter, Rotterdam, The Netherlands, generating all analyses presented in this manuscript.

This study was approved by the local ethics committee at both hospitals and was done in accord with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Procedures

All interventions were done according to current practice guidelines for percutaneous coronary intervention.[29] The operator was responsible for the decision to choose a specific treatment strategy. Patients were prescribed aspirin plus clopidogrel 75 mg per day (after a loading dose of 300 mg or 600 mg) before or during baseline coronary

	Overall (n=8146)	SES (n=3823)	PES (n=4323)	p
Age (years)	62·6 (11·6)	62·5 (11·5)	62·7 (11·6)	0·31
Male	6065/8146 (75%)	2859/3823 (75%)	3206/4323 (74%)	0·53
Hypertension	3745/8144 (46%)	1965/3821 (51%)	1780/4323 (41%)	<0·0001
Family history	2279/8144 (28%)	1112/3821 (29%)	1167/4323 (27%)	0·04
Current smoking	2993/8144 (37%)	1721/3821 (45%)	1272/4323 (29%)	<0·0001
Dyslipidaemia	4079/8144 (50%)	2087/3821 (55%)	1992/4323 (46%)	<0·0001
Diabetes	1315/8144 (16%)	697/3821 (18%)	618/4323 (14%)	<0·0001
Renal failure	134/3309 (4%)	97/2253 (4%)	37/1056 (4%)	0·30
Left ventricular ejection fraction (%)	55 (12)	54 (12)	55 (11)	0·01
Acute coronary syndrome at presentation	2853/4859 (59%)	795/1481 (54%)	2058/3378 (6 1%)	<0·0001
Bifurcation treatment	781/4889 (16%)	267/1488 (18%)	514/3401 (15%)	0·01
Number of stents per patient	1·96 (1·23)	1·87 (1·13)	2·03 (1·31)	<0·0001
Total stent length per patient (mm)	35·9 (25·3)	33·6 (22·6)	37·9 (27·4)	<0·0001
Average stent diameter per patient (mm)	2·93 (1·4)	2·90 (2·1)	2·95 (0·5)	0·11
Duration of clopidogrel prescription (months)*	5·94 (3·1)	4·72 (4·0)	6·36 (2·6)	<0·0001

Data are mean (SD) or n/total with data available (%). *Based on Rotterdam cohort.

Table 1: **Clinical and procedural characteristics of study population stratified by stent type**

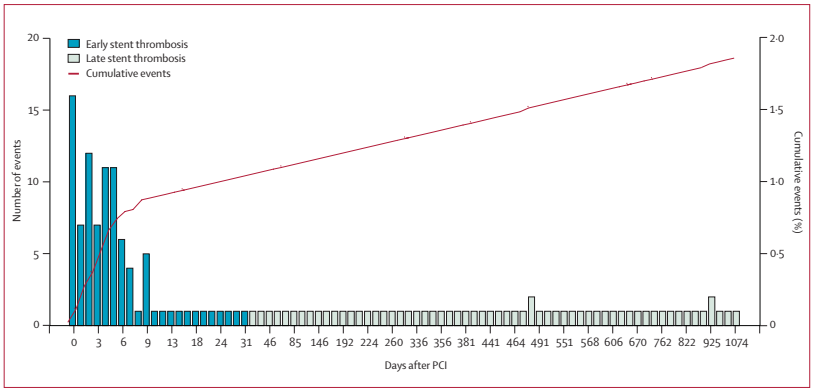

Figure 2: **Occurrence and frequency of stent thrombosis over time**

interventions. After the procedure, all patients were advised to maintain lifelong use of aspirin. In the Dutch institution, patients treated with PES were prescribed at least 6 months of clopidogrel (75 mg per day), on the basis of existing data from a randomised controlled trial.[30] For patients treated with SES, clopidogrel was prescribed for at least 3 months, unless one of the following was present, in which case clopidogrel was maintained for at least 6 months: multiple SES implantation (≥3 stents), total stent length 36 mm or longer, chronic total occlusion, and bifurcations.[5] In the Swiss institution, 12 months of clopidogrel was prescribed irrespective of the stent type used.[6] In a few patients who were on oral anticoagulation therapy, doctors recommended a shorter duration of clopidogrel (eg, 3-month triple therapy with aspirin, clopidogrel, and warfarin).

Patients were contacted according to follow-up schedules specific for each institution for the occurrence of major adverse cardiac events, including all-cause death, myocardial infarction, and repeat revascularisation. Survival data for all patients were obtained from municipal civil registries. A health questionnaire was subsequently sent to all living patients with specific questions on re-admission and major adverse cardiac events. For patients who had an adverse event at another centre, medical records or discharge summaries from other institutions were systematically reviewed. General practitioners, referring cardiologists, and patients were contacted as necessary for additional information. Data were based on a registry at two institutions entered into a database. There was no independent or external monitoring of data entry. However, data were carefully verified and adjudicated by clinicians. Mean follow-up was 1·73 years. Figure 1 shows flow of patients during various follow-up times.

Myocardial infarction was defined as increased creatine kinase by twice the upper limit of normal value and three times the upper limit of normal value of creatine kinase-MB fraction. Repeat revascularisation included target lesion revascularisation (TLR) and non-TLR, irrespective of whether the procedure was clinically or angiographically driven.

Only patients with angiographically proven stent thrombosis were included in the present study. Stent thrombosis was judged to have occurred if thrombolysis

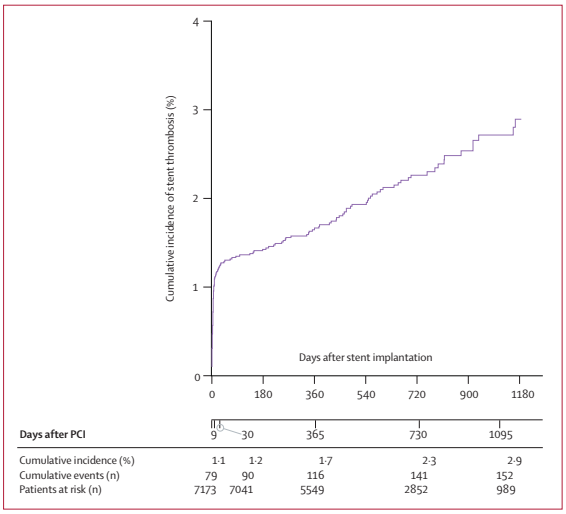

Figure 3: **Kaplan-Meier survival curve showing cumulative incidence of stent thrombosis in patients with SES or PES**

Slope of linear portion of cumulative incidence curve between 30 days and 3 years was 0·6% per year.

in myocardial infarction (TIMI) flow was grade 0 with occlusion originating in the peri-stent region, or grade 1, 2, or 3 in the presence of a thrombus originating in the peri-stent region. Angiographic evidence of thrombus was defined as a discrete, intraluminal filling defect with defined borders and separated from the vessel wall.[31] Additionally, at least one of the following criteria had to be met: acute ischaemic symptoms (typical chest pain with duration >20 min); ischaemic ECG changes (ST-segment elevation in territory of implanted stent, ST-segment depression or T-wave inversion in territory of implanted stent); typical rise and fall in cardiac biomarkers.[32]

All cases of angiographically proven stent thrombosis were reviewed independently by two experienced interventional cardiologists. In case of disagreement, a consensus was established between the two reviewers, or a third interventional cardiologist was consulted.

Stent thrombosis was categorised dependant on the timing of emergence into early (within 30 days) and late (>30 days).

Risk factors and co-morbidities in each patient were determined as classified by the treating physicians. Acute coronary syndrome was defined as the group of clinical symptoms, electrocardiographic changes, and elevation of cardiac biomarkers that is compatible with acute myocardial ischaemia and encompasses an acute myocardial infarction (ST-segment elevation and non-ST segment elevation myocardial infarction) as well as unstable angina.[32] Hypertension was defined as blood pressure of 140 mm Hg or greater systolic or 90 mm Hg or greater diastolic, or current use of antihypertensive treatment. Dyslipidaemia was classified as a concentration of cholesterol in serum of 6·2 mmol/L or greater, or the use of lipid-lowering drugs.

Angiographic success was defined as: achievement of 30% or less residual diameter stenosis within the stented segment by visual assessment; no evidence of residual dissection; no evidence of thrombus; and achievement of final TIMI flow grade 3. For the quantitative angiographic analysis, in-segment analysis was defined as the stented segment plus the adjacent proximal and distal 5-mm peri-stent regions. Premature discontinuation of antiplatelet therapy was characterised as cessation of either aspirin or clopidogrel before the end of the recommended duration of prescription.

	ST (n=152)	No ST (n=7994)	p
Age (years)	60·3 (12·0)	62·5 (11·5)	0·01
Male	115/152 (76%)	5950/7994 (74%)	0·78
Hypertension	63/152 (41%)	3682/7992 (46%)	0·29
Family history	44/152 (29%)	2235/7992 (28%)	0·79
Current smoking	57/152 (38%)	2936/7992 (37%)	0·87
Dyslipidaemia	74/152 (49%)	4005/7992 (50%)	0·74
Diabetes	29/152 (19%)	1286/7992 (16%)	0·32
Renal failure	9/152 (6%)	132/3242 (4%)	1·00
Left ventricular ejection fraction (%)	52 (12)	55 (12)	0·07
Acute coronary syndrome at presentation	67/95 (71%)	2786/4764 (59%)	0·02
Bifurcation treatment	27/96 (28%)	754/4793 (16%)	0·003
Number of stents per patient	2·35 (1·73)	1·95 (1·22)	<0·0001
Total stent length per patient (mm)	42·3 (34·0)	35·8 (25·1)	0·002
Average stent diameter per patient (mm)	2·83 (0·35)	2·93 (1·44)	0·48

Data are mean (SD) or n/total with data available (%). ST=stent thrombosis.

Table 2: **Comparison of clinical and procedural characteristics between patients with and without stent thrombosis**

	Hazard ratio (95% CI)			
	Bern		Rotterdam	
	Univariate	Multivariate	Univariate	Multivariate
Overall stent thrombosis				
Age	0·99 (0·97–1·00)	0·98 (0·96–1·01)	0·98 (0·96–1·00)	0·97 (0·95–1·00)
Male sex	1·06 (0·63–1·79)	1·32 (0·65–2·66)	1·05 (0·62–1·75)	0·90 (0·51–1·58)
Family history	0·74 (0·44–1·25)	0·67 (0·35–1·28)	1·25 (0·77–2·02)	1·23 (0·74–2·15)
Diabetes	1·04 (0·58–1·85)	1·30 (0·67–2·51)	1·43 (0·81–2·53)	2·03 (1·07–3·83)
Hypertension	0·83 (0·54–1·30)	0·78 (0·45–1·34)	0·72 (0·44–1·19)	0·68 (0·38–1·21)
Smoking	1·05 (0·67–1·63)	0·87 (0·50–1·51)	0·89 (0·51–1·55)	0·78 (0·43–1·44)
Dyslipidaemia	0·77 (0·50–1·20)	0·76 (0·44–1·30)	0·93 (0·58–1·47)	1·07 (0·63–1·82)
Left ventricular ejection fraction	0·98 (0·96–0·99)	*	‡	‡
Renal failure†	1·00 (0·24–4·10)	0·96 (0·23–3·99)	‡	‡
Acute coronary syndrome at presentation	‡	‡	1·80 (1·07–3·05)	2·28 (1·29–4·03)
Bifurcation treatment	‡	‡	1·87 (1·04–3·37)	1·47 (0·79 -2·72)
Paclitaxel-eluting stents	1·26 (0·80–1·97)	1·25 (0·73–2·12)	1·47 (0·86–2·51)	1·38 (0·79–2·44)
Number of stents per patient	1·21 (0·97–1·51)	1·11 (0·74–1·67)	1·27 (1·12–1·43)	1·27 (0·98–1·64)
Total stent length per patient	1·01 (1·00–1·02)	1·01 (0·98–1·03)	1·01 (1·01–1·02)	1·00 (0·99–1·01)
Average stent diameter per patient	0·64 (0·26–1·60)	‡	0·70 (0·46–1·07)	0·72 (0·42–1·22)
Absence of clopidogrel	‡	‡	0·59 (0·77–4·48)	0·77 (0·09–6·24)

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Early stent thrombosis				
Age	1·01 (0·98–1·04)	1·00 (0·97–1·04)	0·98 (0·96–1·01)	0·96 (0·94–0·99)
Male sex	1·02 (0·50–2·08)	1·04 (0·44–2·49)	0·82 (0·45–1·52)	0·70 (0·35–1·39)
Family history	0·50 (0·22–1·12)	0·41 (0·14–1·18)	0·94 (0·50–1·78)	0·83 (0·40–1·70)
Diabetes	1·43 (0·70–2·90)	2·03 (0·91–4·52)	1·94 (1·01–3·73)	2·29 (1·07–4·90)
Hypertension	0·51 (0·28–0·94)	0·40 (0·19–0·86)	0·97 (0·54–1·76)	0·80 (0·39–1·63)
Smoking	0·76 (0·41–1·38)	0·85 (0·41–1·78)	0·40 (0·16–1·01)	0·37 (0·14–0·97)
Dyslipidaemia	0·68 (0·37–1·24)	0·82 (0·39–1·68)	1·03 (0·59–1·82)	1·29 (0·66–2·56)
Left ventricular ejection fraction	0·98 (0·95–1·00)	*	‡	‡
Renal failure†	1·64 (0·39–6·82)	1·23 (0·29–5·28)	‡	‡
Acute coronary syndrome at presentation	‡	‡	1·64 (0·86–3·14)	2·29 (1·16–4·52)
Bifurcation treatment	‡	‡	3·17 (1·66–6·05)	2·52 (1·26–5·02)
Paclitaxel-eluting stents	1·11 (0·60–2·05)	1·28 (0·63–2·59)	0·93 (0·49–1·76)	0·86 (0·44–1·71)
Number of stents per patient	1·32 (1·00–1·74)	1·39 (0·85–2·26)	1·34 (1·17–1·55)	1·18 (0·85–1·63)
Total stent length per patient	1·01 (1·00–1·03)	1·00 (0·98–1·03)	1·02 (1·01–1·02)	1·01 (0·99–1·02)
Average stent diameter per patient	0·63 (0·20–1·95)	‡	0·70 (0·45–1·11)	0·66 (0·35–1·24)
Absence of clopidogrel	‡	‡	¶	*
Late stent thrombosis				
Age	0·96 (0·94–0·99)	0·96 (0·92–0·99)	0·97 (0·94–1·01)	0·99 (0·95–1·03)
Male sex	1·11 (0·50–2·43)	1·93 (0·56–6·63)	1·93 (0·66–5·63)	1·52 (0·51–4·56)
Family history	1·06 (0·51–2·15)	1·04 (0·45–2·43)	2·07 (0·95–4·55)	2·40 (1·03–5·58)
Diabetes	0·61 (0·22–1·73)	0·67 (0·20–2·27)	0·69 (0·20–2·30)	1·22 (0·34–4·34)
Hypertension	1·53 (0·77–3·06)	1·75 (0·75–4·09)	0·36 (0·14–0·98)	0·43 (0·15–1·24)
Smoking	1·52 (0·78–2·97)	0·92 (0·40–2·11)	2·13 (0·97–4·70)	1·70 (0·70–4·11)
Dyslipidaemia	0·88 (0·46–1·70)	0·72 (0·32–1·62)	0·80 (0·37–1·76)	0·89 (0·37–2·04)
Left ventricular ejection fraction	0·98 (0·96–1·01)	*	‡	‡
Renal failure†	..	..	‡	‡
Acute coronary syndrome at presentation	‡	‡	2·34 (0·94–5·87)	2·46 (0·87–7·00)
Bifurcation treatment	‡	‡	0·31 (0·04–2·30)	0·22 (0·03–1·72)
Paclitaxel-eluting stents	1·39 (0·72–2·70)	1·21 (0·54–2·75)	2·43 (0·96–6·17)	2·36 (0·92–6·04)
Number of stents per patient	1·07 (0·75–1·54)	0·73 (0·35–1·56)	1·14 (0·90–1·45)	1·57 (1·00–2·46)
Total stent length per patient	1·00 (0·99–1·02)	1·01 (0·98–1·05)	1·00 (0·99–1·01)	0·99 (0·96–1·01)
Average stent diameter per patient	0·63 (0·13–3·00)	‡	0·85 (0·33–2·15)	0·82 (0·33–2·06)
Absence of clopidogrel	‡	‡	0·74 (0·07–7·42)	1·03 (0·08–13·03)

*Not used for multivariate analysis because of colinearity problems. †Defined as creatinine >150 µmol/L. ‡Not used in analysis, <75% of variables available. ¶Could not be estimated.

Table 3: **Univariate and multivariate Cox proportional hazards analysis**

A creatinine value of 150 µmol per L or chronic haemodialysis qualified for the definition of renal impairment.

Statistical analysis

Continuous variables are described as mean and SD or median values with IQR. Dichotomous variables are described as counts and percentages. Continuous variables were compared between SES and PES and between early and late thrombosis with Student's *t* test (for parametric variables) or Mann-Whitney U test (for non-parametric variables) as appropriate in terms of the clinical, angiographic, and procedural demographics.

The incidence of stent thrombosis was calculated as incidence density and as cumulative incidence. Incidence density was defined as the number of patients with stent thrombosis divided by the total number of patient-years, and expressed as a number per 100 patient-years of observation.[33,34] Cumulative incidence was estimated by the Kaplan Meier method and differences were assessed with the log-rank test. A Cox proportional hazards model was used to identify independent predictors of stent thrombosis, with these variables: age, sex, family history of cardiovascular disease, diabetes, hypertension, current smoking, dyslipidaemia, renal impairment, left ventricular ejection fraction, acute coronary syndrome at presentation, stent type (SES or PES), number of stents, total stent length, average stent diameter, bifurcation treatment, and prescribed duration of clopidogrel. Data

on acute coronary syndrome, bifurcation treatment, and average stent diameter in the Bern cohort, and on left ventricular ejection fraction and renal impairment in the Rotterdam cohort, were available in less than 75% of the patients; therefore, we stratified univariate and multivariate Cox regression analysis by centre. Statistical analyses were done with SPSS 12.0.1 for Windows. All p values were two-sided and values less than 0·05 were judged statistically significant.

Role of the funding source

There was no industry involvement in the study design, data collection, data analysis, or writing of the report. The study was supported by research grants from the two institutions; data from both institutions were entered into a common database held at the Thoraxcenter, Rotterdam, the Netherlands. As principal investigators, PWS and SW had full access to the data and take final responsibility for the data as presented in the manuscript.

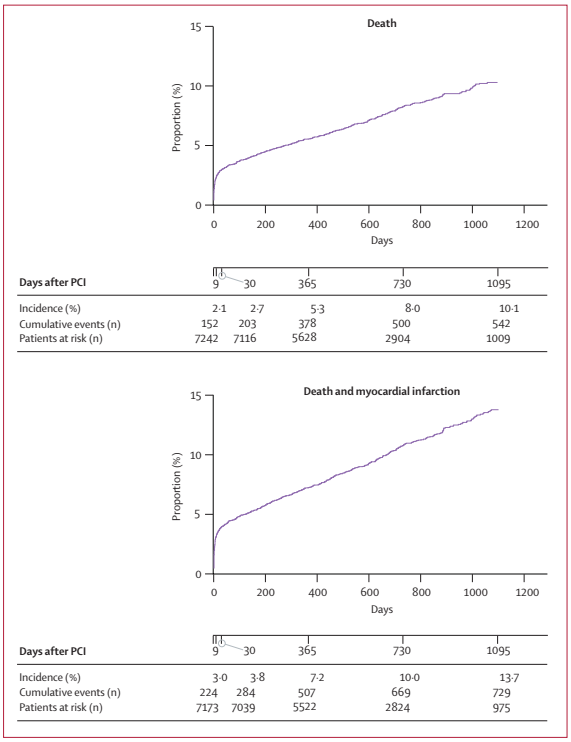

Figure 4: **Kaplan Meier survival curves showing (A) all-cause mortality and (B) all-cause mortality or myocardial infarction in overall population**

	Overall ST (n=152)	Early ST (n=91)	Late ST (n=61)	p
PCI for stent thrombosis	148 (97%)	87 (96%)	61 (100%)	0·51
Additional stenting	59 (39%)	30 (33%)	29 (48%)	0·13
Adjunctive thrombolysis	9 (6%)	5 (6%)	4 (7%)	0·83
Adjunctive thrombectomy	18 (12%)	11 (12%)	7 (12%)	9·85
In-hospital outcome				
Death	11 (7%)	8 (9%)	3 (5%)	0·53
Periprocedural myocardial infarction*	106 (70%)	62 (68%)	44 (72%)	0·99
Reinfarction	2 (1%)	1 (1%)	1 (2%)	0·77
Repeat revascularisation	5 (3%)	3 (3%)	2 (3%)	0·97
Emergency bypass surgery	3 (2%)	2 (2%)	1 (2%)	1·00
Recurrent stent thrombosis	2 (1%)	1 (1%)	1 (2%)	0·77
30-day outcome				
Death	13 (9%)	9 (10%)	4 (7%)	0·40
Reinfarction	3 (2%)	2 (2%)	1 (2%)	1·00
Repeat revascularisation	7 (5%)	4 (4%)	3 (5%)	1·00
Recurrent stent thrombosis	3 (2%)	2 (2%)	1 (2%)	1·00
6-month outcome				
Death	17 (11%)	12 (13%)	5 (8·2%)	0·24
Reinfarction	3 (2%)	2 (2%)	1 (1·6%)	1·00
Repeat revascularisation	10 (7%)	5 (6%)	5 (8·2%)	0·52
Recurrent stent thrombosis	3 (2%)	2 (2%)	1 (1·6%)	1·00
Hierarchical MACE†	117 (76%)	70 (77%)	47 (75·4%)	0·99

PCI=percutaneous coronary intervention. ST=stent thrombosis. MACE=major adverse cardiac events (defined as the composite of death, periprocedural myocardial infarction, reinfarction, and repeat revascularisation). *Myocardial infarction due to stent thrombosis. †Including periprocedural myocardial infarction due to stent thrombosis.

Table 4: **Periprocedural and postprocedural clinical outcomes of patients with stent thrombosis**

Results

Between April, 2002, and December, 2005, 8146 patients underwent percutaneous coronary intervention with SES (3823 patients) or PES (4323 patients) at the two academic hospitals. Table 1 summarises clinical and procedural characteristics of the overall study population. Compared with patients treated with PES, those who received SES were more likely to have hypertension, a family history of coronary heart disease, dyslipidaemia, and diabetes, and were more frequently smokers. Left ventricular ejection fraction was somewhat lower in the SES group than in the PES group. By contrast, patients treated with PES presented more often with an acute coronary syndrome, and received more and longer stents than SES patients.

Angiographically proven stent thrombosis was recorded in 152 of 8146 patients at a median of 9 days (IQR 3–342) after DES implantation during a follow-up period of more than 3 years (mean 1·73 years, SD 0·99). The incidence density of stent thrombosis was 1·3 per 100 person-years. Stent thrombosis occurred early (at 0–30

days) in 91 of 152 (60%) patients, and late (after 30 days) in 61 of 152 (40%) patients. The cumulative incidence of early ST was 1·1% (91 events), whereas late ST occurred at a rate of 0·6 per 100 person-years of observation (61 events). The median time to occurrence of early stent thrombosis was 4 days (IQR 1–6). Of the 61 late ST cases, 36 (59%) patients developed stent thrombosis 1 year or later after stent implantation (median 451 days; IQR 211–665; figure 2). The cumulative incidence of stent thrombosis over time showed an initial steep rise with 50% of cases occurring within 9 days, followed by an almost linear increase in the remaining events up to 3 years. The cumulative incidence of stent thrombosis was 1·2% at 30 days, 1·7% at 1 year, 2·3% at 2 years, and 2·9% at 3 years. The slope of the linear portion of the cumulative incidence curve between 30 days and 3 years was 0·6% per year (figure 3).

Patients with stent thrombosis were younger, presented more often with an acute coronary syndrome, and were treated more frequently for bifurcation lesions, compared with those without stent thrombosis (table 2). The number of stents and total stent length were greater in patients with stent thrombosis than in those without (table 2).

Table 3 summarises the results of Cox proportional hazards analysis. In the Bern group, no independent predictors of overall stent thrombosis emerged. Hypertension was the only independent predictor of early stent thrombosis, and age was the only independent predictor of late stent thrombosis. In the Rotterdam group, acute coronary syndrome at presentation and diabetes were independent predictors of overall stent thrombosis. Age, hypertension, smoking, acute coronary syndrome at presentation, and bifurcation treatment were independently associated with early stent thrombosis. Family history of coronary heart disease was an independent predictor of late stent thrombosis in the Rotterdam group. Absence of clopidogrel treatment did not seem to be associated with an increased risk of total and late stent thrombosis.

In the overall group (n=8146), 3-year cumulative incidences were 10·3% for all-cause mortality, 13·7% for death or myocardial infarction (figure 4), 4·1% for myocardial infarction, 11·7% for target vessel revascularisation, and 22·3% for major adverse cardiac events (ie, death, periprocedural myocardial infarction, reinfarction, and repeat revascularisation). Percutaneous coronary intervention was the initial treatment strategy in almost all patients who developed stent thrombosis (table 4). The majority of patients who presented with stent thrombosis developed myocardial infarction. Notably, recurrent stent thrombosis in two patients and multiple stent thromboses in a different vessel in another patient caused three reinfarctions within 6 months after treatment of stent thrombosis. We noted no differences in clinical outcome between patients with early and late stent thrombosis.

Table 5 shows baseline clinical, angiographic, and procedural characteristics stratified for early or late stent thrombosis. Compared with patients who had late stent thrombosis, patients with early stent thrombosis were slightly younger, more frequently diabetic, less frequently smokers, and had more bifurcation lesions treated, smaller reference vessel diameter, smaller final minimum luminal diameter, and a higher residual diameter stenosis.

Clinical, procedural, and angiographic characteristics of the 152 patients with stent thrombosis are shown in table 6, along with the comparison between SES and PES. More than 70% of stent thrombosis cases occurred in patients who underwent the index percutaneous coronary intervention in the context of acute coronary syndromes. Patients' characteristics, apart from sex and hypertension, were similar for both stent types. The groups were also similar in terms of time course (table 6), 3-year cumulative incidence of total stent thrombosis (SES 2·5%, PES 3·2%, p=0·07; figure 5), and cumulative incidence of early stent thrombosis (SES 1·1%, PES 1·3%, p=0·49). Late stent thrombosis, however, occurred later in the SES group than in the PES group (table 6) and cumulative incidence at 3 years was significantly higher in the PES group (1·9%) than in the SES group (1·4%; p=0.031).

Of patients who had early stent thrombosis, 79 (87%) were on dual antiplatelet therapy, eight (9%) were on a

	Early ST	Late ST	p
Baseline clinical characteristics			
n	91	61	
Age (years)	61·9 (11·7)	58·0 (12·2)	0·05
Male sex	66/91 (73%)	49/61 (80%)	0·34
Clinical presentation			
Stable angina	28/91 (31%)	15/61 (25%)	
Acute myocardial infarction	41/91 (45%)	28/61 (50%)	1·00
Unstable angina	22/91 (24%)	18/61 (30%)	0·57
Cardiogenic shock	8 (9%)	5 (8%)	1·00
Hypertension	35/91 (39%)	28/61 (46%)	0·40
Family history	20/91 (22%)	24/61 (39%)	0·03
Current smoking	25/91 (28%)	32/61 (53%)	0·002
Dyslipidaemia	41/91 (45%)	33/61 (54%)	0·32
Diabetes	25/91 (28%)	5/61 (8%)	0·003
Non-insulin-dependent	18/91 (20%)	4/61 (7%)	0·03
Insulin-dependent	7/91 (7%)	1/61 (2%)	0·15
Renal insufficiency	8/91 (9%)	1/61 (2%)	0·09
Multivessel disease	55/91 (60%)	33/61 (54%)	0·50
Multivessel stenting	31/91 (34%)	17/61 (28%)	0·48
Left ventricular ejection fraction (%)	51 (12)	53 (12)	0·41
Number of stents per patient	2·52 (1·85)	2·08 (1·51)	0·12
Total stent length per patient (mm)	46·4 (37·5)	36·1 (27·2)	0·07
Average stent diameter per patient (mm)	2·82 (0·37)	2·85 (0·32)	0·72
Timing of ST (days)			
Mean (SD)	5·5 (6·5)	459·4 (274·7)	..
Median (IQR)	4·0 (1–6)	442·0 (235–652)	..

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Lesion and procedural characteristics

n*	98	63	
Pre-procedure			
Treated vessel			
Left main coronary artery	0/98 (0%)	1/63 (2%)	..
Left anterior descending artery	53/98 (54%)	34/63 (54%)	0·989
Left circumflex artery	19/98 (19%)	6/63 (10%)	0·092
Right coronary artery	26/98 (27%)	21/63 (33%)	0·378
Saphenous vein graft	0	1 (2%)	..
ACC/AHA lesion class B2/C	81/89 (91%)	51/63 (81%)	0·089
Bifurcation lesions	34/95 (36%)	8/63 (13%)	0·002
Diameter stenosis (%)	81 (17)	82 (19)	0·740
Lesion length (mm)	20·11 (13·36)	20·30 (13·83)	0·940
MLD (mm)	0·49 (0·41)	0·55 (0·57)	0·465
MLD, excluded total occlusion (mm)	0·68 (0·33)	0·77 (0·53)	0·332
RVD (mm)	2·70 (0·53)	2·87 (0·43)	0·041
Periprocedure or postprocedure			
Number of stents per lesion	1·59 (0·87)	1·63 (1·04)	0·746
Average stent diameter per lesion (mm)	2·95 (0·32)	2·94 (0·29)	0·902
Total stent length per lesion (mm)	32·39 (23·05)	31·08 (23·11)	0·729
Maximum balloon inflation pressure (atm)	16·9 (3·7)	16·2 (3·7)	0·250
Periprocedural bolus heparin (units)	7·4 (3·5)	7·3 (2·9)	0·753
In-stent diameter stenosis (%)	14 (14)	10 (8)	0·046
In-stent MLD (mm)	2·39 (0·52)	2·58 (0·40)	0·024
In-segment diameter stenosis (%)	18 (12)	13 (10)	0·030
In-segment MLD (mm)	2·14 (0·51)	2·38 (0·45)	0·006
Ratio of SES to PES	0·8 (43:55)	0·8 (27:36)	0·899
Direct stenting	29/98 (30%)	17/63 (27%)	0·653
Stent overlap	41/98 (42%)	24/63 (38%)	0·392
Use of glycoprotein IIb/IIIa inhibitors	38/98 (39%)	19/63 (30%)	0·218

Data are mean (SD) or n/total with data available (%), unless otherwise specified. MLD=minimum lumen diameter. PCI=percutaneous coronary intervention. RVD=reference vessel diameter. ACC/AHA=American College of Cardiology/American Heart Association. *Multiple lesions in the same patient counted separately.

Table 5: **Clinical, procedural, and angiographic characteristics for patients with early and late stent thrombosis (ST)**

single antiplatelet drug, and four (4%) were not on antiplatelet therapy. By contrast, late stent thrombosis occurred during dual antiplatelet therapy in 14 (23%) patients, during single-drug therapy in 31 (51%), and in 16 (26%) who were not on antiplatelet therapy (p<0·0001 for the comparison of early *vs* late). Stent thrombosis occurred late in 31 patients on aspirin monotherapy, and 97% (30 of 31) experienced the event after the recommended prescription period of clopidogrel had ended. 23 patients prematurely discontinued one or both of the two antiplatelet drugs (seven of 91 early, 16 of 61 late, p=0·008). The reasons for premature discontinuation were poor compliance in 11 patients (48%), surgery in 7 (30%), bleeding in four (17%), and allergy in one (4%).

Discussion

Our findings from a large cohort of patients with stent thrombosis after implantation of drug-eluting stents add to the evidence about late stent thrombosis[23–28,35] with the following observations: stent thrombosis occurred with an incidence density of 1·3 per 100 person-years and a cumulative incidence of 2·9% at 3 years; the incidence of late stent thrombosis did not diminish, but continued at a steady rate of 0·6% per year during the first 3 years; acute coronary syndrome at presentation and diabetes were independent predictors of overall stent thrombosis; and early and late stent thrombosis occurred with both types of drug-eluting stent, but late stent thrombosis was more frequently observed with PES than with SES.

The principal aim of this study was to assess the incidence of stent thrombosis during a follow-up period of up to 3 years in a large group of patients treated with the unrestricted use of drug-eluting stents. Previous data on stent thrombosis after drug-eluting stent implantation were derived from randomised trials and registries, in which low rates of events were reported and early stent thrombosis seemed to occur with similar frequency in drug-eluting and bare metal stents.[17,19–22,36] Similarly, a recent meta-analysis reported similar event rates for drug-eluting and bare metal stents up to 1 year of follow-up.[18] The incidence of early stent thrombosis (1·2%) and the median time to stent thrombosis (9 days) in the present study were similar to rates previously reported in patients treated with bare metal stents.[16,35]

Of more interest are adverse events during long-term follow-up and the occurrence of late stent thrombosis encountered with drug-eluting stents. Late stent thrombosis has also been shown in the long-term follow-up results of early trials comparing SES and PES with bare metal stents. A pooled analysis of RAVEL, SIRIUS, C-SIRIUS, and E-SIRIUS revealed five cases of late stent thrombosis between 1 year and 4 years of follow-up with SES, but no such case with bare metal stents (survival free from stent thrombosis at 3 years: 98·8% *vs* 99·4%, p=0·20).[17] Similarly, a pooled analysis of TAXUS II, IV, V, and VI showed eight cases of late stent thrombosis between 9 months and 3 years with PES and only one case with bare metal stents (survival free from stent thrombosis at 3 years 98·7% *vs* 99·2%, p=0·36).[22] However, concerns have been raised as to whether these data are truly applicable to everyday clinical practice, because of the small number of patients, and the exclusion of acute coronary syndromes and complex lesions in randomised controlled trials. The complexity of the present population is reflected in the high mortality rates. The cumulative incidence of all-cause mortality was 10·3% in the present study, which is higher than the mortality rates reported in previous studies. However, the results of the present study suggest that late stent thrombosis with drug-eluting stents occurs more frequently than expected[19–22,36] and that rates increase steadily during long-term follow-up. The sustained occurrence over a long-term period might be explained in part by the delayed healing response after implantation of drug-eluting stents, as indicated by delayed re-

	Overall (n=152)	SES (n=69)	PES (n=83)	p
Age (years)	60·3 (12·0)	61·3 (13·4)	59·5 (10·8)	0·37
Male sex	115/152 (76%)	46/69 (67%)	69/83 (83%)	0·02
Hypertension	63/152 (41%)	40/69 (58%)	23/83 (28%)	<0·0001
Family history	44/152 (29%)	23/69 (33%)	21/83 (25%)	0·29
Current smoking	57/152 (38%)	27/69 (39%)	30/83 (36%)	0·74
Dyslipidaemia	74/152 (49%)	33/69 (48%)	41/83 (49%)	0·87
Diabetes	29/152 (19%)	16/69 (23%)	13/83 (16%)	0·30
Renal insufficiency	9/143 (6%)	6/68 (9%)	3/84 (4%)	0·30
Left ventricular ejection fraction (%)	52 (12)	53 (12)	51 (13)	0·61
Acute coronary syndrome at presentation	67/95 (71%)	24/35 (69%)	43/60 (72%)	0·82
Multivessel disease	88/149 (59%)	42/65 (65%)	45/83 (54%)	0·24
Bifurcation treatment	27/96 (28%)	9/36 (25%)	18/60 (30%)	0·65
Timing of early ST (days)				
Mean (SD)	5·5 (6·5)	5·9 (6·3)	5·1 (6·4)	0·58
Median (IQR)	4·0 (1–6)	4·0 (2–8)	4·0 (1–5)	
Timing of late ST (days)				
Mean (SD)	459·4 (274·7)	564·8 (310·1)	375·7 (212·5)	0·007
Median (IQR)	442·0 (235–652)	585 (381–801)	343·5 (214–509)	
Recommended duration of clopidogrel (months)				
Mean (SD)	7·9 (3·5)	8·1 (4·1)	7·9 (3·1)	0·84
Median (IQR)	6·0 (6·0–12·0)	6·5 (3·8–12·0)	6·0 (6·0–12·0)	
Number of stents per patient	2·35 (1·73)	2·20 (1·64)	2·47 (1·80)	0·35
Average stent diameter per patient (mm)	2·83 (0·35)	2·75 (0·28)	2·89 (0·39)	0·051
Total stent length per patient (mm)	42·3 (34·0)	38·5 (28·0)	45·5 (38·2)	0·22

Data are mean (SD) or n/total with data available (%), unless otherwise specified.

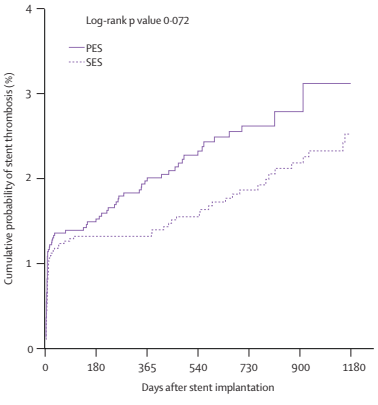
***Table 6*: Clinical, procedural, and angiographic characteristics of patients with stent thrombosis (ST) overall and by type of stent**

endothelialisation[38] and hypersensitivity reactions to the antiproliferative drugs or, more probably, to the synthetic polymers.[12,13]

Stent thrombosis is a multifactorial occurrence that has been attributed to a range of angiographic, lesion-related and vessel-related, technical and clinical factors.[39] Acute coronary syndrome, bifurcation treatment, diabetes and premature discontinuation of anti-platelet therapy were the strongest predictors of overall ST in several previous studies.[19,26–28,40] The present study confirms the predictive value of diabetes and acute coronary syndrome at presentation.

Several clinical risk factors were predictive for development of early stent thrombosis. The increased risk in diabetic patients might be related to the more diffuse and aggressive nature of atherosclerosis, accompanied by longer lesion lengths, smaller vessel size, and greater plaque burden, which might incur less optimal procedural results.[41–44] Additionally, the detrimental effects of smoking on endothelial function[45,46] and the long-term impairment of peri-stent vasoreactivity after drug-eluting stent implantation[14,15] are well known. However, the fact that smoking was independently associated with lower rates of early stent thrombosis might be related to the high number of patients with acute coronary syndrome in the present population. Smokers are likely to stop smoking immediately after such an event, which might remove from their risk-factor profile one of the major determinants of atherosclerosis.[47,48] The fact that the use or implementation of an antihypertensive treatment at the time of percutaneous coronary intervention was sufficient to qualify patients as hypertensive might have resulted in the so-called protective predictive value of hypertension for early stent thrombosis and the trend towards a lower risk for late stent thrombosis. However, overall, late stent thrombosis seemed difficult to predict and its cause remains largely unknown.

Although the cumulative incidence of overall and early stent thrombosis was similar for the two types of drug-eluting stent, late stent thrombosis occurred more frequently in patients treated with PES than in those treated with SES during the 3-year observation period. Up to 90% of paclitaxel remains indefinitely sequestered within the polymer, while 10% of the drug is released in a bimodal manner during a 2-week period. In contrast, sirolimus is completely released from the polymer and slowly elutes over a 90-day period. Whether the differences in drug-release kinetics,[49] distribution within the vessel wall, mechanisms of action,[50] or design of the stent platforms[51] affect the incidence and time course of late stent thrombosis remains unclear. PES were implanted in more complex lesions in this study group,



Days after PCI	9	30	365	730	1095
Incidence, SES (%)	1·0	1·1	1·3	1·9	2·5
Cumulative events (n)	36	41	47	60	69
Patients at risk (n)	3535	3508	2671	1710	903
Incidence, PES (%)	1·2	1·3	2·0	2·7	3·2
Cumulative events (n)	43	49	69	81	83
Patients at risk (n)	3626	3493	2667	1131	68

Figure 5: **Kaplan Meier survival curves showing cumulative incidence of stent thrombosis stratified by type of drug-eluting stent**

whereas SES had been used from an earlier time than had PES, and subsequently the length of follow-up differed between the two devices. Only randomised clinical trials will be able to fairly address potential differences in safety between the two stent types.

In this study, 30 of 31 patients who had late stent thrombosis while on single antiplatelet therapy received lifelong aspirin. Although absence of clopidogrel was not associated with a higher risk of stent thrombosis, 80% of patients with late stent thrombosis developed the problem after completion of the recommended duration of clopidogrel treatment. The question of whether extended or indefinite adjunctive clopidogrel treatment, if well tolerated, might be considered for patients who undergo drug-eluting stent implantation remains open. The effect of antiplatelet treatment on the pathophysiology of stent thrombosis is well established. Platelet aggregation studies have shown that an impaired response to antiplatelet treatment[52] and high post-treatment platelet reactivity[53] are associated with stent thrombosis. Furthermore, late stent thrombosis after cessation of clopidogrel has been reported in several studies.[23,25–27,35] In particular, the withdrawal of antiplatelet treatment in patients undergoing non-cardiac procedures seems problematic, because perioperative stress enhances platelet aggregation and thus the risk of thrombotic stent occlusion.[23,54] In this study, seven patients (one early; six late) discontinued both aspirin and clopidogrel before elective dental work or non-cardiac surgery. However, further evidence of the limited ability of clopidogrel to prevent all stent thrombosis is provided in our study, in which 13 of 61 of patients had late stent thrombosis despite dual antiplatelet therapy with aspirin and clopidogrel. Despite the longer duration of clopidogrel prescription (12 months) in the patients from Bern compared with those in Rotterdam (6 months), the incidence of both early and late stent thrombosis was similar in both centres. Additionally, the increased risk of bleeding complications and the economic burden imposed by long-term clopidogrel administration must be carefully weighed in light of these findings.

Effective antiplatelet treatment has a key role in the prevention of stent thrombosis and randomised controlled trials should be appropriately designed to prospectively address the following questions: which drugs are essential and for how long, what is the role of platelet function tests in patients undergoing drug-eluting stent implantation, and what are the therapeutic consequences?

Our study has several limitations. First, this was a non-randomised cohort study, with the decision about stent type and antiplatelet therapy largely determined by local institutional practice. The main purpose of the present study was to investigate the incidence and time course of stent thrombosis in unselected patients treated with drug-eluting stents. A comparison with stent thrombosis after bare metal stent implantation was beyond the scope of the present manuscript. The study was observational in nature and has the same disadvantages as any other observational study, including confounding by indication.[55] SES and PES have been used in both centres at different times, and PES were available for commercial use 1 year later than were SES. This difference in follow up might have biased our results. Nevertheless, results from comparisons of these two stent types should be viewed as hypothesis-generating and have to be confirmed in long-term follow-up of randomised controlled trials directly comparing these devices. Longer-term follow-up of the group of patients we studied will be needed to better understand the time course and incidence of this overall rare problem.

Second, our data provide an estimate of the incidence of stent thrombosis after drug-eluting stent implantation during routine clinical practice at two tertiary care centres. In this study we recorded a high number of stents per patient, small average stent diameter, and overall long total stent length, so our findings might not apply to institutions with more restricted use of drug-eluting stents. Nevertheless, previous randomised trials certainly underestimated the true incidence of stent thrombosis because of their less complex population of patients. Some stent thrombosis might have been undetected in our study despite our attempts at an active surveillance of harms.[56]

Additionally, we only reported angiographically documented cases, using a definition consistent with our previous reports on stent thrombosis after drug-eluting or bare metal stent implantation.[16,17,19–22,36] This practice might have led to an underestimation of the actual incidence of stent thrombosis—for example, if patients had sudden cardiac death or silent stent occlusion. Because of resource limitations it was impossible to ascertain retrospectively characteristics of patients and procedures that were not prospectively collected as part of routine procedures. Therefore, some variables were unavailable. In particular, the actual use of clopidogrel at each time point was not available for a substantial proportion of patients and therefore was not used in the final analysis. By contrast, the duration of clopidogrel prescription was available for all patients in Rotterdam and was included in the final Cox regression models. The value of clopidogrel in preventing stent thrombosis needs to be established in sufficiently powered dedicated trials. Intravascular ultrasound examination was not routinely done and the underlying mechanism contributing to the occurrence of stent thrombosis was not specifically investigated.

In conclusion, our data suggest that late stent thrombosis occurs at a steady rate during follow-up up to 3 years, tends to be more frequent with PES than with SES, and can unpredictably occur at any time point despite antiplatelet therapy. Late stent thrombosis complicating the use of drug-eluting seems to be a distinct entity with pathophysiological factors that differ from those of early stent thrombosis.

Contributors

The first two authors contributed equally to the manuscript. K Tschuchida, P Wenaweser, J Daemen, S Windecker, and P W Serruys were responsible for conception and design of the study, analysis and interpretation of data, and drafting of the manuscript. S Vaina, L Abrecht, C Morger, K Kukreja, P Jüni, G Sianos, G Hellige, R T van Domburg, O M Hess, E Boersma, and B Meier critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript. Statistical expertise was provided by J Daemen, P Jüni, R T van Domburg, and E Boersma. S Windecker, B Meier, and P W Serruys obtained public funding. Administrative, technical, and logistic support were provided by O M Hess, R T van Domburg, B Meier, S Windecker, and P W Serruys. K Tschuchida, P Wenaweser, J Daemen, S Vaina, L Abrecht, C Morger, N Kukreja, G Sianos, and G Hellige acquired data.

Conflict of interest statement

We declare that we have no conflict of interest.

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Chapter 18

Incidence and correlates of drug-eluting stent thrombosis in routine clinical practice: 4 year results from a large two-institutional cohort study

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Incidence and Correlates of Drug-Eluting Stent Thrombosis in Routine Clinical Practice

4-Year Results From a Large 2-Institutional Cohort Study

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Objectives We sought to determine the risk of late stent thrombosis (ST) during long-term follow-up beyond 3 years, searched for predictors, and assessed the impact of ST on overall mortality.

Background Late ST was reported to occur at an annual rate of 0.6% up to 3 years after drug-eluting stent (DES) implantation.

Methods A total of 8,146 patients underwent percutaneous coronary intervention with a sirolimus-eluting stent (SES) (n = 3,823) or paclitaxel-eluting stent (PES) (n = 4,323) and were followed up to 4 years after stent implantation. Dual antiplatelet treatment was prescribed for 6 to 12 months.

Results Definite ST occurred in 192 of 8,146 patients with an incidence density of 1.0/100 patient-years and a cumulative incidence of 3.3% at 4 years. The hazard of ST continued at a steady rate of 0.53% (95% confidence interval [CI]: 0.44 to 0.64) between 30 days and 4 years. Diabetes was an independent predictor of early ST (hazard ratio [HR]: 1.96; 95% CI: 1.18 to 3.28), and acute coronary syndrome (HR: 2.21; 95% CI: 1.39 to 3.51), younger age (HR: 0.97; 95% CI: 0.95 to 0.99), and use of PES (HR: 1.67; 95% CI: 1.08 to 2.56) were independent predictors of late ST. Rates of death and myocardial infarction at 4 years were 10.6% and 4.6%, respectively.

Conclusions Late ST occurs steadily at an annual rate of 0.4% to 0.6% for up to 4 years. Diabetes is an independent predictor of early ST, whereas acute coronary syndrome, younger age, and PES implantation are associated with late ST. (J Am Coll Cardiol 2008;52:1134–40) © 2008 by the American College of Cardiology Foundation

Drug-eluting stents (DES) reduce angiographic restenosis and the clinical need for repeat revascularization procedures (1,2). Recent systematic reviews and large-scale registries observed similar rates of death and myocardial infarction (MI) for patients treated with either a DES or bare-metal stent (BMS) during long-term 4-year follow-up (3–5). However, very late stent thrombosis (ST) has emerged as a distinct entity overshadowing the use of DES, and concerns persist as to whether this phenomenon might jeopardize the long-term outcome after DES implantation, particularly after discontinuation of dual antiplatelet therapy (6–11).

Drug-eluting stents delay healing and impair endothelialization as evidenced in necropsy studies and clinical investigations (12,13). Vessel remodeling (14) in concert with local drug release enhancing endothelial tissue factor expression (15,16) after DES implantation might result in a prothrombotic milieu predisposing to late ST. Previously, we reported on the frequency and timing of ST after the unrestricted use of DES implantation in a cohort of 8,146 consecutive patients treated at 2 academic institutions (10). Late and very late ST was encountered steadily at an annual rate of 0.6% with no evidence of diminution up to 3 years of follow-up. During extension of the follow-up period to 4 years in the current study, we investigated whether the risk of very late ST would change beyond 3 years, identified

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correlates of early as opposed to late ST, and assessed the impact of ST-related mortality after DES implantation on overall mortality in the entire cohort.

Methods

Study cohort, design, and follow-up. Between April 16, 2002, and December 31, 2005, a total of 8,146 consecutive patients underwent percutaneous coronary intervention with the 2 Food and Drug Administration–approved DES at 2 academic referral hospitals in Switzerland and the Netherlands, comprising 3,823 patients treated with sirolimus-eluting stents (SES) (Cypher, Cordis Corp., Johnson & Johnson, Warren, New Jersey) and 4,323 patients treated with paclitaxel-eluting stents (PES) (TAXUS Express2 or Liberté, Boston Scientific, Natick, Massachusetts). The use of the respective stent platforms at the 2 institutions has been reported previously (10). For the present extended 4-year follow-up, patients were again contacted 1 year after the last contact with specific questions addressing repeat hospital stay and major adverse cardiac events (MACE) with a health questionnaire. Patients who did not return the questionnaire were contacted by phone, at which time the questionnaire was completed. Moreover, survival data were obtained from municipal civil registries. If necessary, medical records and discharge summaries from other institutions were systematically reviewed and primary care physicians were contacted for additional or missing information. The median follow-up was 2.53 years/patient, and a complete clinical follow-up was achieved in 96.4% (n = 7,857). The common database was held and analyzed at the Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland. There was no industry involvement in the design, conduct, or analysis of the study.

This study was approved by the local ethics committee in both hospitals and is in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Definitions. Definite ST was defined as follows:

1. Presence of Thrombolysis In Myocardial Infarction (TIMI) flow:
   a. Grade 0 with occlusion originating in the peri-stent region
   b. Grade 1, 2, or 3 in the presence of a thrombus originating in the peri-stent region. Angiographic evidence of thrombus was defined as a discrete, intraluminal filling defect with defined borders and separated from the vessel wall.

And at least 1 of the following criteria had to be met:

1. Acute ischemic symptoms (typical chest pain with duration >20 min)
2. Ischemic electrocardiographic changes
   a. ST-segment elevation in territory of implanted stent
   b. ST-segment depression or T-wave inversion in territory of implanted stent
3. Typical rise and fall in cardiac biomarkers (17).

All cases of definite ST were reviewed independently by 2 experienced interventional cardiologists, and in case of disagreement, a consensus was established between the 2 reviewers or a third interventional cardiologist was consulted. Moreover, ST was categorized into early (within 30 days), late (>30 days and ≤365 days), and very late (>365 days) depending on the timing of occurrence of the event. For the definition of probable ST, the Academic Research Consortium (ARC) criteria were applied (18).

Abbreviations and Acronyms

ACS = acute coronary syndrome
ARC = Academic Research Consortium
ASA = acetylsalicylic acid
BMS = bare-metal stent(s)
CI = confidence interval
DES = drug-eluting stent(s)
MACE = major adverse cardiac event
MI = myocardial infarction
PES = paclitaxel-eluting stent(s)
SES = sirolimus-eluting stent(s)
ST = stent thrombosis
TIMI = Thrombolysis In Myocardial Infarction

The diagnosis of MI was based on the presence of new Q waves in at least 2 contiguous leads with an elevated creatine kinase-myocardial band fraction. In the absence of pathologic Q waves, the diagnosis of MI was based on an elevation in creatine kinase to more than twice the upper limit of normal with an elevated creatine kinase-myocardial band fraction of more than 3 times the upper limit of normal. Premature discontinuation of antiplatelet therapy was referred to as cessation of acetylsalicylic acid (ASA) or clopidogrel or both before the recommended duration of prescription. A creatinine value ≥150 μmol or chronic hemodialysis qualified as definition of renal impairment.

Interventional procedure and antiplatelet prescription. All interventions were performed according to current practice guidelines for percutaneous coronary intervention. The decision to choose a specific treatment strategy was left to the discretion of the operator. Patients were prescribed ASA 100 mg once daily plus clopidogrel 75 mg/day (after a loading dose of 300 or 600 mg) before or during baseline coronary interventions. After the procedure, all patients were advised to maintain ASA 100 mg once daily lifelong. In the Swiss institution, 12 months of clopidogrel therapy was prescribed irrespective of the stent type used. In the Dutch institution, PES-treated patients received at least 6 months of clopidogrel (75 mg/day), whereas patients treated with SES were prescribed clopidogrel for at least 3 months, unless 1 of the following was present (in which case clopidogrel was maintained for at least 6 months): ≥3 SES implantations, total stent length ≥36 mm, chronic total occlusion, and bifurcations. In a minority of patients under oral anticoagulation therapy, a shorter duration of clopidogrel (e.g.,

3-month triple therapy with ASA, clopidogrel, and warfarin) was recommended.

Statistical analysis. Continuous variables are expressed as mean ± SD or median values with the corresponding interquartile range. Dichotomous variables are expressed as counts and percentages. For comparison of continuous variables between SES and PES as well as early and late thrombosis, a Student *t* test for continuous variables was used.

The incidence of ST was calculated in 2 different ways: 1) incidence density, defined as the number of patients with ST divided by the total number of patient-years under observation (expressed as a number of events/100 patient-years); and 2) cumulative incidence, estimated according to the Kaplan-Meier method and the log-rank test for the differences in survival curve. Univariable and multivariable Cox proportional hazards models were used to assess predictors of ST, with the following variables: age, gender, family history of cardiovascular disease, diabetes, hypertension, current smoking, dyslipidemia, renal impairment, left ventricular ejection fraction, acute coronary syndrome (ACS) at presentation, stent type, number of stents, total stent length, average stent diameter, bifurcation treatment, and prescribed duration of clopidogrel. Statistical analyses were performed with Stata version 9 for Windows (Stata Corp., College Station, Texas). All p values were 2-sided and values <0.05 were considered statistically significant.

Results

Baseline clinical and procedural characteristics of patients with and without ST are summarized in Table 1. Compared with patients without ST, those suffering from definite ST were younger (59.4 ± 12.1 years vs. 62.9 ± 11.5 years, p < 0.001), had a lower left ventricular ejection fraction (52 ± 12% vs. 55 ± 12%, p = 0.035) and more often an ACS (67.7% vs. 54.9%, p < 0.001) at the time of stent implantation, and had received longer (total stent length: 44.0 ± 38.8 mm vs. 36.1 ± 25.5 mm, p < 0.001) and more stents (number of stents: 2.33 ± 1.71 vs. 1.95 ± 1.21, p < 0.001), which were smaller in diameter (2.88 ± 0.32 mm vs. 2.94 ± 0.38 mm, p = 0.048). The status of antiplatelet therapy as recorded during early and late and very late ST is summarized in Figure 1.

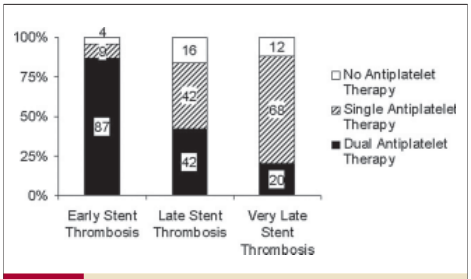


Figure 1 **Status of Antiplatelet Treatment at Time of Definite Stent Thrombosis**

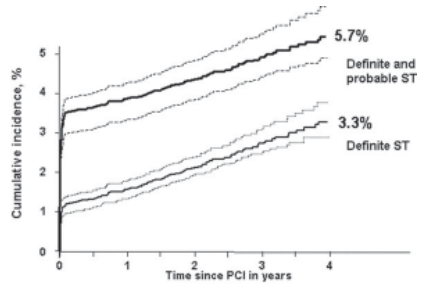
Proportion of patients with early and late stent thrombosis treated with dual, single, or no antiplatelet therapy.

Incidence and time course of ST. During a follow-up period of 4 years, definite ST was encountered in 192 of 8,146 patients after a median of 56 (interquartile range 4 to 593) days (Fig. 2). Early ST was observed in 92 (48%), late ST in 31 (16%), and very late ST in 69 (36%) of 192 patients. Definite ST occurred with an incidence density of 1.0/100 patient-years and a cumulative incidence of 3.3% at 4 years of follow-up. The hazard of late ST (between 30 days and 1 year) amounted to 0.46% (95% confidence interval [CI]: 0.32% to 0.65%), the hazard of very late ST (between 1 and 4 years) to 0.57% (95% CI: 0.45% to

Table 1 **Clinical and Procedural Characteristics of Patients With and Without Definite ST**

	Overall Population (n = 8,146)	ST (n = 192)	No ST (n = 7,954)	p Value
Age (yrs), mean ± SD	62.8 ± 11.5	59.4 ± 12.1	62.9 ± 11.5	<0.001
Male gender, %	74.5	75.0	74.5	0.88
Hypertension, %	46.5	42.2	46.6	0.23
Current smoking, %	36.8	41.7	36.7	0.16
Family history of CAD, %	28.1	29.2	28.1	0.75
Dyslipidemia, %	50.9	50.0	50.9	0.81
Diabetes, %	16.3	20.8	16.2	0.09
Left ventricular ejection fraction (%), mean ± SD	55 ± 12	52 ± 12	55 ± 12	0.035
Renal impairment, %	4.1	2.6	4.2	0.48
ACS at presentation, %	55.2	67.7	54.9	<0.001
Bifurcation treatment, %	11.8	17.9	11.6	0.06
Sirolimus-eluting stent, %	47.9	43.2	48.0	0.19
Total stent length/patient (mm), mean ± SD	36.3 ± 25.9	44.0 ± 38.8	36.1 ± 25.5	<0.001
Number of stents/patient, mean ± SD	1.96 ± 1.23	2.33 ± 1.71	1.95 ± 1.21	<0.001
Average stent diameter/patient (mm), mean ± SD	2.94 ± 0.38	2.88 ± 0.32	2.94 ± 0.38	0.048

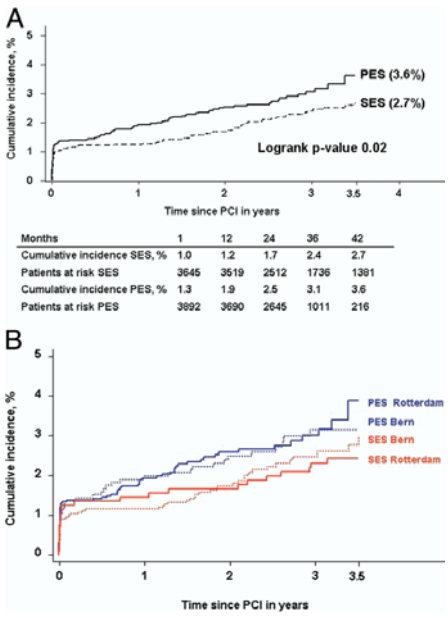
ACS = acute coronary syndrome; CAD = coronary artery disease; ST = stent thrombosis.



Months	1	12	24	36	48
Cumulative incidence definite ST, %	1.2	1.6	2.1	2.7	3.3
Cumulative incidence probable and definite ST, %	3.7	4.1	4.6	5.2	5.7
Patients at risk	7537	7209	5157	2747	1051

Figure 2 **Cumulative Incidence of Definite ST in 8,146 Patients During a 4-Year Follow-Up Period**

PCI = percutaneous coronary intervention; ST = stent thrombosis.



Months	1	12	24	36	42
Cumulative incidence SES, %	1.0	1.2	1.7	2.4	2.7
Patients at risk SES	3645	3519	2512	1736	1381
Cumulative incidence PES, %	1.3	1.9	2.5	3.1	3.6
Patients at risk PES	3892	3690	2645	1011	216

Figure 3 **Cumulative Incidence of Definite ST Stratification**

(A) Cumulative incidence of definite stent thrombosis (ST) stratified by stent type. **(B)** Cumulative incidence of definite ST stratified by stent type and treatment site. PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent(s); SES = sirolimus-eluting stent(s).

0.72%), and the hazard of the combined rate for late and very late ST (between 30 days and 4 years) was 0.53% (95% CI: 0.44% to 0.64%)/year. The rate of definite and probable ST after 4 years amounted to 5.7% (95% CI: 5.15% to 6.39%) with an incidence of 3.68% (95% CI: 3.29% to 4.12%) after 30 days and 4.09% (95% CI: 3.67% to 4.55%) after 1 year (Fig. 2).

Baseline demographic data for SES- and PES-treated patients differed widely (Table 2). The cumulative incidence of ST up to 3.5 years amounted to 2.7% for SES-treated and 3.6% for PES-treated patients (HR: 0.7; 95% CI: 0.53 to 0.95, p = 0.02) (Fig. 3A). Whereas early ST occurred with similar frequency in SES- (1.0%) and PES-treated

Table 2 **Clinical and Procedural Characteristics of Patients Stratified by Stent Type**

	SES (n = 3,823)	PES (n = 4,323)	p Value
Age (yrs), mean ± SD	62.6 ± 11.4	63.0 ± 11.5	0.31
Male gender, %	74.9	74.2	0.51
Hypertension, %	41.9	51.6	<0.0001
Current smoking, %	44.9	29.5	<0.0001
Family history of CAD, %	29.0	27.3	0.09
Dyslipidemia, %	55.8	47.3	<0.0001
Diabetes, %	18.3	14.6	<0.0001
Left ventricular ejection fraction (%), mean ± SD	54 ± 12	55 ± 12	0.01
Renal impairment, %	4.3	3.9	0.58
ACS at presentation, %	52.1	58.0	<0.0001
Bifurcation treatment, %	10.3	12.3	0.09
Total stent length/patient (mm), mean ± SD	33.8 ± 23.0	38.6 ± 28.1	<0.0001
Number of stents/patient, mean ± SD	1.87 ± 1.14	2.03 ± 1.30	<0.0001
Average stent diameter/patient (mm), mean ± SD	2.86 ± 0.32	3.00 ± 0.40	<0.0001
Duration of clopidogrel prescription (days), mean ± SD	144 ± 120	194 ± 80	<0.0001

PES = paclitaxel-eluting stent(s); SES = sirolimus-eluting stent(s); other abbreviations as in Table 1.

(1.3%) patients (HR: 0.76; 95% CI: 0.50 to 1.15, p = 0.19), late and very late ST occurred with an annual rate of 0.44% (95% CI: 0.33% to 0.59%) after SES and 0.63% (95% CI: 0.49% to 0.83%) after PES implantation (HR: 0.66; 95% CI: 0.44 to 0.99, p = 0.047). A stratified analysis according to treatment site revealed a similar frequency and time course of definite ST after SES (Bern: 2.9% vs. Rotterdam: 2.4%, p = 0.49) and PES (Bern: 3.1% vs. Rotterdam: 3.9%, p = 0.83) implantation at both institutions (Fig. 3B).

Predictors of ST. The results of multivariate analyses to identify overall, early, and late definite ST are summarized in Table 3. Acute coronary syndrome at the time of stent implantation (HR: 1.81; 95% CI: 1.32 to 2.49), diabetes (HR: 1.61; 95% CI: 1.11 to 2.33), younger age (HR: 0.98; 95% CI: 0.96 to 0.99), and use of PES (HR: 1.51; 95% CI: 1.10 to 2.04) were independent predictors of overall ST. Diabetes (HR: 1.96; 95% CI: 1.18 to 3.28) was the only predictor of early ST, whereas ACS at time of stent implantation (HR: 2.21; 95% CI: 1.39 to 3.51), younger age (HR: 0.97; 95% CI: 0.95 to 0.99), and use of PES (HR: 1.67; 95% CI: 1.08 to 2.56) were independently associated with an increased risk of late ST.

Long-term clinical outcome. Mortality after definite ST amounted to 15.6% at 2 years and tended to be higher in patients suffering from early (20.3%) as opposed to late and very late ST (10.4%) (Fig. 4). At 4 years of follow-up, rates of death, MI, and the composite of death or MI were 10.6%, 4.6%, and 14.6%, respectively, in the overall population (Fig. 5). During the entire observation period of 4 years, 27 patients suffering from definite ST subsequently died. Death after the diagnosis of definite ST occurred in 0.4% of the entire population and accounted for 3.9% of all 702 deaths.

Discussion

The results of the present study indicate a continuous hazard of late and very late ST at an annual rate of 0.4% to 0.6% extending to 4 years after DES implantation. The only independent predictor of early ST was diabetes, whereas ACS, younger age, and use of PES were independently associated with an increased risk of late ST. Mortality due to definite ST accounted for only a small fraction of overall mortality.

Autopsy studies and clinical investigations using angioscopy and assessment of endothelial function indicate that DES delay healing and impair endothelialization (12,13,19–22). Intravascular ultrasound studies demonstrate a higher incidence of stent malapposition and evidence of vessel remodeling after DES implantation in patients with very late ST (14). Furthermore, drugs released from the drug-polymer combination might be thrombogenic on their own, because both sirolimus and paclitaxel enhance endothelial tissue factor expression, the principal activator of the coagulation cascade that activates factors IX and X (15,16). Therefore, it has been suggested that DES might create a prothrombotic milieu predisposing to thrombotic stent occlusion.

Previously, we reported the phenomenon of late ST after DES implantation occurring continuously without diminu-

Table 3 Hazard Ratio and 95% CI for Risk Factors Associated With Definite ST During the Entire Follow-Up Period From Multivariable Cox Regression

Variables	Hazard Ratio	95% CI
ACS at presentation	1.8	1.3–2.5
Diabetes	1.6	1.1–2.3
Number of stents/patient	1.2	0.95–1.4
Current smoking	1.1	0.78–1.5
Family history of CAD	1.0	0.73–1.4
Total stented length/patient	1.0	1.00–1.01
Age	0.98	0.96–0.99
Dyslipidemia	0.95	0.70–1.28
Female	0.89	0.63–1.25
Hypertension	0.85	0.62–1.16
Use of PES	1.67	1.08–2.56

CI = confidence interval; other abbreviations as in Tables 1 and 2.

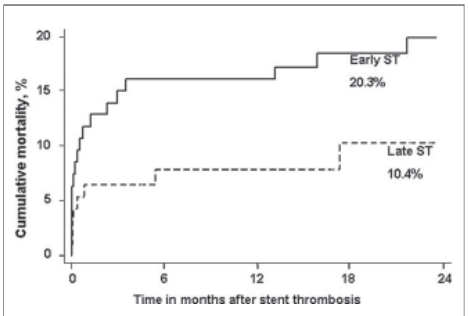


Figure 4 Cumulative Incidence of Death in Patients With Definite ST Stratified According to Early and Late ST

ST = stent thrombosis.

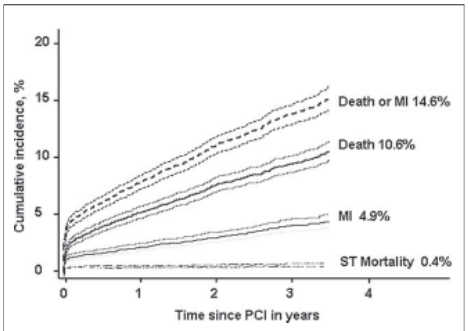


Figure 5 Cumulative Incidence of Ischemic Adverse Events in 8,146 Patients During 4 Years of Follow-Up

MI = myocardial infarction; PCI = percutaneous coronary intervention; ST = stent thrombosis.

tion up to 3 years of follow-up in a large cohort of consecutive patients treated with the unrestricted use of DES (10). The present study extends these findings to a longer-term follow-up and shows that the steady annual rate of 0.4% to 0.6% remains unchanged between 3 and 4 years of follow-up. A continuous linear hazard of late ST comparable to the present study has been corroborated more recently in the extended follow-up of 21,717 DES-treated patients included in the SCAAR (Swedish Coronary Angiography and Angioplasty Registry) with an annual rate of ST of 0.5% during a follow-up of 2 years (23,24). Moreover, several systematic reviews reported a significantly higher rate of very late ST in disfavor of both SES and PES compared with BMS, although the overall rate of ST was not different between the different stent types (3,4,25). Accordingly, very late ST is a distinct entity complicating the use of DES, and arterial healing remains incomplete up to 4 years after DES implantation in humans.

Although late and very late ST complicated the clinical course of both DES types, it was more frequent with PES than SES, and use of PES emerged as independent of late ST. Of note, PES was implanted in more complex lesions in this cohort, whereas SES had been used earlier than PES, and subsequently the length of follow-up was different between the 2 devices, which might have biased the results in disfavor of PES. Yet, Bavry et al. (7) made a similar observation and found the risk of very late ST more pronounced with PES (5.9 of 1,000 patient-years) than SES (3.6 of 1,000 patient-years) in a meta-analysis of 14 trials with 6,675 patients. A meta-analysis directly comparing SES (4,391 patients) with PES (4,304 patients) also reported a higher risk of protocol-defined ST with PES (1.9%) than SES (1.2%; HR: 0.66, 95% CI: 0.46 to 0.94, $p = 0.02$) (26). Finally, a network meta-analysis of 38 trials comparing BMS, SES, and PES reported an increased risk of late ST with PES compared with BMS (HR: 2.11; 95% credibility interval: 1.2 to 4.2, $p = 0.02$), whereas the risk was less pronounced with SES (HR 1.1; 95% credibility interval: 0.6 to 2.3, $p = 0.71$) (5). It can only be speculated whether the different drug-release kinetics, distribution within the vessel wall, mechanisms of action, inhomogeneity of strut coverage, or design of the stent platforms impact on the incidence and time course of late ST.

Previous studies identified clinical characteristics such as premature discontinuation of antiplatelet therapy (27–29), ACS (10,30), diabetes (10,27,30), and renal failure (27,28) as independent risk factors of DES-associated ST. In addition, lesion characteristics including smaller reference vessel diameter, stent length (29), thrombus burden (31), and bifurcation lesions (27,28) were identified as predictive of ST. The present study not only confirms the hazard related to diabetes and ACS in the largest cohort of patients with definite ST to date but also identifies diabetes as a predictor of early ST and ACS as a predictor of late ST. The reasons for a predisposition of diabetic patients to early ST might be related to smaller vessel size (32), longer lesion length, a higher rate of residual dissections, and an increased platelet aggregation (11,33). Conversely, patients with ACS might be predisposed to late and very late ST due to a higher thrombus burden at the time of stent implantation (31), which upon dissolution might result in late acquired stent malapposition and altered flow dynamics around stent struts (14).

The contribution of definite ST to overall mortality was small in the present study (<5%). A similar observation has been made in a pooled analysis of pivotal trials comparing DES with BMS (25), where mortality due to ST accounted for <10% of overall mortality. It might be speculated that the overall outcome regarding death or MI of patients treated by percutaneous coronary interventions might be determined in large part by causes other than target lesion revascularization or ST. Along this line, a pooled analysis of 4 randomized trials comparing SES with BMS in 1,748 patients found that the majority of death or MI in both stent groups was unrelated to either target lesion revascularization or ST, suggesting another etiology, such as disease progression (34). However, it is important to note that the definition of definite ST requiring angiographic or autopsy confirmation of thrombotic stent occlusion leads to a considerable underestimation of the true incidence of ST-related mortality. Because only those patients reaching the catheterization laboratory alive qualify for the diagnosis of definite ST, all deaths before angiographic or autopsy confirmation are missed and not classified as "definite ST"–related. In other words, the presented data only reflect the mortality toll of definite ST after initial survival.

Study limitations. The findings of this study have to be interpreted in light of several limitations. First, the study was nonrandomized, with the decision regarding stent type and antiplatelet therapy largely determined by local institutional practice. The principal purpose was to investigate the incidence and time course of definite ST in unselected patients treated with DES during long-term follow-up rather than a comparison of ST as encountered after BMS implantation. This is an observational study, which suffers from confounding by indication. The SES and PES were used in both centers during different time periods, and PES was available for commercial use 1 year later than SES. This might have resulted in bias due to differences in follow-up. Due to the continuous enrollment of patients into this registry between 2002 and 2005, not all patients had completed the 4-year follow-up. Accordingly, estimates of the risk of ST are less precise during later time points, and the data should be carefully interpreted by considering the corresponding CIs. Second, the data were obtained from a patient population at 2 tertiary care centers with a high number of stents/patient, a small average stent diameter, and an overall long total stent length, which might not apply to institutions with a more restricted DES use. Third, it is possible that some ST went undetected in our study despite our attempts at an active surveillance of harms. In addition, the focus of the present study was on definite ST, which might have led to an underestimation of the actual incidence

of ST as well as mortality related to definite ST. The latter requires angiographic or autopsy confirmation of thrombotic stent occlusion and therefore ignores any death without these prerequisites. However, the definition is in line with previous reports from our group on ST either after DES or BMS implantation and allows for appropriate comparisons. Moreover, the composite of definite and probable ST, suggested as a useful parameter to avoid underestimation and overestimation of ST, is provided in the present study as are the ischemic end points of death and MI. Finally, only the prescribed duration of antiplatelet therapy was available in the present study, whereas the exact duration of dual antiplatelet therapy could not reliably be ascertained in the whole patient population. Therefore, it cannot be excluded that we missed an important relation between the actual duration of thienopyridine therapy and ST.

Conclusions

Late ST is a distinct entity complicating the use of DES and occurs steadily at an annual rate of 0.4% to 0.6% for up to 4 years of follow-up. Diabetes is an independent predictor of early ST, whereas ACS, younger age, and use of PES are associated with late ST.

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Key Words: drug-eluting stent ▪ mortality ▪ stent thrombosis.

Chapter 19

Angiographic stent thrombosis after routine use of drug-eluting stents in ST-segment elevation myocardial infarction: the importance of thrombus burden

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Angiographic Stent Thrombosis After Routine Use of Drug-Eluting Stents in ST-Segment Elevation Myocardial Infarction

The Importance of Thrombus Burden

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Objectives This study sought to investigate the impact of thrombus burden on the clinical outcome and angiographic infarct-related artery stent thrombosis (IRA-ST) in patients routinely treated with drug-eluting stent (DES) implantation for ST-segment elevation myocardial infarction (STEMI).

Background There are limited data for the safety and effectiveness of DES in STEMI.

Methods We retrospectively analyzed 812 consecutive patients treated with DES implantation for STEMI. Intracoronary thrombus burden was angiographically estimated and categorized as large thrombus burden (LTB), defined as thrombus burden ≥2 vessel diameters, and small thrombus burden (STB) to predict clinical outcomes. Major adverse cardiac events (MACE) were defined as death, repeat myocardial infarction, and IRA reintervention.

Results Mean duration of follow-up was 18.2 ± 7.8 months. Large thrombus burden was an independent predictor of mortality (hazard ratio [HR] 1.76, $p = 0.023$) and MACE (HR 1.88, $p = 0.001$). The cumulative angiographic IRA-ST was 1.1% at 30 days and 3.2% at 2 years, and continued to augment beyond 2 years. It was significantly higher in the LTB compared with the STB group (8.2% vs. 1.3% at 2 years, respectively, $p < 0.001$). Significant independent predictors for IRA-ST were LTB (HR 8.73, $p < 0.001$), stent thrombosis at presentation (HR 6.24, $p = 0.001$), bifurcation stenting (HR 4.06, $p = 0.002$), age (HR 0.55, $p = 0.003$), and rheolytic thrombectomy (HR 0.11, $p = 0.03$).

Conclusions Large thrombus burden is an independent predictor of MACE and IRA-ST in patients treated with DES for STEMI. (J Am Coll Cardiol 2007;50:573–83)

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Primary percutaneous coronary intervention (PCI) with bare metal stent (BMS) implantation is established as the treatment of choice for ST-segment elevation myocardial infarction (STEMI) (1,2). There are limited data regarding the use of drug-eluting stents (DES) in a STEMI setting. Initial small registries showed superiority of sirolimus-eluting stents (SES) compared with BMS up to 1 year of follow-up (3–8). Two randomized trials confirmed these results (9,10). The findings regarding paclitaxel-eluting stents (PES) are less clear with positive small single-center reports (11,12), but a negative randomized trial (13). There are no data on the routine use of DES for STEMI with midterm outcomes.

The etiology of stent thrombosis is multifactorial, involving stent thrombogenicity and procedure-, lesion-, and patient-related factors (14). Acute coronary syndromes have been recognized as a factor of increased rates of stent thrombosis both for BMS (15–17) and DES (18–20). Limited data exist regarding the incidence and predictors of DES thrombosis during STEMI (9,10,13,18).

In patients with acute coronary syndromes, angiographic presence of thrombus increases the incidence of in-hospital major adverse cardiac events (MACE) (21,22). Mechanical treatment of thrombotic lesions, by means of thrombectomy and distal protection devices, has been proposed to prevent the complications caused by thrombus and improve clinical outcomes, but randomized trials failed to show any beneficial

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Abbreviations and Acronyms

BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
IRA-ST = infarct-related artery stent thrombosis
LTB = large thrombus burden
MACE = major adverse cardiac events
MI = myocardial infarction
PES = paclitaxel-eluting stents
PCI = percutaneous coronary intervention
RT = rheolytic thrombectomy
SES = sirolimus-eluting stent(s)
STB = small thrombus burden
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombosis In Myocardial Infarction
TLR = target lesion revascularization (of the infarct-related artery)
TVR = target vessel revascularization (of the infarct-related artery)

effect of routine use in "all comers" on myocardial reperfusion or clinical outcome during STEMI (23,24). There is no angiographic thrombus classification validated to predict clinical outcomes.

In a large unselected cohort of consecutive patients with STEMI treated with PCI and DES, we propose a simple angiographic thrombus classification, and we report the 2-year clinical outcome and incidence and predictors of infarct-related artery stent thrombosis (IRA-ST).

Patients and Methods

Patients and procedure. From April 2002, when DES were introduced, until December 2004, 900 consecutive patients presented with STEMI and underwent PCI (primary or rescue) within 12 h after the onset of chest pain; 37 (4.1%) were treated with balloon angioplasty, 51 (5.7%) with BMS, and 812 (90.2%) with DES. The BMS were implanted because of unavailability of all DES sizes (length or diameter) in the initial period of their approval. This analysis focuses on patients treated exclusively with DES. All patients were pretreated with 250 mg aspirin and 300 mg clopidogrel. Preprocedural intracoronary nitrates were systematically administered. A PCI was performed according to standard clinical practice. The use of rheolytic thrombectomy (RT) (Possis Medical, Inc., Minneapolis, Minnesota), the only thrombectomy or aspiration system used, and periprocedural pharmacological treatment (e.g., glycoprotein IIb/IIIa antagonists) were at the operator's discretion. All patients received dual antiplatelet therapy: aspirin 325 mg/day indefinitely and clopidogrel 75 mg/day for 3 and 6 months after SES and PES implantation, respectively.

Clinical follow-up. Information regarding baseline clinical characteristics, procedural details, and in-hospital events was obtained from electronic databases maintained at Erasmus Medical Center. Postdischarge survival status was obtained from the Municipal Civil Registry. A questionnaire was mailed to all living patients focusing on rehospitalization and MACE. Referring cardiologists, general practitioners, and patients were contacted when necessary for additional information. All patients provided written informed consent.

Angiographic analysis. Intracoronary thrombus was angiographically identified and scored in 5 grades as previously described (25). According to this classification, in thrombus grade 0 (G0), no cineangiographic characteristics of thrombus are present; in thrombus grade 1 (G1), possible thrombus is present, with such angiography characteristics as reduced contrast density, haziness, irregular lesion contour, or a smooth convex meniscus at the site of total occlusion suggestive but not diagnostic of thrombus; in thrombus grade 2 (G2), there is definite thrombus, with greatest dimensions $\leq$1/2 the vessel diameter; in thrombus grade 3 (G3), there is definite thrombus but with greatest linear dimension $>$1/2 but $<$2 vessel diameters; in thrombus grade 4 (G4), there is definite thrombus, with the largest dimension $\geq$2 vessel diameters; and in thrombus grade 5 (G5), there is total occlusion (unable to assess thrombus burden due to total vessel occlusion).

In patients presenting with an open IRA, thrombus was scored in the preintervention angiographic sequence more clearly depicting its size. In patients presenting with an occluded IRA (G5; essentially no flow and not thrombus classification), thrombus was reclassified into one of the other categories after flow achievement with either guidewire crossing or a small (diameter 1.5 mm) deflated balloon passage or dilation. After reclassification of the G5 group, thrombus burden was stratified in 2 categories, scored as a small thrombus burden (STB) for thrombus $<$G4 and a large thrombus burden (LTB) for thrombus G4, based on clinical outcomes.

Thrombosis In Myocardial Infarction (TIMI) flow and myocardial blush were assessed as previously reported (26,27). No reflow was defined as reduced antegrade flow (TIMI flow grade $<$2) in the absence of occlusion at the treatment site or evidence of distal embolization. Distal embolization was defined as migration of a filling defect to distally occlude the infarct-related vessel or one of its branches, or a new abrupt cutoff of the distal vessel/branch.

Stent thrombosis was defined as a complete or partial occlusion within the stented segment with evidence of thrombus and reduced antegrade flow (TIMI flow grade $<$3) with a concurrent acute clinical ischemic event. The stent thrombosis cases were categorized according to the timing of occurrence into acute (from the end of the procedure up to 24 h), subacute (from 24 h up to 30 days), late (between 30 days and 6 months), and very late ($>$6 months).

All procedural parameters, including thrombus classification, were assessed by 2 experienced interventional cardiologists reviewing the angiograms together. Both reviewers were blinded to clinical outcomes. Consensus was achieved in all patients. Half of the films were randomly selected and reanalyzed by the same analysts for intraobserver variability, and by a third experienced interventional cardiologist for interobserver variability of the proposed LTB and STB classification.

Definitions. Repeat myocardial infarction (MI) (nonfatal) was defined as new clinical symptoms or electrocardiogram changes associated with an increase in the creatine kinase level to more than twice the upper normal limit with an increased creatine kinase-MB. In cases in which the creatine kinase level had not returned to normal values after the index event, a second peak was defined as repeat MI. Target lesion revascularization (TLR) was defined as any repeat revascularization of the IRA involving the stent and/or its 5-mm proximal or distal edges.

Target vessel revascularization (TVR) was defined as any repeat revascularization of the IRA. A MACE was defined as death, repeat MI, and TVR.

Statistics. Categorical variables (presented as counts and percentages) were compared using the chi-square test or Fisher exact test where the expected value in any cell was <5. The unpaired *t* test was used for comparing continuous variables (presented as the mean ± SD). Cumulative event rates were estimated using the Kaplan-Meier method, and differences between groups were assessed by the log-rank test of significance. Variables associated with event rates on univariate analysis at a level of $p \leq 0.2$ were entered in a multivariate Cox model with a stepping algorithm, and then the variables referring to thrombus burden and RT were forced into the model to estimate their independent effect along with the other predictors of clinical outcome (mortality, MACE, stent thrombosis). In-hospital events were included in the survival analysis. All tests were 2-tailed, and a value of $p < 0.05$ was considered significant. The SPSS statistical software package (version 12.0 for Windows, SPSS Inc. Chicago, Illinois) was used for the analysis.

Table 1 Baseline Clinical, Angiographic, and Procedural Characteristics

Characteristic	Total Population (n = 792)	STB (n = 567)	LTB (n = 225)	p Value*
Age (yrs)	59.4 ± 11.5	59.6 ± 11.6	58.8 ± 11.1	0.38
Female	166 (21%)	122 (21.5%)	44 (19.6%)	0.54
Diabetes	80 (10.1%)	50 (8.8%)	30 (13.3%)	0.057
Hypertension	215 (27.1%)	148 (26.1%)	67 (29.8%)	0.294
Hypercholesterolemia	240 (30.3%)	177 (31.2%)	63 (28.0%)	0.374
Smoking	299 (37.8%)	223 (39.3%)	76 (33.8%)	0.146
Family history of CAD	207 (26.1%)	144 (25.4%)	63 (28.0%)	0.452
Previous MI	80 (10.1%)	54 (9.5%)	26 (11.6%)	0.392
Previous PCI	46 (5.8%)	24 (4.2%)	22 (9.8%)	0.003
MI presentation				
Infarct duration (h)†	4.5 ± 11.3	4.3 ± 8.5	4.9 ± 14.9	0.659
Peak CK-MB (IU/l)	314.5 ± 303.6	305.3 ± 292.4	335.9 ± 328.2	0.699
Primary PCI	712 (89.9%)	503 (88.7%)	209 (92.9%)	0.079
Rescue PCI	80 (10.1%)	64 (11.3%)	16 (7.1%)	0.079
Cardiogenic shock	76 (9.6%)	50 (8.8%)	26 (11.6%)	0.238
Stent thrombosis	22 (2.8%)	6 (1.1%)	16 (7.1%)	<0.001
Prehospital resuscitation	21 (2.7%)	15 (2.6%)	6 (2.7%)	0.987
Multivessel disease	309 (39.0%)	229 (40.4%)	80 (35.6%)	0.209
Infarct-related artery				0.007
Left main stem	11 (1.4%)	10 (1.8%)	1 (0.4%)	
Left anterior descending	404 (51%)	299 (52.7%)	105 (46.7%)	
Right coronary artery	297 (37.5%)	199 (35.1%)	98 (43.6%)	
Circumflex coronary artery	75 (9.5%)	58 (10.2%)	17 (7.6%)	
Vein or IMA graft	5 (0.6%)	1 (0.2%)	4 (1.8%)	
Multivessel PCI	85 (10.7%)	69 (12.2%)	16 (7.1%)	0.038
Pacemaker	107 (13.5%)	46 (8.1%)	61 (27.1%)	<0.001
IABP	91 (11.5%)	57 (10.1%)	34 (15.1%)	0.044
Inotropes	90 (11.4%)	59 (10.4%)	31 (13.8%)	0.177
Glycoprotein IIb/IIIa antagonists	401 (50.6%)	251 (44.3%)	150 (66.7%)	<0.001
Distal protection device	15 (1.9%)	2 (0.4%)	13 (5.8%)	<0.001
Drug-eluting stent type				0.004
Sirolimus-eluting stent	200 (25.3%)	159 (28.0%)	41 (18.2%)	
Paclitaxel-eluting stent	592 (74.7%)	408 (72.0%)	184 (81.8%)	
Bifurcational stenting	51 (6.4%)	33 (5.8%)	18 (8.0%)	0.26
Direct stenting	442 (55.8%)	321 (56.6%)	121 (53.8%)	0.469
Rheolytic thrombectomy	63 (8.0%)	4 (0.7%)	59 (26.2%)	<0.001

*STB versus LTB group. †Infarct duration was available in 531 patients (361 in the STB and 170 in the LTB group).

CAD = coronary artery disease; CK = creatine kinase; IABP = intra-aortic balloon pump; IMA = internal mammary artery; LTB = large thrombus burden; MI = myocardial infarction; PCI = percutaneous coronary intervention; STB = small thrombus burden.

Kappa statistics were calculated for estimating the intraobserver (kappa = 0.95) and interobserver (kappa = 0.91) variability of the proposed thrombus classification after selecting randomly and reanalyzing half of the films.

Results

Complete follow-up information was obtained in 798 (98.3%) patients treated with DES (mean duration 18.2 ± 7.8 months), and both clinical follow-up and thrombus burden classification was available in 792 (97.5%) patients. Minimum follow-up for patients who survived the index hospitalization was 12 months. Baseline demographic and procedural characteristics of the total population and according to thrombus burden are presented in Table 1.

Angiographic classification of thrombus burden. Thrombus burden grading is presented in Table 2. More than half of the patients (57%) presented with an occluded IRA (G5). Reclassification into a thrombus category (G0 to G4) was achieved in 449 (98.7%) patients; in 305 (67.9%) after some flow achievement with guidewire crossing, and in 144 (32.1%) after a deflated 1.5-mm balloon passage or dilation (mean dilation pressure was 6.8 atm and mean duration of dilation was 16.6 s). An example of thrombus reclassification after wire crossing is presented in Figure 1. In 2 patients, thrombus G5 was sustained (no flow achievement), and in 4 patients reclassification was not possible because of inadequate angiographic documentation. Finally, thrombus burden was estimated in 792 (99.2%) patients.

In the reclassified G5 group, there were more G4 patients compared with the group with open IRA (33.0% vs. 22.4%, p = 0.001).

Clinical outcome. The 2-year cumulative clinical outcomes of the total population are presented in Figure 2, and 2-year cumulative mortality and MACE rate according to thrombus score after G5 reclassification are depicted in Figures 3A and 3B. Patient groups G1, G2, and G3 had similar 2-year cumulative mortality (7.8% vs. 9.6% vs. 7.9%, respectively, p = 0.95) and MACE rates (15% vs. 13.8% vs. 12.8%, respectively, p = 0.78), whereas groups G0 and G4 had higher rates (mortality 14.6% and 13%, respectively, p = 0.22; MACE rate 24.4% and 24.9%, respectively, p = 0.001) compared with the former groups. The G0 group compared with G1 to G3 had more multivessel PCI (20.6% vs. 11.1%, p = 0.029) and more left main stem and less right coronary artery involvement (4.8% vs. 1.4% and 19% vs. 37.1%, respectively, p < 0.001).

Based on the aforementioned results, we stratified thrombus burden in 2 groups of patients with STB, combining

Table 2 Classification of Thrombus Burden

Thrombus Score	Thrombus Burden* Reference (n = 798)	Reference Non-G5† (n = 343)	G5 Reclassified† (n = 455)	Reclassified Final (n = 798)
G5	455 (57.0)	0 (0)	2 (0.4)	2 (0.3)
G4	77 (9.6)	77 (22.4)	148 (32.5)	225 (28.2)
G3	61 (7.6)	61 (17.8)	80 (17.6)	141 (17.7)
G2	95 (11.9)	95 (27.7)	113 (24.8)	208 (26.1)
G1	68 (8.5)	68 (19.8)	87 (19.1)	155 (19.4)
G0	42 (5.3)	42 (12.2)	21 (4.6)	63 (7.9)
Not available‡	0 (0)	0 (0)	4 (0.9)	4 (0.5)

Data are presented as n (%). *Reference is the classification that includes patients with occluded vessels at presentation (G5), and reclassified is the one after thrombus evaluation in this group following minimal intervention. †p < 0.001 for the comparison of G0, G1, G2, G3, G4 between "Reference Non-G5" and "G5 Reclassified" groups. ‡In 4 patients, reclassification was not possible because of inadequate angiographic documentation.

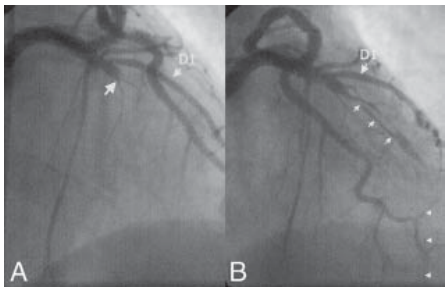

Figure 1 Thrombus Burden Evaluation in a Patient Presenting With an Occluded Infarct-Related Artery

(A) An occluded left anterior descending coronary artery **(arrow)** after the take-off of the first diagonal branch (D1) in a patient who presented with anterior myocardial infarction. **(B)** After crossing the occlusion with an angioplasty guidewire **(arrowheads)** and without further intervention, Thrombolysis In Myocardial Infarction flow grade 1 was restored, allowing the visualization of a large thrombus **(arrows)**.

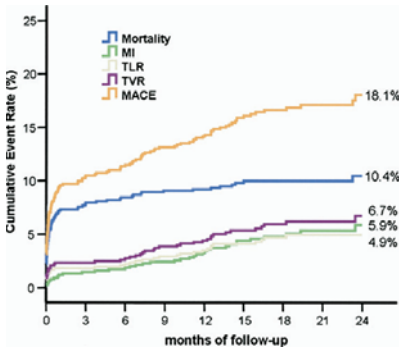

Figure 2 Overall Clinical Outcomes

Two-year cumulative mortality, repeat nonfatal myocardial infarction (MI), infarct-related artery lesion repeat revascularization (TLR), infarct-related artery repeat revascularization (TVR), and major adverse cardiac event (MACE) (death, MI, TVR) rates of patients treated with drug-eluting stents.

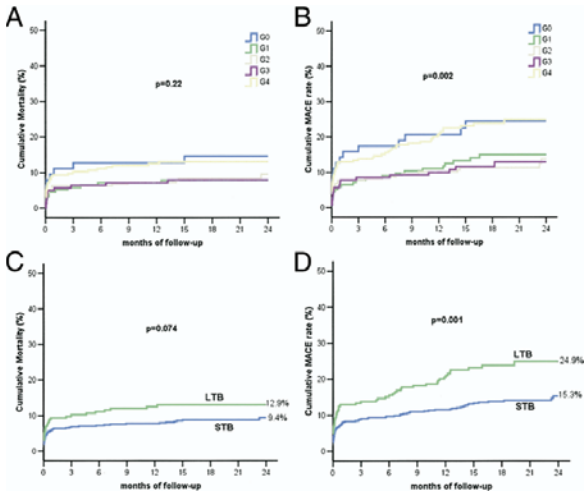

Figure 3 **Mortality and MACE According to Thrombus Burden**

Two-year cumulative mortality and MACE (death, repeat nonfatal myocardial infarction, or infarct-related artery repeat revascularization) rates according to the reclassified thrombus grades before **(A, B)** and after stratification in large thrombus burden (LTB) and small thrombus burden (STB) **(C, D)**. Other abbreviations as in Figure 2.

groups G0 to G3, and LTB, same as G4. The LTB group had higher in-hospital mortality (7.6% vs. 5.1%, p = 0.18). Two-year mortality and MACE rate were increased in LTB patients compared with the STB patients (Figs. 3C and 3D). The difference in mortality became evident early, at 30 days (Fig. 4A), and there was no difference beyond 30 days between the 2 groups (Fig. 4B). An LTB was an independent predictor of 30-day mortality (hazard ratio 1.96, 95% confidence interval 1.12 to 3.43, p = 0.019), as well as 2-year mortality and MACE (Table 3).

Procedural outcome. There were 7 (0.9%) procedural deaths (procedural mortality: LTB group 1.8% vs. STB group 0.5%, p = 0.1). Patients with LTB had a worse final TIMI flow grade, myocardial blush, and complete thrombus removal, as well as more cases of no reflow and distal embolization compared with STB patients (Table 4).

Incidence and predictors of stent thrombosis. Two-year cumulative stent thrombosis, IRA-ST (Fig. 5), and non–IRA-ST rates were 3.8 ± 0.7% (26 events), 3.2 ± 0.7% (22 events), and 0.6 ± 0.3% (4 events), respectively.

IRA-ST. The 2-year cumulative IRA-ST rate was significantly higher in LTB (16 events) compared with STB (6 events) patients (Fig. 5). An LTB was the most hazardous independent predictor of IRA-ST (Table 5). The LTB patients treated with RT had a lower 2-year cumulative IRA-ST (0% vs. 11.3%, p < 0.001) compared with LTB patients without RT.

In relation to antiplatelet medication, 9 (40.9%) IRA-STs occurred under dual antiplatelet therapy, 4 (18.2%) shortly (≤30 days) and 9 (40.9%) long (>30 days) after clopidogrel discontinuation. Chronologically, 4 (18.2%) patients had acute, 5 (22.7%) subacute, 2 (9.1%) late, and 11 (50%) very late IRA-ST. There were 3 additional events beyond the 2 years at 884, 1,067, and 1,074 days; 2 of them with LTB at baseline procedure.

There was no difference in the 2-year cumulative IRA-ST rate between PES and SES both for the total population (PES 3.7 ± 0.9% [18 events] vs. SES 2.1 ± 1.06% [4 events], p = 0.314) and the LTB group (PES 7.5 ± 2.1% [12 events] vs. SES 10.5 ± 4.9% [4 events], p = 0.598).

In patients presenting with stent thrombosis at the index procedure, the 2-year cumulative IRA-ST rate was 20.5 ± 9.2% (4 events), all with LTB. Stent thrombosis at presentation was an independent predictor of IRA-ST (Table 5).

Impact of IRA-ST on clinical outcome. Of the 22 IRA-ST patients, 4 (18.2%) presented with unstable angina, 16 (72.7%) suffered a nonfatal repeat MI, and there were 2 (9.1%) deaths; all underwent TLR. Two-year cumulative mortality attributable to IRA-ST was only 0.3%.

The LTB patients had increased 2-year cumulative repeat MI (Fig. 6A) and TLR (Fig. 6C) rates compared with STB patients. The 2-year cumulative repeat MI rate attributable to IRA-ST (2.4%, 16 events) accounted for 40.7% of the

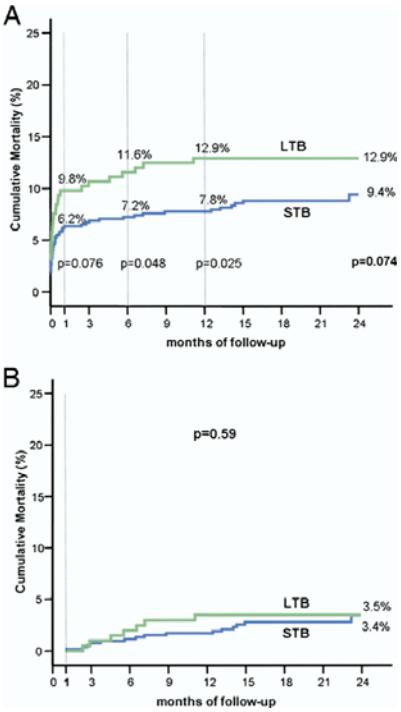

Figure 4 **Impact of Thrombus Burden on Mortality**

Two-year **(A)** and post-30-days cumulative mortality **(B)** according to the presence of large thrombus burden (LTB) or small thrombus burden (STB) at the index procedure.

total 2-year cumulative repeat MI rate (5.9%, 36 events). The 2-year cumulative TLR rate attributable to IRA-ST (3.2%, 22 events) accounted for 67.3% of the total 2-year cumulative TLR rate (4.9%, 34 events). After excluding patients with IRA-ST, there was no significant difference between LTB and STB patients in the 2-year cumulative repeat MI and TLR rates (Figs. 6B and 6D).

The LTB patients had a worse 2-year and post-30-days cumulative MACE rate compared with STB patients (Figs. 7A and 7B). The 2-year cumulative MACE rate attributable to IRA-ST (3.2%, 22 events) accounted for 17.7% of the total 2-year cumulative MACE rate (18.1%, 132 events). The post-30-days cumulative MACE rate attributable to IRA-ST (1.2%, 13 events) accounted for 21.9% of the total post-30-days cumulative MACE rate (9.6%, 58 events). After excluding patients with IRA-ST, there was no significant difference in the post-30-days cumulative MACE rate between LTB and STB patients (Fig. 7C). The LTB patients treated with RT had a lower MACE rate compared with LTB patients without RT (10.7% vs. 30% at 2 years, $p = 0.006$) but similar to that of STB patients (10.7% vs. 15.3% at 2 years, $p = 0.5$).

Discussion

We report our experience on a large cohort of consecutive patients presenting with STEMI and treated with PCI and DES. This is the first report accounting for thrombus burden. An LTB is a fundamental factor for adverse clinical outcomes because it is related to increased 30-day mortality and very high rates of IRA-ST, which account for the majority of the post-30-days MACE.

Thrombus burden. Almost 60% of the patients with STEMI presented with an occluded IRA (G5). This is essentially a flow classification (TIMI flow grade 0), and consequently excludes these patients from any analysis focusing on thrombus burden. We propose a method that allows thrombus burden estimation in almost 99% of these patients after flow restoration with minimal intervention. Minimal antegrade flow (even TIMI flow grade 1) allowing contrast penetration beyond the occlusion is adequate to allow thrombus evaluation.

There was no difference in the clinical outcome of patients with thrombus G1 to G3, both in the univariate and the multivariate analysis. This was the rationale for stratifying these groups as a single category defined as STB. Patients with no thrombus (G0) at presentation showed worse outcomes compared with G1 to G3 patients and similar outcomes compared with G4 patients. Despite their increased risk, these patients were included in the STB group because it is obvious that therapeutic strategies to improve their clinical outcome should not target thrombus.

Incidence of stent thrombosis during STEMI. Randomized trials of elective BMS implantation using dual antiplatelet therapy reported stent thrombosis rates of 0.4% to 1.3% (28,29). Stent thrombosis rates were reported to be similar (around 0.6%) between BMS and DES in a meta-analysis of 10 randomized trials of elective angioplasty (30). Concerns were recently raised that DES might be more thrombogenic compared with BMS in the long-term, especially when implanted in more complex patient subsets (31).

Acute coronary syndromes have been associated with increased rates of stent thrombosis. In registries representing "real world" practice, which included patients with acute coronary syndromes and STEMI treated either with BMS (16,17) or DES (18,32,33), higher rates of stent thrombosis (1.2% to 1.9%) were reported. In 4,607 patients treated with BMS for acute coronary syndromes, an even higher rate of 2.9% of stent thrombosis was observed (15). In the TYPHOON (Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated With Angioplasty) trial, which randomized STEMI patients to SES or BMS, the nonangiographic stent thrombosis was 3.4% and 3.6%,

Table 3 Independent Predictors of Clinical Outcomes

Outcome	Variable	Hazard Ratio	95% Confidence Interval	p Value
2-yr mortality*	Age (per 10-yr increase)	1.76	1.4–2.22	<0.001
	Cardiogenic shock	9.47	5.87–15.28	<0.001
	Prehospital resuscitation	4.28	1.99–9.2	<0.001
	Infarct-related artery			0.024
	Right coronary artery (reference)	1.00		
	Left anterior descending coronary artery	1.66	0.97–2.82	0.064
	Circumflex coronary artery	2.07	0.94–4.55	0.069
	Left main coronary artery	4.06	1.64–10.03	0.002
	Graft	3.9	0.51–29.76	0.189
	Large thrombus burden	1.76	1.08–2.87	0.023
	Thrombus burden‡			0.168
	Grade 4 (reference)	1.00		
	Grade 3	0.51	0.25–1.05	0.066
	Grade 2	0.62	0.34–1.16	0.135
	Grade 1	0.47	0.23–0.95	0.034
	Grade 0	0.78	0.35–1.73	0.543
2-yr major adverse cardiac event†	Age (per 10-yr increase)	1.19	1.01–1.4	0.036
	Female	1.68	1.13–2.48	0.01
	Cardiogenic shock	6.31	4.28–9.28	<0.001
	Stent thrombosis presentation (at index procedure)	3.95	1.95–7.98	<0.001
	Bifurcational stenting	2.24	1.33–3.77	0.002
	Prehospital resuscitation	2.84	1.46–5.52	0.002
	Rheolytic thrombectomy	0.37	0.17–0.78	0.009
	Large thrombus burden	1.88	1.3–2.72	0.001
	Thrombus burden‡			0.005
	Grade 4 (reference)	1.00		
	Grade 3	0.5	0.29–0.88	0.016
	Grade 2	0.45	0.27–0.73	0.001
	Grade 1	0.52	0.31–0.87	0.014
	Grade 0	0.91	0.5–1.66	0.755

*Additional variables entered in the multivariate model but not found to be significant were: female gender, hypercholesterolemia, smoking, multivessel disease, multivessel percutaneous coronary intervention, intra-aortic balloon pump, glycoprotein IIb/IIIa antagonists, bifurcational stenting, direct stenting, final Thrombolysis In Myocardial Infarction flow grade, and stent type. †Additional variables entered in the multivariate model but not found to be significant were: hypercholesterolemia, previous myocardial infarction, previous percutaneous coronary intervention, infarct-related artery, multivessel disease, multivessel percutaneous coronary intervention, intra-aortic balloon pump, glycoprotein IIb/IIIa antagonists, direct stenting, final Thrombolysis In Myocardial Infarction flow grade, and stent type. ‡Similar results in the multivariate analysis (data not provided for the other predictors) were also shown when thrombus burden was inserted as a variable with 5 categories (grade 0, grade 1, grade 2, grade 3, grade 4) instead of 2 (large and small).

whereas the angiographic stent thrombosis was 2.0% and 3.4%, respectively, at 1 year (10). Similarly, in the SESAMI (Sirolimus-Eluting Stent Versus Bare-Metal Stent In Acute Myocardial Infarction) trial, 1-year stent thrombosis rates were 3.1% and 3.7% for SES and BMS, respectively (9).

Table 4 Procedural Outcome

Outcome	Total (n = 792)	STB (n = 567)	LTB (n = 225)	p Value*
Final Thrombolysis In Myocardial Infarction flow grade 3	726 (91.7)	538 (94.9)	188 (83.6)	<0.001
Myocardial blush grade 3†	290 (47.6)	222 (53.2)	68 (35.4)	<0.001
Complete thrombus removal	757 (95.6)	556 (98.1)	201 (89.3)	<0.001
No reflow	12 (1.5)	3 (0.5)	9 (4.0)	0.001
Distal embolization	59 (7.4)	20 (3.5)	39 (17.3)	<0.001

Data are presented as n (%). *Small thrombus burden (STB) versus large thrombus burden (LTB) group. †Myocardial blush assessment was achieved in 609 patients (417 in the STB and 192 in the LTB group).

We observed an incidence of angiographically documented stent thrombosis of 3.2% at 2 years. The angiographically documented stent thrombosis underestimates the true incidence of stent thrombosis because sudden deaths and repeat MIs also may be related to this complication. Moreover, patients continued to present with stent thrombosis beyond the 2-year time window. Similar cases of very late DES thrombosis in STEMI patients recently have been reported (34,35).

Mechanisms of early and late stent thrombosis during STEMI. Stent underexpansion, malapposition, residual dissections, and inflow/outflow disease have been well established by intravascular ultrasound as mechanical causes related to early stent thrombosis for BMS (16,36–39) and DES (40).

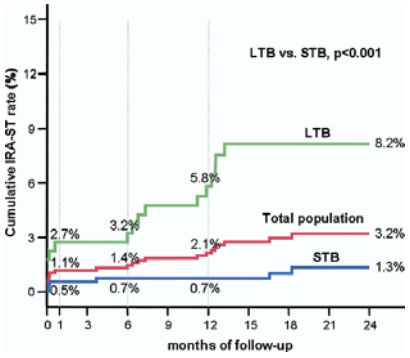

Figure 5 Infarct-Related Artery Stent Thrombosis

Two-year cumulative infarct-related artery stent thrombosis (IRA-ST) rate for the total population and according to the existence of large thrombus burden (LTB) or small thrombus burden (STB) at the index procedure.

Primary stenting during acute MI has been recognized as an independent predictor of late stent malapposition both after BMS (41) and DES (42) with an incidence 2- to 3-fold higher compared with elective stenting. Thrombus compression/displacement by the stent struts in the acute phase with abluminal thrombus resolution in the long term has been proposed as a potential mechanism. However, its incidence with DES was 31.8%, 3 times higher compared with BMS (11.5%). These intravascular ultrasound observations may well explain the negative late loss observed in STEMI trials with DES implantation and angiographic follow-up (3,6). An LTB was the strongest predictor of stent thrombosis, and LTB patients experienced an extremely high IRA-ST rate of 8.2%. It is rational that the larger the thrombotic burden, the higher will be the incidence of incomplete stent apposition that might account for the higher rates of late stent thrombosis in LTB patients in the long term. Moreover, the presence of thrombus has been clearly identified as a factor predisposing to stent thrombosis (14,36,39). Persistence of thrombus was an independent predictor of early repeat MI in the PAMI (Primary Angioplasty in Myocardial Infarction) trials (43). Patients with STB had an IRA-ST rate of 1.3%, similar to that reported during elective stenting (14,28,29).

Mechanical reasons may be inadequate to explain the stent thrombosis rates during STEMI; their incidence is common but the incidence of stent thrombosis remains relatively low. Increased platelet activity and aspirin resistance have been shown during STEMI (44). Furthermore, stent thrombosis has been associated with an impaired response to antiplatelet therapy, particularly in ACS patients (45). There is evidence that preintervention plaque composition resembling that of a STEMI setting predisposes to stent thrombosis (46).

Procedural and periprocedural factors related to stent thrombosis. Discontinuation of dual antiplatelet therapy after DES implantation has been related to an increased risk for stent thrombosis (32,33). In our study, 59% of our patients experienced IRA-ST while on aspirin monotherapy; 18% within the first 30 days after discontinuation of clopidogrel. Stent thrombosis occurred in patients while stable for very long on antiplatelet monotherapy. Dual antiplatelet therapy was not able to prevent 41% of the events. Whether it would have prevented the late cases of stent thrombosis remains unclear. The efficacy of dual antiplatelet therapy and its duration remains unclear in a STEMI setting.

Bifurcation stenting has been recognized previously as a risk factor for stent thrombosis in stable patients treated with DES (18,32). It was the second strongest independent predictor of stent thrombosis in our study, and therefore it should be avoided if not absolutely necessary.

The worse procedural outcomes observed in LTB compared with STB patients were translated into increased short-term mortality. Mortality after 30 days was comparable between the 2 groups. Similar results were recently reported in a large cohort of patients (47).

The use of thrombectomy devices during STEMI remains controversial. There were positive results reported when surrogate markers, such as ST-segment resolution, TIMI flow, or left ventricular remodeling (48–50), were used as end points, but there are no randomized studies reporting positive outcomes in hard clinical end points such as survival and MACE (23,24). The majority of these trials were underpowered for clinical outcomes, a fact that is indicative of the relative paucity of evidence, and thrombus burden was not considered. Safety issues were recently raised regarding routine application of thrombectomy in all comers with STEMI (24). Based on the current results, the potential of thrombectomy devices in STEMI should be explored selectively in patients at higher risk, such as those with LTB, in a prospective randomized fashion.

Efficacy of DES and thrombus burden. The rate of TVR with BMS implantation for STEMI has been reported to be 8% to 10% (51–53). Experience with DES for STEMI

Table 5 Independent Predictors of Infarct-Related Artery Stent Thrombosis

Variable*	Hazard Ratio	95% Confidence Interval	p Value
Age (per 10-yr increase)	0.55	0.37–0.82	0.003
Stent thrombosis at presentation	6.24	2.06–18.92	0.001
Bifurcational stenting	4.06	1.64–10.02	0.002
Rheolytic thrombectomy	0.11	0.01–0.81	0.03
Large thrombus burden	8.73	3.39–22.47	<0.001

*Additional variables entered in the multivariate model but not found to be significant were diabetes mellitus, previous myocardial infarction, previous percutaneous coronary intervention, and direct stenting.

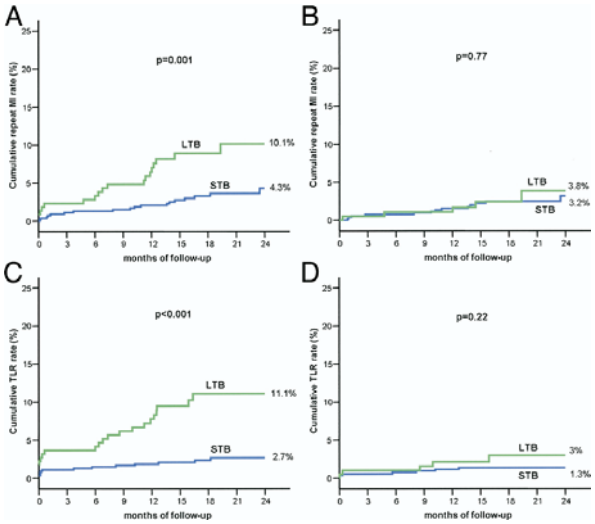

Figure 6 **Impact of Thrombus Burden and IRA-ST on Repeat MI and TLR**

Two-year cumulative **(A)** repeat myocardial infarction (MI) and **(C)** infarct-related artery lesion repeat revascularization (TLR) rates in relation to large thrombus burden (LTB) or small thrombus burden (STB) at the index procedure. The corresponding rates after excluding patients with infarct-related artery stent thrombosis (IRA-ST) are presented in **(B)** and **(D)**, respectively. After excluding IRA-ST, the total 2-year cumulative repeat MI and TLR rates are 3.3% and 1.7%, respectively.

showed lower TLR rates, around 2% to 4% (3,4,7,8,11,12). In our patients the 2-year TLR rate was 4.9%, and it was significantly higher in LTB compared with STB patients. It has been reported that thrombus can modulate stent-based drug elution and significantly alter vessel wall drug levels and potentially efficacy (54). Such concerns do not seem to be confirmed because excluding reintervention caused by IRA-ST, which is not related to restenosis, the overall TLR rate was very low (1.7%) and was comparable in LTB and STB patients.

Study limitations. This is a retrospective analysis with all of the limitations arising from such an approach. Potential thrombus burden modification related to preprocedural pharmacotherapy cannot be excluded. Angiography has inherent limitations for assessing thrombus burden, and there is no gold standard method to be compared with. However, it is the imaging modality used for decision making during PCI for STEMI, and in that respect this classification is clinically relevant. The poor outcome of G0 patients is poorly understood and should be further explored. Established parameters related to clinical outcomes such as infarct duration and myocardial blush were not available for all patients and were not included in the multivariate analysis model. No quantitative angiographic analysis was performed, and parameters such as lesion characteristics and stent length also were not accounted for.

Discontinuation of antiplatelet medication is a well-established risk factor for stent thrombosis. In our analysis, the antiplatelet medication status of the patients who developed stent thrombosis was well established, but no reliable information was possible to be obtained for patients who did not experience stent thrombosis, and therefore this parameter also was not included in the multivariate analysis. Of note, 6 months of double antiplatelet medication, the maximum prescribed in our patients, is regarded as inadequate today. All patients who developed stent thrombosis beyond 6 months were on aspirin monotherapy. We currently prescribe 12 months of double antiplatelet medication in all STEMI patients treated with DES.

Conclusions

In patients presenting with STEMI, minimal intervention with either guidewire crossing or a small (diameter 1.5 mm) deflated balloon passage or predilation restores flow enough to allow intracoronary thrombus estimation in angiographically occluded vessels. Thrombus stratification in LTB (≥2 vessel diameters) and STB has prognostic value.

Patients with STEMI treated with PCI and DES experience a high 2-year rate (3.2%) of IRA-ST, which continues to occur even beyond that time window. An LTB is a predictor of MACE. This is because of increased 30-day

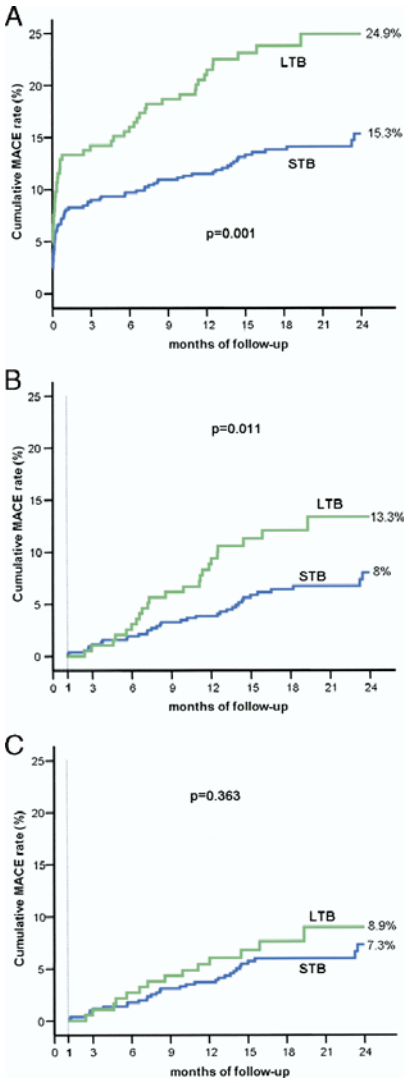

Figure 7 **Impact of Thrombus Burden and IRA-ST on MACE**

Two-year cumulative major adverse cardiac event (MACE) rate **(A)**, post-30-days cumulative MACE rate **(B)**, and post-30-days cumulative MACE rate after excluding patients with infarct-related artery stent thrombosis **(C)** in relation to large thrombus burden (LTB) and small thrombus burden (STB) at the index procedure.

mortality related to worse procedural outcome and very high rates of early and late IRA-ST in LTB patients. An LTB does not influence the clinical antirestenotic efficacy of DES.

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Chapter 20

A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents

Spaulding C, Daemen J, Boersma E, Cutlip D, Serruys PW

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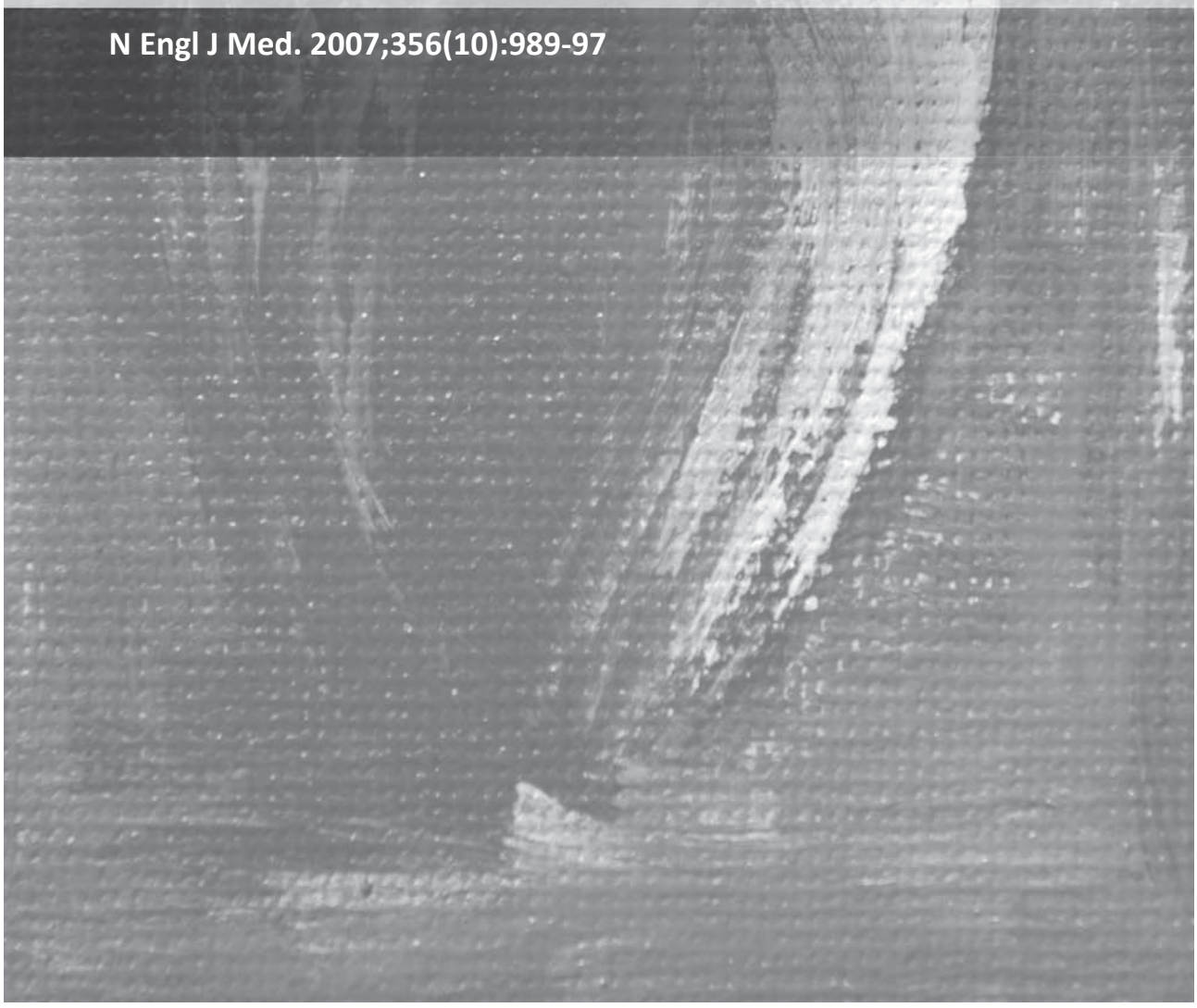

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A Pooled Analysis of Data Comparing Sirolimus-Eluting Stents with Bare-Metal Stents

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ABSTRACT

BACKGROUND

Although randomized studies have shown a beneficial effect of drug-eluting stents in reducing the risk of repeated revascularization, these trials were underpowered to compare rates of death and myocardial infarction. The long-term safety of drug-eluting stents has been questioned recently.

METHODS

We performed a pooled analysis of 1748 patients in four randomized trials evaluating the safety of sirolimus-eluting stents as compared with bare-metal stents. Patient-level data were obtained and analyzed at independent statisticians at two academic institutions. The primary safety end point was survival at 4 years. We tested for heterogeneities in treatment effect in patient subgroups.

RESULTS

The survival rate at 4 years was 93.3% in the sirolimus-stent group, as compared with 94.6% in the bare-metal–stent group (hazard ratio for death, 1.24; 95% confidence interval [CI], 0.84 to 1.83; P=0.28). In the 428 patients with diabetes, a significant difference in the survival rate was observed in favor of the bare-metal–stent group over the sirolimus-stent group (95.6% vs. 87.8%; hazard ratio for death in the sirolimus-stent group, 2.9; 95% CI, 1.38 to 6.10; P=0.008). The lower survival rate among patients with diabetes who were treated with sirolimus-eluting stents was due to increased numbers of deaths from both cardiovascular and noncardiovascular causes. No difference in survival rate was detected among the patients without diabetes. Rates of myocardial infarction and stent thrombosis were similar in the two groups.

CONCLUSIONS

In a pooled analysis of data from four trials comparing sirolimus-eluting stents and bare-metal stents, no significant differences were found between the two treatments in rates of death, myocardial infarction, or stent thrombosis. (ClinicalTrials.gov numbers, NCT00233805, NCT00381420, NCT00232765, and NCT00235144.)

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Since April 2002, randomized trials and registries have shown that drug-eluting stents, as compared with bare-metal stents, reduce the need for subsequent revascularization procedures.[1-6] As a result, the use of drug-eluting stents has increased rapidly, with current rates up to 80% of all stenting procedures in some countries. However, two recent meta-analyses have suggested that rates of death and myocardial infarction may be increased in patients who have received drug-eluting stents.[7,8] Impaired reendothelialization, late endothelial dysfunction, hypersensitivity reactions to the stent or its coating, and stent thrombosis have been suggested as potential causes.[9-17] The consequences of even a slight increase in the rates of death and myocardial infarction would be dramatic, considering the current high rate of use of drug-eluting stents.

The early and pivotal randomized studies that led to approval of stents for marketing were individually not adequately powered to detect differences in the rates of death, myocardial infarction, or stent thrombosis. However, reliable long-term data, including information about these end points, are now available and can be pooled to conduct analyses with greater power than those in the original trials. We therefore performed a safety analysis of patient-level data collected, in four randomized trials comparing sirolimus-eluting stents and bare-metal stents, during a follow-up period of 4 years for 1748 patients.

Methods

Original Trials

Our analysis is based on pooled patient-level data from the Randomized Study with the Sirolimus-Coated Bx Velocity Balloon Expandable Stent in the Treatment of Patients with De Novo Native Coronary Artery Lesions (RAVEL), the Sirolimus-Eluting Balloon-Expandable Stent in the Treatment of Patients with De Novo Native Coronary-Artery Lesions (SIRIUS) trial, the European SIRIUS (E-SIRIUS) trial, and the Canadian SIRIUS (C-SIRIUS) trial, all of which were performed between August 2000 and April 2002. Each of these four trials compared a sirolimus-eluting stent (Cypher, Cordis, a Johnson & Johnson company) with a bare-metal stent of identical design (Bx Velocity, Cordis), but without polymer and drug coatings, implanted in single, previously untreated lesions in native coronary arteries, using a double-blind study design with a 1:1 randomization process.

The designs of these trials, as well as short-term angiographic and clinical outcomes, have been reported previously.[1-4] In summary, RAVEL included patients in clinically stable condition with relatively low-risk lesions, whereas the three SIRIUS trials involved patients with higher-risk and more complex lesions. Patients with acute myocardial infarction were excluded in all four trials. A total of 428 patients with diabetes (treated through diet, with an oral hypoglycemic agent, or with insulin) were included.

Dual antiplatelet therapy with aspirin and clopidogrel or ticlopidine was prescribed per protocol for a minimum of 2 months in RAVEL and the E-SIRIUS and C-SIRIUS trials and for a minimum of 3 months in the SIRIUS trial. Aspirin was prescribed indefinitely; doses ranged from 81 to 325 mg daily.

The protocols called for complete angiographic follow-up at 6 months (in RAVEL) or at 8 months (in the SIRIUS, E-SIRIUS, and C-SIRIUS studies) and clinical follow-up yearly. The primary end points differed among the studies and included purely angiographic end points (in-stent late loss in RAVEL and in-stent minimal lumen diameter at 8 months in the E-SIRIUS and C-SIRIUS trials) as well as the clinical end point of target-vessel failure (a composite of death, myocardial infarction, and target-vessel revascularization) in the SIRIUS trial. Secondary end points included death, myocardial infarction, and repeated revascularization.

The study protocols were approved by the ethics committee at each participating institution and were conducted according to the principles of the Declaration of Helsinki. All patients gave written informed consent before enrollment. The studies were sponsored and monitored by Cordis.

The design of each trial specified in advance that data would be collected for up to 5 years, with adjudication of events by the independent end-points committee of the original trial. Four-year follow-up data are currently available from all four studies. All clinical follow-up information was collected at the investigating centers in a blind fashion.

Current Analysis

The databases of the individual studies were obtained from Cordis. Study coordination and data management were performed at two independent central research organizations (Cardialysis, Rotterdam, the Netherlands, for RAVEL, and Harvard

Clinical Research Institute, Boston, for the SIRIUS, E-SIRIUS and C-SIRIUS studies). The patient-level data were pooled and then analyzed by one independent statistician at Harvard Clinical Research Institute and another at Erasmus University Medical Center, Rotterdam. The authors were given unrestricted access to the data by Cordis and made all decisions about analysis and publication independently of the company.

STUDY END POINTS

The primary safety end point was death from any cause. Information on the circumstances of all deaths was obtained from each of the sites, and narratives were developed. These narratives were reviewed by the clinical events committees for the trials and, for the conduct of our analysis, by three of the authors.

Secondary safety end points were death from cardiovascular causes and noncardiovascular causes, death from any cause or Q-wave myocardial infarction, and death from any cause or any type of myocardial infarction. The following definitions of events were used in all four trials.

Death from cardiovascular causes was defined either as death due to acute myocardial infarction, cardiac perforation or pericardial tamponade, arrhythmia or conduction abnormality, cerebrovascular accident within 30 days or related to the procedure, or a complication of the procedure or as any death in which a cardiovascular cause could not be ruled out. Death from noncardiovascular causes was defined as any death not due to a cardiovascular cause.

Q-wave myocardial infarction was defined as the development of new, pathologic Q-waves in two or more contiguous leads as assessed by the electrocardiography core laboratory, with creatine kinase or creatine kinase MB levels elevated above the upper limit of the normal range. Non–Q-wave myocardial infarction was defined as an elevation of the creatine kinase MB level to three times the normal value in the absence of new, pathologic Q-waves; if no assay for creatine kinase MB was performed, elevation of the creatine kinase level to a value that was twice the normal value in the absence of new Q-waves was also considered a non–Q-wave myocardial infarction.

In the study protocols, stent thrombosis was defined as acute if it occurred within 24 hours after the index procedure, subacute if it occurred between 1 and 30 days after the procedure, and late if it occurred more than 30 days after the procedure. Acute and subacute stent thromboses were classified on the basis of vessel occlusion on angiography, any recurrent Q-wave myocardial infarction in an area irrigated by the stented vessel, or death from cardiac causes. Late stent thrombosis was diagnosed on the basis of any recurrent myocardial infarction with vessel occlusion on angiography. In the original trial protocols, secondary stent thrombosis — stent thrombosis in a patient who had previously undergone target-lesion revascularization — was not considered to be a stent thrombosis.

Stent thrombosis was reclassified in a blind fashion by an independent research organization (Harvard Clinical Research Institute) according to a set of definitions developed during summer 2006 by an academic research consortium (ARC) of academic investigators, regulators, and industry representatives. These definitions were proposed to serve as standard criteria for stent thrombosis for the comparison of event rates across different trials and studies. According to the ARC definitions, stent thrombosis was classified as acute if it occurred within 24 hours after the index procedure, subacute if it occurred between 1 and 30 days after, late if it occurred between 31 days and 1 year after, and very late if it occurred more than 1 year after the procedure.

Furthermore, stent thrombosis was considered definite if there was angiographic confirmation of thrombus, with or without vessel occlusion, associated with clinical or electrocardiographic signs of acute ischemia or elevation of creatine kinase levels to twice the normal value within 48 hours of angiography. Stent thrombosis was classified as probable if unexplained death occurred within 30 days after the index procedure or if a myocardial infarction, occurring at any time after the index procedure, was documented in an area irrigated by the stented vessel in the absence of angiographic confirmation of stent thrombosis. Stent thrombosis was classified as possible if unexplained death occurred more than 30 days after the index procedure. During the readjudication of stent thrombosis according to the ARC definitions, events occurring after repeated target-lesion revascularization were included.

STATISTICAL ANALYSIS

The effectiveness analysis and safety evaluation were both performed in a modified intention-to-treat population, including all patients who actually underwent stent placement (whether the pro-

Table 1. Baseline Clinical and Angiographic Characteristics.*

Characteristic	Sirolimus-Stent Group	Bare-Metal–Stent Group	P Value
Age — yr			
Median	61	62	0.91
IQR	54–70	54–70	
Range	24–92	32–89	
Male sex — no./total no. (%)	629/878 (71.6)	622/870 (71.5)	0.95
Diabetes mellitus — no./total no. (%)	195/878 (22.2)	233/868 (26.8)	0.02
Insulin-dependent diabetes mellitus — no./total no. (%)	51/195 (26.2)	62/233 (26.6)	0.92
Previous MI — no./total no. (%)	287/865 (33.2)	308/862 (35.7)	0.26
Previous PCI — no./total no. (%)	201/878 (22.9)	184/869 (21.2)	0.39
Previous coronary-artery bypass graft — no./total no. (%)	66/878 (7.5)	64/870 (7.4)	0.90
Hyperlipidemia — no./total no. (%)	613/866 (70.8)	617/859 (71.8)	0.63
Hypertension — no./total no. (%)	557/873 (63.8)	548/866 (63.3)	0.82
Current smoker — no./total no. (%)	183/862 (21.2)	210/858 (24.5)	0.11
Congestive heart failure — no./total no. (%)	36/869 (4.1)	49/861 (5.7)	0.14
CCS angina classification III or IV — no./total no. (%)†	344/831 (41.4)	344/831 (41.4)	1.00
Silent ischemia — no./total no. (%)	152/783 (19.4)	155/793 (19.5)	0.95
Ejection fraction — %			
Median	59	60	0.55
IQR	50–64	50–65	
Range	25–91	25–89	
Coronary artery disease — no./total no. (%)			
Single-vessel	538/876 (61.4)	531/868 (61.2)	0.92
Double-vessel	216/876 (24.7)	236/868 (27.2)	0.23
Triple-vessel	122/876 (13.9)	101/868 (11.6)	0.15
Procedure success — no./total no. (%)	858/877 (97.8)	852/868 (98.2)	0.63
Target vessel — no./total no. (%)			
LAD	408/878 (46.5)	407/870 (46.8)	0.98
LCx	210/878 (23.9)	207/870 (23.8)	0.90
RCA	254/878 (28.9)	254/870 (29.2)	0.96
LMCA	3/878 (0.3)	3/870 (0.3)	1.00
SVG	0	1/870 (0.1)	0.31
Severe calcification — no./total no. (%)	37/755 (4.9)	26/754 (3.4)	0.16
Total occlusion — no./total no. (%)	25/875 (2.9)	20/870 (2.3)	0.46
Disease of branch vessel — no./total no. (%)	55/755 (7.3)	46/755 (6.1)	0.35
Modified ACC–AHA lesion class — no./total no. (%)‡			
A	61/875 (7.0)	61/870 (7.0)	0.98
B1	297/875 (33.9)	317/870 (36.4)	0.28
B2	320/875 (36.6)	332/870 (38.1)	0.50
C	197/875 (22.5)	161/870 (18.5)	0.04

Table 1. (Continued.)

Characteristic	Sirolimus-Stent Group	Bare-Metal–Stent Group	P Value
Reference-vessel diameter — mm			
Median	2.7	2.7	0.98
IQR	2.4–3.0	2.4–3.0	
Range	1.5–4.5	1.7–5.4	
Lesion length — mm			
Median	12.7	13.1	0.96
IQR	10.0–16.6	9.8–16.5	
Range	3.2–41.5	3.4–48.9	

* Data for some characteristics were missing for some patients. IQR denotes interquartile range, MI myocardial infarction, PCI percutaneous coronary intervention, LAD left anterior descending coronary artery, LCx left circumflex coronary artery, RCA right coronary artery, LMCA left main coronary artery, and SVG saphenous-vein graft.
† Canadian Cardiovascular Society (CCS) angina classifications III and IV are defined as angina on mild exertion and angina at any level of physical exertion, respectively.
‡ Modified American College of Cardiology (ACC) and American Heart Association (AHA) lesion classes A, B1, B2, and C are defined as a low-risk lesion, a moderate-risk lesion with one or with two or more risk factors, and a high-risk lesion, respectively.

cedure was successful or not). Patients who were randomly assigned to treatment but who did not undergo a procedure were not included in the analysis.

Summary statistics for all continuous variables are presented as medians and interquartile ranges. Categorical data are summarized as frequencies and percentages. Differences in baseline characteristics between the sirolimus-stent group and the bare-metal–stent group were analyzed using the Wilcoxon–Mann–Whitney test or Fisher's exact test.

The incidence of events over time was studied with the use of the Kaplan–Meier method, whereas log-rank tests and Cox proportional-hazards regression analyses were applied to evaluate differences between the two groups. In the main analysis, hazard ratios and 95% confidence intervals (CIs) were adjusted for differences in outcome between trials. Follow-up at 1, 2, and 3 years was completed for 99.1%, 97.8%, and 96.3% of the patients, respectively. Because follow-up data for the period between 1441 and 1460 days were lacking in 675 patients, we decided to count events through 1440 days, which was interpreted as 4 years of follow-up. This 4-year follow-up was completed in 90.7% of patients (90.5% of those who received sirolimus-eluting stents and 90.9% of those who received bare-metal stents).

Exploratory analyses (not prespecified) were performed to evaluate possible heterogeneities in treatment effects on mortality according to the trial in which the patient was enrolled and the following 10 clinically relevant characteristics: age, sex, diabetes, dyslipidemia, hypertension, prior myocardial infarction, heart failure, angina classification by the Canadian Cardiovascular Society, number of diseased vessels, and left ventricular ejection fraction.[5] Since a clinically relevant difference in treatment effect on mortality was observed in relation to diabetes status, we decided to study other end points in patients with and those without diabetes. Treatment effects were evaluated with the use of Cox regressions that included a term for the interaction between each characteristic of interest and the assigned treatment, adjusted for differences in outcome between trials. More extensive regression models incorporating predictive baseline characteristics were applied to estimate the adjusted treatment effects.[18]

All statistical tests were two-sided, without correction for multiple testing. P values of less than 0.05 and less than 0.01 were considered to indicate statistical significance for the results of nonheterogeneity tests and tests for heterogeneity in treatment effect, respectively. All statistical analyses were performed with the use of SAS software, version 8.2 (SAS Institute).

RESULTS

A total of 1748 patients were included in this analysis (238 in RAVEL, 1058 in the SIRIUS study, 100 in the C-SIRIUS study, and 352 in the E-SIRIUS

study). In total, 878 patients underwent placement of a sirolimus-eluting stent, and 870 patients underwent placement of a bare-metal stent. The clinical and angiographic characteristics of the study patients are summarized in Table 1. Complex lesions were more frequent in patients with sirolimus-eluting stents than in patients with bare-metal stents (22.5% vs. 18.5%, P=0.04), and diabetes was more common in the bare-metal–stent group than in the sirolimus-stent group (26.8% vs. 22.2%, P=0.02).

Results for all patients are shown in Table 2 and Figure 1. The 4-year cumulative survival rate was slightly, but not significantly, lower in the sirolimus-stent group than in the bare-metal–stent group (93.3% and 94.6%, respectively; hazard ratio for death in the sirolimus group, 1.24; 95% CI, 0.84 to 1.83; P=0.28). Narratives of all patient deaths revealed that mortality from both cardiovascular and noncardiovascular causes was slightly, but not significantly, higher in the sirolimus-stent group (Table 2 and the Supplementary Appendix, available with the full text of this article at www.nejm.org). Rates of myocardial infarction overall were similar between the two groups. Rates of Q-wave myocardial infarction were also slightly, but not significantly, higher in the sirolimus-stent group.

Table 2. Incidences of Death, Myocardial Infarction, and Stent Thrombosis after 1440 Days of Follow-up.*

End Point	Sirolimus-Stent Group (N=878)	Bare-Metal–Stent Group (N=870)	Adjusted Hazard Ratio (95% CI)	P Value
	number (percent)			
Death	57 (6.7)	46 (5.4)	1.24 (0.84–1.83)	0.28
Cardiovascular cause	29 (3.5)	23 (2.7)	1.26 (0.73–2.18)	0.40
Noncardiovascular cause	28 (3.3)	23 (2.8)	1.22 (0.70–2.11)	0.49
MI	55 (6.4)	53 (6.2)	1.03 (0.71–1.51)	0.86
Q-wave	18 (2.1)	11 (1.3)	1.64 (0.78–3.47)	0.20
Non–Q-wave	37 (4.3)	43 (5.0)	0.85 (0.55–1.33)	0.48
Death or Q-wave MI	70 (8.2)	55 (6.5)	1.28 (0.90–1.82)	0.17
Death or any MI	100 (11.6)	90 (10.5)	1.11 (0.83–1.47)	0.48
Stent thrombosis as defined in protocols†				
Acute	0	0	—	
Subacute	4 (0.5)	1 (0.1)	4.02 (0.45–35.98)	0.21
Late	6 (0.7)	4 (0.5)	1.50 (0.42–5.30)	0.53
Stent thrombosis as defined by the ARC‡				
Acute	0	0	—	
Subacute	4 (0.5)	3 (0.5)	1.34 (0.30–5.93)	0.70
Late	3 (0.3)	11 (1.3)	0.18 (0.04–0.81)	0.03
Very late	23 (2.8)	14 (1.7)	1.65 (0.85–3.20)	0.14
Definite	10 (1.2)	7 (0.8)	1.43 (0.54–3.76)	0.47
Definite or probable	13 (1.5)	15 (1.8)	0.87 (0.41–1.82)	0.70
Any	30 (3.6)	28 (3.3)	1.07 (0.64–1.79)	0.80

* All percentages are based on Kaplan–Meier estimates. Numbers of patients for death or Q-wave myocardial infarction (MI) and death or any MI do not total the sums for each end point alone because some patients had both end points. CI denotes confidence interval.

† Definitions of stent thrombosis according to the study protocols were as follows: acute, within 24 hours after the procedure; subacute, within 1 to 30 days after; and late, more than 30 days after.

‡ Definitions of stent thrombosis according to the academic research consortium (ARC) were as follows: acute, within 24 hours after the procedure; subacute, within 1 to 30 days after; late, between 31 days and 1 year after; and very late, more than 1 year after. See text for details on stent-thrombosis adjudication per protocol and per ARC definitions.

According to the protocol definitions, there were 10 stent thromboses in the sirolimus-stent group and 5 in the bare-metal–stent group (Table 2). Five of the thromboses in the sirolimus-stent group, but none in the bare-metal–stent group, occurred after 1 year. In contrast, according to the ARC definitions, there were 30 stent thromboses in the sirolimus-stent group and 28 in the bare-metal–stent group (Fig. 2). Stent thrombosis was more frequent in the bare-metal–stent group in the first year (14, vs. 6 in the sirolimus-stent group), whereas very late stent thrombosis (occurring after the first year) was more frequent in the sirolimus-stent group (23, vs. 14 in the bare-metal–stent group).

Significant heterogeneity in the treatment effects was not found for any of the prespecified subgroups except patients with diabetes (P value for interaction = 0.008) (see the Supplementary Appendix). The 4-year cumulative survival rates among patients without diabetes did not differ significantly between the two groups. However, the survival rate for patients with diabetes was significantly lower in the sirolimus-stent group (87.8%, vs. 95.6% in the bare-metal–stent group; hazard ratio for death, 2.90; 95% CI, 1.38 to 6.10; P=0.008) (Fig. 3 and the Supplementary Appendix). A large heterogeneity in the causes of death of the patients with diabetes precluded the identification of a clear pattern of mortality (see the Supplementary Appendix). Among the patients with diabetes, there was a small excess of very late stent thrombosis as defined by the ARC (occurring more than 1 year after the procedure) in the sirolimus-stent group (11 patients, vs. 3 in the bare-metal–stent group) (see the Supplementary Appendix).

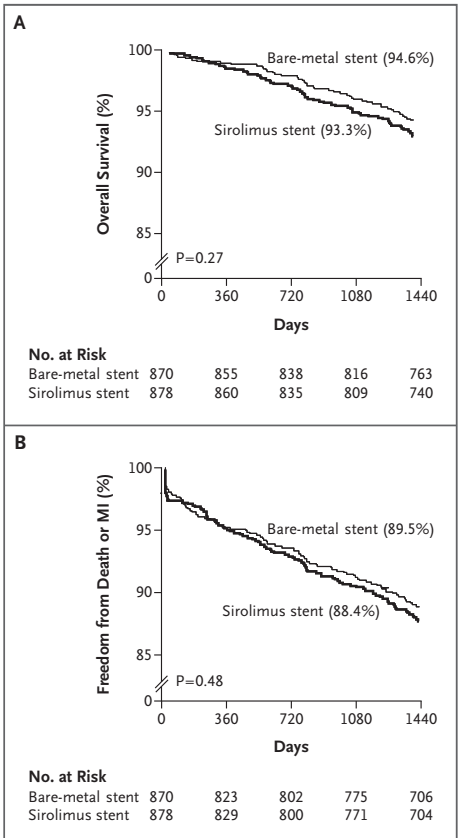

Figure 1. Kaplan–Meier Survival Curves for Patients Who Received a Sirolimus-Eluting Stent and Those Who Received a Bare-Metal Stent.

Panel A shows overall survival; Panel B shows freedom from death or myocardial infarction (MI). The survival rates at 1440 days are shown in parentheses. P values were calculated with the use of the log-rank test.

DISCUSSION

In this study, we performed a pooled analysis of four randomized trials comparing sirolimus-eluting stents and bare-metal stents in 1748 patients with 4 years of follow-up. We did not find evidence of a significantly higher rate of death, myocardial

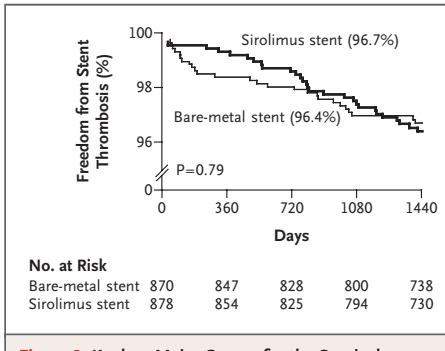

Figure 2. Kaplan–Meier Curves for the Survival of Patients without Stent Thrombosis as Defined by the Academic Research Consortium.

All first episodes of stent thrombosis were counted, including those that occurred after revascularization of the target lesion. The survival rates at 1440 days are shown in parentheses. The P value was calculated with the use of the log-rank test.

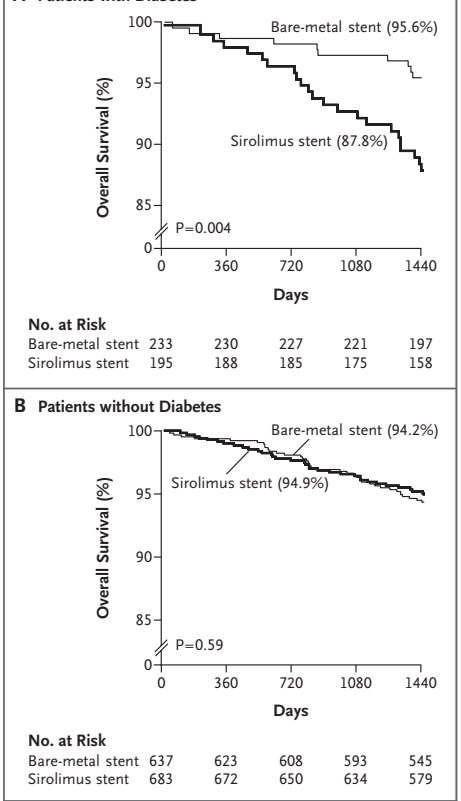

Figure 3. Kaplan–Meier Survival Curves for Patients with Diabetes (Panel A) and Those without Diabetes (Panel B).

The survival rates at 1440 days are shown in parentheses. P values were calculated with the use of the log-rank test.

infarction, or stent thrombosis in the patients treated with sirolimus-eluting stents. The divergence of the Kaplan–Meier survival curves over time could be interpreted as a growing trend toward a lower survival rate among patients treated with sirolimus-eluting stents as compared with those treated with bare-metal stents, although a larger number of patients, a longer follow-up period, or both would be necessary to confirm this interpretation.

In our study, we analyzed rates of stent thrombosis adjudicated according to the definitions in the original protocols and those of the ARC. We believe that this provides a more accurate picture of the incidence of stent thrombosis with either type of stent, for two reasons. First, late events such as unexplained death, which were not considered in the original protocols, were adjudicated as possible stent thrombosis. Second, all episodes of stent thrombosis, including those occurring after target-lesion revascularization, were included in the readjudicated event rates.

A significant heterogeneity of the treatment effect was found with respect to diabetes. A significantly reduced survival rate was found among patients with diabetes (but not patients without diabetes) treated with sirolimus-eluting stents. Deaths from cardiovascular and noncardiovascular causes were more frequent in the sirolimus-stent group. In the subgroup of patients with diabetes, very late stent thrombosis was adjudicated more frequently among the patients with sirolimus-eluting stents than among those with bare-metal stents. Owing to the low number of events, these findings should be interpreted with caution; it does not appear that they adequately explain the observed difference in survival among patients with diabetes in the two groups.

Previous studies have reached different conclusions regarding the benefit of drug-eluting stents in patients with diabetes. The 9-month results of a dedicated randomized trial of patients with diabetes showed that sirolimus-eluting stents were superior to bare-metal stents in reducing rates of both restenosis and repeated revascularization.[19] Mortality at 9 months was only 1% in the sirolimus-stent group, as compared with 2% in the bare-metal–stent group. Conversely, the 2-year follow-up of 708 patients with diabetes from a large registry on the use of drug-eluting stents revealed a mortality of 13.3% among patients treated with sirolimus-eluting stents, as compared with 9.8% among patients treated with bare-metal stents.[20] Although the difference in mortality was not significant, a hazard ratio for death of 1.55 remained after a propensity analysis. In addition, the rate of angiographically proven stent thrombosis in that study was 4.4% in the sirolimus-stent group but only 0.8% in the bare-metal–stent group. Finally, diabetes has been shown to be a consistent independent predictor of stent thrombosis in patients treated with drug-eluting stents.[21,22]

Several limitations of our study should be considered. The analysis was underpowered to detect a clinically significant difference in mortality; more than 11,000 patients would have been need-

ed for such an analysis. Patients included in the four randomized trials were highly selected and are representative of only about 25% of patients currently treated with drug-eluting stents. Treatment with clopidogrel was required for at least 2 or 3 months, according to the original trial protocols, but no information on actual use by individual patients, even by those who had adverse events, was available. Thus, we cannot provide any specific insight into the question of whether prolonging dual antiplatelet therapy further would reduce the risk of such events. We performed multiple subgroup analyses that were not prespecified, including one for diabetes. The number of fatal events in patients with diabetes was small, so the related findings may be due to chance. Finally, lower-than-expected mortality was noted among the patients with diabetes in the bare-metal–stent group, for reasons that remain unclear.

In summary, in our pooled analysis of data from four randomized trials, we compared the effects of sirolimus-eluting stents with those of bare-metal stents on clinical events at 4 years. No significant differences in the rates of death, myocardial infarction, or stent thrombosis were found.

Dr. Spaulding reports receiving consulting and lecture fees from Cordis, Boston Scientific, and Guidant. No other potential conflict of interest relevant to this article was reported.

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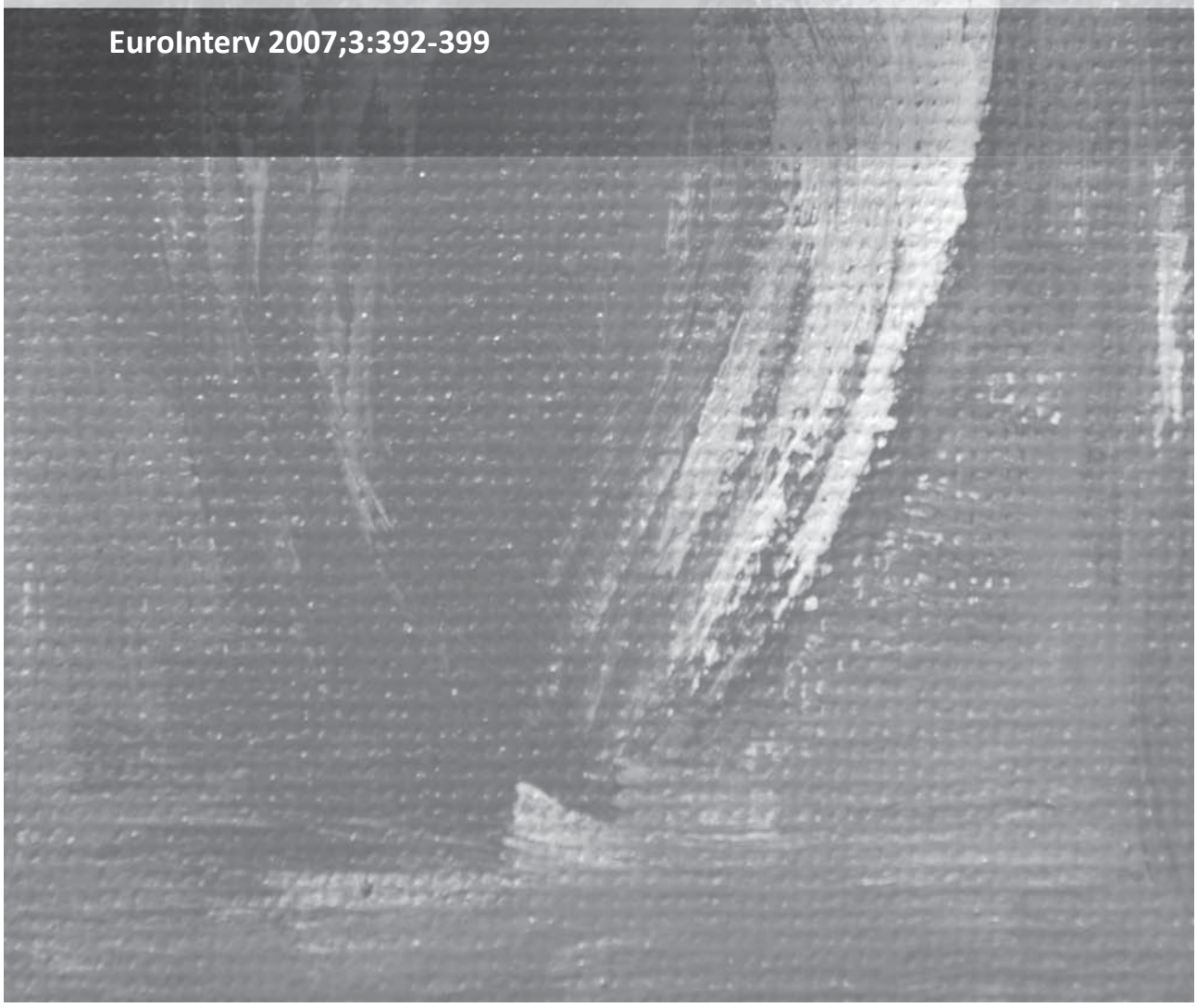
Chapter 21

A pooled safety analysis of data comparing paclitaxel-eluting stents with bare-metal stents

Daemen J, Spaulding C, Jacob S, Boersma E, Varenne O, Serruys PW

EuroInterv 2007;3:392-399



A pooled safety analysis of data comparing paclitaxel-eluting stents with bare-metal stents

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Dr Spaulding reports having received consulting or lecture fees from Cordis, Johnson & Johnson and Dr Varenne reports having received consulting or lecture fees from Cordis, Johnson & Johnson, Abbott and Boston Scientific. The studies were sponsored by Boston Scientific. Drs Daemen, Boersma, Jacob, and Serruys have no disclosures.

Drs J Daemen and C Spaulding contributed equally to the manuscript.

KEYWORDS
Coronary disease, angioplasty, safety, paclitaxel-eluting stent, mortality, stent thrombosis, drug-eluting stent

Abstract

Background: Randomised studies have demonstrated the beneficial effect of drug-eluting stents in reducing repeat revascularisation at one year. However, they were individually underpowered to assess long-term safety endpoints such as death and myocardial infarction. The long-term safety of drug-eluting stents has been recently questioned.

Methods and results: We performed a pooled analysis of 2,797 patients included in four randomised trials to assess the safety of slow-release paclitaxel-eluting stents as compared with bare metal stents. Patient level data were obtained and analysed by two independent academic statistical institutions. The primary safety endpoint was survival at four years. Secondary endpoints were myocardial infarction and stent thrombosis. Heterogeneities in treatment effect were tested in subgroups.

Survival at four years was 93.4% in the paclitaxel-eluting stent group versus 93.0% in the bare-metal stent group (Hazard ratio for survival 0.95; 95% confidence interval [CI] 0.96 - 1.30; P=0.75). Myocardial infarction occurred at a similar rate between both treatment groups. Whereas the total rates of stent thrombosis were equal between the two groups, there was a trend towards a higher rate of stent thrombosis occurring after repeat target lesion revascularisation in the bare-metal stent group. No heterogeneity of treatment effect was found in the subgroups, including diabetic patients and complex lesions.

Conclusions: In a pooled analysis of four trials comparing paclitaxel-eluting stents with bare metal stents, no significant differences were found in the rates of death, myocardial infarction or stent thrombosis.

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Introduction

Pivotal randomised clinical trials and registries have shown that drug-eluting stents reduce the need for subsequent revascularisation procedures when compared with bare metal stents[1-10]. More than four million patients have been treated worldwide with drug-eluting stents. However, the pivotal randomised trials were individually underpowered to detect differences in death and myocardial infarction. Recently, several meta-analyses of published randomised trials with three to four years of follow-up have shown a small, albeit consistent increase in the rates of death, myocardial infarction and late stent thrombosis in patients receiving drug-eluting stents[11-13]. To specifically address the long-term safety of the paclitaxel-eluting stent, we performed a safety meta-analysis of patient level data derived from four randomised controlled trials comparing a slow-release paclitaxel-eluting stent with a bare-metal stent during a follow-up period of four years in 2,797 patients.

Methods

The original studies

The present analysis is based on pooled patient level data from the TAXUS I, II, IV, and V trials, all comparing a polymer-based, slow-release paclitaxel-eluting stent to a bare metal stent in lesions in native coronary arteries using a double-blind study design with a 1:1 randomisation process. The design of these trials, as well as short-term angiographic and clinical outcomes, have been reported previously[7-10,14]. Patients treated with the moderate-release paclitaxel-eluting stent, which was never commercialised, were excluded from the present analysis. For this reason, patients treated with the moderate-release paclitaxel-eluting stent and their control group of cohort II of TAXUS II and patients included in TAXUS VI were excluded. Acute myocardial infarction was an exclusion criteria in all trials. A total of 715 patients with diabetes (defined as patients which were medically treated and/or insulin treated) were included. Angiographic inclusion criteria were variable: TAXUS I, II and IV included patients with low risk lesions whereas TAXUS V included prespecified subgroups of patients with lesions in small vessels (≤ 2.25 mm), long lesions (> 26 mm), and lesions treated with large diameter stents. In both TAXUS IV and V, randomisation of diabetics was stratified by group. TAXUS I and II compared the paclitaxel TAXUS NIR™ stent to the bare metal NIR™ stent and TAXUS IV and V compared the TAXUS Express™ stent to a bare metal Express™ stent (all from Boston Scientific, Natick, Mass, USA). The primary endpoints for TAXUS I as a Phase I feasibility study was 30-day MACE (a composite endpoint of all-cause death, q-WAVE myocardial infarction and stent thrombosis at 30 days). The primary endpoint for TAXUS II as a Phase II study was % in-stent net volume obstruction measured by intravascular ultrasound at six months. TAXUS IV and V as Phase III and Phase IIIb studies were powered for nine-month target vessel revascularisation as primary endpoints. Cardiac death and myocardial infarction were collected as secondary endpoints in all studies. All-cause death and stent thrombosis by protocol definition were also collected in all studies.

Dual antiplatelet therapy with aspirin and clopidogrel or ticlopidine was mandated per protocol for a minimum of six months in all studies. Aspirin was mandated indefinitely. Aspirin doses ranged from 81 to 325 mg daily.

The protocol called for angiographic follow-up at six months (for all patients in TAXUS I and II), at nine months for all patients in TAXUS V and for a prespecified subgroup of patients in TAXUS IV, and clinical follow-up data up to five years was prespecified. Clinical status was checked yearly and five year follow-up is currently available for TAXUS I, four-year for TAXUS II and IV and Two years for TAXUS V. Median follow-up was 1,430 days (IQR 1,072 to 1,452) The study protocols were approved by the ethics committee at each participating institution and were conducted according to the principles of the Declaration of Helsinki. All patients gave written informed consent before enrolment. The studies were performed between October 2000 and December 2002.

Current analysis

All studies were sponsored and monitored by the Boston Scientific Corporation. Follow-up was performed by the investigating centres in a blinded fashion. Core lab analysis for angiographic and intravascular ultrasound was performed by independent research organisations (Cardialysis, Rotterdam, The Netherlands, for the TAXUS II trial, and by Harvard Clinical Research Institute, Boston, MA, for the TAXUS I, IV and V trials). Independent clinical event committees adjudicated the events. For this specific post-hoc analysis, the patient level based data were pooled and than analysed by two independent academic statisticians. The authors had unrestricted access to the data and made all decisions about publication independently of the sponsor or the principal investigators of the studies.

Study endpoints

The primary safety endpoint was all cause death. Secondary safety endpoints were cardiovascular and non-cardiovascular death, stent thrombosis, and all cause death or Q-wave myocardial infarction and all cause death or all myocardial infarction. The same definitions of events given below were used for all four trials.

Cardiovascular death was defined as death due to any of the following: 1) acute myocardial infarction, 2) cardiac perforation or pericardial tamponade, 3) arrhythmia or conduction abnormality, 4) cerebrovascular accident within 30 days or related to the procedure, 5) complication of the procedure or 6) any death in which a cardiac cause cannot be excluded. Non-cardiovascular death was defined as any death not due to a cardiovascular cause.

Q-wave myocardial infarction was defined as the development of new, pathological Q-waves in two or more contiguous leads as assessed by the ECG core laboratory with creatine kinase (CK) or CKMB levels elevated above the upper limit of normal. Non-Q-wave myocardial infarction was defined as an elevation of CK two times the normal value with positive CKMB in the absence of new pathological Q-waves.

In the study protocols stent thrombosis was defined as an acute coronary syndrome with angiographic documentation of either vessel occlusion or thrombus within or adjacent to a previously successfully stented vessel or, in the absence of angiographic confirmation, either acute myocardial infarction in the distribution of

the treated vessel or death from cardiac causes within 30 days. A thrombotic occlusion subsequent to a repeat target lesion intervention did not quality as stent thrombosis in these definitions. Stent thrombosis was re-classified in a blinded fashion by an independent research organisation (Harvard Clinical Research Institute, Boston, MA, USA) according to a set of definitions developed during the summer of 2006 by a consortium of academic investigators, regulators and industry representatives. These definitions (referred to as the Academic Research Consortium or ARC definitions) were proposed to serve as standard criteria for stent thrombosis for the comparison of event rates across different trials and studies. Using the ARC definitions, stent thrombosis was classified as acute if it occurred within 24 hours after the index procedure, subacute if it occurred between one and 30 days, late between 30 days and one year and very late after one year. Furthermore, stent thrombosis was considered definite if there was angiographic proof of thrombus with or without vessel occlusion associated with clinical or electrocardiographic signs of acute ischaemia, or a rise of CK twice the normal value within the 48 hours of the angiogram. Stent thrombosis was classified as probable if unexplained death occurred within 30 days of the index procedure or if a myocardial infarction, irrespective of the time after the index procedure, was documented in the territory of the implanted stent without angiographic confirmation of stent thrombosis. Stent thrombosis was classified as possible in the presence of any unexplained death occurring after 30 days of the index procedure. Stent thrombotic events occurring after the index procedures were classified as primary stent thrombosis and events occurring after repeat target lesion revascularisations were adjudicated as secondary stent thrombosis.

Statistical analysis

All analyses were based on the intention-to-treat principle. Summary statistics for continuous variables are presented as medians and interquartile ranges. Categorical data are summarised as frequencies and percentages. Differences in baseline characteristics between patients randomised to paclitaxel-eluting stents versus bare metal stents were analysed using Wilcoxon-Mann-Whitney tests or Fisher's exact tests, as appropriate.

The incidence of events over time was with the use of the Kaplan-Meier method, whereas log-rank tests and Cox proportional-hazards regression analyses were applied to evaluate differences between the two groups. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. In the main analysis, hazard ratios and 95% confidence intervals (CIs) were adjusted for differences in outcome between trials. Owing to the differences in the follow-up per study with a mean of 1,762, 1,384, 1,345 and 690 days in TAXUS I, II, IV and V respectively we decided to count events through 1,440 days for TAXUS-I, II and IV and through 730 days for TAXUS-V. Finally, two-year follow-up was available for 95.2% of the patients in TAXUS-V, and four-year follow-up was available for 100%, 96.1% and 94.1% in the TAXUS-I, II and IV respectively. No events occurred beyond 1,440 days.

Exploratory analyses (not prespecified) were performed to evaluate possible heterogeneities in treatment effects according to the trial-of-enrolment and the following clinically and angiographic relevant characteristics: age, gender, diabetes, dyslipidaemia, hypertension, prior MI, clinical presentation, diseased vessel, left ventricular ejection fraction, AHA/ACC lesion type and number of implanted stents. Treatment effects were evaluated by Cox' PH regressions that included a characteristic times allocated treatment interaction term, with adjustment for between-trial outcome differences. More extensive regression models were applied to estimate adjusted treatment effects[15].

All statistical tests were two-sided, without correction for multiple testing. P values of less than 0.05 and less than 0.01 were considered to indicate statistical significance for the results of non-heterogeneity tests and tests for heterogeneity in treatment effect, respectively. All statistical analyses were performed with the use of SAS software, version 8.2 (SAS Institute).

Results

A total of 2,797 patients were included in this analysis (TAXUS I: 61 patients, TAXUS II cohort I comparing the slow release formulation and its respective control: 266, TAXUS IV: 1,314, TAXUS V: 1,156). In total, 1,400 patients received a paclitaxel-eluting stent, and 1,397 patients were treated with a bare metal stent. The clinical and angiographic characteristics of the study patients are summarised in Table 1. Except for silent ischaemia at presentation, which was slightly more frequent in the bare metal stent group as compared with the paclitaxel-eluting stent group (18.4% versus 14.9%; P=0.015), there were no significant differences in baseline clinical and procedural characteristics between both treatment groups.

Results for all patients are shown in Table 2. The four-year cumulative survival rate was similar in the paclitaxel-eluting stent group as compared to the bare metal stent group (92.9% vs. 92.6% respectively; hazard ratio for survival for the paclitaxel-eluting stent group 0.95, 95% CI 0.70 -1.31; p=0.77). Subsequently, there were no differences in both cardiovascular and non-cardiovascular mortality. There were no differences in the occurrence of myocardial infarction and total stent thrombosis between the two treatment groups. Using the protocol definitions, stent thrombosis occurred in 16 patients in the paclitaxel-eluting stent group and 10 patients in the bare metal stent group (Table 2). When the ARC definitions were applied, stent thrombosis (either definite, probable or possible) was noted in 39 patients in the paclitaxel-eluting stent group and 41 patients in the bare metal stent group. Events occurring after repeat revascularisation for restenosis accounted for stent thrombosis in three patients with paclitaxel-eluting stents and eight patients with bare-metal stents. Of note, all these events occurred after 30 days. In the bare-metal stent group five definite or probable stent thrombotic events occurred following repeat target lesion intervention versus one on the paclitaxel-eluting stent group. Worth mentioning was that in four out of five cases brachytherapy was used whereas a new bare-metal stent was implanted in only one case. In the sole event occurring post repeat intervention in the paclitaxel-eluting stent group, brachytherapy was used as well.

No significant heterogeneity in the treatment effects was observed in any of the prespecified characteristics, including complex lesions and diabetes (Figure 2). While in the overall population diabetics

Table 1. Baseline clinical and angiographic characteristics*.

	Paclitaxel-eluting stent group (1,400 patients)	Bare-metal stent group (1,397 patients)	P-value
Age (years)			
Median	63	62	0.15
IQR	55 - 71	55 - 70	
Range	31 - 92	34 - 88	
Men	71.4% (1,011/1,400)	71.7% (1,002/1,397)	0.30
Diabetes mellitus	25.4% (356/1,400)	25.7% (359/1,397)	0.90
IDDM	30.1% (107/356)	31.7% (114/359)	0.63
Previous MI	31.4% (440/1400)	29.6% (414/1397)	0.30
Previous PCI #	33.0% (406/1,232)	31.9% (390/1,222)	0.60
Previous CABG #	10.0% (137/1,369)	10.1% (138/1,365)	0.95
Hyperlipidaemia	70.1% (978/1,396)	70.1% (978/1,395)	1.00
Hypertension	72.1% (1,009/1,400)	70.6% (984/1,393)	0.40
Current smoker	23.8% (333/1,397)	22.2% (310/1,397)	0.32
Clinical presentation			
Stable angina	54.4% (743/1,367)	54.4% (743/1,366)	1.00
Unstable angina	33.9% (464/1,369)	31.5% (430/1,366)	0.18
Silent ischaemia	14.9% (202/1,356)	18.4% (249/1,355)	0.015
Ejection fraction			
Median	55	55	0.31
IQR	50-60	50-60	
Range	25 - 90	10 - 88	
Number of diseased vessels			0.39
1	82.1% (1,150/1,400)	83.4% (1,165/1,397)	
2	17.9% (250/1,400)	16.6% (232/1,397)	
Target vessel			
LAD	40.2% (558/1,389)	39.8% (554/1,391)	0.88
LCX	27.2% (378/1,389)	26.4% (367/1,391)	0.67
RCA	32.6% (453/1,389)	33.8% (470/1,391)	0.49
Modified ACC-AHA Lesion Class §, #			
A	9.4% (118/1,262)	7.9% (99/1,255)	0.20
B1	27.5% (347/1,262)	27.0% (339/1,255)	0.79
B2	35.8% (452/1,262)	36.6% (459/1,255)	0.71
C	27.3% (345/1,262)	28.5% (358/1,255)	0.54
Reference vessel diameter (mm)			
Median	2.7	2.7	0.81
IQR	2.4 - 3.1	2.4 - 3.1	
Range	1.2 - 4.8	1.2 - 4.5	
Lesion length (mm)			
Median	12.5	12.5	0.64
IQR	9.5 - 18.0	9.2 - 17.9	
Range	2.4 - 58.2	2.0 - 67.3	
Number of stents			
Median	1 (1 - 1)	1 (1 - 1)	0.45
IQR	1 - 1	1 - 1	
Range	0 - 5	0 - 5	
Total stented length (mm)			
Median	20	16	0.30
IQR	16 -32	16 - 32	
Range	8 - 84	8 - 76	

* Data for some characteristics were missing for some patients. IQR denotes interquartile range, MI myocardial infarction, PCI percutaneous coronary intervention, CABG coronary-aortic bypass graft, LAD left anterior descending coronary artery, LCx left circumflex coronary artery, and RCA right coronary artery.

§ Modified American College of Cardiology (ACC) and American Heart Association (AHA) lesion classes A, B1, B2, and C are defined as a low-risk lesion, a moderate-risk lesion with one B1 or with two or more B2 risk factors, and a high-risk lesion, respectively.

Information on previous CABG/PCI was not collected in TAXUS I and previous PCI and AHA/ACC lesion type were not collected in TAXUS II.

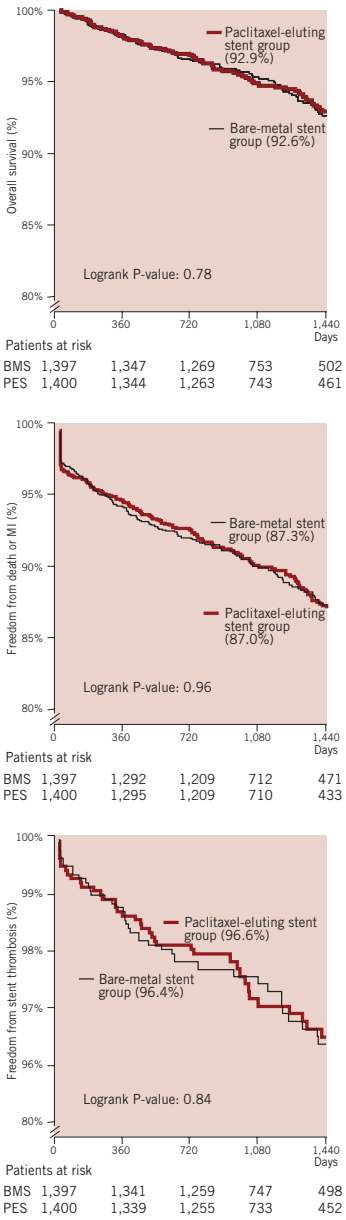

Figure 1. Kaplan Meier survival curves for patients who received a paclitaxel-eluting stent and those who received a bare-metal stent. Survival rates at 1,440 days are shown in parenthesis. P-values were calculated with the use of the log-rank test.

Table 2. Rates of death and myocardial infarction at four-year follow-up*.

	Paclitaxel-eluting stent group (1,400 patients)		Bare-metal stent group (1,397 patients)		Adjusted HR (95% CI)		P-value
	N	%	N	%			
Death	75	7.1	79	7.4	0.95	(0.70 - 1.31)	0.77
Cardiac	31	2.7	35	3.1	0.89	(0.55 - 1.44)	0.63
Non-cardiac	44	4.4	44	4.4	1.00	(0.66 - 1.53)	0.98
Myocardial infarction	82	6.9	80	6.4	1.03	(0.75 - 1.39)	0.87
Q wave MI	13	1.0	12	1.1	1.09	(0.50 - 2.39)	0.83
Non-Q wave MI	71	6.1	70	5.5	1.01	(0.73 - 1.41)	0.94
Death or Q-wave MI	86	7.9	89	8.3	0.97	(0.72 - 1.31)	0.86
Death or any MI	148	13.0	149	12.7	1.02	(0.75 - 1.39)	0.89
Thrombosis by Protocol definition#	16	1.3	10	0.8	1.60	(0.73 - 3.54)	0.24
Acute ST (within 24 hours)	2	0.1	1	0.1	2.00	(0.18 - 22.03)	0.57
Subacute ST (within 1 - 30 days)	5	0.4	6	0.4	0.83	(0.25 - 2.73)	0.76
Late ST (after 30 days)	9	0.8	3	0.3	3.03	(0.82 - 11.20)	0.096
Thrombosis by Dublin definitions§							
Acute ST (within 24 hours)	2	0.1	1	0.1	2.00	(0.18 - 22.03)	0.57
Subacute ST (within 1 - 30 days)	5	0.4	6	0.4	0.83	(0.25 - 2.73)	0.76
Late ST (within 30 days - 1 year)	12	0.9	13	0.9	0.92	(0.42 - 2.03)	0.84
Very late ST (after 1 year)	20	2.0	21	2.2	0.96	(0.52 - 1.77)	0.90
Definite ST	16	1.3	14	1.1	1.15	(0.56 - 2.35)	0.71
Definite or probable ST	22	1.9	18	1.5	1.23	(0.66 - 2.29)	0.52
Any ST	39	3.5	41	3.6	0.96	(0.62 - 1.48)	0.84
Primary thrombosis by Dublin definitions ¶							
Acute ST (within 24 hours)	2	0.1	1	0.1	2.00	(0.18 - 22.03)	0.57
Subacute ST (within 1 - 30 days)	5	0.4	6	0.4	0.83	(0.25 - 2.73)	0.76
Late ST (within 30 days - 1 year)	11	0.8	11	0.8	1.00	(0.43 - 2.31)	1.00
Very late ST (after 1 year)	18	1.9	15	1.6	1.21	(0.61 - 2.41)	0.58
Definite ST	15	1.2	10	0.8	1.50	(0.68 - 3.35)	0.32
Definite or probable ST	21	1.8	13	1.1	1.62	(0.81 - 3.24)	0.17
Any ST	36	3.2	33	2.9	1.10	(0.68 - 1.76)	0.70

* All percentages are based on Kaplan-Meier estimates. Numbers of patients for death or Q-wave myocardial infarction (MI) and death or any MI do not total the sums for each endpoint alone because some patients had both endpoints. CI denotes confidence interval.

Definitions of stent thrombosis according to the study protocols were as follows: acute, within 24 hours after the procedure; subacute, within one to 30 days after; and late, more than 30 days after.

§ Definitions of stent thrombosis of the academic research consortium (ARC) were as follows: acute, within 24 hours after the procedure; subacute, within one to 30 days after; late, between 31 days and one year after; and very late, more than one year after. See text for details on stent-thrombosis adjudication per protocol and per ARC definitions.

¶ Stent thrombosis events occurring post target-lesion revascularisation were censored.

had a worse overall survival as compared with the non-diabetic patients, overall survival in both the bare-metal stent group and paclitaxel-eluting stent group was comparable in both the diabetic and non-diabetic subset (hazard ratio for survival for paclitaxel-eluting stent treated diabetics 0.82, 95% CI 0.54-1.23; P for interaction 0.71) (Figure 3). Additionally, in the diabetic patients stent thrombosis occurred at an identical rate between the diabetic patients receiving a bare-metal stent and a paclitaxel-eluting stent (11 versus 13 events respectively according to the ARC definitions).

Discussion

In this pooled analysis of four randomised trials comparing paclitaxel-eluting stents to bare metal stents in 2,797 patients with four years of follow-up, we found similar rates of death, myocardial infarction and stent thrombosis in both groups. No heterogeneity of the treatment effect was found in the higher risk subsets, such as diabetics or patients treated for complex lesions.

Recent concerns were raised about the long-term safety of drug-eluting stents. Meta-analysis using published data and registries suggested that their use would lead to marked increases in death, myocardial infarction, stent thrombosis and even cancer. Shortly after, physician derived independent patient level based meta-analysis of randomised trials tempered these premature contentions and a dedicated two-day Food and Drug Administration panel meeting undermined the concept that the hypothesised safety concerns outweighed the benefits of drug-eluting stents for on-label use.[16,17] The panelists' opinions were more divided, and left open the possibility that death and myocardial infarction due to stent thrombosis might be increased in patients with off-label drug eluting stent use.

In this analysis, angiographically proven stent thrombosis occurred at a yearly rate of 0.2%. Similar results were noted in a pooled analysis of randomised trials, which assessed the sirolimus-eluting stent[17]. In contrast, the rate was 0.6% per year in a two-centre all-

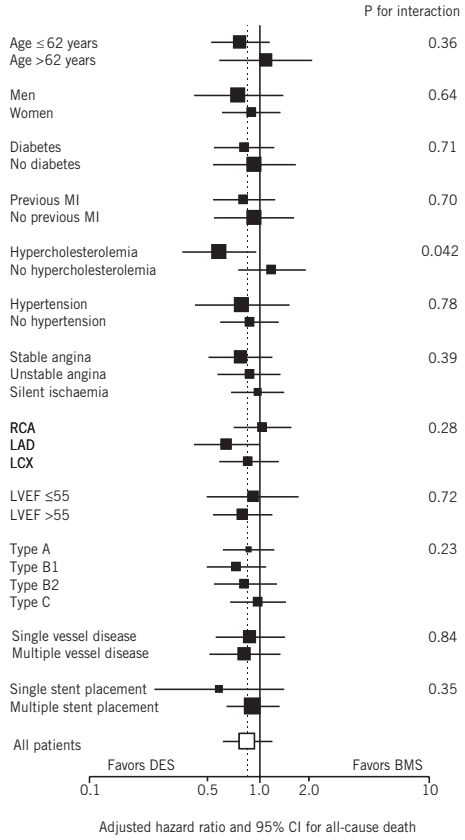

Figure 2. All-cause mortality in selected subgroups. Exploratory analyses to evaluate possible heterogeneity in treatment effects on mortality according to the trial of enrolment and the following clinically relevant characteristics: age, gender, diabetes, dyslipidaemia, hypertension, prior MI, clinical presentation, diseased vessel, left ventricular ejection fraction, AHA/ACC lesion type and number of implanted stents. The size of the squares corresponds to the amount of statistical information. For the continuous variables (age and left ventricular ejection fraction), medians were used as cut-off. Results of tests for heterogeneity in treatment effect were considered significant if P was <0.01. MI=myocardial infarction, LVEF=left ventricular ejection fraction, RVD=reference vessel diameter.

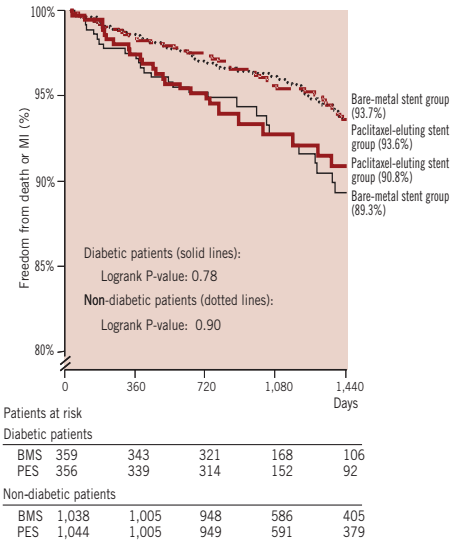

Figure 3. Kaplan Meier curve showing freedom from stent thrombosis according to the Dublin definitions. Survival rates at 1,440 days are shown in parenthesis. P-values were calculated with the use of the log-rank test.

comers registry with a three-year follow-up.[18] Careful selection and follow-up of patients in randomised trials may account for this difference. Primary angioplasty for acute myocardial infarction, stent length, diabetes, bifurcation treatment and premature antiplatelet discontinuation proved to be the strongest predictors of stent thrombosis following drug-eluting stent implantation[6,18-25]. Despite the inclusion of more complex patients in the more recent TAXUS studies, these characteristics were absent or less frequently observed in the present analysis. Therefore, extrapolation of our findings to a real world patient population might be far-fetched. To better define the relative contribution of stent thrombosis to the mortality rate in both groups, the events were adjudicated according to definitions recently developed by a consensus group. Classification in three categories (definite, probable, and possible) allows uniform description and reliable comparison of stent thrombosis rates between studies and registries. Late events such as unexplained death, which were not considered in the initial protocol definitions, were adjudicated as possible stent thrombosis. Thrombotic occlusion occurring after repeat revascularisation were also adjudicated as thrombosis of the original stent. In the bare metal stent group, 28% (5/18) of the definite or probable stent thrombosis occurred following a target lesion revascularisation compared with 5% (1/22) in the paclitaxel-eluting stent group. The validity of adjudicating events occurring after repeat revascularisation to stent thrombosis of the original stent is debatable, and it is worth mentioning that a thrombotic occlusion following a repeat target lesion intervention was not considered a stent thrombosis in the initial per protocol definitions. However, stent thrombosis following repeat revascularisation emphasises the potentially severe consequences of restenosis, which is still often considered as a purely benign process. Dedicated studies of hospitalisation for in-stent restenosis showed that up to 10% of these patients presented with a myocardial infarction or sudden death[26,27]. Additionally, two studies demonstrated a close correlation between the rate of restenosis and late mortality.[28,29] One

could therefore expect to find a decrease in the rates of death and myocardial infarction in the long-term follow-up of drug-eluting stents due to a reduction in repeat revascularisation. However, our analysis and data from large-scale real world registries shows that there is no benefit at four years on these hard clinical endpoints. It remains to be determined whether the long-term restenosis reduction gained with DES use, outweighs a possibly slightly higher incidence of late stent thrombosis[5,30-32].

Recent concerns were raised about the long-term safety of sirolimus-eluting stents in patients with diabetes mellitus. In a pooled analysis of the pivotal randomised sirolimus-eluting stent trials, a significantly reduced survival rate was found among diabetic (but not nondiabetic) patients treated with sirolimus-eluting stents[17]. Analysis of the causes of death and the occurrence of stent thrombosis in this high-risk subset could not adequately explain the observed difference in survival, and the four-year survival rate of diabetic patients receiving bare-metal stents was surprisingly high as compared to previous studies or the present analysis (95.6% versus 90.1% respectively). Nevertheless, in the present analyses, the overall survival was similar between the bare metal and paclitaxel-eluting stent group and although larger trials with long-term follow-up in diabetics are needed to settle this issue, there seems so far no cause of concern for a reduced safety of drug-eluting stents in diabetics.

The present analysis exclusively studied the slow-release PES, which is the only commercially available TAXUS stent. In the TAXUS II trial, the moderate-release PES, characterised by an three-fold greater amount of in vivo drug release over the first 30 days, proved to have a similar efficacy as the slow-release PES and the authors thereby suggested that the dosing threshold for prevention of restenosis had already been reached with the slow release version, at least for low-risk lesions[8].

Several limitations need to be addressed. The present analysis was underpowered to detect a clinically significant difference in mortality, however, it is worth mentioning that ten thousand patients would be needed based on the results of the present study. Treatment with clopidogrel was required for at least six months by the original trial protocols, but no information on actual individual patient use was available, especially in patients with adverse events. Thus, we cannot provide any specific insight into the question of whether further prolonging dual antiplatelet therapy would reduce the risk of such events. We performed multiple subgroup analyses, including those for diabetes and complex lesions, which were not pre-specified. The number of fatal events in these subgroups was numerically small, so that the findings may still be due to the play of chance.

In summary, in this pooled analysis of four randomised trials, we compared the effects of paclitaxel-eluting stents with those of bare metal stents on clinical events at four years. No significant differences in the rates of death, myocardial infarction or stent thrombosis were demonstrated.

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The contribution of the authors is as follows. Drs J Daemen and P Serruys contacted the sponsor of these trials (Boston Scientific, Natick, Mass, USA) and the patient level data was transferred and subsequently analysed by two independent statistical institutions (Drs Olivier Varenne and Sophie Jacob, Paris Medical School, Paris, France and E Boersma, Erasmus University, Rotterdam, The Netherlands). The results were analysed by J Daemen, C Spaulding and P Serruys. The manuscript was written by Drs J Daemen, C Spaulding and P Serruys. All authors agree that two of them (C Spaulding and J Daemen) have contributed equally to the work. The authors had full access to the data and took decisions regarding analysis and publication independently of the sponsor. The disclosures of interest are as follows: Dr Spaulding reports having received consulting or lecture fees from Cordis, Johnson & Johnson and Dr Varenne reports having received consulting or lecture fees from Cordis, Johnson & Johnson, Abbott and Boston Scientific. The studies were sponsored by Boston Scientific. Drs. Daemen, Boersma, Jacob, and Serruys have no disclosures.

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Chapter 22

The relative safety and efficacy of bare-metal and drug-eluting stents in low- and high-risk patient subsets

An epidemiological analysis of three sequential cohorts of all-comers (n=6129)

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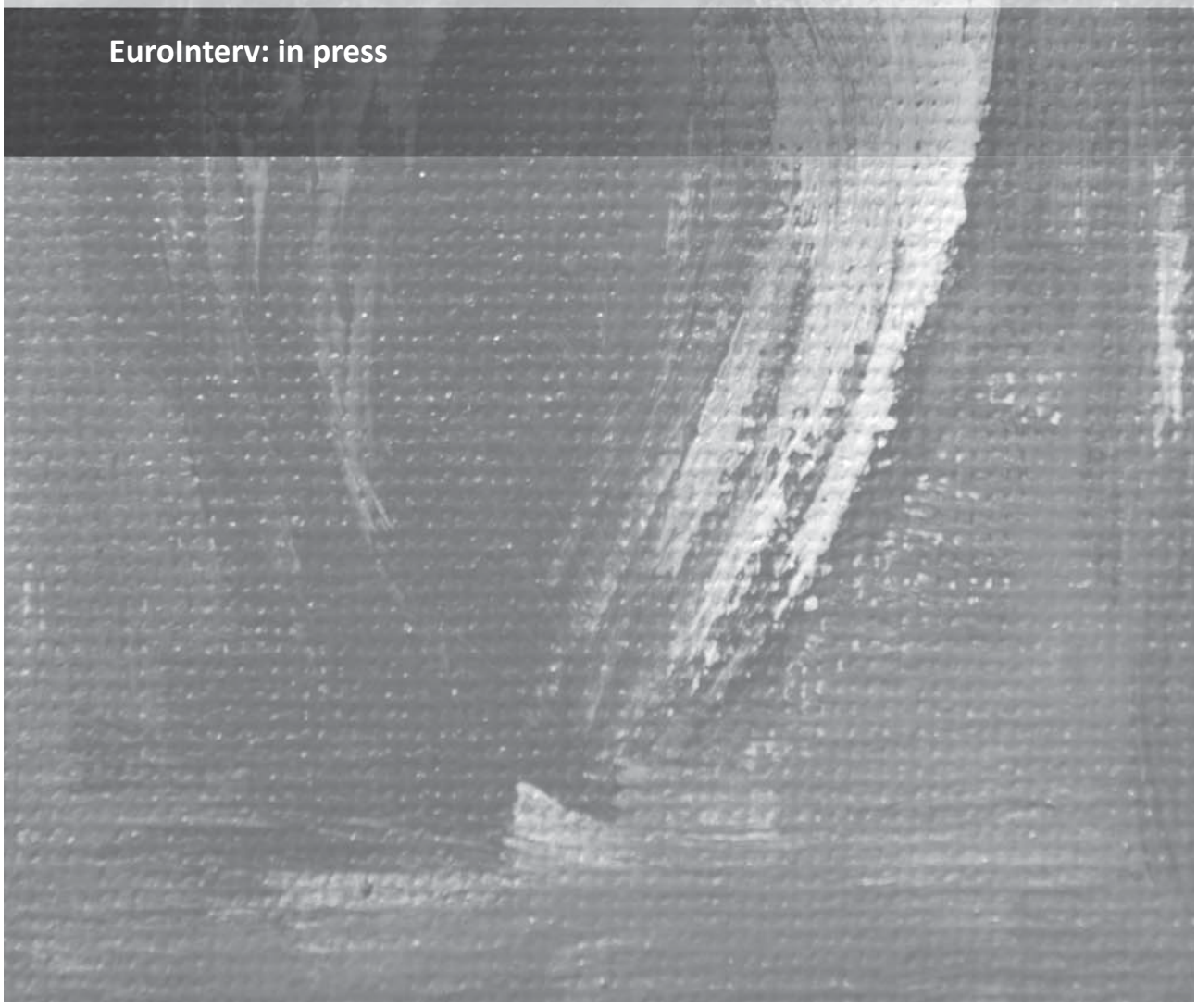

The relative safety and efficacy of bare-metal and drug-eluting stents in low- and high-risk patient subsets

An epidemiological analysis of three sequential cohorts of consecutive all comers (n=6129)

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None of the authors have a conflict of interest as it relates to this study.

KEYWORDS
Sirolimus-eluting stent, paclitaxel-eluting stent, long-term safety

Abstract

Background: Sirolimus- and paclitaxel- eluting stents (SES and PES respectively) have been shown to produce a sustained reduction in restenosis and repeat revascularisations as compared to bare-metal stents (BMS) up to four years. There is still limited data about the long-term safety and efficacy of DES in high-risk subgroups.

Methods and results: A total of 6,129 consecutive patients were treated during three sequential periods with BMS (n=2,428; January, 2000 to April, 2002), SES (n=866; April 2002 to February 2003) or PES (n=2,835; February 2003 to December 2005). A stratified analysis (including age, gender, diabetes, clinical presentation, treated vessel, multivessel disease, AHA lesion class, bifurcation, in-stent restenosis, average stent diameter ≤2.5 mm and total stented length ≤30 mm) was performed to evaluate possible heterogeneities in treatment effect. At four years, all-cause mortality was identical between the drug-eluting stent (DES) and BMS cohorts (13.5% vs. 13.4%, respectively; Adjusted HR 1.10, 95% CI 0.90 - 1.34) without evidence of heterogeneity in the high-risk patient subsets. Both DES significantly reduced the risk for target vessel revascularisation (TVR) as compared to BMS (TVR: 11.9% vs. 15.7% respectively; Adjusted HR 0.69, 95% CI 0.58 - 0.82) along with a reduced risk for post-operative MI (adjusted HR 0.75, 95% CI 0.57 - 0.98), but counterbalanced by a non-significantly higher risk for stent thrombosis (3.1% vs. 1.6%; adjusted HR 1.26, 95% CI 0.82 - 1.95). DES failed to show superiority to BMS in patients with acute myocardial infarction (TVR 10.5% vs. 9.2% respectively; Adjusted HR 1.26, 95% CI 0.82 - 1.93).

Conclusions: In a real world patient population, after four years, the overall use of DES was associated with similar all-cause mortality rates and a significantly reduced risk for post-operative MI and TVR as compared to BMS.

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Introduction

While the superior anti-restenotic properties of drug-eluting stents (DES) have been extensively demonstrated, their impact on hard clinical endpoints like death and myocardial infarction (MI) was never appropriately studied. Although pivotal randomised controlled trials and meta-analyses demonstrated similar rates of death, post-operative MI and stent thrombosis in DES as compared to bare-metal stents (BMS), they were underpowered to detect meaningful differences in these hard clinical endpoints, particularly when the relative safety and efficacy were questioned in high-risk subgroups.[1-4] Although the randomisation was a key feature, the main limiting factors in the pivotal randomised trials were the highly selected patient populations (approximately 40% of the daily clinical practice) and the use of angiographic primary endpoints in many of them. These constraints limited the ability to generalise the conclusions to an all-comer population and precluded proper subgroup analysis. Meta-analyses of randomised controlled trials, including trials in higher risk patients, using aggregate data rather than patient-level data, partially resolved the long-term safety concerns but were again unable to study high-risk subgroups.

Registries including higher risk patients have recently shown a consistent trend towards an increased rate of late stent thrombosis, but an improved survival rate when DES are used.[5-9] However, the majority of the registries suffer from a severe selection bias due to concomitant non-randomised use of DES and BMS. Thereby, the "DES" cohorts in these studies were often a mixture of different types of DES (often mixed with BMS), and ignored the fact that there is a clear difference in the safety and efficacy of different types of DES.[4,10-12]

In the present study, we analysed the relative safety and efficacy of three sequential cohorts of all-comers (n=6.129) treated with either BMS, sirolimus- or paclitaxel-eluting stents (SES and PES respectively). In particular, we performed a stratified analysis to study the efficacy of both types of DES among high-risk patient subsets.

Methods

Study design and patient population

Between January 1, 2000 and December 31, 2005, a total of 7,217 percutaneous coronary interventions were performed in our institution using BMS, SES or PES. From January 2000 until April 16th 2002, 2,681 percutaneous coronary interventions were performed using exclusively bare metal stents, from April 16, 2002, until February 23, 2003, 1,035 interventions were performed using SES (Cypher®, Cordis Corp., Johnson & Johnson, Warren, NJ, USA), as part of RESEARCH registry[13], and from February 23, 2003 to December 31, 2005, 3,339 interventions using PES (TAXUS™ Express2™ or Liberté™, Boston Scientific, Natick, MA, USA), as part of the T-SEARCH registry.[14] Procedures in which two different types of stents (BMS and either SES or PES; SES and either BMS or PES; PES and either SES or BMS) were used were excluded (n=162).

Although a total of 784 patients underwent multiple procedures, only patients initially enrolled in one of the sequential cohorts (BMS, SES or PES group) were maintained for analytical purposes throughout the follow-up period in their original cohort, even if a repeat intervention was performed using a different type of stent. A total of 6,129 patients fulfilled these criteria. (Figure 1)

This study was approved by the local ethics committee and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Procedures and post-intervention medications

All procedures were performed following previously defined current standard procedural guidelines.[15] Baseline, clinical and procedural patient characteristics were prospectively entered into a dedicated database.

Patients were prescribed aspirin plus clopidogrel 75 mg/day (after a loading dose of 300 mg) before or during baseline coronary interventions. Patients treated with BMS received at least one month of clopidogrel (mean 2.4±2.3 months). Patients treated with SES, received at least three months of clopidogrel (mean 4.5±3.2 months), and patients treated with PES received at least six months of clopidogrel (mean 6.4±3.4 months). All patients were advised to remain on aspirin indefinitely.

Planned angiographic follow-up was performed in 12.0%, 25.9% and 14.3% in the BMS, SES and PES groups respectively.

Baseline definitions

Angina was categorised according to the Canadian Cardiovascular Society (CCS) classification for stable angina and according to the Braunwald classification for unstable angina.[16,17] Hypertension was defined as a blood pressure ≥140 systolic or ≥90 mmHg diastolic or based on the current use of antihypertensive treatment. Dyslipidaemia was classified as a total serum cholesterol level ≥6.2 mmol/l or the use of lipid lowering drugs. Diabetes was defined as treatment with either an oral hypoglycaemic agent, insulin, or through diet. Complete procedural success was defined as the achievement of <50% diameter stenosis (visual assessment) and Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow in all

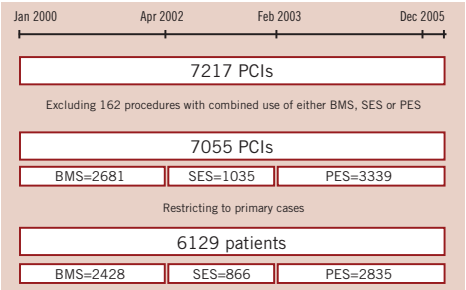

Figure 1. Flowchart depicting the number of procedures in the three sequential periods and the number of patients fulfilling the inclusion criteria in each cohort. Primary cases indicates the number of patients undergoing their first intervention in the study period (2000-2005). SES indicates sirolimus-eluting stent, BMS bare metal stent, PES paclitaxel-eluting stent, PCI percutaneous coronary intervention.

lesions intended to treat. Clinical success was defined as procedural success without death or (re) infarction during the index hospitalisation.

Endpoint definitions and clinical follow-up

The primary safety endpoint was all-cause death and post-operative MI and the primary efficacy endpoint was target vessel revascularisation (TVR) at 4-years of follow-up. Secondary endpoints were the itemised outcome parameters: all-cause death, cardiac death and death from cancer, post-operative MI, TVR and stent thrombosis. Survival data for all patients were obtained from municipal civil registries on a yearly basis for each of the three patient cohorts. The most recent follow-up was performed in October 2007. Causes of death were obtained from the Central Bureau of Statistics, The Hague, The Netherlands. Causes of death were classified according to the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10).[18] For the present analysis, death from ischaemic heart disease (I-20 - I-25), sudden cardiac death (I-46), sudden death undefined (R-96), or death from heart failure (I-50) were considered to be cardiac. Death from cancer was defined as any death from malignant neoplasms (C-00 - C-97). All the remaining deaths were classified as being due to other causes and no further distinctions were made. Follow-up was complete for 98.7% of the BMS patients, 100% of the SES patients and 98.4% of the PES patients. Target vessel revascularisation was defined as a re-intervention driven by any lesion located in the same epicardial vessel.[19] Myocardial infarction at follow-up was diagnosed by a rise in creatine kinase-MB fraction (CK-MB) of three times the upper limit of normal, according to American Heart Association/American College of Cardiology guidelines.[20] Stent thrombosis (ST) was defined as angiographically defined thrombosis with TIMI grade 0 or 1 flow or the presence of a flow limiting thrombus, accompanied by acute symptoms, irrespective of whether there had been an intervening reintervention.[21] The timing of ST was categorised as early (within 30 days after implantation), late (between 30 days and 1 year) or very late (more than 1 year).[22] Additionally, a difference was made between primary stent thrombosis (occurring directly after the index procedure) and secondary stent thrombosis (stent thrombosis occurring following a repeat target vessel revascularisation).

Statistical analysis

Continuous variables are presented as mean ±standard deviation. Categorical variables are expressed as percentages. Comparisons among the three groups were performed by the F-test from an analysis of variance for continuous variables and Pearson's Chi-Square test for categorical variables. All statistical tests are 2-tailed. The incidence of events over time was studied with the use of the Kaplan-Meier method, whereas log-rank tests were applied to evaluate differences between the treatment groups. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. Cox proportional-hazards regression analyses were applied to further study treatment effects, adjusting for potential confounders listed in Table 1. The number of co-variables in the final model was limited to variables ($p<0.10$) in Cox multivariable regression, and variables considered clinically relevant for each specific endpoint. Final results are presented as adjusted hazard ratios with 95% confidence interval. Subsequent analyses were performed to evaluate possible heterogeneities in treatment effects on mortality and TVR according to the following clinically relevant characteristics: age, gender, diabetes, clinical presentation, treated vessel, multivessel disease, AHA lesion class, bifurcation, in-stent restenosis, average stent diameter≤2.5 mm and total stented length >30 mm. Treatment effects were evaluated with the use of Cox regressions that included a term for the interaction between each characteristic of interest and the assigned treatment, adjusted for the previously defined clinically relevant characteristics. Given the differential follow-up in the three treatment cohorts, additional stepwise logistic regression analyses were performed on the 2-year endpoints of all-cause mortality and TVR to check whether these results were in line with the Cox proportional hazards regression analyses on the 4-year endpoints.

Results

Baseline and procedural characteristics

Both baseline and procedural characteristics are depicted in Table 1. Mean age increased slightly over time from 61.5±11.8 in the BMS group to 62.2±11.5 in the PES group (p=0.04). Treatment for acute MI increased from 22.4% in the BMS group to 36.1% in the PES group (P<0.001). Procedural complexity increased over time, illustrated by an increase in the treatment of type C lesions, bifurcations and left main stem lesions. Over time, total stented length and number of stents increased, while the average stent diameter decreased.

Clinical outcomes

At thirty days, the cumulative incidence of all-cause mortality was 3.5% in both the DES and BMS groups (adjusted HR 0.84, 95% CI 0.63 - 1.13). However, there was a trend towards a lower 30-day mortality rate in the SES group (2.2%) compared to the PES group (4.0%) (adjusted HR 0.73, 95% CI 0.44 - 1.22). At four years, the mortality rates in the DES and BMS group remained remarkably similar (13.5% vs. 13.4% respectively; adjusted HR 1.10, 95% CI 0.90 - 1.34); however, a trend remained towards a lower mortality rate in the SES group as compared to the PES group (11.2% vs. 14.0% respectively; adjusted HR 1.16, 95% CI 0.88 - 1.53) (Table 2, Figure 2).

The majority (57%) of all deaths were due to cardiac causes, 15% were due to cancer and 28% of the patients died of other causes. While cardiac mortality was similar in the overall DES group as compared with the BMS group, the cardiac mortality rate was significantly lower in the SES group as compared with the PES group (5.8% vs. 8.0% respectively, adjusted HR 0.69 95% CI 0.49 - 0.97). Death due to cancer occurred at a similar rate in both DES groups as in the BMS group (Table 2).

Although the cumulative incidence of post-operative MI was similar among the DES and BMS groups (4.8% vs. 4.9% respectively)

Table 1. Clinical and procedural characteristics of the study population stratified according to stent type.

Variables	Bare metal stent (n=2428)	Drug-eluting stent (n=3701)	Sirolimus-eluting stent (n=866)	Paclitaxel-eluting stent (n=2835)	p* value
Age, years (SD)	61.5 (11.8)	62.1 (11.4)	61.5 (11.0)	62.2 (11.5)	0.04
Male gender	1768/2428 (72.8)	2767/3701 (72.3)	609/866 (70.3)	2067/2835 (72.9)	0.30
Indication SA	1005/2428 (41.4)	1444/3701 (39.0)	373/862 (43.3)	1071/2832 (37.8)	0.003
Indication UA	878/2428 (36.2)	1043/3701 (28.2)	303/862 (35.2)	740/2832 (26.1)	<0.001
Indication MI	545/2428 (22.4)	1207/3701 (32.6)	186/862 (21.6)	1021/2832 (36.1)	<0.001
Cardiogenic shock	24/2428 (1.0)	75/3701 (2.0)	24/862 (2.8)	51/2832 (1.8)	<0.001
DM	320/2428 (13.2)	619/3701 (16.7)	150/866 (17.3)	469/2835 (16.5)	0.001
IDDM	32/2428 (1.3)	155/3701 (4.2)	47/866 (5.4)	108/2835 (3.8)	<0.001
NIDDM	288/2428 (11.9)	471/3701 (12.7)	104/866 (12.0)	367/2835 (12.9)	0.46
Hypertension	793/2428 (32.7)	1944/3701 (33.0)	357/866 (41.2)	1172/2835 (41.3)	<0.001
Hypercholesterolaemia	1057/2428 (43.5)	1944/3701 (52.5)	479/866 (55.3)	1465/2835 (51.7)	<0.001
Family history	523/2428 (21.5)	1220/3701 (33.0)	267/866 (30.8)	953/2835 (33.6)	<0.001
Current smoking	588/2428 (24.1)	997/3701 (26.9)	254/866 (27.9)	743/2835 (25.7)	0.011
Previous PCI	384/2422 (15.9)	416/3675 (11.2)	102/864 (11.8)	314/2811 (11.2)	<0.001
Previous CABG	289/2425 (11.9)	286/3675 (7.7)	61/865 (7.1)	225/2810 (8.0)	<0.001
Previous MI	847/2403 (35.2)	965/3636 (26.1)	269/859 (31.3)	696/2777 (25.1)	<0.001
Treated vessel					
RCA	957/2428 (39.4)	1415/3701 (38.2)	351/866 (40.5)	1064/2835 (37.5)	0.18
LAD	1291/2428 (53.2)	2009/3701 (54.3)	514/866 (59.4)	1495/2835 (52.7)	0.002
LCX	732/2428 (30.1)	115/3701 (30.1)	283/866 (32.7)	832/2835 (29.3)	0.17
LM	86/2428 (3.5)	174/3701 (4.7)	27/866 (3.1)	147/2835 (5.2)	0.003
Bypass graft	135/2428 (5.6)	118/3701 (3.2)	17/866 (2.0)	101/2835 (3.6)	<0.001
AHA Lesion class					
Type A	432/2428 (17.8)	421/3701 (11.4)	162/866 (18.7)	259/2835 (9.1)	<0.001
Type B1	814/2428 (33.5)	978/3701 (26.4)	295/866 (34.1)	683/2835 (24.1)	<0.001
Type B2	1109/2428 (45.7)	1610/3701 (43.5)	426/866 (49.2)	1184/2835 (41.8)	<0.001
Type C	883/2428 (36.4)	1556/3701 (42.0)	372/866 (43.0)	1184/2835 (41.8)	<0.001
Bifurcation	87/2428 (3.6)	437/3701 (11.8)	88/866 (10.2)	349/2835 (12.3)	<0.001
Multivessel disease	1280/2426 (52.8)	1911/3692 (51.6)	40/866 (54.3)	1441/2826 (51.0)	0.18
Multivessel treatment	690/2428 (28.4)	1014/3701 (27.4)	284/866 (32.8)	730/2835 (25.7)	<0.001
ISR	164/2417 (6.8)	132/3605 (3.6)	43/864 (5.0)	89/2741 (3.2)	<0.001
Previous brachytherapy	150/2428 (6.2)	23/3701 (0.6)	11/866 (1.3)	12/2835 (0.4)	<0.001
Number of stents (SD)	1.8 (1.1)	2.2 (1.4)	2.2 (1.5)	2.2 (1.4)	<0.001
Average stent diameter	3.3 (0.6)	2.9 (0.5)	2.8 (0.3)	2.9 (0.6)	<0.001
Total stented length	28.3 (20.0)	42.7 (31.0)	42.8 (30.1)	42.7 (31.1)	<0.001
Clinical success rate	2377/2424 (98.1)	3467/3541 (97.9)	838/859 (97.6)	2629/2682 (98.0)	0.64
Complete procedural success rate	2314/2425 (95.4)	3373/3547 (95.1)	819/862 (95.0)	2554/2685 (95.1)	0.84
IIb/IIIa Inhibitor	791/2428 (32.6)	371/3701 (19.8)	184/866 (21.2)	547/2835 (19.3)	<0.001
Duration of clopidogrel in months (SD)	2.4 (2.3)	6.1 (3.5)	4.5 (3.2)	6.6 (3.4)	<0.001
Planned angiographic follow-up	280/2330 (12.0)	602/3521 (17.1)	221/854 (25.9)	381/2667 (14.3)	<0.001

Figures are represented as absolute numbers and percentages or means and standard deviations as appropriate. SD indicates standard deviation; IDDM: insulin dependant diabetes mellitus; NIDDM: Non-insulin dependent diabetes mellitus; SA: stable angina; UA: unstable angina; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; LAD: left anterior descending coronary artery; LCx: left circumflex coronary artery; RCA: right coronary artery: LM: left main coronary artery; SVG: saphenous vein bypass graft; AHA: American Heart Association and ISR in-stent restenosis. * P-values are based on comparison BMS, SES and PES.

adjusting for independent predictors resulted in a significantly lower risk for post-operative MI in the DES group (adjusted HR 0.75, 95% CI 0.57 - 0.98). No statistically significant differences were observed between the SES and PES group (adjusted HR 0.84, 95% CI 0.57 - 1.24). (Table 2)

The cumulative incidence of angiographic stent thrombosis was significantly higher in the DES group as compared to the BMS group (3.1% vs. 1.6%; HR 1.80, 95% CI 1.23 - 2.64)(Figure 3). Cox multivariable regression analysis revealed that in the BMS group previous brachytherapy and MI at presentation were significant

Table 2. All cause and specified mortality rates at 4 years.

	Bare metal stent (n=2428)		Drug-eluting stent (n=3701)		Sirolimus-eluting stent (n=866)		Paclitaxel-eluting stent (n=2835)		Drug-eluting vs. bare-metal stent	Sirolimus- vs. Paclitaxel-eluting stent
	N	%	N	%	N	%	N	%	Adjusted HR [95% CI]	Adjusted HR [95% CI]
All-cause death	318	13.4	400	13.5	93	11.2	307	14.0	1.10 [0.90-1.34]	1.16 [0.88-1.53]
Cardiac death	176	7.5	233	7.5	48	5.8	185	8.0	1.00 [0.80-1.25]	0.69 [0.49-0.97]
Death due to cancer	50	2.3	58	2.3	16	2.1	42	2.4	1.16 [0.77-1.75]	0.98 [0.53-1.81]
Myocardial infarction (MI)	111	4.9	153	4.8	34	4.1	119	5.1	0.75 [0.57-0.98]	0.84 [0.57-1.24]
Cardiac death or MI	274	11.7	370	11.7	79	9.5	291	12.4	0.90 [0.75-1.07]	0.76 [0.58-0.90]
Angiographic stent thrombosis	37	1.6	93	3.1	22	2.7	71	3.2	1.26 [0.82-1.95]	0.82 [0.50-1.34]
Target vessel revascularisation (TVR)	355	15.7	356	11.9	99	12.2	257	12.0	0.69 [0.58-0.82]	0.99 [0.77-1.28]
All-cause death, MI or TVR	676	28.4	778	25.3	189	22.4	589	26.6	0.83 [0.74-0.94]	0.85 [0.71-1.01]

SES: sirolimus-eluting stent; BMS: bare metal stent; PES: paclitaxel-eluting stent; HR: hazard ratio; CI: confidence interval. Percentages are based on Kaplan Meier estimates. All hazard ratios are adjusted hazard ratios considering potential confounders listed in Table 1.

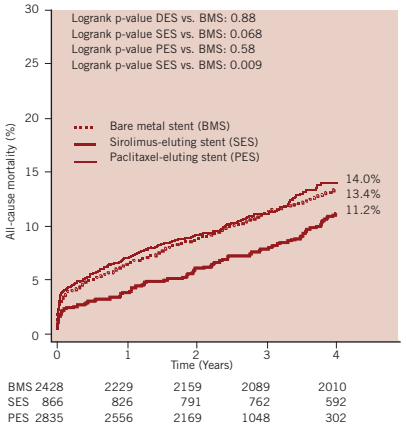

Figure 2. Kaplan Meier all-cause mortality curves for all patients receiving bare-metal stents (BMS), sirolimus-eluting stents (SES) or paclitaxel-eluting stents (PES).

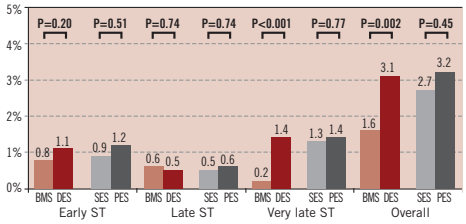

Figure 3. Chart depicting the cumulative incidence of early (<30 days), late (>30 days, <365 days) and very late (>365 days) angiographic stent thrombosis in the bare-metal stent group (BMS), sirolimus-eluting stent (SES) group, paclitaxel-eluting stent group (PES) and drug-eluting stent (DES) group (combined SES and PES). P values are based on the Logrank test.

predictors of stent thrombosis while in the DES group, MI at presentation, diabetes, treatment of the LAD and age significantly increased the risk for stent thrombosis (Table 3). When correcting for independent predictors of stent thrombosis, the adjusted risk for stent thrombosis in the DES group decreased to 1.26 (95% CI 0.82 - 1.95). Additionally, there were no significant differences in the occurrence of stent thrombosis between both DES groups (adjusted HR 0.82, 95% CI 0.50 - 1.34). Among patients with stent thrombosis, secondary stent thrombosis (stent thrombosis occurring after a target lesion revascularisation) occurred in 10.8% of the BMS patients compared to the 4.3% of the DES patients (p=0.22). None (0%) of the patients in the BMS group vs. one (0.1%) patient in the SES group and eight (0.3%) patients in the PES group experienced a second episode of stent thrombosis. In the BMS group 22/111 (19.8%) post-operative MIs were due to ST versus 59/153 (38.6%) in the DES group (p=0.016).

TVR was performed significantly more often in the BMS group (15.7%) as compared to the two DES groups (12.2% vs. 12.0% in the SES and PES groups, respectively)(Table 3, Figure 4). The use of DES was associated with a 31% lower risk for TVR at 4-years compared to BMS (adjusted HR 0.69, 95% CI 0.58 - 0.82). As compared to PES, the use of SES was associated with an equal risk for TVR at 4-years (adjusted HR 0.99, 95% CI 0.77 - 1.28).

Finally, given the differential follow-up between the three treatment cohorts, a stepwise logistic regression analyses with follow-up truncated at two years was used to test the estimated 4-year treatment effect using Cox proportional hazards regression analyses. At two years, the adjusted HR for all-cause mortality in the DES group was 0.92, 95% CI 0.77 - 1.10, which was comparable to initial adjusted HR of 1.04, 95% CI 0.80 - 1.34 derived from a Cox proportional hazards regression model including all univariate significant (p<0.1) predictors of all-cause mortality. Similarly, for TVR, the adjusted HR at two years was 0.55, 95% CI 0.46 - 0.65, which was comparable to initial adjusted HR of 0.60, 95% CI 0.50 - 0.73 derived from a Cox proportional hazards regression model including all univariate significant (p<0.1) predictors of TVR.

Table 3. Univariate and multivariate predictors of stent thrombosis at 4 years in the bare metal- and drug-eluting stent groups.

	BMS		DES	
	Univariate HR [95% CI]	Adjusted HR [95% CI]	Univariate HR [95% CI]	Adjusted HR [95% CI]
Age	–	–	0.97 [0.95-0.98]	0.97 [0.95-0.99]
Clinical presentation				
Stable angina (ref)	–	–	–	–
Unstable angina	2.46 [1.06-5.70]	2.54 [1.08-5.97]	1.86 [1.07-3.24]	2.04 [1.17-3.57]
Myocardial infarction	3.00 [1.23-7.35]	3.56 [1.40-9.09]	2.62 [1.57-4.39]	3.45 [1.99-5.97]
Diabetes	–	–	1.50 [0.92-2.44]	1.83 [1.10-3.00]
Family history	–	–	1.42 [0.94-2.14]	1.44 [0.94-2.19]
Previous brachytherapy	2.84 [1.18-6.80]	3.70 [1.48-9.29]	–	–
Treatment of RCA	0.24 [0.09-0.61]	0.42 [0.14-1.23]	–	–
Treatment of LAD	2.11 [1.04-4.26]	2.01 [0.80 -5.03]	2.15 [1.36-3.38]	1.92 [1.20-3.05]
Treatment of bypass graft	2.65 [1.03-6.79]	3.22 [0.99-10.4]	–	–
Bifurcation treatment	–	–	1.77 [1.06-2.96]	1.33 [0.77-2.31]
Number of stents	0.69 [0.45-1.03]	1.01 [0.50-2.05]	1.22 [1.09-1.37]	1.19 [0.89-1.61]
Total stented length	0.98 [0.95-1.00]	0.98 [0.98-1.02]	1.01 [1.00-1.01]	1.00 [0.99-1.02]
AHA lesion type B2/C	–	–	1.97 [1.10-3.54]	1.48 [0.81-2.70]

BMS: indicates bare-metal stent; DES: drug-eluting stent; RCA: right coronary artery; LAD: left anterior descending coronary artery; AHA: American Heart Association

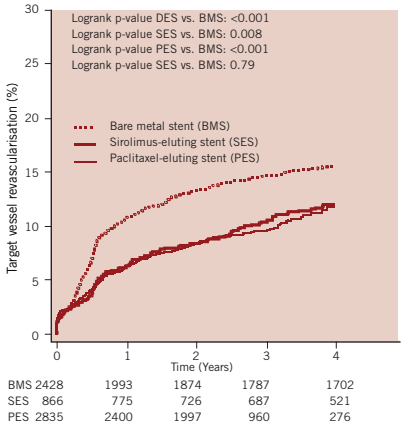

Figure 4. Kaplan Meier curves for target vessel revascularisation up to 4 years for all patients receiving bare-metal stents (BMS), sirolimus-eluting stents (SES) or paclitaxel-eluting stents (PES).

Stratified analysis among subgroups

When more specifically analysing the heterogeneity of the treatment effect (DES vs. BMS) on the 4-year TVR rates, a trend towards heterogeneity was observed among patients presenting with MI (p heterogeneity 0.086).(Figure 5a) When assessing the treatment effect of SES vs. PES, which was remarkably similar in the overall population (Figure 4), significant heterogeneity was observed in patients with diabetes (p heterogeneity 0.045), and bifurcation lesions (p heterogeneity 0.036).(Figure 5b)

A stratified analysis to detect heterogeneity in the treatment effect between DES vs. BMS and SES vs. PES did not reveal any significant differences in the 4-year all-cause mortality rates.

ST segment elevation MI subgroup

While in patients presenting with stable or unstable angina, the risk for TVR at 4-years was 38% lower in patients treated with DES as compared to BMS (adjusted HR 0.62, 95% CI 0.51 - 0.75), the risk for TVR in patients presenting with MI was 26% higher (adjusted HR 1.26; 95% CI 0.82 - 1.93) in patients treated with DES as compared with BMS (p heterogeneity 0.086). There was no difference between SES and PES at four years (Figure 5b). The cumulative incidence of all-cause mortality was 16.9% in the DES group vs. 18.7% in the BMS group (Adjusted HR 1.15, 95% CI 0.76 - 1.74) with no significant difference between the SES and PES groups (14.8% vs. 17.0% respectively; adjusted HR 0.82, 95% CI 0.53 - 1.29). Furthermore, there was no difference in the combined endpoint of cardiac death or post-operative MI in DES (18.6%) and BMS (17.9%) group (Adjusted HR 1.05, 95% CI 0.60 - 1.84). Stent thrombosis however, occurred in 5.0% of the DES (SES: 4.9%, PES 4.7%) patients as compared to 2.4% of the BMS patients (p=0.06) and very late stent thrombosis (>1 year) was significantly more frequent in the DES as compared to the BMS group (2.7% vs. 0% respectively; p=0.0007).

Diabetes subgroup

Although the 4-year cumulative incidence of TVR in the diabetic subset was significantly lower in the overall DES group as compared to the BMS group (16.2% vs. 24.6%; Adjusted HR 0.53, 95% CI 0.36 - 0.78) significant heterogeneity in the treatment effect was found between SES and PES.(Figure 5b) While in the non-diabetics, the risk for TVR in the SES group was 11% lower than in the PES group (adjusted HR 0.89, 95% CI 0.67 - 1.19), the risk was 41%

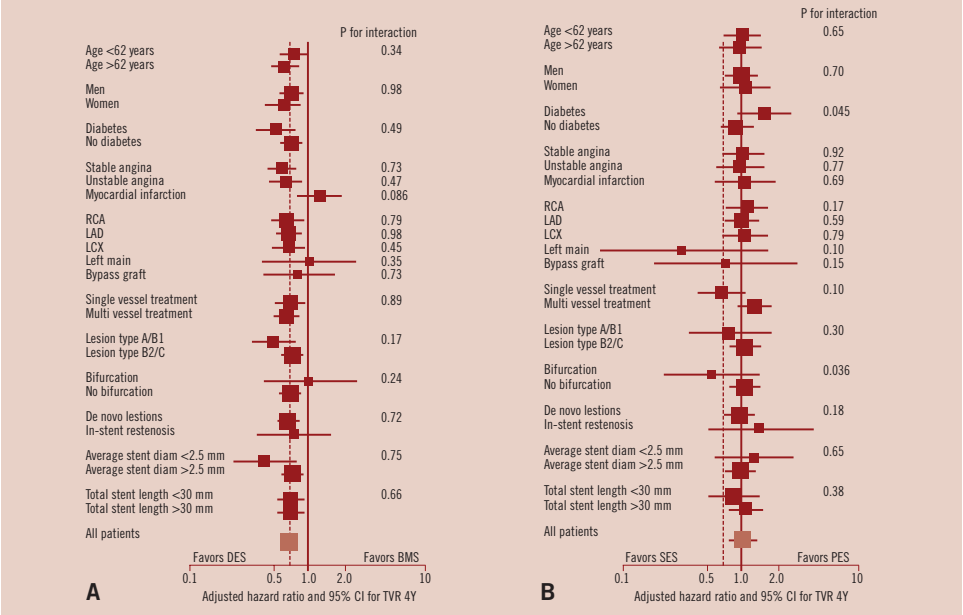

Figure 5. Exploratory analyses to evaluate possible heterogeneity in treatment effects on 4-year target vessel revascularisation rates according to drug-eluting vs. bare-metal stent cohort (A) and according to the sirolimus- vs. paclitaxel-eluting stent treatment cohort (B) and the following clinically relevant characteristics: age, gender, diabetes, clinical presentation, treated vessel, multivessel disease, AHA lesion class, bifurcation, in-stent restenosis, average stent diameter≤2.5 mm and total stented length≤30 mm. The size of the squares corresponds to the amount of statistical information. For the continuous variables (age, average stent diameter and total stented length), medians were used as cut-off. Results of tests for heterogeneity in treatment effect were considered significant if P was <0.05. SES indicates sirolimus-eluting stent, BMS bare metal stent, PES paclitaxel-eluting stent, AHA American Heart Association, LAD left anterior descending coronary artery, LCx left circumflex coronary artery, RCA right coronary artery.

higher in the patients with diabetes (adjusted HR 1.41, 95% CI 0.85 - 2.35) (p heterogeneity 0.045). In diabetics, the cumulative incidence of TVR at 4-years was 20.9% in the SES patients as compared with 13.9% in the PES group (Logrank p-value 0.048). There were no significant differences in the hard clinical endpoints between SES and PES treated patients: four-year all-cause mortality was 19.4% in the SES group as compared to 18.4% in the PES group (Adjusted HR 1.38, 95% CI 0.86 - 2.19), whilst the cumulative incidence of cardiac death or post-operative MI was 17.7% in the SES group as compared to 14.6% in the PES group (Adjusted HR 1.09 95% CI 0.64 - 1.83) and stent thrombosis occurred in 6.5% of the SES patients as compared to 4.1% of the PES patients (adjusted HR 1.41; 95% CI 0.56 - 3.56).

Bifurcation lesions

Finally, significant heterogeneity in the 4-year TVR rates between SES and PES was observed in patients treated for bifurcation lesions. While in patients without bifurcations there was no difference between the TVR rates in both DES groups (12.7% in the SES group vs. 11.7% in the PES group; adjusted HR 1.04, 95% CI 0.80 - 1.36), in patients with bifurcation lesions conversely, there was a strong trend towards a lower TVR risk in patients treated with SES as compared to PES (7.1% vs. 14.3% respectively; adjusted HR 0.56, 95% CI 0.23 - 1.36) (p heterogeneity 0.036).(Figure 5b) The difference in all-cause mortality did not reach statistical significance (SES: 6.2% vs. PES: 15.2%; adjusted HR 0.62, 95% CI 0.21 - 1.84). However, the cumulative incidence of cardiac death or post-operative MI was significantly lower in the SES group as compared to the PES group (4.5% vs. 14.2%; adjusted HR 0.30, 95% CI 0.10 - 0.88). Additionally, the cumulative incidence of stent thrombosis was lower in the SES group (1.3%) than in the PES group (5.2%) (adjusted HR 0.21, 95% CI 0.03 - 1.67).

Discussion

The results of the present study show that in a real world patient population, after four years, the overall use of DES was associated with similar all-cause mortality rates and a significantly reduced risk of post-operative MI and TVR as compared to BMS. As compared to patients treated with PES, the use of SES was associated with a significantly lower cardiac mortality and a strong trend towards

lower all-cause mortality as compared to PES. Although the cumulative incidence of stent thrombosis was significantly higher in the DES group, adjustment for confounders resulted in a non-significant 26% increased risk for stent thrombosis at four years in the DES group.

The findings of the present study need to be interpreted in the context of a tertiary referral centre that decided to adopt a policy of default DES use for all-comers (including acute MI at presentation, post-CABG, in-stent restenosis etc.) since the first day of commercial availability of the first approved drug-eluting (Cypher®) stent in Europe on April 16, 2002. On February 23, 2003, for financial reasons, our institution replaced the Cypher® stent by the second CE-mark approved drug-eluting stent (TAXUS™).[23] These two sequential cohorts were complemented by an equally sized cohort of consecutive patients treated with BMS in the two years preceding the commercial introduction of the Cypher® stent.

With the exception of a slightly longer follow-up in the pivotal randomised trials of the two DES[24], the follow-up of the present registry (mean 3.8 years) exceeds that of previously reported registries.[5,6,25-28] Another unique feature of this registry is that it was conducted in a small European country with a sedentary population and a very accurate registration of the vital status and cause of death of its citizens by a well-organised governmental administration. These features reinforce the strength of our observations.

Comparing our results to a recently performed network meta-analyses of 38 drug-eluting stent trials revealed a significantly lower absolute risk reduction for TVR at four years in the present study (3.8% vs. approximately 12% in the meta-analysis). Additionally, a higher overall mortality rate was observed in the present study as compared to the network meta-analysis (13.3% vs. approximately 7.5%, without significant differences between DES and BMS).[4] Yet, it is difficult to compare our results to other published meta-analyses and registries for three reasons. First, meta-analyses using patient level data of the pivotal randomised trials included only highly selected patients, and are representative of only ~40% of the clinical population of a tertiary medical centre.[29] Secondly, in comparable registries, the use of either a DES or BMS was often operator and procedure dependent, resulting in an even greater degree of heterogeneity of the patients treated with DES or BMS, thereby introducing a major potential for selection bias. For example, whereas diabetics would be likely to receive a DES because they are at increased risk of restenosis following BMS placement, patients presenting with acute MI are generally more likely to receive a BMS. It is unlikely that extensive regression and propensity analyses can completely compensate for this inherent type of bias. Thirdly, the vast majority of these registries pooled the outcomes of different devices into one "DES" group, despite the widely acknowledged differences between different types of DES.[4,10-12]

Recently, at least six large-scale real world registries demonstrated similar to significantly lower mortality rates in patients treated with DES compared to BMS.[5-8,30,31] Considering the different features of the present study, our findings demonstrated a similar safety profile for DES and BMS with a significantly lower risk of cardiac death (or post-operative MI) in patients treated with SES compared to PES. The survival benefit in patients treated with SES was already apparent at one week and remained so at one month. Exploring clinical- and procedural success rates, including mortality due to cardiogenic shock at presentation could not account for this difference, and clopidogrel was mandated for at least one month in all patients. Of note, both the short- and long-term survival in the PES group was remarkably similar to the BMS. Several other large-scale registries have also found a similar survival benefit with DES in the first six months which sustained in the longer term.[6,7,25] Our sequential registry analysis does not eliminate the possibility of confounders, but sheds additional light on the late survival after BMS, SES and PES implantation in all comers and demonstrates that pooling the outcomes of different types of DES may not always be appropriate. This is an important lesson as new DES, eluting different drugs form different polymers over different periods of time, enter the market.

We performed a stratified analysis to assess the relative safety of DES. The safety of DES appeared to be consistent among several pre-selected high-risk patient subsets, without a significantly superior safety profile, as expressed by all-cause mortality, between SES and PES. However, we found a strong trend towards heterogeneity in the 4-year TVR rates between DES and BMS in patients presenting with MI. As compared to BMS, the adjusted risk for TVR was 26% higher in patients treated with DES. Although this difference in performance did not reach statistical significance, the observation was in clear contrast to the non-MI population, in which the adjusted risk for TVR in the DES group was significantly (38%) lower. Pivotal randomised controlled trial data revealed that the use of SES was equally safe and more efficacious in reducing TVR in this setting as compared to BMS at 1-year, however, PES failed to demonstrate a superior performance as compared to BMS at one and two years.[32-34] These latter controversial findings, together with the fact that MI at presentation appeared to be a strong predictor of stent thrombosis in patients treated with DES[12,27,35,36], inevitably leading to repeat revascularisations, together with the results of the present study including 1,752 MI patients (DES group with over 80% PES use), makes the use of DES in this high-risk patient subset disputable.

There was significant heterogeneity in the 4-year TVR risk between SES and PES in patients with diabetes and bifurcation treatment. While both drug-eluting devices had a similar safety profile, there was a trend towards a 41% higher risk for TVR in diabetic patients treated with SES. Several smaller subgroup analyses of randomised controlled trials and registries concur with our findings. In the 1-year results from the SOLACI and MILAN registry and the REALITY trial, the use of PES was associated with non-significantly lower rates of target lesion revascularisation as compared to SES in diabetics.[37,38] The Kaiser Permanente and TC-Wyre registries conversely, even demonstrated a significant difference between SES and PES in reducing target lesion revascularisation in diabetics, in favour of PES.[39,40] Indirect evidence of a possible superiority of paclitaxel as compared to the -limus family drugs was derived from a pooled analysis of the randomised SPIRIT-II and III trials, which showed a strong trend towards lower major adverse cardiac events rates in patients treated with PES as compared to the Everolimus-eluting XIENCE V stent. [FDA Executive Summary Memo. FDA Panel 29 November

2007; http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4333b1-00-index.html] The sole randomised ISAR-Diabetes trial did not show any significant differences in the clinical endpoints with SES and PES.[41] Large-scale randomised controlled trials are needed to assess the possible superiority of PES as compared to SES in diabetics. The randomised controlled FREEDOM trial (using PES and SES) vs. coronary artery bypass surgery will shed additional light on this issue. [42]

Finally, significant heterogeneity in the treatment effect was observed in patients treated for bifurcation lesions, in which there was a strong trend towards a lower TVR risk and a significantly lower risk (70%) to suffer from cardiac death or post-operative MI when treated with SES as compared to PES. These findings confirm the results of a randomised trial by Pan et al evaluating the safety and efficacy of SES vs. PES in bifurcation lesions.[43] The authors concluded that the overall system of the SES is better than the PES in terms of main vessel restenosis rates, late loss, and neointimal proliferation assessed using intravascular ultrasound.

The present single centre study has several limitations. First, the clinical and procedural complexity increased over time, which resulted in substantial differences in clinical and procedural characteristics between the sequential patient cohorts. Despite the use of extensive regression models, it remains uncertain whether we were able to completely adjust for the differences between the groups. However, the likelihood of a randomised trial comparing BMS with DES in an all-comer population is already remote and will become even more unlikely with the advent of the second and third generation of DES.

A substantial amount of pivotal experiences with DES in several high risk patient and lesion subsets were reported based on the RESEARCH and T-SEARCH registries. Subsequently, late angiographic evaluation was eventually obtained from "complex" patients, typically with DES implanted in bifurcations, left main coronary, chronic total occlusions, very small vessels, long stented length (>36 mm), and acute myocardial infarction (in total, 25.9% patients in the SES group had angiographic follow-up between six and 12 months).[44-50] In the BMS and PES groups, planned angiography was performed in 12.0% and 14.3% respectively. In all other cases, coronary angiography during follow-up was obtained as clinically indicated by symptoms or documentation of myocardial ischaemia. Of note, planned angiographic re-evaluation was used as a co-variable in the Cox proportional hazards regression models.

Due to the sequential nature of the three patient cohorts in the present study, the follow-up in the PES group was shorter than the follow-up in both the BMS and SES groups resulting in a lower number of patients at risk at three years in the PES group. Kaplan Meier survival analyses were performed to reconcile this limitation.

The per patient clinical- and procedural risk profile was linearly associated with time. Given the sequential nature of the three patient cohorts in our study, propensity analyses were considered inappropriate. However, the overall risk profile was more favourable for the BMS group than for either DES group and might even underestimate the real difference.

Finally, the findings derived from the stratified analyses to detect possible heterogeneity in the treatment effect of the different devices should be seen as hypothesis generating. The non-randomised nature of our study precludes any definite statements about the true superiority of one DES above the other in several high-risk subgroups. However it was remarkable that our findings concurred with the few comparative data available in these high-risk subgroups, despite the longer follow-up and subsequent higher event rates in the present study. With the exception of the FREEDOM trial, there are currently no comparative randomised controlled trials ongoing comparing either SES or PES or one of both with BMS in patients with acute MI, bifurcations and/or diabetes properly powered for hard clinical endpoints to confirm our findings.

Conclusion

The results of the present study show that in a real world patient population, after four years, the overall use of DES was associated with similar all-cause mortality rates and a significantly reduced risk for post-operative MI and TVR as compared to BMS. This finding appeared to be consistent among several high-risk patient subsets, with the exception of patients presenting with MI. Furthermore, the use of SES resulted in significantly lower rates of cardiac death and post-operative MI as compared to PES.

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The contribution of the authors is as follows: Conception and design: Daemen, van Domburg, Serruys. Analysis and interpretation of data: Daemen, van Domburg, Boersma, Serruys. Drafting of the manuscript: Daemen, van Twisk, Kukreja, Serruys. Critical revision of the manuscript for important intellectual content: van Twisk, Kukreja, van Domburg, de Jaegere, Daemen, Serruys. Statistical expertise: Boersma, van Domburg, Daemen. Administrative, technical, or logistic support: van Twisk, van Domburg, Serruys. Acquisition of data: van Twisk, Kukreja, van Domburg, Daemen.

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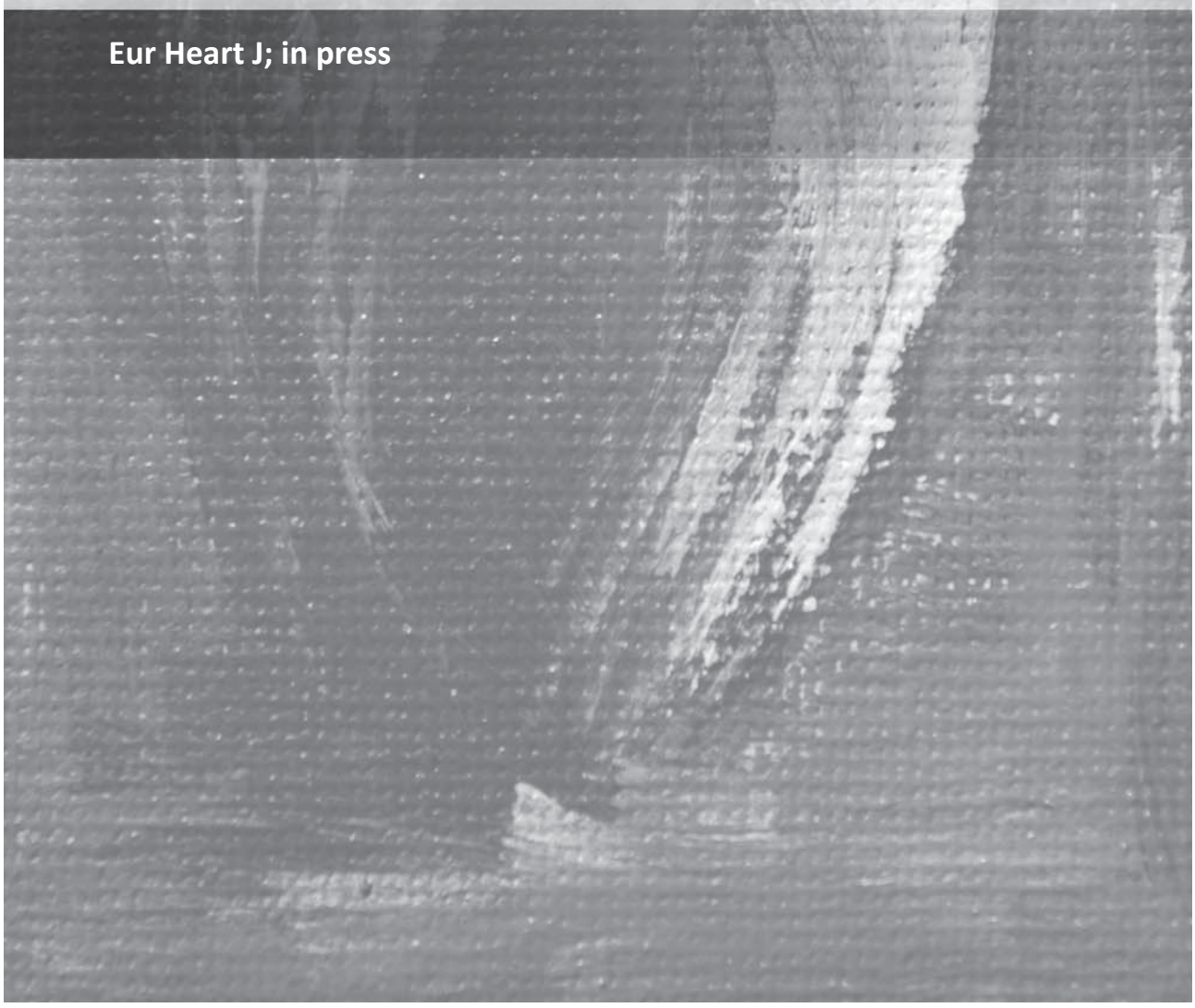
Chapter 23

Meeting report: ESC Forum on drug eluting stents; European Heart House Nice, 27 – 28 September 2007

Daemen J, Simoons ML, Wijns W, Baczynsak A, Bagust A, Bos G, Boam A, Bowen JM, Braunwald E, Camenzind E, Carter A, Chevalier B, DiMario C, Fajadet J, Ghislain JC, Gitt A, Guagliumi G, Hillege H, James S, Jüni P, Kastrati A, Kloth S, Kristensen SD, Krucoff M, Legrand V, Lekehal M, Pfisterer M, Raveau-Landon C, Rothman M, Serruys PW, Silber S, Steg PG, Tariah I, Wallentin L, Windecker SW

Eur Heart J; in press



Meeting Report

ESC Forum on Drug Eluting Stents European Heart House Nice, 27 – 28 September 2007

Daemen J, MD; Simoons M.L. , MD, PhD; Wijns W., MD, PhD; Bagust A. ; Bos G. ; Boam, A., MD; Bowen J.M., MSc; Braunwald E., MD; Camenzind E., MD; Farb, A. MD; Chevalier B., MD; DiMario C, MD; Fajadet J., MD; Ghislain J.C.; Gitt A., MD; Guagliumi G., MD; Hillege H., MD, PhD; James S., MD; Jüni P. MD; Kastrati A., MD; Kloth S. MD, PhD; Kristensen S.D., MD; Krucoff M., MD; Legrand V., MD; Lekehal M. ; Pfisterer M, MD; Raveau-Landon C. ; Rothman M., MD; Serruys P.W., MD, PhD; Silber S., MD; Steg P.G., MD, PhD; Tariah I. ; Wallentin L, MD, PhD; Windecker S.W., MD, PhD.

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INTRODUCTION

Drug eluting stents (DES) were introduced into clinical practice in 2002 in order to reduce restenosis which occurred in 15% to 25% of patients receiving bare-metal stents (BMS).(2, 3) Subsequent trials with different types of DES confirmed their efficacy in this regard.(4) However, late stent thrombosis was reported as early as 2004, typically in patients discontinuing dual antiplatelet therapy.(5) At the European and World Congress of Cardiology in Barcelona 2006, alarming data were presented on a worse long-term prognosis following DES implantation as compared to BMS.(6-8) As a result both randomized controlled trials and registry data were scrutinized to validate these concerns, bearing in mind the differential values of both types of studies. Furthermore, the worldwide discussion on the long-term safety and efficacy of DES triggered the European Society of Cardiology together with the European Association for Percutaneous Cardiovascular Interventions to organize a forum on DES. On September 27 and 28, 2007, key opinion leaders in (interventional) cardiology and representatives from industry and regulatory bodies gathered in the European Heart House with the intention to review: 1) the most recent data on the long-term efficacy (reduction of restenosis, re-intervention and possibly improved survival) and safety (late stent thrombosis, myocardial infarction, mortality) of DES; 2) specific indications for DES; 3) health economical analyses currently performed with DES; 4) the DES registration process in Europe; 5) current and possible future trial designs. The overall goal was to provide general recommendations to the medical community for the use, clinical development and future assessment of DES.

SAFETY

In several randomized controlled trials comparing sirolimus-eluting stents or paclitaxel-eluting stents and bare-metal stents, no significant differences were found in the rates of death or myocardial infarction, although RAVEL showed a trend towards more death and MI at 5 year follow up.(9-12) The overall similar safety was confirmed in several pooled analyses of individual patient level data from these trials.(13-15) The long-term safety of DES was further assessed in a network meta-analysis including 38 randomized controlled

trials in over 18.000 patients. (16) While there was no difference in mortality up to 4 years in patients initially treated with either BMS, sirolimus-eluting stents (SES) or paclitaxel-eluting stents (PES), the SES was associated with a 19% lower risk for myocardial infarction (MI) as compared to BMS and 17% as compared to PES.

In the latest report of the Swedish SCAAR registry (n=35.262) presented at the ESC congress in Vienna 2007, the incidence of death and MI was similar between DES and BMS up to four years.(17) However, the survival curves showed a short-term survival benefit with DES up to ~1 year followed by a late catch-up.(8) Thus the apparent early benefit is lost by an excess of subsequent events. It is noteworthy that the impaired overall outcome with DES that was reported earlier by the SCAAR investigators in patients treated up to 2004, was no longer present in the more recent analysis, which included patients treated in 2005.(18) Additionally, the Western-Denmark registry (n=12.395), Ontario registry data (n=13.353), and data from the state of Massachusetts demonstrated a trend towards a lower mortality rate following DES in the first months, which was maintained up to 2 years.(19-21)

A pattern of lower initial and increased late mortality rates following DES use was also reported by the Basel Stent Kosten Effektivitäts Trial (BASKET-LATE; DES: n=545; BMS: n=281) investigators. While there was again no difference in death and MI at 3 years, this was the net result of a higher 6 months survival and a higher incidence of late (>1 month) death or MI following DES. According to the authors, this latter might be the consequence of the discontinuation of clopidogrel at 6 months.(22) In an analysis of 6.129 consecutive patients from Rotterdam, the Netherlands, the use of SES was associated with a significantly higher survival as compared to BMS.(23) The survival benefit with SES became apparent as early as 3 months, a finding which was in line with the Danish registry and the last follow-up of the SCAAR and Massachusetts registries.(17, 21) The ENDEAVOR program, evaluating a zotarolimus-eluting stent showed significantly lower cardiac death and MI rates for the DES as compared with BMS up to 3 years.(11)

It should be appreciated that follow up in different trials, meta-analyses and registries varies from one or two years to five years. These differences should be taken into consideration when comparing these studies. If the trend of an early benefit with some DES, with a later excess of death and MI as observed in some studies, would persist, long term outcome beyond five years might gradually favor BMS. This is, of course, highly speculative! Nevertheless we do hope that the investigators will continue to provide such very long term follow-up data.

LATE STENT THROMBOSIS

Stent thrombosis has been linked to a wide variety of pathophysiological mechanisms and clinical and procedural risk factors.(6, 24-27) It has been associated with mortality rates varying between 15% and 45%.(28, 29) Data from registries and meta-analyses indicated that there is no difference in the risk of early (<30 days) and late (>30 days, <365 days) stent thrombosis between DES and BMS, but that an excess risk emerges after more than one year of follow-up (very late stent thrombosis). The incidence of definite stent thrombosis in the combined Bern-Rotterdam experience with PES and SES was 0.6% per year, without any sign of reduction up to 4 years after stent implantation, and with slightly higher rates for PES than SES.(29, 30) A comparable rate of 0.5% was observed in the SCAAR registry. This suggests that endothelial healing remains impaired up to 4 years, at least in some patients. Of interest were the recently presented 2- and 3-year follow-up of the ENDEAVOR I, II and III trials, which showed remarkably low rates of stent thrombosis (0.0% to 0.3%) and no cases of stent thrombosis after 30 days.(11) Of note, these

pivotal studies evaluating the relative safety and efficacy of the zotarolimus-eluting stent were restricted to relatively simple lesions and patients. The results of the large E-Five registry and the 8000 patient randomized PROTECT trial are eagerly awaited.

It should be appreciated that ´definite´ stent thrombosis underestimates the real incidence of such event, since some of the patients with stent thrombosis develop myocardial infarction, or die without angiographic documentation of stent thrombosis. To address this issue, new definitions were formulated by a consortium of interventional cardiologists from both sides of the Atlantic, representatives of the Food and Drug Administration, central research organizations, and representatives from major stent manufacturers.(31)

EFFICACY

The clinical trials as well as registries consistently confirm lower (target lesion) revascularization rates at follow-up with DES compared with BMS.(9, 10, 15, 17, 19, 20) However, the reduction of subsequent revascularization in registries was less than in clinical trials. The absolute reduction in target vessel revascularization at 4 years in a network meta-analysis of 38 clinical trials was about 12% versus 2 – 4% in the Swedish SCAAR registry at 3 years.(16) While the target lesion revascularization (TLR) rate in SCAAR (Swedish Coronary and Angioplasty Registry) did not reach 6% at 3 years in the DES arm(8), the network meta-analysis(16) showed TLR rates up to 9% at 3 years with DES, a discrepancy that was even more apparent in patients treated with BMS and is most probably explained by systematic angiographic follow-up in many trials, and the lack of such angiography in the `real world` registries. Thereby, data quality in the registries may be limited by absence of event adjudication by blinded outcome assessors and lack of data query and verification. Furthermore, patient and device selection is often operator dependent. This phenomenon is further enhanced by the arbitrary allocation of patients treated with at least one DES into the DES cohort regardless of the number of simultaneously or previously implanted BMS. Clinical events in the mixed cohort may be related to either stent type. In many registries, the BMS group is a mixture of many different types of bare metal devices, with different outcomes. This was illustrated from the SCAAR registry reporting restenosis rates per individual BMS types ranging from 7 to 11% at 3 years. [Figure 1] For different DES 3 year restenosis rates varied between 3 and 4.5 %. Finally, the interpretation of long-term follow-up data is hampered by cross-overs: patients who receive first one type of stent and another type of stent at a later point in time, for example for in-stent restenosis. In the original trial protocols, secondary stent thrombosis — stent thrombosis in a patient who had previously undergone target-lesion revascularization — was not reported as a stent thrombosis. Clear consensus should be reached on how these events should be classified and reported.

DES AND BMS IN SPECIFIC PATIENT GROUPS

In interventional cardiology, as well as in other fields of medicine, post-hoc subgroup analyses should be interpreted with caution. These may provide important directions for additional research, but the conclusions may only be accepted if these are very strong, consistent among all studies, and based on plausible pathophysiology and experimental data. In general, the treatment effects in subgroups with limited numbers of patients and events, are best estimated by the overall effects in the trials. Yet, a few subgroups should be discussed in this report.

ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

Two-year follow-up of the STEMI cohort of the GRACE registry showed a lower in-

hospital mortality in the DES cohort, a similar mortality rate from the time of discharge up to 6-months, but a significantly higher mortality rate from 6-months to 2 years in patients treated with DES (n=569) as compared to BMS (n=1.729) (HR 6.69, 95% CI 2.05 – 21.8).(32) Survival rates following DES or BMS were similar in both the overall population and in the non-STEMI group. A recent meta-analysis of trials including patients presenting with ST segment elevation MI (8 trials – 2.786 patients) showed no difference in the hard clinical endpoints of death and MI in these high-risk patients. However, most of the trials had a follow-up limited to 1 year.(33)

MULTIVESSEL CORONARY ARTERY DISEASE

The recently presented 3-year results of the Arterial Revascularization Therapies Study (ARTS-II) reported on the safety and efficacy of PCI using SES (n=607) as compared with the randomized surgical (n=605) and percutaneous arms (n=600) of ARTS-I for patients with multivessel coronary artery disease.(34) The authors concluded that despite the higher clinical and angiographic risk profile of the ARTS-II population, the incidence of death/CVA/MI was significantly lower than in the ARTS-I PCI arm and similar to the ARTS-I CABG arm. Despite the significantly lower repeat intervention rates in ARTS-II as compared to ARTS-I PCI, CABG remained associated with the lowest reintervention rates compared with both PCI groups. These findings were in line with the 3-year results of the Argentine Randomized Study Coronary Angioplasty versus Coronary Bypass Surgery in Multiple Vessel Disease (ERACI-III trial; n=675) showing similar rates of death, CVA and MI up to three years in patients treated with DES as compared to either CABG or PCI with BMS and significantly lower repeat revascularization in the CABG group as compared to both PCI arms.(35)

SMALL VESSELS, LONG LESIONS, DIABETICS AND BYPASS GRAFTS

Heterogeneity of the treatment effect was suggested by an analysis of the randomized BASKET-LATE trial, observational data from Ontario, Canada (n=16.498)(36), and data from a continuous registry of all PCI's in Belgium (n=15.237). In these studies the DES benefit was apparent particularly in small vessels, long lesions, diabetics and bypass grafts. Among patients with diabetes, DES proved effective in reducing the need for revascularization in almost all lesion types and regardless of recent MI status. Among non-diabetic patients, the benefit of DES was more limited but was apparent in long lesions, small vessels and particularly when both adverse features co-existed. Also in the meta-analysis the number needed to treat to prevent target lesion revascularization was lower in diabetic patients as compared to non-diabetic patients.(16). Of note, in a meta-analysis of pivotal randomized controlled Cypher trials, significant heterogeneity in the treatment effects was found for patients with diabetes. The 4-year cumulative survival rates among patients without diabetes did not differ significantly between the stent types. However, deaths from both cardiovascular and non-cardiovascular causes were more frequent in the SES-group and the survival rate for patients with diabetes was significantly lower in the SES group (P = 0.008). In the subgroup of patients with diabetes, very late stent thrombosis was adjudicated more frequently among the patients with sirolimus-eluting stents than among those with BMS. Owing to the low number of events, these findings should be interpreted with caution; it does not appear that they adequately explain the observed difference in survival among patients with diabetes in the two groups.(13) Conversely, in the larger scale network meta-analysis, no significant difference in all-cause mortality was observed in patients with diabetes.(16)

CONCLUSIONS, PERSPECTIVES AND RECOMMENDATIONS REGARDING EFFICACY AND SAFETY OF DES

- DES, when compared with BMS as an initial treatment strategy are associated with lower subsequent revascularization rates, but an excess risk of late stent thrombosis, which thus far, does not seem to impact on the occurrence of hard clinical endpoints like death and myocardial infarction up to 4 years.
- Thus far the overall relative *safety and efficacy* of DES compared with BMS appears to be consistent across different groups of patients, albeit at various levels of absolute benefit and risk. The long-term safety of DES in diabetics and patients presenting with myocardial infarction remains to be established.
- Data about the long-term safety and efficacy of DES in high-risk subgroups like diabetics, and patients with (non) ST segment elevation MI remain limited. This has implications for cost-effectiveness analyses as illustrated below.
- There are important differences between the various types of stents, with dissimilar mechanical and pharmacological properties and subsequent differences in clinical outcome. "Not all DES are equal, nor are BMS".
- Interpretation of long-term follow-up data is hampered by cross-overs and mixed DES and BMS use: patients who receive first one type of stent and another type of stent at a later point in time, for example for in stent restenosis.
- These new findings attenuate the initial reports which have led to the creation of this Task Force and call for greater attention to scientific scrutiny and caution in the communication to the public of sensitive scientific information. However, the current conclusions regarding the safety and efficacy of DES should not divert the attention from the importance to continue development of less- or non-thrombogenic stents.

HEALTH ECONOMICAL ANALYSES

With respect to the discussions about effectiveness and risks of DES, and the higher costs of DES compared with BMS, health economical analyses have been initiated in different countries. Three analyses were presented, showing consistent results.

In Ontario, Canada, since 2003, the Ministry of Health & Long-Term Care has allocated a funding of $12 Million for DES annually between the 12 Cardiac Care Centres in that province.(36) Cost-effectiveness was analyzed using data from 16.498 patients with a least 12 months follow-up receiving only BMS or DES from Dec 1, 2003 – March 31, 2005.(20) Overall the incremental cost-effectiveness ratios (ICER) of DES vs. BMS, were "fairly high" (ICER ranging from $2.630,- for very long and narrow lesions to $133.937,- for short lesions in larger vessels). A significant benefit (reduction of repeat revascularization) at acceptable costs appeared in a limited group of patients with adverse lesion characteristics (long lesions, small vessels) and/or diabetes.

In its first appraisal of DES reported in October 2003, the English National Institute for Clinical Health and Excellence (N.I.C.E.) restricted the use of DES to small vessels (<3mm) and long lesions (>15mm) based on cost effectiveness assessment using a QALY-based Incremental Cost-Effectiveness methodology. The expected use of DES at that time was approximately 30%, while in practice the usage increased up to more than 60% of patients in the UK. In July 2007 N.I.C.E. issued its 2nd appraisal of DES in draft form and concluded that DES are not cost-effective in any population and cannot be recommended for patients with coronary artery disease. This recommendation was driven by a lower than expected need for repeat revascularization with BMS in unselected patient populations, markedly lower than in the randomized controlled trials, contrasting with the very high price of DES which did not fall as expected.

Furthermore, the conclusion was driven by an increase in the cost differential between DES and BMS. This recommendation has been challenged by professional societies and industry alike, and has been the subject of extensive debate. It should be appreciated that the more successful the new technology, the more rapidly and further the price of the old technology that it is replacing is likely to fall. This may reduce the relative cost/effectiveness of the new technology, unless its price is similarly reduced.

The appraisal committee reviewed their draft guidelines in October 2007 and N.I.C.E. subsequently made their 3 year review with the latest draft document issued in Jan 2008 (see textbox below) and will issue final guidelines in June 2008. In the 18-month data presented from the BASKET trial, follow-up costs were similar for both DES and BMS and relatively low overall. Due to higher stent costs, the use of DES was associated with an incremental cost-effectiveness ratio (ICER) of €64.732. In terms of clinical endpoints, DES proved most effective in high-risk patients and lesions, while the study showed no improved outcome in low-risk patients and lesions in terms of efficacy. Subgroup analyses revealed that at 18 months, the ICER for DES was favorable if the use was limited to high-risk patients with small vessel / bypass graft stenting (only one third of the patients fall into these groups)..

Ong et al. evaluated the cost-effectiveness of SES in the Rapamycin Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry and concluded that the SES was not cost-effective at one, or two years follow-up when compared to BMS.(37) The incremental cost-effectiveness ratio per target vessel revascularization avoided would be €29.373 at 1 year, and €22.267 at 2 years in the total cohort. Based on these results, the calculated maximum cost-effective price after 1-year of follow-up is €1.336 per SES for all-comers, or €1.023 to achieve cost-neutrality in the Netherlands.

The findings of these health-economic analyses are consistent, indicating that DES are not cost-effective at the current price levels for most patients undergoing PCI for stable angina, while the use of DES can be cost-effective in a subset of patients at high risk for restenosis. It was discussed that DES would become cost-effective for most patients if the price-premium, relative to BMS, would not exceed €300 - €450 (£300 Pounds sterling). No cost-effectiveness data on the use of DES for the life-saving indications of PCI (unstable angina, NSTEMI or STEMI) as compared to either BMS use or conventional treatment are currently available.

THE DES REGISTRATION PROCESS

DES are combination products that consist of a medical device with a medicinal substance as an integral part. DES were classified as class III medical devices and require a consultation with the Competent Authorities of the member states prior to CE certification by the Notified Body. Therefore, the Competent Authority will assess the clinical data related to quality, safety and usefulness of the medicinal substance. The positive assessment report of the Competent Authority is the pre-requisite for the certification of DES by the Notified Body.

In 2007, at least 19 different DES have received Conformité Européenne (CE) mark approval, while at the time of the conference only the first two DES (Cypher and Taxus) were approved by the US FDA for commercial use. Of note, the US Food and Drug Administration has recently given a positive review for the Endeavor and Xience-V DES.

In a recent publication from the German Society of Cardiology the data were reviewed supporting 19 DES with CE mark, reported in 76 randomized controlled trials. A distinction was made between studies

CONCLUSIONS, PERSPECTIVES AND RECOMMENDATIONS ON COST-EFFECTIVENESS

- Cost-effectiveness analyses are essential to fully understand the value of BMS versus DES and enlighten health care policies. However, careful interpretation is needed when analyzing specific patient subsets derived from clinical trials which might not reflect real world clinical practice.
- At the current price level, DES can be cost-effective when applied in high-risk patients. Alternatively, DES would be cost-effective in the majority of patients undergoing percutaneous coronary intervention at a price premium around €450 (£300 Pounds sterling) above the price of comparable BMS, or less.
  It is worth noting that the ICER will be heavily influenced by the costs of both the new and old technology. The more successful the new technology, the more rapidly and further the price of the old technology is likely to fall. This may reduce the relative cost/effectiveness of the new technology, unless its price is similarly reduced.
- Importantly, the available cost-effectiveness analyses do not pertain to high-risk patients such as NSTEMI and STEMI. Under those circumstances, PCI with BMS was shown to portend a survival benefit over non-interventional conventional therapy.(1) It is unknown whether this survival benefit will be amplified by the use of DES.

UPDATE: NICE APPRAISAL JAN 2008 ***NOT DISCUSSED AT THE MEETING***

- The recommendation continues to support the use of DES in small vessels and long lesions, with no recommendation for the volume of DES that can be implanted. There has been some debate about the cost-effectiveness and relative pricing of BMS and DES in the UK. NICE used price differentials between £300 and £600 as input in their model to determine the cost per QALY. Considering a differential of £300 is the subject of a current appeal to NICE, the outcome of which will become public in mid 2008.

with angiographic or clinical primary endpoints. The authors used a predefined decision tree to assess the level of evidence gained with the individual trials. Although the used score was not an internationally validated assessment tool for clinical studies and disregarded the fact that several studies were also powered for secondary endpoints, the authors concluded that only 3, or at best 5 out of the 19 CE marked DES had adequate clinical documentation supporting their use. They concluded that there is significant heterogeneity in the requirements that are set for obtaining a CE-mark certificate.(38)

With the intention to harmonize the views and interests of the notified bodies on the one hand and the medical profession on the other hand, speakers from KEMA, BSI, TÜV SÜD Product Service, CETF, EMEA and the FDA presented their views on the current approval process and their thoughts for modification of the process for assessment of next generation devices. There was agreement that novel stent technologies will be developed, and should be made available for patient use in Europe, but also that more extensive pre-marketing (pre-clinical and clinical) as well as post-marketing studies might be required. A balance should be found between pre-marketing and post-marketing evaluation with differential follow-up timescales, also accounting for the expected relatively short lifetime of the drug-device combination products. Additional guidance documents are required to achieve uniformity and consistency on the type of 'short term' (pre-approval) data needed to receive CE Mark decision and 'long term' (post-approval) data that are needed. Such documents are under development both by the Notified

Bodies and by the EMEA. It was suggested by the clinical professionals that initial (CE mark) approval might be obtained based on assessment of the effects of a stent (DES or BMS) on coronary lesions (angiography, intravascular ultrasound), stent coverage by intima (optical coherence tomography, or endothelial function studies) as well as one-year clinical follow-up. In addition post-market clinical follow-up should be considered for devices where identification of possible emerging risks and the evaluation of long-term safety and performance are critical. Careful attention should also be paid to differences in the populations enrolled in pre-market studies as compared to the actual use after release. Finally, the interplay between a device and long-term medical treatment, in particular the duration and level of anti-platelet therapy should also be taken into consideration.

According to the EMEA, there are at present substantial differences in the amount and quality of submitted data. The authority emphasized the need for properly performed randomized controlled trials. While there is clearly a role for both patient based endpoints such as death, myocardial infarction and repeat revascularization as well as for lesion/device based endpoints such as late lumen loss, binary restenosis and target lesion revascularization, there is no consensus on how best to use both of these categories for trials at different stages in the development and approval processes. Furthermore, there are many unresolved issues with regard to the selection of comparators when evaluating new DES platforms. First, there are studies that should use surgery or medical therapy most appropriately as the standard of care for the control group. Second, if DES are compared to BMS, data presented from the SCAAR registry made the point that outcomes vary greatly depending on the brand of BMS selected.[Figure 1] In future studies it may be relevant to compare new, investigational DES platforms to already approved DES platforms in so-called “active control” study designs. Yet, there is no specific requirement for either BMS or DES as a control device. When acceptable treatment alternatives exist, safety concerns can tip the balance in the risk-benefit assessment.

A proper randomization process with adequate concealment of allocation and blind adjudication of clinical endpoints is needed to avoid bias in the interpretation of data, but this can only be achieved in larger trials at relatively high costs. The balance between the need for robust pre-market evaluation and the speed of innovation in cardiovascular devices such as DES is a critical one that needs to be directly addressed in order to ensure patient safety and preserve the advance of medical technology.

Representatives of the United States Food and Drug Administration (FDA) confirmed that this organization also considers a two staged approach: trials with a clinically relevant composite endpoint at 1 year (cardiac death, myocardial infarction, target lesion revascularization) as well as assessment of death and MI and stent thrombosis over longer follow-up (at yearly intervals up to 5 years). The recently established ARC-criteria for definite and probable stent thrombosis should be applied.[Figure 2] Furthermore, the actual use and possible interruption of adjunctive antiplatelet therapy should be registered. Both randomized clinical trials, as well as properly organized registries of clinical practice might contribute to the post-marketing assessment of DES. In this process it should be appreciated that new devices often are built on already existing platforms, polymers or drugs. A completely new approval process may not be required for every small modification of an existing device, although this approach requires thorough characterizations of DES through pre-clinical evaluation. Processes can be tailored for novel devices that incorporate already existing and approved platforms, polymers or drugs.

In order to reach a consensus on these issues, notified bodies indicated that they will encourage and dialogue with scientific societies, in an attempt to harmonize the relevant requirements coming from both a device-oriented and a pharmaceutical approach. There is a need for harmonization in interpretation and applying requirements for quality, safety and efficacy and guidance to applicants and/or sponsors in planning the overall product development. Of note, the lifecycle of medicinal products and medical devices differ considerably; while new medicinal substances require time frames up to 15 years, the lifecycle of medical devices is shorter, ranging between 3 to 5 years.

A GLIMPSE INTO FUTURE TRIAL DESIGN

Currently, various innovative DES types are emerging and will become available in the coming years with the intention to avoid the current limitations of DES. A wide variety of modifications to the stent platform, coating, drugs and eluting techniques are under investigation. Abolition of neointimal hyperplasia is no longer the ultimate goal, but rather the development of more biocompatible or bioabsorbable stents facilitating adequate endothelialization.(39) At the same time also the development of BMS continues, with new materials and geometry. Thus future trials should not only compare new and established DES, but also new DES with new BMS."

Several proposals for large-scale randomized controlled trials are under development. These trials aim at an adequate power/sample size for hard clinical end-points and are often conceived in a 2x2 factorial design to compare different stents and to simultaneously assess the optimal duration of (dual) antiplatelet therapy. For example, the PRACTICA trial, might include approximately 12.000 all-comer patients, with a factorial design, randomizing first to treatment with either a DES or a BMS and subsequently for receiving 12 or 36 months of dual antiplatelet therapy. FIESTA has a similar factorial design, with a 5-year follow-up for death, MI and repeat revascularization and 10 years follow-up for all-cause mortality. Only public funding will be obtained for financing the trial. In the currently enrolling PROTECT trial, approximately 8.800 patients will be randomized to receive either a zotarolimus-eluting stent or a SES. Primary endpoint of this trial will be stent thrombosis at 3 years.

On a broader scale, the Cardiac Safety Critical Path Initiative, in which academics, industry and regulatory authorities are joining, is initiating a program focused on DES thrombosis and optimal dual anti-platelet therapy. The core of this program is to develop a more formalized registration approach to concomitant evaluation of a drug and a device when there is an obligate interaction between the drug and the safety behavior of the device.

Large scale randomized trials (eg. TRITON, OASIS 7, PLATO, CHAMPION) are currently evaluating the pros and cons of new antiplatelet agents and will shed light on the balance between a possible reduction of adverse cardiac events by more intensive long term anti-platelet therapy, perhaps at the costs of higher bleeding. Dual antiplatelet therapy with the P2Y12 receptor inhibitor clopidogrel and aspirin substantially reduces the risk of stent thrombosis. However, low response to clopidogrel is common and increases the risk for stent thrombosis. Clopidogrel is a prodrug requiring conversion to an active metabolite resulting in a slow onset of effect. Multiple studies have demonstrated that the response to antiplatelet therapy with either clopidogrel and aspirin is highly variable when the responsiveness to clopidogrel is measured with ADP-induced aggregation.(40) A low level of inhibition has been reported in 20-40% of the patients. Prasugrel like clopidogrel is also a pro-drug, but with substantially more rapid onset of P2Y12 inhibition and greater and more consistent platelet inhibition without

the low responders seen with clopidogrel. Recently the TRITON-TIMI 38 trial (n=13.608) compared prasugrel with clopidogrel when given before or during PCI and continued for 15 months in patients with acute coronary syndrome. Prasugrel reduced the risk of myocardial infarction and halved the rate of stent thrombosis both with DES as well as with BMS. Prasugrel was, however associated with an increased rate of major bleeding and transfusion, particularly in the elderly, in patients with a low body weight, and in those with documented cerebrovascular disease.(41) The net clinical benefit (death, MI, stroke and major bleeding) favoured Prasugrel in most patients, except in the three subgroups mentioned above. Ongoing trials will reveal whether the new direct P2Y12 inhibitors, e.g. cangrelor, and AZD6140, or alternative doses of clopidogrel and prasugrel might overcome these limitations. Subsequently several of these agents should be tested at different treatment durations in combination with existing or new stents. Finally, the hypothesis has been developed that longer term dual antiplatelet therapy will not only reduce the risk for stent thrombosis but will also slow down disease progression.

CONCLUSIONS, PERSPECTIVES AND RECOMMENDATIONS FOR TRIAL DESIGN, REGISTRATION PROCESSES AND ANTI-PLATELET THERAPY

- The EU Commission is asked to initiate the development of a unified guidance document for assessment of DES. The participation of Competent Authorities of the Member States, Notified Bodies & EMEA and expert societies such as ESC and EAPCI is strongly encouraged in the development of such unified guidance for assessment. This standard should be homogeneous in Europe and flexible in order to allow new devices on the market. If appropriate, the guidance document might be written in consultation with the FDA.
- Randomized controlled trials pre-registration should strive to include all-comers which should be followed by large-scale all-comer registries to assess both the benefits and late complications. Attention should be given to the choice of comparator stents, since both DES as well as BMS continue to develop.
- In view of the superior common goal of having complete unbiased longitudinal results after current and future DES, Industry, National Departments of Health and Scientific Societies should cooperate to implement prospective independent registries of all PCI's, ideally country-wide or continent-wide, with appropriate quality control and follow-up connected to official demographic registries.
- Both randomized trials and registries, reflecting real world clinical practice, are valuable, however, they need to be put in their appropriate context. Rules for reporting events, endpoint definitions and quality control need to be agreed upon and harmonized. Reinterventions should be categorized as clinically driven or non-clinically driven (eg. angiographic follow-up, staged procedures and evaluation prior to non-cardiac surgery).
- Market access should be based on efficacy as part of "usefulness". Initial approval might be based on assessment of restenosis (angiography, IVUS) or neointima formation and stent coverage (OCT, endothelial function) including one-year clinical follow up. These data should be followed by the assessment of death, MI and stent thrombosis over longer follow-up (at yearly intervals up to 5 years).
- Randomized trials are required to assess the benefit, cost-effectiveness and "optimal" dose and duration of long-term (dual) anti-platelet therapy including the new more potent agents. Currently, the preferred design seems to be a 2x2 factorial design that incorporates a double randomization to device and antiplatelet regimen.
- Data from clinical trials and registries should be in the public domain and academic investigators should have access to all relevant data for independent analyses and/or pooled analyses.

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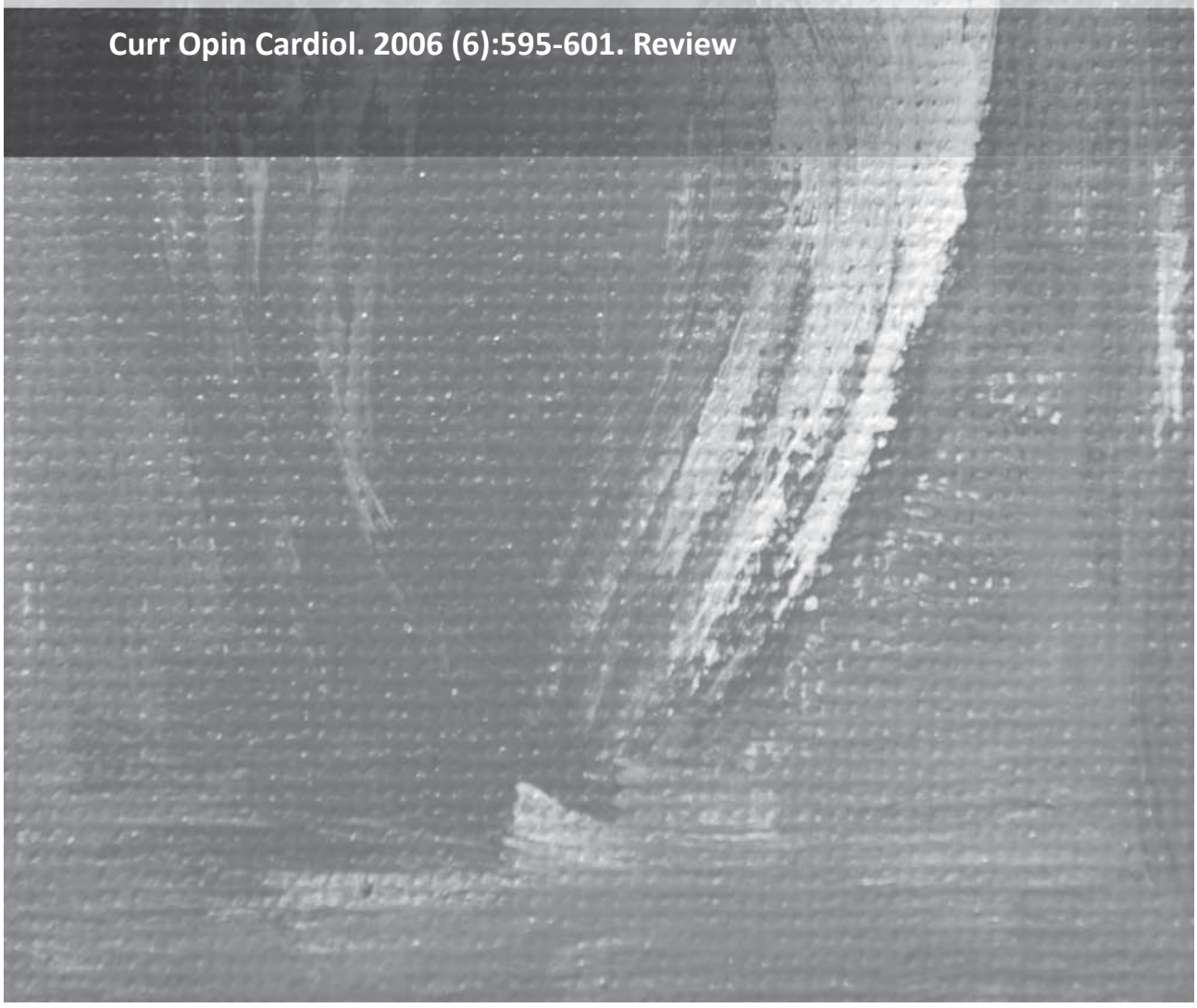
Chapter 24

Optimal revascularization strategies for multi-vessel coronary artery disease

Daemen J, Serruys PW

Curr Opin Cardiol. 2006 (6):595-601. Review



Optimal revascularization strategies for multivessel coronary artery disease

Joost Daemen and Patrick W. Serruys

Purpose of review
The aim of this article is to review the current status of optimal revascularization strategies in patients presenting with multivessel coronary artery disease.
Recent findings
Coronary artery bypass surgery is the gold standard for patients with multivessel disease. Recent developments in the interventional field, like drug-eluting stents, which significantly reduced restenosis and the need for repeat revascularizations, have cut back one of the largest limitations of percutaneous coronary intervention.
Summary
There is currently little evidence to believe that in a general population, opting for either coronary artery bypass surgery or percutaneous coronary intervention would imply a better long-term survival. Coronary artery bypass surgery is still associated with higher rates of complete revascularization and a higher durability than percutaneous coronary intervention, resulting in lower rates of repeat revascularization. The current evidence, however, is based on sub-optimal inconclusive data from single center or multicenter registries. Until the results of several dedicated ongoing randomized trials are presented, the choice for a revascularization strategy should be made not only on the basis of feasibility but also by taking into account each patient's co-morbidities and risk factors. Careful monitoring of glycemic control and lipid concentrations and an optimal pharmacological treatment are at least as important in achieving an optimal outcome.
Keywords
complete revascularization, coronary artery bypass surgery, coronary artery disease, multivessel disease, percutaneous coronary intervention

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All authors have approved the final manuscript, which has not been published and is not under consideration elsewhere.

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Abbreviations

ARTS	Arterial Revascularization Therapy Study
BARI	Bypass Angioplasty Revascularization Investigation
CABG	coronary artery bypass grafting
CTO	chronic total occlusion
DES	drug-eluting stent
ERACI	Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty Versus Coronary Artery Bypass Surgery in Multivessel Disease
MI	myocardial infarctions
PCI	percutaneous coronary intervention

0268-4705

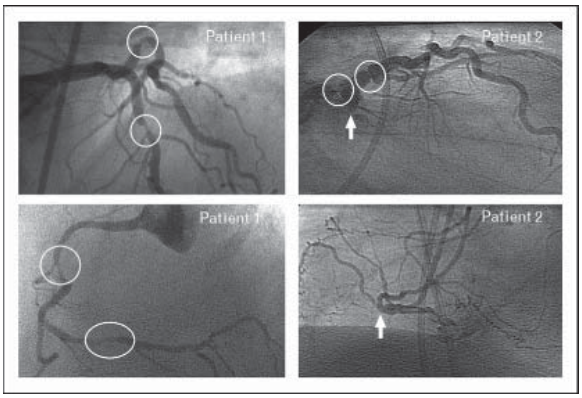
Introduction

In the predrug-eluting stent era, in-stent restenosis and the need for repeat revascularizations have been shown to be the major limitations of the percutaneous treatment of multivessel coronary artery disease [1,2]. Drug-eluting stents (DESs) have been shown to reduce both angiographic and clinical restenosis, resulting in a significant reduction in the need for repeat revascularizations [3–8,9••,10]. Evidence stemmed from the use of DESs in low-risk patients presenting with relatively simple lesions, but soon afterwards, their use was extended to higher-risk populations and lesions. Currently, the presence of diabetes, severely calcified lesions, left main or multivessel disease, chronic total occlusions, bifurcation lesions, acute myocardial infarctions (MIs) and in-stent restenotic lesions do not hold back the interventionalist from using DES [11,12]. Like percutaneous coronary revascularization, coronary artery bypass surgery has also been optimized in the last decade, illustrated by a less invasive approach, the use of off-pump coronary artery bypass grafting (CABG), the improvement of perioperative care and the extensive use of longer-lasting arterial grafts instead of saphenous vein grafts. Traditionally, CABG is the gold standard for the patient with multivessel disease, albeit repeatedly challenged by various percutaneous coronary intervention (PCI) modalities (balloon angioplasty, bare stents, and DESs). Several dedicated randomized trials are ongoing, but until their results are presented we have to rely on sub-optimal inconclusive evidence from single-center or multicenter registries.

Coronary artery bypass grafting or percutaneous coronary intervention?

Let us imagine two patients with multivessel disease (Fig. 1). Patient 1 has a right dominant system with

Figure 1 Two types of three-vessel disease



three-vessel disease consisting of four focal lesions, two in the right coronary, one in the mid-left anterior descending and one in the proximal circumflex. Patient 2 conversely, whilst also having a right dominant system with three-vessel disease, has a significant left main stenosis, a proximal left anterior descending stenosis, and a totally occluded right coronary and circumflex. There is no argument that patient 2 forms a much greater challenge for the interventionalist than patient 1. Whether patient 2 would be better off with CABG is disputable, however, and depends also on the individual patient characteristics like age and comorbidity.

Regarding the risks of long-term mortality or MI, no differences have been found between CABG and PCI. This latter can be illustrated by many trials from the past like Randomized Intervention Treatment of Angina (RITA; 1993) [13], Emory Angioplasty versus Surgery Trial (EAST; 1994) [14], Coronary Angioplasty versus Bypass Revascularisation Investigation (CABRI; 1995) [15], Bypass Angioplasty Revascularization Investigation (BARI; 1996) [16], Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty Versus Coronary Artery Bypass Surgery in Multivessel Disease (ERACI; 1996) [17], Arterial Revascularization Therapy Study (ARTS; 2001) [1], ERACI-II (2001) [18] and Stent or Surgery (SOS; 2002) [19]. Even when patients were followed for many years, no difference in these endpoints could be noticed [20,21]. Nevertheless, PCI was associated with a significantly higher risk for subsequent revascularization.

With the introduction of DESs in 2002, the parameters of the PCI–CABG equation changed. With significantly lower rates of clinical and angiographic restenosis as compared with bare metal stents, DES partly cut back the major limitation of PCI [3–8,9••,10,21]. Soon after the disclosure of the amazingly low revascularization needs following PCI with DESs, the first PCI–CABG trials started to add DES arms to previously published trials. One of the first to do so was the ARTS-II trial, which added a prospectively collected arm of 607 consecutive patients to the ARTS-I study [22•]. The ARTS-I trial randomized 1205 patients with stable or unstable angina or silent ischemia presenting with two or three-vessel disease to CABG or PCI with bare stents [23]. The ARTS-II 1-year results showed that PCI with DES was not inferior to CABG in terms of the combined endpoint of major adverse cardiac and cerebrovascular events. The need for repeat revascularizations, however, was still significantly higher than in the CABG arm of ARTS-I [22•]. Shortly after the ARTS-II trial, the smaller ERACI-III study was conducted maintaining a similar approach as ARTS-II by adding a group of 225 DES patients to the ERACI-II trial [24]. At 1 year, the need for repeat PCI was significantly higher in the DES arm than in the ERACI-II CABG arm. Due to the significantly lower incidence of death and MI, however, the overall major adverse cardiac or cerebrovascular events rate was significantly lower in the DES arm than in the CABG arm ($P = 0.047$). Another study worth mentioning is that of Hannan and colleagues [25••], who evaluated the 3-year outcome of 59 314 patients with multivessel disease from New York's cardiac registries treated with either PCI or CABG. The authors concluded that both the risk-adjusted survival rates and the rates of revascularization were significantly higher among the CABG patients. Remarkable was that there were almost no significant differences in the unadjusted survival rates. Thereby, this observational report attempts to equalize the two

groups by using risk-adjusted survival methods. This methodology attempts to adjust an unadjustable characteristic, namely the judgment of the treating physician regarding the revascularization strategy that is not correctable by adjusting for clinical variables. Given the results of the contemporary randomized trials, these results have to be interpreted with caution and could be misleading. In conclusion we can say that there is no evidence to believe that the PCI-treated multivessel-diseased patient would be at higher risk for future mortality and MI than their surgical counterparts. This leaves us with the problem of the need for repeat revascularization, which is potentially connected to an initially less complete revascularization. In fact, PCI is a local, topical, endoluminal treatment, which does not preclude the progression of the disease proximal or distal to the treated focus, whereas bypass surgery inherently prevents reintervention for most of the disease progression upstream to the bypass.

The optimal method for complete revascularization

Although essential for comparing modalities of revascularization, a clear demonstration of the completeness of revascularization is lacking. Differences have been pointed out between anatomical and functional revascularization, depending on whether the reperfused ischemic myocardial territory is taken into consideration [26]. Other definitions also looked at the size or type (main vessel or side branch) of the revascularized coronary arteries. Furthermore, scoring systems have been used, weighing the different vessels and locations [26]. Of note, these definitions are based on immediate procedural success rates and in contrast to PCI patients, CABG patients will seldom undergo routine angiographic restudy, and functional failure following an initially successful revascularization cannot be measured.

CABG is still associated with higher rates of complete revascularization and a higher durability than PCI [27–29]. It is mainly because of this durability that the difference in long-term outcome is found largely in the need for repeat revascularization.

Whether a more complete revascularization automatically implies a better survival remains controversial. In the BARI trial, complete revascularization was achieved in 91% of the CABG patients versus only 51% of the PCI patients. The 5-year results, however, showed that the excess mortality in angioplasty patients occurred solely in the diabetic subgroup; the overall and cardiac survival rates were similar among nondiabetic CABG and angioplasty patients. Of interest was that when Vander Salm and colleagues [26] applied four definitions of complete revascularization to the BARI trial results, no independent advantage existed from complete revascularization by either the traditional or functional definitions.

The ARTS trial confirmed that randomization to stenting in patients with incomplete revascularization was not associated with a worse late mortality [29]. Hannan *et al.* [30••], however, when evaluating the impact of complete revascularization on the long-term outcome following PCI, found that complete revascularization was associated with significant short and long-term survival benefit as compared with incomplete revascularization. Although the study is based on a population of almost 22 000 patients, it suffers from several limitations. Only in-hospital information is entered in the database, there is no outcome data collection, no monitoring, and the causes of death are unknown. Furthermore, the registry does not comprise a surgical arm, so it is unclear whether these patients would have benefited from bypass surgery, also given the increased risk profile of the patients with incomplete revascularization.

Another item that has to be taken into consideration is the cost-effectiveness of both therapeutic strategies. Recently, the 10–12-year follow-up of the BARI study revealed that in patients with multivessel disease, the cost-effectiveness of PCI relative to CABG becomes less unfavorable at long-term. The initial revascularization costs of the PCI arm were 35% lower than in the CABG arm, but after 5 years, this benefit shrank to no more than 5% due to the higher frequency of repeat revascularizations in the PCI arm [31]. Ten years after randomization, the differences between PCI and CABG in the economic and quality-of-life outcomes were no longer significant. Nevertheless, the study was limited by the fact that the patients were included before the introduction of coronary stents. Although many thought that with the introduction of DESs this item would be resolved by a shift from CABG to PCI, several studies provided inconclusive results [24,25••,26–29,30••,31,32•,33–35].

Coronary artery bypass grafting or percutaneous coronary intervention for chronic total occlusions?

In a registry of 8004 patients presenting for diagnostic catheterization, at least 52% of the patients with a stenosis of 70% or greater had a chronic total occlusion (CTO), which illustrates the incidence of this challenging lesion [36]. Indeed, the presence of a CTO remains the major hurdle in achieving complete revascularization although successful recanalization of the CTO has been shown to result in a relief of clinical symptoms, and improvement of left ventricular function and long-term survival [37–40].

Although bare metal stents significantly reduced the need for repeat revascularizations in CTOs when

compared with balloon angioplasty, Kastrati *et al.* [41,42] showed that even when bare metal stents were used, the treatment of a CTO was highly predictive of developing restenosis. Hoye *et al.* [43] reported on the 10-year single-center percutaneous CTO experience and showed that the procedural success rates did not improve over time. Nevertheless, many new devices and techniques to successfully recanalize the CTO followed each other rapidly and proved to be of variable efficacy. Laser-tipped guidewires resulted in disappointing success rates [44]. Catheters capable of locally delivering thrombolytic therapy [45] and retrograde recanalization using septal collaterals, on the other hand, proved more promising. Of note, higher rates of technical success do not necessarily result in higher rates of procedural success, which also includes the avoidance of complications.

Additionally, much is to be expected from further developments in the field of noninvasive coronary imaging. Multislice computed tomographic scan and magnetic guidance have already been shown to facilitate the recanalization of the CTO [46•]. In terms of improving the outcome of successfully recanalized CTOs, both sirolimus and paclitaxel-eluting stents proved to be associated with lower clinical and angiographic restenosis rates [47,48]. Despite all progress, PCI of CTOs still remains a predictive factor for the development of restenosis, irrespective of the use of DES [49••]. Thereby, the CTO success rates still do not approximate those for nonocclusive disease.

For many operators with a limited experience in the treatment of CTOs, CABG is probably still the procedure of first choice, definitely in patients with multivessel disease. For those who do feel confident enough to treat the CTO percutaneously, however, it is important to keep in mind several drawbacks. The lack of a tapered stump, a CTO in close vicinity of a sidebranch, bridging collaterals, lengths of more than 15 mm and severe calcification have all proved to result in a substantial amount of failures [50]. Besides these percutaneous limits, the choice for the optimal treatment strategy should again depend not only on the feasibility of re-opening the CTO but also on the patient's individual risk factors and comorbidities.

Coronary artery bypass grafting or percutaneous coronary intervention for diabetic patients?

Diabetic patients are known to have an accelerated and more aggressive form of atherosclerosis and they showed high restenosis rates and less favorable long-term survival following both PCI and CABG as compared with nondiabetic participants [51–54]. Due to their smaller vessel size, longer lesion length, greater plaque burden and a possibly differently acting restenotic cascade as compared to nondiabetic individuals they are inextricably connected to multivessel disease [55,56].

Selection of the most optimal revascularization strategy has been controversial. Confirming the results of the randomized BARI trial, Niles and colleagues [54] showed that after 5 years of follow-up, diabetics undergoing initial PCI were significantly more likely to die during follow-up than patients treated with CABG. Conversely, in the BARI registry, all-cause survival was not significantly different between both groups [57]. The ARTS-I trial, which in contrast to the BARI trial included patients treated with bare metal stents, showed that in the subgroup of diabetic patients ($n = 208$), patients treated with stenting had a significantly lower event-free survival (63.4%) than those treated with CABG (84.4%), again due to the higher need for repeat revascularizations in the PCI arm [58]. The separate endpoints of death and MI did not differ significantly between both groups. The more recent nonrandomized diabetes subgroup of the ARTS-II trial, which included patients with sirolimus-eluting stents, showed that the 1-year event-free survival was equal in the CABG arm (85.4%) and ARTS-II arm (84.3%). The need for repeat revascularization, however, was still in favor of the CABG-treated patients (4.2% ARTS-I CABG versus 12.6% ARTS-II; $P = 0.027$) [59].

The above mentioned results are disputable since they are all derived from indirect comparisons and subgroup analyses of randomized controlled trials. There seems reason, however, to believe that due to the rapid disease progression and greater atherosclerotic burden of the diabetic patient with multivessel disease, CABG should be the preferred treatment, mainly because of its ability to bypass this large amount of plaque burden, which could make repeat revascularizations necessary.

Currently, the first randomized controlled trials, specifically designed to compare the outcomes of diabetic patients treated with either CABG or PCI with DESs, are ongoing. The Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial, a randomized unblinded two-sided superiority trial, is enrolling 2400 diabetic patients with multivessel disease to treatment with PCI with sirolimus-eluting stent (SES) or paclitaxel-eluting stent (PES) versus CABG. Another ongoing trial is the Coronary Artery Revascularisation in Diabetes (CARDIA) study, a prospective, randomized, multicenter UK investigation of 600 diabetes mellitus patients, designed to address the hypothesis that PCI with SES is not inferior to CABG as a revascularization strategy.

Until the results of these trials are published the choice for either strategy should be based on the patient's individual risk profile and anatomy. Additionally, it is

imperative to say that carefully monitoring glycemic control and lipid concentrations is at least as important in achieving an optimal outcome [60].

Adjunctive pharmacological treatment

Recent developments in periprocedural and postprocedural adjunctive drug therapy have led to a significant improvement in both short and long-term survival following PCI. In a recent meta-analysis of 19 randomized trials evaluating the impact of the use of IIb/IIIa inhibitors in a total of 20 137 patients, mortality was significantly reduced by 31% at 30 days (RR 0.69; 95% CI 0.53–0.90) and 21% at 6 months (RR 0.79; 95% CI 0.64–0.97) [61]. Additionally, there was no excessive risk of bleeding if heparin was discontinued. Regarding the use of clopidogrel, the randomized PCI–CURE trial showed that long-term administration of clopidogrel after PCI was associated with a lower rate of cardiovascular death, MI, or any revascularization ($P = 0.03$), and of cardiovascular death or MI ($P = 0.047$). Overall (including events before and after PCI) there was a 31% reduction in cardiovascular death or MI ($P = 0.002$) [62]. What has to be remarked is that the PCI–CURE trial, supported by the Clopidogrel for the Reduction of Events During Observation (CREDO) trial, showed that clopidogrel given before a PCI is effective and cost-effective in reducing major adverse cardiac events up to 1 month [62,63]. There was, however, no significant difference in death or MI between the clopidogrel and placebo-treated groups between 1 and 6 months [64]. Herewith, the long-term continuation of clopidogrel and the protective effect on stent-thrombosis remains controversial when also taking into account the increased costs, the higher bleeding risk and the possibility of aspirin or clopidogrel resistance [64–66]. Additionally, worth mentioning is the Lescol Intervention Prevention Study (LIPS), which randomized PCI patients to treatment with fluvastatin or a placebo [67]. The presence of multivessel disease markedly increased the risk of cardiac atherosclerotic events compared with single-vessel disease among patients allocated to placebo (RR 1.67; 95% CI 1.24–2.25). In patients treated with fluvastatin, however, no significant differences in long-term outcomes were observed between patients with multivessel disease and single-vessel disease (RR 1.28; 95% CI 0.90–1.81) [68•,69]. The additional cost-effectiveness of fluvastatin following successful first PCI was shown to be US$13 505 per life–year (US$15 454 per quality adjusted life–year) saved [70].

Conclusion

As outlined above there is little evidence to believe that opting for either CABG or PCI would imply a better survival in the general population. What we do know is that the interventionalist should try to strive for a complete revascularization, which has proved to be the surgeon's best asset. This implies that improving one's skills in the treatment of chronic total occlusions is essential and is a goal that might be difficult to achieve for many interventionalists operating in a smaller-scale setting with limited access to high-tech tools and techniques. It is noteworthy that new scoring systems and reports of surgeon-based procedural mortality rates tend to cause a shift of high-risk patients from surgery towards a percutaneous approach.

Taken all together, surgical coronary revascularization remains a valuable technique that will certainly not disappear and does not have to be restricted to the severely diseased diabetic patient or the patient with CTOs.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 629–630).

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Chapter 25

Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient level data from the ARTS, ERACI-II, MASS-II and SoS trials

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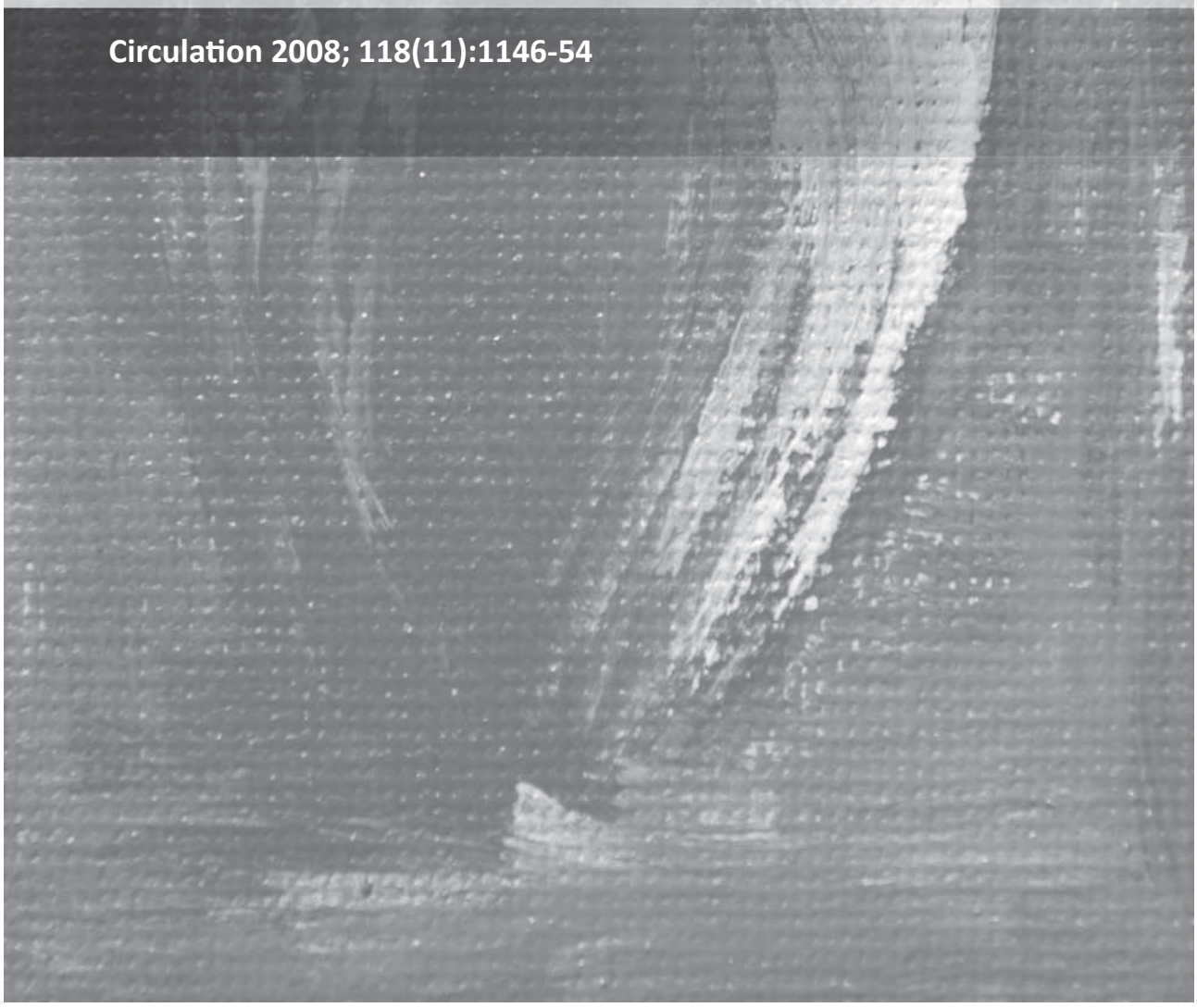

Long-Term Safety and Efficacy of Percutaneous Coronary Intervention With Stenting and Coronary Artery Bypass Surgery for Multivessel Coronary Artery Disease

A Meta-Analysis With 5-Year Patient-Level Data From the ARTS, ERACI-II, MASS-II, and SoS Trials

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Background—Randomized trials that studied clinical outcomes after percutaneous coronary intervention (PCI) with bare metal stenting versus coronary artery bypass grafting (CABG) are underpowered to properly assess safety end points like death, stroke, and myocardial infarction. Pooling data from randomized controlled trials increases the statistical power and allows better assessment of the treatment effect in high-risk subgroups.

Methods and Results—We performed a pooled analysis of 3051 patients in 4 randomized trials evaluating the relative safety and efficacy of PCI with stenting and CABG at 5 years for the treatment of multivessel coronary artery disease. The primary end point was the composite end point of death, stroke, or myocardial infarction. The secondary end point was the occurrence of major adverse cardiac and cerebrovascular accidents, death, stroke, myocardial infarction, and repeat revascularization. We tested for heterogeneities in treatment effect in patient subgroups. At 5 years, the cumulative incidence of death, myocardial infarction, and stroke was similar in patients randomized to PCI with stenting versus CABG (16.7% versus 16.9%, respectively; hazard ratio, 1.04, 95% confidence interval, 0.86 to 1.27; $P=0.69$). Repeat revascularization, however, occurred significantly more frequently after PCI than CABG (29.0% versus 7.9%, respectively; hazard ratio, 0.23; 95% confidence interval, 0.18 to 0.29; $P<0.001$). Major adverse cardiac and cerebrovascular events were significantly higher in the PCI than the CABG group (39.2% versus 23.0%, respectively; hazard ratio, 0.53; 95% confidence interval, 0.45 to 0.61; $P<0.001$). No heterogeneity of treatment effect was found in the subgroups, including diabetic patients and those presenting with 3-vessel disease.

Conclusions—In this pooled analysis of 4 randomized trials, PCI with stenting was associated with a long-term safety profile similar to that of CABG. However, as a result of persistently lower repeat revascularization rates in the CABG patients, overall major adverse cardiac and cerebrovascular event rates were significantly lower in the CABG group at 5 years. **(*Circulation*. 2008;118:1146-1154.)**

Key Words: bypass ■ coronary disease ■ prognosis ■ stents ■ surgery

Coronary artery bypass grafting (CABG) has been considered the gold standard for treating multivessel coronary artery disease, mainly because of its higher rate of complete revascularization, reflected by a lower need for repeat revascularizations compared with percutaneous coronary intervention (PCI).[1–4]

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Whereas the risk difference of CABG versus balloon angioplasty for repeat revascularization in a large-scale meta-analysis proved to be 34% at 3 years, this difference decreased to 15% when coronary stents were used.[1] In terms of clinical safety end points, the recently reported 5-year follow-up of the Arterial Revascularization Therapies Study (ARTS),[5] Argentine Randomized Trial of Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Patients With Multiple Vessel Disease (ERACI-II),[6] and the Medicine, Angioplasty or Surgery Study for Multi-Vessel Coronary Artery Disease (MASS-II)[7] reported no difference in death rates between the 2 revascularization strategies.

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Conversely, the Stent or Surgery (SoS) trial recently demonstrated a significantly lower survival in patients treated with PCI compared with CABG at 6 years.[7a]

In the present study, patient-level data of the above-mentioned randomized trials were pooled to make a more precise estimate of the relative long-term safety and efficacy of PCI with stenting and CABG for multivessel coronary artery disease, to assess the relative treatment effect in several high-risk subgroups, and to assess the heterogeneity of the treatment effect.

Methods

Study Design and Patient Population

The methodology of the present meta-analysis has been described previously.[8] In brief, a MEDLINE search using the keywords *coronary stenting*, *coronary artery bypass surgery*, and *multisystem/multivessel disease* was performed with the intention of selecting and including all randomized clinical trials comparing PCI with stenting and CABG in patients with multivessel coronary artery disease. Four trials were selected: ARTS,[9] SoS,[10] ERACI-II,[11] and MASS-II.[12]

Principal investigators of each study group were contacted, and individual patient data were requested on a broad range of baseline characteristics, medication usage, procedural results, and clinical outcome at 5 years. Clinical outcome included data on death, stroke, myocardial infarction (MI), and repeat revascularization (either PCI or CABG) at 5 years for ARTS, MASS-II, and ERACI-II. For the SoS trial, 5-year follow-up data were restricted to survival data. Data on the occurrence of stroke, MI, and repeat revascularization between 1 and 5 years were not collected by the SoS investigators.

Clinical events were adjudicated by independent clinical event committees. The patient-level–based data were subsequently transferred to Erasmus University Medical Center (Rotterdam, the Netherlands; E.B.) to 2 researchers (J.D., P.W.S.) who analyzed and interpreted the data.

Definitions and Clinical End Points

No attempt was made to readjudicate the events in the different trials to compensate for the differences in the individual end-point definitions. Given the randomized design of the 4 trials, no bias was expected. The primary end point was the composite end point of death, stroke, or MI at 5 years. The secondary end points included major adverse cardiac and cerebrovascular events (defined as the occurrence of major adverse cardiac and cerebrovascular accidents: all-cause death, stroke, MI, and repeat revascularization); the combined end point of all-cause death, MI, or repeat revascularization; and the itemized end points of death, stroke, MI, and repeat revascularization (PCI or CABG).

Statistical Analysis

All analyses were performed on an intention-to-treat population. Most continuous variables had nonnormal distribution (as evaluated by Kolmogorov-Smirnov tests). For reasons of uniformity, summary statistics for all continuous variables are therefore presented as medians and 25th and 75th percentiles. Categorical data are summarized as frequencies and percentages. Differences in baseline characteristics between patients randomized to PCI with stenting versus CABG were analyzed with Wilcoxon–Mann–Whitney tests or Fisher's exact tests as appropriate.

The incidence of events over time was studied by the Kaplan–Meier method, and log-rank tests were applied to evaluate differences between patients allocated to PCI with stenting or CABG. Additionally, Cox proportional-hazards regression models were applied to further evaluate the effects of allocated treatment on the incidence of events over time. Because aggregated estimates of treatment effect that are based on small numbers of studies are sensitive to the chosen pooling method, we applied a variety of such methods, which showed quite consistent results. First, hazard ratios (HRs) for study end points were determined from the proportional-hazards model stratified by trial with a single fixed effect according to the Yusuf–Peto[13] approach. Subsequently, nonstratified models were fitted with study membership as a covariate in the model, allowing for the adjustment of trial effects and variations in the standards of practice across participating institutions.[14] Then, trial-by-treatment interaction terms were added to evaluate heterogeneity in treatment effect across trials. Interaction terms also were added to study heterogeneities in treatment effects according to clinically relevant characteristics, including age, gender, diabetes, dyslipidemia, hypertension, prior MI, number of diseased vessels, left ventricular ejection fraction, and peripheral vascular disease. Because the −2 log likelihood of the regression models was not improved by adding interaction terms (except for death in relation to trial; see the Results section), we decided to stick to the fixed-effects approach and to remove any interaction term from further models. The HRs that are finally reported (together with the 95% confidence intervals [CIs]) are based on regression models with allocated treatment as the main effect and with the above-mentioned clinical characteristics as covariates.[15]

All tests are 2 sided with a significance level of 0.05. All statistical analyses were performed with the SAS System version 8.2 (SAS Institute Inc, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patients, Baseline, and Procedural Characteristics

A total of 3051 patients were included in this analysis between June 1995 and June 2000 (1205 in ARTS, 450 in ERACI-II, 408 in MASS-II, and 988 in SoS). In total, 1533 were randomized to CABG, and 1518 were randomized to PCI. Eighty-nine percent of patients allocated to PCI underwent the assigned treatment compared with 96% of those assigned to CABG.

Baseline and procedural characteristics are summarized in Table 1. Although 3-vessel disease was more frequent in the CABG group compared with the PCI group (40.0% versus 36.1%, respectively; $P=0.017$), complete revascularization was performed in 89.4% of the CABG patients compared with 62.0% of the PCI patients ($P<0.001$). The hospital stay was significantly longer in the CABG group (median, 8 days; interquartile range, 1 to 4 days) compared with the PCI group (median, 3 days; interquartile range, 6 to 11) ($P<0.001$).

Clinical Outcome

Clinical event rates are summarized in Table 2 and Figure 1. Five-year follow-up was complete for 97% of all patients (100% in ARTS and ERACI-II, 97.5% in MASS-II, and 91.6% in SoS). At 5 years, the cumulative incidence of death, MI, and stroke was similar in patients randomized to PCI with stenting versus CABG (16.7% versus 16.9%, respectively; HR, 1.04; 95% CI, 0.86 to 1.27; $P=0.69$). Repeat revascularization, however, occurred significantly more frequently after PCI compared with CABG (29.0% versus 7.9%, respectively; HR, 0.23; 95% CI, 0.18 to 0.29; $P<0.001$). Because of the substantial difference in the repeat revascularization rates between both treatment modalities, major adverse cardiac and cerebrovascular event rates were significantly higher in the PCI group than in the CABG group (39.2% versus 23.0%, respectively; HR, 0.53; 95% CI, 0.45 to 0.61; $P<0.001$).

Table 1. Baseline and Procedural Characteristics and Medications

	PCI With Stenting (n=1518 Patients)	CABG (n=1533 Patients)	*P*
Age, y			
Median	61.6	61.6	0.37
IQR	53.5–68.0	54.6–68.3	
Range	30.2–85.4	31.9–86.0	
Men, %	76.5 (1162/1518)	77.1 (1182/1533)	0.73
Diabetes mellitus, %	18.1 (275/1518)	17.5 (268/1533)	0.67
Hyperlipidemia, %	60.1 (910/1515)	56.5 (866/1532)	0.051
Hypertension, %	50.5 (766/1518)	51.7 (792/1533)	0.52
Family history of CAD, %	38.1 (498/1307)	38.7 (514/1327)	0.75
Current smoker, %	28.3 (429/1516)	26.5 (406/1533)	0.27
Previous MI, %	42.8 (650/1518)	41.4 (635/1533)	0.44
Peripheral vascular disease, %	7.0 (107/1518)	8.2 (126/1533)	0.25
Aspirin, %	93.5 (1419/1518)	90.2 (1382/1533)	0.001
β-Blockers, %	79.4 (1205/1518)	81.7 (1252/1533)	0.11
Calcium channel blockers, %	37.3 (566/1518)	40.2 (617/1533)	0.095
Nitrates, %	68.1 (1033/1518)	69.7 (1068/1533)	0.35
Statins, %	40.9 (621/1517)	39.5% (606/1533)	0.44
Enrollment diagnosis, %*			
Stable angina	68.2 (1036/1518)	68.9 (1057/1533)	0.70
Unstable angina	28.5 (432/1518)	27.3 (418/1533)	0.47
Silent ischemia	3.5 (48/1358)	2.6 (34/1330)	0.15
Ejection fraction, %			0.91
Median	60	60	
IQR	52–68	51–67	
Range	27–92	26–91	
Segments with >50% stenosis, n			0.92
Median	3	3	
IQR	2–3	2–3	
Range	1–9	1–8	
Diseased vessels, n			0.017
1	4.6 (70/1518)	3.0 (46/1533)	
2	59.3 (900/1518)	57.0 (874/1533)	
3	36.1 (548/1518)	40.0 (613/1533)	
Vessel territory with stenosis, %			
RCA	74.2 (1127/1518)	78.0 (1195/1533)	0.017
LAD	89.9 (1364/1518)	91.8 (1408/1533)	0.06
LCx	63.2 (959/1518)	67.7 (1038/1533)	0.009
LMCA	1.0 (15/1518)	0.7 (10/1533)	0.32
Length of hospital stay, d			<0.001
Median	3	8	
IQR	1–4	6–11	
Range	1–70	1–110	
Complete revascularization, %	62.0 (809/1304)	89.4 (1180/1320)	<0.001

IQR indicates interquartile range; CAD, coronary artery disease; RCA, right coronary artery; LAD, left anterior descending artery; LCx, left circumflex artery; and LMCA, left main coronary artery. Values are mean±SD when appropriate. The difference between the total number in each group and the denominator used to calculate the percentages for each variable is due to missing data.

*Stable angina was defined according to the Canadian Cardiovascular Society system; unstable angina was classified according to the Braunwald classification.

Table 2. Event Rates at 5 Years

	Crude Event Rates, %			Kaplan–Meier Estimates, %			
Variables	PCI (n=1518 Patients)	CABG (n=1533 Patients)	*P*	PCI (n=1518 Patients)	CABG (n=1533 Patients)	HR (95% CI)*	*P*
Death	8.5 (129/1518)	8.2 (125/1533)	0.74	8.5	8.2	0.95 (0.73–1.23)	0.69
Stroke	2.5 (38/1518)	2.9 (45/1533)	0.51	3.1	3.6	1.16 (0.73–1.83)	0.54
MI	6.6 (100/1518)	6.1 (94/1533)	0.66	7.3	7.6	0.91 (0.68–1.23)	0.54
Repeat revascularization	25.0 (379/1518)	6.3 (96/1533)	<0.001	29.0	7.9	0.23 (0.18–0.29)	<0.001
Repeat PCI	18.3 (278/1518)	5.4 (83/1533)	<0.001	21.5	6.9	0.29 (0.22–0.37)	<0.001
Repeat CABG	9.1 (138/1518)	1.2 (18/1533)	<0.001	10.4	1.5	0.12 (0.07–0.21)	<0.001
Death, stroke, or MI	14.2 (215/1518)	14.6 (224/1533)	0.76	16.7	16.9	1.04 (0.86–1.27)	0.69
Death, MI, or repeat revascularization	32.5 (494/1518)	17.5 (268/1533)	<0.001	37.1	20.4	0.50 (0.43–0.58)	<0.001
Death, stroke, MI, or repeat revascularization	34.2 (519/1518)	19.6 (301/1533)	<0.001	39.2	23.0	0.53 (0.45–0.61)	<0.001

*Adjusted for between-trial outcomes and the following predetermined clinical characteristics: age, gender, diabetes, dyslipidemia, hypertension, prior MI, number of diseased vessels, left ventricular ejection fraction, and peripheral vascular disease.

Heterogeneity

As far as the composite end point of death, stroke, and MI is concerned, there was no evidence of heterogeneity in the treatment effect between the 4 trials. However, we found significant heterogeneity in the treatment effect for death at 5 years between SoS and the other trials ($P=0.0074$; Figure 2A). In SoS, CABG was associated with a 44% reduction in 5-year mortality rate compared with PCI with stenting (cumulative survival, 95.5% versus 92.1%, respectively; HR, 0.56; 95% CI, 0.33 to 0.95), whereas no such reduction was observed in the remaining trials (91.2% versus 90.0%, respectively; HR, 1.15; 95% CI, 0.86 to 1.52). No heterogeneity was observed between SoS and ARTS with respect to the effects of CABG versus PCI with stenting on 5-year mortality rate ($P=0.09$). Furthermore, no significant heterogeneity for the composite end point of death, stroke, and MI was found for any of the clinical and anatomic subgroups of interest shown in Figures 2B and 3.

Patients With Diabetes

For the composite end point of death, stroke, and MI, no heterogeneity in treatment was found between patients with diabetes and those without diabetes (Figure 3). In patients with diabetes, the cumulative incidence of death was 12.4% in the PCI group compared with 7.9% in the CABG group ($P=0.09$). In patients without diabetes, the cumulative incidence of death was 7.7% in the PCI group compared with 8.3% in the CABG group ($P=0.55$). The cumulative incidence of death, stroke, or MI in diabetics was similar after PCI with stenting and CABG (21.4% versus 20.9%, respectively; $P=0.9$). However, the HR for repeat revascularization in the diabetic subgroup was 0.18 (95% CI, 0.11 to 0.29) as a result of a 3-fold-higher cumulative incidence of repeat revascularization in the PCI group (29.7% versus 9.2%; $P<0.001$).

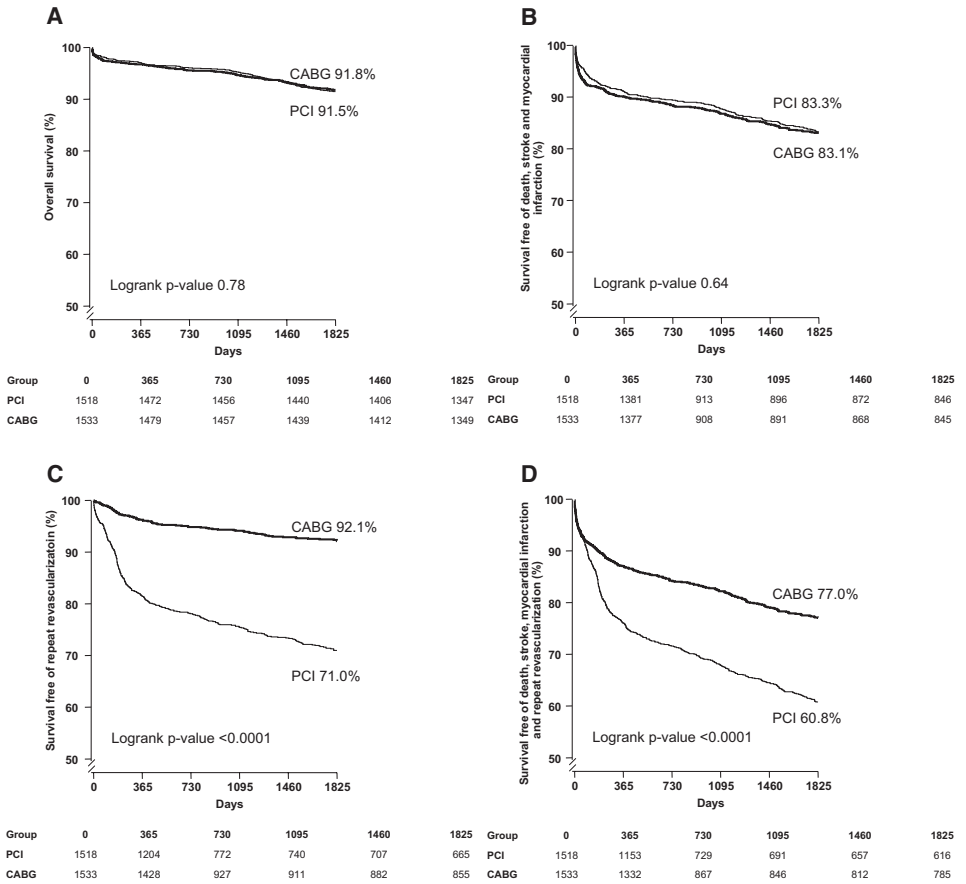
2-Vessel Versus 3-Vessel Disease

The cumulative 5-year incidence of death was similar between PCI and CABG in both the 2-vessel disease (7.6% versus 7.3%, respectively; $P=0.87$) and the 3-vessel disease (10.2% versus 9.5%, respectively; $P=0.71$) subgroups. The cumulative incidence of death, stroke, and MI was similar between PCI and CABG in both the 2- and 3-vessel subgroups. However, repeat revascularization rates were significantly higher in the PCI group in patients with 2-vessel and in those with 3-vessel disease (29.0% versus 7.2%, $P<0.001$; and 28.9% versus 7.8%, $P<0.001$, respectively), resulting in a significantly lower incidence of the combined major adverse cardiac and cerebrovascular events in the CABG cohort for both 2- and 3-vessel disease.

Discussion

The present study was conducted using individual patient-based data with complete follow-up until 5 years. We demonstrated that at 5 years PCI and CABG were associated with a similar safety profile, expressed by hard clinical end points like death, stroke, and MI. These results confirm the previous findings of a large-scale review of 23 PCI (with and without stenting) versus CABG trials by Bravata et al,[16] which demonstrated no difference in the 5-year survival rates between both treatment modalities. No differences in survival rates between PCI and CABG were noted even up to 13 years.[17–20]

A nonrandomized study that reached different conclusions was a large-scale registry (n=59 314) by Hannan and colleagues.[21] Risk-adjusted survival rates in this study were significantly higher in patients treated with CABG than in those treated with PCI with stenting. Bearing in mind that all baseline characteristics collected in this study were significantly different between the PCI and CABG groups and the unadjustable characteristic "judgment of the treating physician to chose for either PCI or CABG," we must interpret these results with caution. Furthermore, the shorter follow-up and the higher-risk profile (higher age, higher incidence of diabetes, lower ejection fraction) of patients included in the study by Hannan and colleagues compared with the present meta-analysis make it difficult to put the results into perspective.



Group	0	365	730	1095	1460	1825
PCI	1518	1472	1456	1440	1406	1347
CABG	1533	1479	1457	1439	1412	1349

Group	0	365	730	1095	1460	1825
PCI	1518	1381	913	896	872	846
CABG	1533	1377	908	891	868	845

Group	0	365	730	1095	1460	1825
PCI	1518	1204	772	740	707	665
CABG	1533	1428	927	911	882	855

Group	0	365	730	1095	1460	1825
PCI	1518	1153	729	691	657	616
CABG	1533	1332	867	846	812	785

Figure 1. Kaplan–Meier event-free survival analysis of death (A); death, stroke, or MI (B); repeat revascularization (C); and major adverse cardiac and cerebrovascular events (death, stroke, MI, and repeat revascularization (D).

All 4 randomized trials included in the present meta-analysis studied the safety and effectiveness of PCI with bare metal stents. Since 2002, drug-eluting stents have been shown to halve repeat reinterventions rates without affecting the short- and long-term safety of the treatment.[22–25] Moreover, because of their significantly lower revascularization rates, sirolimus-eluting stents proved to be capable of narrowing the gap in major adverse cardiac event rates between PCI and CABG, as demonstrated by the ARTS-II and ERACI-III studies.[26,27] In contrast to the ARTS-I study, the recently presented 3-year results of the ARTS-II study showed similar major adverse cardiac event rates after PCI with sirolimus-eluting stents and CABG. However, the need for repeat revascularization was still significantly lower after CABG.[28] Although both ERACI-III and ARTS-II showed a clear impact of drug-eluting stents on the relative efficacy of PCI and CABG, it must be noted that both studies were nonrandomized comparisons. Along these lines, a recent registry by Javaid et al[29] reported significantly higher mortality rates and a trend toward higher MI rates in patients treated with PCI with drug-eluting stents compared with those treated with CABG at 1 year regardless of the amount of vessels diseased and the presence of diabetes.[29] It is worth mentioning that the 1-year results of none of the 4 randomized trials in the present study concurred with these latter findings.[9–12] Given the similar, if not superior, safety profile of drug-eluting stents compared with bare metal stents, it is unlikely that the use of drug-eluting stents in this study accounted for this dissimilarity.[22,23,30] Several large-scale randomized trials such as Future Revascularization Evaluation in Patients With Diabetes: Optimal Management of Multivessel Disease (FREEDOM), Coronary Artery Revascularization in Diabetics (CARDIA), and

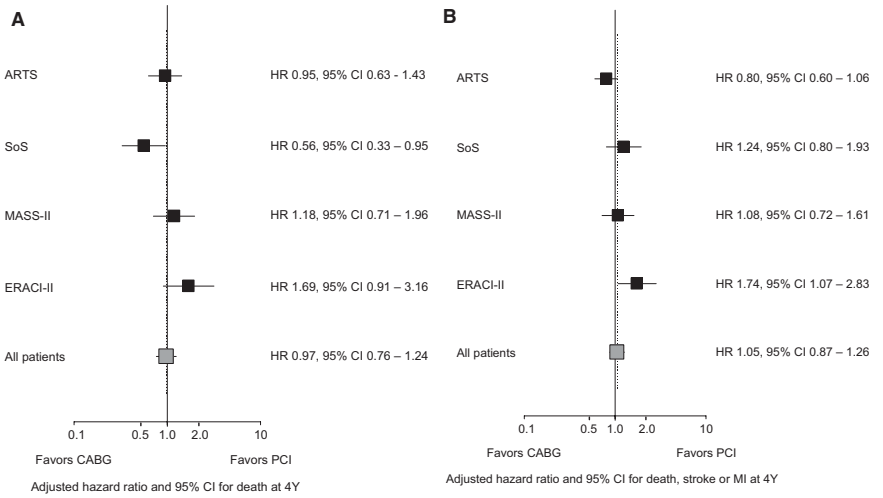


Figure 2. HRs for each trial individually and the pooled estimate for all trials (corrected for between-trial outcome) for the end points of all-cause mortality (A) and all-cause death, stroke, and MI (B).

Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) are currently comparing the safety and effectiveness of CABG and PCI with drug-eluting stents.[31]

Of note, despite the improvement in durability of more contemporary PCI with (drug-eluting) stents, long-term survival rates do not seem to improve in a similar fashion and remain equal between PCI and CABG. This finding recalls a major goal of treating (multivessel) coronary artery disease: the relief of angina. Despite the fact that at 1 year after CABG significantly more patients were free of angina compared with PCI in all 4 trials,[9–12] 5-year reports of the ARTS, ERACI-II, and MASS-II demonstrated similar incidences of angina at 5 years after CABG and PCI.[5–7] Additionally, the final results from the Bypass Angioplasty Revascularization Investigation (BARI) trial proved that even up to 10 years, angina rates were still equal between both treatment modalities.[17] However, in the PCI group, these similar angina rates were achieved only after a significantly higher rate of repeat revascularizations compared with the CABG group.

Significant heterogeneity in treatment effect was noted between SoS and the remaining trials with respect to survival at 5 years. Although the 5-year cumulative survival in the PCI arm of SoS (92.1%) was similar to the ARTS, ERACI-II, and MASS-II trials (92.2%, 92.9%, and 86.3% respectively), the survival in the CABG arm of SoS (95.5%) was remarkably higher than in ARTS, ERACI-II, and MASS-II (92.6%, 88.5%, and 84.1%, respectively). The exact reason for this superior survival rate remains puzzling, and a play of chance cannot be excluded. A speculative reason for the heterogeneity might be the difference in the inclusion criteria and procedural requirements in the different studies. In ARTS, higher-risk patients were excluded; 67% of the patients had 2-vessel disease; and an equivalent revascularization rate was required.[9,32] Conversely, in MASS-II, almost 58% of the patients had 3-vessel disease, and a proximal left anterior descending artery lesion was required.[12] Additionally, the SoS trial protocol stated that the study was intended to be a "pragmatic trial," including enrollment of a wide range of patients with minimal restriction on postrandomization patient management. However, both patient groups in SoS were well matched, and it is unlikely that the pragmatic nature of the trial was the reason for the unexpected difference in death rates, which are not confirmed by the larger sample of this meta-analysis.[10]

Coronary artery disease in diabetics has been shown to be more aggressive and to be associated with an impaired event-free survival after both CABG and PCI because of smaller vessel sizes, longer lesion length, greater plaque burden, and a possibly differently acting restenotic cascade than in nondiabetics.[33–38] Given this higher-risk profile, which is most often associated with multivessel disease, CABG was regarded as the preferred revascularization method because of its ability to bypass this large amount of plaque burden and to achieve more complete revascularization rates, making the need for repeat revascularizations less likely. Attempting to demonstrate the most optimal treatment strategy for diabetics, a subgroup analysis of the randomized BARI trial and a large observational registry demonstrated significantly impaired survival among patients treated with PCI compared with those treated with CABG.[36,39] Interestingly, in the BARI registry, all-cause survival was not significantly different between both groups.[40] Furthermore, all the above-mentioned studies were performed in the present era and may no longer be applicable in current clinical practice. In the present analysis, using pooled patient-level–based 5-year follow-up data from 4 randomized controlled trials, we found no significant heterogeneity of the

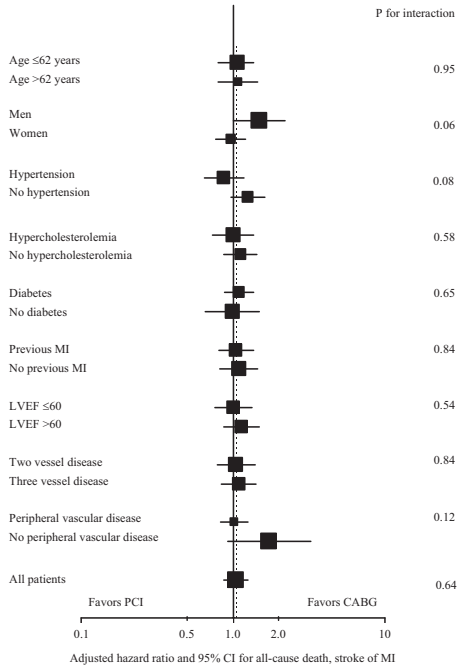


Figure 3. Primary end point of death, stroke, or MI in selected subgroups. Exploratory analyses to evaluate possible heterogeneity in treatment effects on 5-year event rates according to 2 of the 3 treatment cohorts and the following clinically relevant characteristics: age, gender, hypertension, diabetes, previous MI, left ventricular ejection fraction (LVEF), vessel disease, and peripheral vascular disease. For the continuous variables (age and total stented length), medians were used as cutoffs. Results of tests for heterogeneity in treatment effect were considered significant at $P<0.01$.

treatment effect in diabetics compared with nondiabetics, although our analysis might have suffered from a lack of power. The ongoing FREEDOM and CARDIA trials will further address the relative safety and efficacy of CABG and more contemporary PCI with drug-eluting stents in diabetics.

Two randomized controlled trials comparing PCI with CABG, the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME) and a Randomized Comparison of Stent Implantation and Off-Pump Bypass Surgery in Patients Referred for Coronary Angioplasty (OCTOSTENT) trials,[41,42] were excluded from the present meta-analysis. The AWESOME trial (n=454) included only high-risk patients with refractory myocardial ischemia and a high risk of adverse outcomes, generating a study population clearly different from the present one. Moreover, 54% of the patients in AWESOME were treated with balloon angioplasty only. The OCTOSTENT trial (n=280), with only 30% of the population having multivessel disease, was not yet published when the initial meta-analysis by Mercado et al[8] was performed. Of note, neither AWESOME nor OCTOSTENT completed the 5-year follow-up at the time of the present meta-analysis.

Pooling data from 4 multicenter randomized controlled trials with diversity in inclusion and exclusion criteria resulted in a diverse and high-risk patient population. However, patients with severe 3-vessel disease presenting with an acute coronary syndrome, left main lesions, previous coronary interventions, heart failure, or renal disease were excluded in all 4 trials. Although no heterogeneity in the treatment effect was found among several high-risk subgroups in the present analysis, the results of several large-scale, dedicated, randomized controlled trials are eagerly awaited to determine the external validity of our findings. Until the relatively short-term findings of these large trials are presented, the results from the present meta-analysis constitute the highest amount of clinical evidence regarding the relative long-term safety of PCI using stents and CABG.

Conclusions

In this pooled analysis of 4 randomized trials, PCI was associated with a long-term safety profile, expressed by death, stroke, and MI, similar to that of CABG. However, because of the persistently lower repeat revascularization rates in the CABG patients, overall major adverse cardiac and cerebrovascular event rates were significantly lower in the CABG group at 5 years. Dedicated trial data on the impact of drug-eluting stents, the relief of angina, and the role of PCI in higher-risk patients are warranted.

Disclosures

Dr Stables received research grants from Cordis, Boston Scientific, Medtronic, and Abbott and has served as a consultant or on the advisory board for Cordis, Boston Scientific, Medtronic, and Abbott. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Randomized trials that studied clinical outcome after percutaneous coronary intervention (PCI) with bare metal stenting versus coronary artery bypass grafting (CABG) are underpowered to properly assess safety end points like death, stroke, and myocardial infarction. Pooling data from randomized controlled trials increases the statistical power and allows better assessment of the treatment effect in high-risk subgroups. The present pooled analysis of 3051 patients in 4 randomized trials evaluating the relative safety and efficacy of PCI with stenting and CABG for the treatment of multivessel coronary artery disease demonstrates that both treatment modalities provided similar long-term safety profiles. At 5 years, the cumulative incidence of death, myocardial infarction, and stroke was similar in patients randomized to PCI with stenting versus CABG (16.7% versus 16.9%, respectively; hazard ratio, 1.04; 95% confidence interval, 0.86 to 1.27; $P=0.69$). Repeat revascularization, however, occurred significantly more frequently after PCI than CABG (29.0% versus 7.9%, respectively; hazard ratio, 0.23; 95% confidence interval, 0.18 to 0.29; $P<0.001$). Several large-scale randomized trials like the Future Revascularization Evaluation in Patients With Diabetes: Optimal Management of Multivessel Disease, and Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery are currently comparing the safety and effectiveness of CABG and PCI with drug-eluting stents. Whether drug-eluting stents will tip the balance between safety and efficacy of PCI and CABG is to be examined.

Chapter 26

Three-year follow-up of the ARTS-II – Sirolimus-eluting stents for the treatment of patients with multivessel coronary artery disease

Serruys PW, Daemen J, Morice MC, de Bruyne B, Colombo A, Macaya C, Richardt G, Fajadet J, Hamm C, Dawkins K, Vranckx P, Bressers M, van Domburg R, Schuijer M, Wittebols K, Pieters M, Stoll HP, on behalf of the ARTS II Investigators

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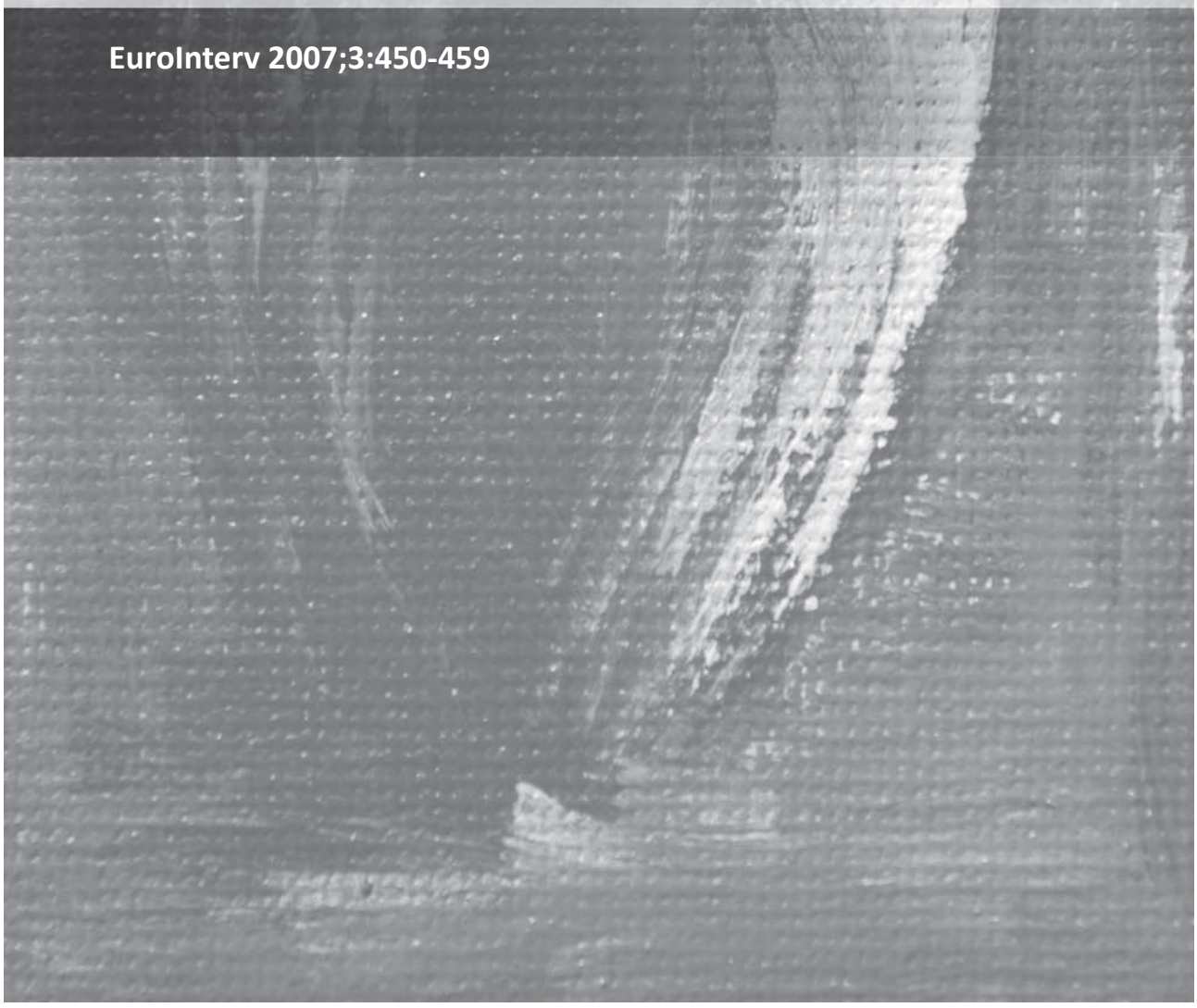

Three-year follow-up of the ARTS-II# – sirolimus-eluting stents for the treatment of patients with multivessel coronary artery disease

 # Arterial revascularisation therapies study

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KEYWORDS
Coronary revascularisation, sirolimus-eluting stents, coronary artery bypass graft surgery, ARC, SYNTAX score

Abstract

Aims: Late stent thrombosis has been documented in on- and off-label populations. Stent thrombosis is more frequently in higher risk patients and there is still scarce data about the impact on late adverse cardiac events. The aim therefore is to determine the 3-year safety and effectiveness of Sirolimus-Eluting Stent (SES) (Cypher®) implantation in patients with multivessel disease and to compare outcomes with the historical results of the two arms of the Arterial Revascularisation Therapies Study (ARTS-I).

Methods and results: ARTS-II is a 45 centre, 607 patient single-arm study. Three years outcomes were compared to the outcome of the historical cohorts of ARTS-I using the same inclusion and exclusion criteria and major adverse cardiac and cerebrovascular events (MACCE) definitions. Patients were stratified by clinical site to ensure that at least 1/3 had 3-vessel disease to achieve a number of treated lesions per patient comparable to ARTS-I. Stent thrombosis was re-adjudicated using the ARC definitions. An angiographic coronary score to characterise lesion complexity was applied to allow the identification of patients who might benefit the most from multivessel stenting.

In ARTS-II, 46.6% of the patients underwent 3-vessel treatment as compared to 18.0% in ARTS-I percutaneous coronary intervention (PCI) (n=600) with bare metal stents (BMS). Diabetes was present in 26.2% in ARTS-II as compared to 17.3% in ARTS-I. In ARTS-II, patients received on average 3.7 stents resulting in a mean total stented length of 72.5 mm. The 3-year survival rate in ARTS-II was 97.0%, comparable to the 95.6% and 96.0% of the historical surgical (n=605) and PCI cohorts of ARTS-I. The death/cerebrovascular accident (CVA)/myocardial infarction (MI) event free survival rate in ARTS-II was 91.7%, versus 89.1% (p=0.1) and 87.2% (p=0.007) in ARTS-I coronary artery bypass graft (CABG) and PCI cohorts, respectively. Freedom from revascularisation in ARTS-II was 85.5%, lower than in ARTS-I CABG (93.4%; p<0.001) but higher than in ARTS-I PCI (73.7%; p<0.001) cohorts. MACCE free survival was 80.6% in ARTS-II, comparable to ARTS-I CABG (83.8%; p=0.21) but superior to ARTS-I PCI (66.0%; p<0.0001). The incidence of stent thrombosis (ARC any) in ART-II was 6.4% (39/607 patients).

Conclusions: Despite the higher clinical and angiographic risk profile, the overall MACCE rate at three years was lower in ARTS-II than in the ARTS-I PCI and comparable to ARTS-I CABG. However, the re-intervention rate in ARTS-I CABG remained significantly lower than in ARTS-II.

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Introduction

In September 2001, the results of the pivotal randomised trial comparing bare metal stents (BMS) and sirolimus-eluting stents (SES) were presented at the scientific sessions of the European Society of Cardiology and subsequently published in 2002.[1] Shortly after the commercialisation of this first drug-eluting stent (Cypher®) in Europe in April 2002, European investigators requested the manufacturer to sponsor a randomised comparison between bypass surgery and stenting with SES for multivessel disease, using a similar study design as in the Arterial Revascularisation Therapies Study ARTS-I.[2-4] However, the project was considered to be premature, hazardous and expensive. As a surrogate, the ARTS-II registry was designed applying the same inclusion and exclusion criteria, the same protocol definitions and the same primary endpoint, in order to make the registry as comparable as possible to the randomised ARTS-I trial of coronary artery bypass surgery and BMS.[5]

Despite the non-randomized nature of the ARTS-II trial, the 3-year results can be interpreted today in the context of the current concerns raised about the long-term safety of SES, since the ARTS-II population is so far one of the most complex populations of patient treated with SES. Since the first seminal observation of very late stent thrombosis, a large number of reports have raised concerns about the safety of the treatment, particularly in off-label use.[6-10] ARTS-II clearly represents "off-label" use of SES with an average use of 3.7 stents per patients resulting for a mean total stented length of 72.5 mm per patient, a length of stenting unparalleled by any randomised trial or current registry reported thus far. In the meantime, the Academic Research Consortium (ARC), working with the FDA and major stent manufacturers, created new definitions for the major adverse clinical events, including stent thrombosis.[11]

In October 2006 the FDA requested that the events in the pivotal Cypher and Taxus trials be re-adjudicated using these definitions.[12-15] In ARTS-II, events were re-adjudicated by a new independent critical event committee, focusing on the incidence and timing of stent thrombosis. The present study reports on the 3-year safety and effectiveness of the SES in patients with multivessel disease compared to the outcomes of the historical results of the two arms of ARTS-I applying the ARC definition to determine the incidence of definite, probable or possible stent thrombosis.

Methods

Study design

ARTS-II is a multicentre, non-randomised, open-label trial, designed to compare the safety and efficacy of the SES in patients with *de novo* multivessel coronary artery disease with the surgical group of ARTS-I acting as a historical control.[5] In order to obtain a population comparable to ARTS-I, patients were stratified by clinical site in order to ensure the inclusion of at least 1/3 of patients with three-vessel disease.

Patient selection

Patients were eligible for coronary revascularisations if they had either stable angina (Canadian Cardiovascular Society class I-IV), unstable angina (Braunwald class I-III B or C), or if they had silent ischaemia and at least two lesions located in different major epicardial vessels and/or their side branches (not including the left main coronary artery) that were potentially amenable to stent implantation.[16,17] Patients were required to have multivessel disease including treatment of the left anterior descending (LAD) artery and at least one other significant lesion (>50% diameter stenosis) in another major epicardial coronary artery. The goal was to achieve complete anatomic revascularisation.[18] One totally occluded major epicardial vessel or side branch could be included. The stenosis had to be amenable to stenting using a SES with a diameter of 2.5 to 3.5 mm and length of 13 to 33 mm, without restriction on the total implanted stent length. Decisions to place stents in lesions with bifurcations, fresh thrombus, calcification, diffuse disease, complex anatomy or stenting of side branches were left to the discretion of the operators. Patients with previous coronary intervention, left main coronary disease, overt congestive heart failure or a left ventricular ejection fraction of less than 30 percent were excluded. Additional exclusion criteria were: history of a cerebrovascular accident, transmural myocardial infarction in the preceding week, severe hepatic or renal disease, neutropenia or thrombocytopenia, an intolerance or contraindication to acetylsalicylic acid or thienopyridines, the need for concomitant major surgery and life-limiting major concomitant non-cardiac diseases. Written, informed consent was obtained from each patient prior to enrolment. The study was approved by the ethics committee of each participating site.

Study objectives

The primary objective of ARTS-II was to compare the safety and effectiveness of coronary stent implantation using the SES with the surgical arm of ARTS-I.[19,20] Endpoints are measured in terms of major adverse cardiac and cerebrovascular events (MACCE) comprising all-cause death, any cerebrovascular event, non-fatal MI, or any repeat revascularisation.

The secondary objectives of this study were to compare the ARTS-II patients to both arms of ARTS-I with respect to MACCE at 30 days, one, three and five years; the composite end point death, CVA and myocardial infarction, and the itemised outcomes death, CVA, myocardial infarction and repeat revascularisation; resource utilisation at 30 days and one year; cost effectiveness at one year, and quality of life at six months, and one, three and five years.[21] Finally, the study aimed at describing the prognostic value of the Syntax score on the MACCE rates in the ARTS-II population.

Endpoint definitions

Death was categorised as cardiac or non-cardiac. Cerebrovascular events were divided into three main categories: stroke, transient ischaemic attacks, and reversible ischaemic neurologic deficits. In the first seven days after the intervention, a definite diagnosis of myocardial infarction was made if there was documentation of new abnormal Q-waves and either a ratio of serum creatine kinase MB (CK-MB) isoenzyme to total cardiac enzyme that was greater than 0.1 or a CK-MB value that was five times the upper limit of normal[22] Serum creatine kinase and CK-MB isoenzyme concentrations were measured six, 12, and 18 hours after the intervention. Commencing eight days after the intervention (the length of the hospital stay after

surgery), either abnormal Q waves or enzymatic changes, as described above, were sufficient for a diagnosis of myocardial infarction. A myocardial infarction was confirmed only after the relevant electrocardiograms had been analysed by the core laboratory and adjudicated by the clinical-events committee. This two-part method of defining myocardial infarction was developed for ARTS-I to address the difficulty of diagnosing a myocardial infarction after cardiac surgery.[5] These definitions have been adopted by the ARC Consortium and are applied whenever a comparison between DES and surgery is performed.[11] In the final report, the window of seven days is not specifically mentioned and this window has been maintained for the sake of comparison with the historical data from ARTS-I. All repeat revascularisation procedures were recorded.

Secondary measures of efficacy were assessed by means of the EQ-5D questionnaire, which allows patients to grade their general health status.[23]

Endpoint measurement

In ARTS-II, the interventional procedure was performed within 48 hours of inclusion, while in ARTS-I patients were randomised after informed consent had been obtained and then entered a waiting list, with three deaths in the ARTS-I CABG arm occurring whilst patients were awaiting revascularisation. To compensate for the temporal difference since allocation between groups, events for the present report were counted from the time of the procedure for all three arms and not from the time of allocation as previously published.[3,4,24]

In ARTS-I and ARTS-II, only data on subacute thrombotic occlusion (<30 days) were collected in the case record form (CRF). In ARTS-II, stent thrombosis was re-adjudicated according to the ARC definitions.[11] In this process, all coronary angiograms, both procedure-related (n=104) and non-procedure related (n=165) were reviewed by an independent core laboratory and adjudicated by an independent critical event committee. Thus far, no attempt has been made to assess data on stent thrombosis in ARTS-I in a similar fashion.

In addition, a detailed coronary risk score which had been previously published and tested in a subgroup of ARTS-II patients with 3-vessel disease (the Syntax score) was used to characterise the complexity of the coronary anatomy.[25,26] In brief, each coronary lesion producing ≥ 50% luminal obstruction lumen in vessels ≥ 1.5 mm was separately scored and added to provide the overall Syntax. The Syntax score was calculated using a dedicated software that integrates the number of lesions with their specific weighting factors based on the amount of myocardium distal to the lesion according to the score of Leaman et al,[27] and the morphologic features of each single lesion, as previously reported[26] (available at http://www.europcronline.com/eurointervention/2nd_issue/36/). This Syntax score is now available for the entire ARTS-II population and its implications in terms of prognosis at three years are reported in the present document.

Statistical analysis

The sample size justification was based on the comparison of 1-year MACCE rates in the ARTS-II patients and the ARTS-I surgery patients for the primary endpoint. A MACCE-free survival rate of 90.9% was assumed in the ARTS-II trial, requiring a sample size of 600 patients to guarantee a power of at least 90%.[5,20] Binary variables are reported as percentages, and the difference between groups was presented with 95% confidence intervals. Time-to-event variables are presented as Kaplan-Meier curves and incidences were compared using the log-rank test. Safety data up to three years are presented as Kaplan-Meier estimates, with relative risks and 95% confidence intervals. The final analyses will be performed at five years.

A separate multivariate regression analysis was performed to determine independent predictors of MACCE and ST within the ARTS-II population only. Baseline and procedural characteristics listed in Table 1 were tested on a per patient basis by univariate analysis to determine suitability for inclusion in the multivariate model. Finally, a logistic regression model was built using the significant univariate predictors (p<0.1).

Results

Baseline and procedural characteristics

Between April 1997 and June 1998 a total of 1,205 patients were randomly assigned to PCI with BMS (n=600) or CABG (n=605) in 67 participating centres in the ARTS-I trial. Between February 2003 and November 2003, 607 patients at 45 participating centres were treated (Figure 1). Table 1 presents their baseline demographic and angiographic characteristics. Patients treated in ARTS-II were significantly older than those in ARTS-I. ARTS-II had a significantly higher incidence of diabetes mellitus, hypertension, hypercholesterolaemia and silent ischaemia, and a lower percentage of current smokers or patients with a history of prior myocardial infarction as compared to the ARTS-I CABG groups. Seven patients did not receive any stents during the index procedure (four underwent elective CABG, one required emergent CABG, one underwent percutaneous treatment 35 days later and one remained on medical therapy).

The percentage of percutaneous 3-vessel treatment was 46.6% in ARTS-II versus 18.0% in ARTS-I PCI (p<0.001). The mean number of

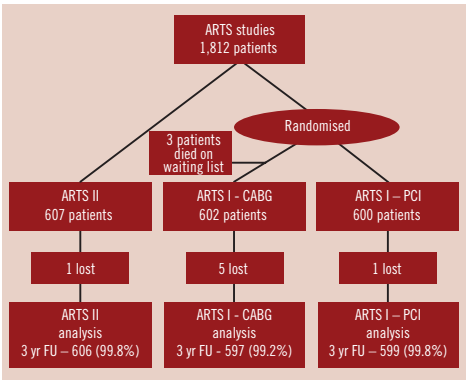

Figure 1. Flowchart of ARTS-I and ARTS-II.

Table 1. Baseline and procedural characteristics of ARTS II and ARTS I population (expressed per patient unless stated otherwise).

	ARTS II (n=607)	ARTS I CABG (n=605)	ARTS I-PCI (n=600)	ARTS II:I-CABG Difference (95% CI)		ARTS II:I-PCI Difference (95% CI)	
Baseline characteristics							
Male gender (%)	77	76	77	0.6%	(−4.2%, 5.4%)	−0.4%	(−5.2%, 4.4%)
Age (years±SD)	63±10	61±9	61±10	1.5	(0.4, 2.6)	2.1	(1.0, 3.2)
Body mass index±SD	27.5±4.1	27.4±3.7	27.2±3.7	0.2	(−0.3, 0.6)	0.3	(−0.1, 0.8)
Risk factors							
Myocardial infarction (%)	34	42	44	−7.6%	(−13.0%, −2.1%)	−9.9%	(−15.4%, −4.4%)
Diabetes (%)	26	16	19	10.3%	(5.8%, 14.9%)	7.5%	(2.8%, 12.2%)
Hypertension (%)	67	45	45	22.3%	(16.8%, 27.7%)	22.5%	(17.1%, 28.0%)
Hypercholesterolaemia (%)	74	58	58	16.4%	(11.2%, 21.7%)	16.1%	(10.8%, 21.4%)
Family history of MI or sudden death < 55 years (%)	36	42	39	−6.0%	(−11.5%, −0.5%)	−3.2%	(−8.7%, 2.2%)
Current smoker (%)	19	26	28	−6.5%	(−11.2%,−1.8)	−8.7%	(−13.4%, −3.9%)
Peripheral vascular disease (%)	7	5	6	1.8%	(−0.9%, 4.5%)	1.4%	(−1.3%, 4.2%)
Indication for treatment							
Stable angina (%)	53	58	56	−4.8%	(−10.4%, −0.8%)	−3.1%	(−8.7%, 2.5%)
Unstable angina (%)	36	37	38	−0.8%	(−6.2%, 4.6%)	−1.3%	(−6.7%, 4.2%)
Silent ischaemia (%)	10	5	6	5.6%	(2.6%, 8.5%)	4.4%	(1.3%, 7.5%)
Angiographic characteristics							
Ejection fraction (%)	60±12	60±13	61±12	−0.2	(−1.6, 1.3)	−0.8	(−2.2, 0.7)
No. of lesions with stenosis > 50%	3.6±1.3	2.8±1.0	2.8±1.0	0.8	(0.6, 0.9)	0.8	(0.6, 0.9)
No. of diseased vessels (%)							
1	0	4	4	−3.4%	(−5.0%, −1.8%)	−3.6%	(−5.3%, −2.0%)
2	46	66	69	−20.1%	(−25.6%, −14.6%)	−22.4%	(−27.9%, −17.0%)
3	54	30	27	23.5%	(18.1%, 28.9%)	26.1%	(20.7%, 31.4%)
Vessel territory with stenosis (% of lesions)							
Right coronary artery	29	29	31	−0.4%	(−3.3%, 2.5%)	−2.1%	(−5.0%, 0.9%)
Left main	0	0	0	−0.1%	(−0.2%, 0.1%)	−0.1%	(−0.2%, 0.1%)
Left anterior descending	42	41	39	0.4%	(−2.7%, 3.6%)	2.1%	(−1.1%, 5.3%)
Left circumflex artery	29	29	29	0.0%	(−2.9%, 3.0%)	0.0%	(−2.9%, 3.0%)
Lesion length (visual) (% of lesions)							
Discrete	61	68	66	−7.3%	(−10.4%, −4.2%)	−4.7%	(−7.9%, −1.5%)
Tubular	27	25	27	2.0%	(−0.9%, 4.9%)	−0.1%	(−3.0%, 2.8%)
Diffuse	12	7	7	5.3%	(3.4%, 7.2%)	4.8%	(2.9%, 6.7%)
Lesion classification (% of lesions)							
Type A	7	7	6	0.0%	(−1.6%, 1.6%)	0.9%	(−0.7%, 2.5%)
Type B1	23	31	26	−7.9%	(−10.8%, −5.1%)	−3.0%	(−5.8%, −0.2%)
Type B2	56	54	60	1.9%	(−1.3%, 5.1%)	−3.7%	(−6.9%, −0.5%)
Type C	14	8	8	6.0%	(4.0%, 8.0%)	5.9%	(3.9%, 7.8%)
Procedural characteristics							
Bifurcation requiring double wiring	34	32	35	2.2%	(−0.9%, 5.3%)	−0.6%	(−3.7%, 2.6%)
Number of stents implanted±SD	3.7±1.5	–	2.8±1.3	–		0.9	(0.7, 1.0)
Total stent length (mm)	72.5±32.1	–	47.6±21.7	–		24.9	(21.8, 28.1)
Maximum dilatation pressure (atm±SD)	16.4±2.9	–	14.6±2.8	–		1.7	(1.4, 2.1)
Direct stenting (% of lesions)	34.6	–	3.3	–		31.3%	(29.1%, 33.6%)
Duration of procedure (mins±SD)	85±43	193±67	99±50	−108.2	(−114.6, −101.8)	−13.6	(−18.9, −8.3)
Post procedural hospital stay (days±SD)	3.4±2.7	9.6±4.9	3.9±3.7	−6.2	(−6.6, −5.8)	−0.5	(−0.9, −0.2)

CI stands: confidence interval; SD: standard deviation; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft

significant lesions per patient was 3.6±1.3 in ARTS-II versus 2.8±1.0 in ARTS-I CABG (p<0.001) and 2.8±1.0 in ARTS-I PCI. ARTS-II patients received 3.7±1.5 stents with average total stented length of 72±32 mm vs. 2.8±1.3 and 48±22 mm in ARTS-I PCI (p<0.001).

Post-procedure creatinine kinase (CK) release was within the normal range (≤ 1 x Upper limit of normal (ULN)) in 81.7% (496/607). Fourteen percent (85/607) of the patients had a CK release of >1 and ≤ 2 x ULN and only 4.3% (26/607) of the patients had a post-procedure CK release of > 2 x ULN, thereby fulfilling the ARC criteria for peri-procedural MI.

Three-year follow-up

MAJOR ADVERSE CARDIAC AND CEREBROVASCULAR EVENTS

The 3-year event rates are depicted in Table 2 and Figure 2. In brief, the survival rate in ARTS-II was comparable to those of the historical surgical and PCI cohorts of ARTS-I. The death/CVA/MI

Table 2. Clinical endpoints at 3 years (hierarchical and non-hierarchical MACCE up to 1080 days, per patient) counted since date of procedure.

	ARTS II N=607 N (%)	ARTS I CABG N=602 * N (%)	ARTS I PCI N=600 N (%)	ARTS II: I-CABG Difference (95% CI) (%)	ARTS II: I-PCI Difference (95% CI) (%)
Hierarchical					
Death	18 (3.0)	26 (4.3)	24 (4.0)	−1.4 (−3.5, 0.8)	−1.0 (−3.1, 1.0)
Cardiac	9 (1.5)	16 (2.7)	16 (2.7)	−1.2 (−2.8, 0.4)	−1.2 (−2.8, 0.4)
Non-cardiac	9 (1.5)	10 (1.7)	8 (1.3)	−0.2 (−1.6, 1.2)	0.1 (−1.2, 1.5)
CVA	15 (2.5)	15 (2.5)	18 (3.0)	0.0 (−1.8, 1.7)	−0.5 (−2.4, 1.3)
MI	17 (2.8)	24 (4.0)	35 (5.8)	−1.2 (−3.2, 0.9)	−3.0 (−5.3, −0.7)
MI Q-wave	10 (1.6)	22 (3.7)	30 (5.0)	−2.0 (−3.8, −0.2)	−3.4 (−5.4, −1.3)
MI non-Q-wave	7 (1.2)	2 (0.3)	5 (0.8)	0.8 (−0.1, 1.8)	−0.3 (−0.8, 1.4)
Death / CVA / MI	50 (8.2)	65 (10.8)	77 (12.8)	2.6 (−5.9, 0.7)	−4.6 (−8.1, −1.1)
Revascularisation	67 (11.0)	32 (5.3%)	127 (21.2)	5.7 (2.7, 8.8)	−10.1 (−14.2, −6.0)
(re) CABG	13 (2.1)	5 (0.8)	40 (6.7)	1.3 (0.0, 2.7)	−4.5 (−6.8, −2.2)
(re) PTCA	54 (8.9)	27 (4.5)	87 (14.5)	4.4 (1.6, 7.2)	−5.6 (−9.2, −2.0)
Any MACCE	117 (19.3)	97 (16.1)	204 (34.0)	3.2 (−1.1, 7.5)	−14.7 (−19.6, −9.8)
Non-hierarchical					
CVA	17 (2.8)	19 (3.2)	20 (3.3)	−0.4 (−2.3, 1.6)	−0.5 (−2.5, 1.4)
MI	22 (3.6)	30 (5.0)	41 (6.8)	−1.4 (−3.6, 0.9)	−3.2 (−5.8, −0.7)
MI Q-wave	13 (2.1)	27 (4.5)	35 (5.8)	−2.3 (−4.4, −0.3)	−3.7 (−5.9, −1.5)
MI non-Q-wave	10 (1.6)	3 (0.5)	7 (1.2)	1.1 (0.0, 2.3)	0.5 (−0.8, 1.8)
Revascularisation	87 (14.3)	39 (6.5)	158 (26.3)	7.9 (4.4, 11.3)	−12.0 (−16.5, −7.5)
(re) CABG	14 (2.3)	7 (1.2)	55 (9.2)	1.1 (−0.3, 2.6)	−6.9 (−9.5, −4.3)
– Target lesion**	4 (0.7)	5 (0.8)	40 (6.7)	−0.2 (−1.1, 0.8)	−6.0 (−8.1, −3.9)
– Non target lesion	10 (1.6)	2 (0.3)	15 (2.5)	1.3 (0.2, 2.4)	−0.9 (−2.5, 0.8)
(re) PTCA	75 (12.4)	36 (6.0)	118 (19.7)	6.4 (3.1, 9.6)	−7.3 (−11.4, −3.2)
– Target lesion**	48 (7.9)	22 (3.7)	86 (14.3)	4.3 (1.6, 6.9)	−6.4 (−10.0, −2.9)
– Non target lesion	37 (6.1)	15 (2.5)	42 (7.0)	3.6 (1.3, 5.9)	−0.9 (−3.7, 1.9)

N stands: number of events

* Three patients died on the waiting list.

** In the ARTS-I PCI cohort, 12 out of 126 (8.7%) target lesion revascularisations were due to a myocardial infarction. In the ARTS-II cohort, 10 out of 52 (19.2%) of the target lesion revascularisations were due to a myocardial infarction.

event free survival was 91.7% in ARTS-II, versus 89.1% (log rank p=0.1) and the 87.2% (log rank p=0.007) in the ARTS-I CABG and PCI cohorts, respectively. Freedom from revascularisation in ARTS-II was 85.5%, which was lower than ARTS-I CABG (93.4%; log rank p<0.0001) but higher than the ARTS-I PCI (73.3%; log rank p<0.0001). The MACCE free survival was 80.6% in ARTS-II and did not differ significantly from the MACCE event free survival rate of 83.8% in ARTS-I CABG (log rank p=0.21) but was superior to ARTS-I PCI (66.0%; log rank p <0.0001).

STENT THROMBOSIS ACCORDING TO THE ARC DEFINITIONS

In ARTS-II, a total of 39 patients (Table 3) experienced at least one stent thrombotic event (definite, probable or possible). One patient experienced two probable ST events (on day 331 and day 399), one patient experienced a definite ST on day 1,020 and a probable ST on day 1,079, one patient experienced definite ST on day 562 and day 984 and probable ST on day 983, and one patient experienced probable ST on day 468 and possible ST on day 479 accounting for 44 ST events in total. The rate of stent thrombosis (definite or probable or possible) in ARTS-II was 1.5% at 30 days, 3.1% at one year, 4.4% at two years and 6.4% at three years, respectively. The rate of definite stent thrombosis in our study rose from 1.0% at 30 days to 1.6% at one year, 2.1% at two years and 3.5% at three years. By contrast, the rate of angiographically documented (definite) stent thrombosis in the ARTS -I PCI cohort was 2.8% at 30 days.[3]

Among the 21 patients with definite ST, six were subacute (within 30 days), four late (within 30 days – one year) and 11 very late (after one year). Four of the subacute thrombotic events occurred within the first four days post procedure. Three of these were due to suboptimal treatment, according to the independent CEC. No clear cause for the thrombotic event in the remaining three patients could be identified. Five of the subacute thrombotic events were treated with repeat intervention (four PCI, one CABG) and one lesion was left untreated. Two patients experienced a non-Q wave MI and four patients experienced a Q wave MI. There were four late definite ST (day 30-365). In one patient, the index procedure failed due to a wide dissection and on day 40 the patient was admitted with angina (CCS 3) and a total occlusion of the failed PCI was diagnosed. No increase in enzymes or appearance of a Q wave was documented. The three remaining patients presented with in-stent restenosis and (un)stable angina but an in-stent thrombus was diagnosed by the CEC, who adjudicated the in-stent stenotic lesion as stent thrombosis. Eleven very late definite stent thromboses occurred: three were

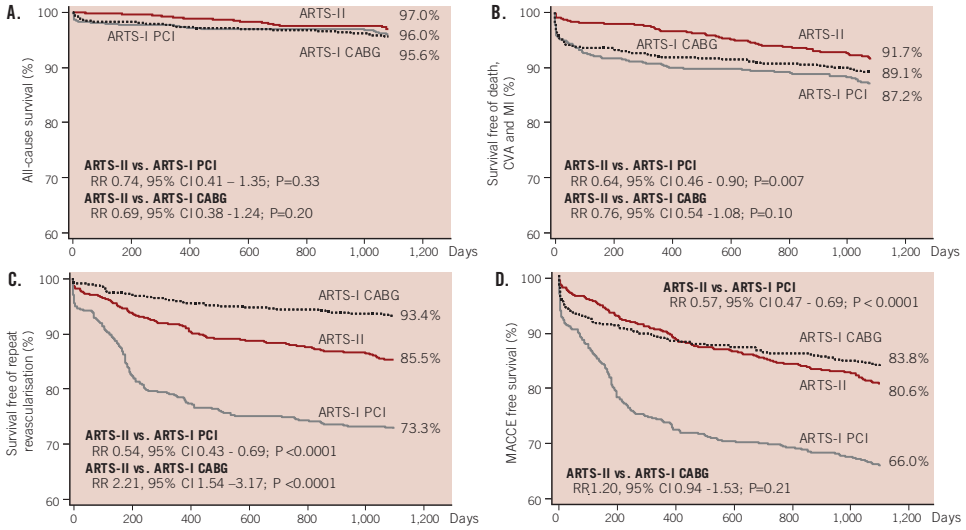

Figure 2. Kaplan-Meier curves out to three years in ARTS-I and ARTS-II; all-cause survival (A); freedom from all-cause death, cerebrovascular accident (CVA) or myocardial infarction (MI) (B); freedom from repeat revascularisation (C) and freedom from all-cause death, CVA, myocardial infarction or repeat revascularisation (MACCE) (D). Thick black line depicts the ARTS-II cohort. The thin black line depicts the ARTS-I PCI cohort and the dotted line the ARTS-I CABG cohort. P-values are Log rank.

Table 3. Stent thrombosis according to the ARC definitions.

Stent thrombosis defined by ARC	ARTS-II	Death up to 1080 days	MI** up to 1080 days	MI*** up to 1080 days
(Sub)acute	9 (23.1%)	0/9 (0.0%)	9/9 (100%)	5/9 (55.6%)
Late	10 (25.6%)	3/10 (30.0%)	4/10 (40.0%)	2/10 (20.0%)
Very late	20 (51.3%)	5/20 (25.0%)	13/20 (65.0%)	12/22 (54.5%)
Definite	21 (53.8%)	0/21 (0.0%)	15/21 (71.4%)	12/21 (57.1%)
Definite or probable	32 (82.1%)	1/32 (3.1%)	25/32 (78.1%)	19/32 (59.4%)
Definite, probable or possible*	39 (100%)	8/39 (20.5%)	25/39 (64.1%)	19/39 (48.7%)

* One patients experienced two probable ST events (on day 331 and day 399), one patient experienced a definite ST on day 1020 and a probable ST on day 1079, one patient experienced definite ST on day 562 and day 984 and probable ST on day 983, and one patient experienced probable ST on day 468 and possible ST on day 479 accounting for 44 ST events in total; ** MI according to ARC definition; *** MI according to protocol

described as restenoses with intrastent thrombus, eight as total occlusion; four presented with unstable angina, seven as STEMI with enzyme elevation and/or new Q-waves.

There was no relation between the use of periprocedural GP IIb/IIIa inhibitors and ST. GP IIb/IIIa inhibitors were used in 197 out of 607 cases in ARTS-II. In this group, 9.1% (18 patients) experienced stent thrombosis. In the group without IIb/IIIa inhibitor use (n=410), 5.1% (21 patients) experienced stent thrombosis (p=0.08). Early stent thrombosis occurred in 1.2% (five patients) in the no GP IIb/IIIa inhibitor group versus 2.0% (four patients) in the GP IIb/IIIa inhibitor group (p=0.48).

Although clopidogrel was only recommended for three months, a total of 266 were still using clopidogrel or thienopyridine at one year. A stratified analysis revealed that the survival free of MACE (79.2% vs. 80.7; log rank p=0.70) and ST (92.4% vs. 95.4%; Logrank p=0.13) was identical between patients who were still on clopidogrel or thienopyridine at one year versus those without. The impact of stent thrombosis on the clinical event rates is depicted in Figure 3a and b.

Including only pre-procedural risk factors, type B2 and C lesions and the presence of an intracoronary thrombus at baseline on the diagnostic film emerged as independent predictors of stent thrombosis. Including post-procedure risk factors, the presence of an intracoronary thrombus, maximum CK post-procedure and stent length per 10 mm increase emerged as independent predictors of stent thrombosis re-adjudicated according to the ARC definitions.

Impact of Syntax score on clinical outcome

Multivariate analysis was performed on the ARTS-II population to determine independent predictors of MACCE (Table 4). The Syntax score proved to be among the strongest predictors of MACCE

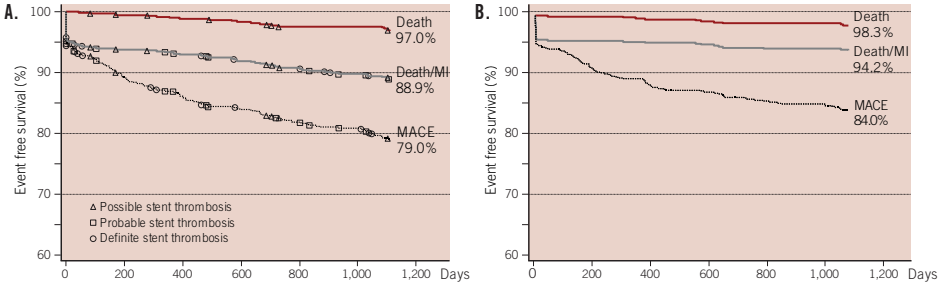

Figure 3. Kaplan Meier survival curves for death; death or myocardial infarction (MI) and death, MI or repeat revascularisation (MACE), with superimposed on the curves, individual hierarchical thrombotic event (definite or probable or possible stent thrombosis according to the ARC definitions) (A); (B) shows the same Kaplan Meier curve, after removal of the individual clinical events related to stent thrombosis – resulting in an upward shift of the three curves, reflecting higher event free rates.

Table 4. Independent predictors of MACCE and stent thrombosis in the ARTS-II group.

	Univariable predictors of MACCE at 3 years*			Multivariable predictors of MACCE at 3 years*		
Variable	Odds ratio	95% confidence interval	P-value	Odds ratio	95% confidence interval	P-value
Pre-procedure						
Diabetes (%)	1.97	1.28-3.02	0.002	1.76	1.13-2.74	0.012
Syntax score (per group increase)	1.62	1.26-2.09	0.0002	1.43	1.08-1.90	0.014
Peripheral vascular disease (%)	2.01	1.01-3.99	0.047	1.76	0.86-3.60	0.12
Nr. of lesions type B2 or C	1.25	1.07-1.47	0.006	1.11	0.88-1.41	0.37
Nr. of lesions with stenosis >50%	1.20	1.03-1.40	0.018	1.01	0.80-1.26	0.95
Age (years±SD)	1.02	1.00-1.05	0.033	***	***	***
Pre + peri-procedure						
Nr. of lesions with direct stenting	0.81	0.67-0.98	0.032	0.80	0.65-0.99	0.037
Diabetes (%)	1.97	1.28-3.02	0.002	1.64	1.02-2.63	0.042
Max post proc CK	1.35	1.08-1.68	0.008	1.25	1.00-1.57	0.053
Syntax score (per group increase)	1.62	1.26-2.09	0.0002	1.34	0.98-1.83	0.06
Peripheral vascular disease (%)	2.01	1.01-3.99	0.047	1.79	0.85-3.78	0.13
Total stent length (mm)	1.09	1.03-1.16	0.006	1.03	0.94-1.13	0.48
Duration of procedure (mins±SD)	1.00	1.00-1.00	0.09	1.00	1.00-1.01	0.56
Nr. of lesions with stenosis >50%	1.20	1.03-1.40	0.018	1.05	0.80-1.36	0.74
Bifurcation requiring double wiring	1.19	0.98-1.44	0.08	1.05	0.82-1.33	0.72
Nr. of lesions type B2 or C	1.25	1.07-1.47	0.006	0.97	0.74-1.26	0.81
Complete revascularisation	0.67	0.45-1.01	0.055	0.98	0.59-1.62	0.93
Age (years±SD)	1.02	1.00-1.05	0.033	***	***	***

	Univariable predictors of stent thrombosis at 3 years**			Multivariable predictors of stent thrombosis at at 3 years**		
Variable	Odds ratio	95% confidence interval	P-value	Odds ratio	95% confidence interval	P-value
Pre-procedure						
Total stent length (mm)	1.13	1.04-1.23	0.005	1.11	1.00-1.24	0.053
Nr. of lesions type B2 or C	1.44	1.13-1.84	0.004	1.40	0.94-2.08	0.095
Nr. of lesions with stenosis >50%	1.26	1.00-1.59	0.051	0.74	0.49-1.13	0.16
Syntax score (per group increase)	1.04	1.01-1.07	0.008	1.02	0.99-1.06	0.20
Pre + peri-procedure						
Max post proc CK	1.47	1.15-1.88	0.002	1.36	1.06-1.74	0.016
Nr. of lesions type B2 or C	1.44	1.13-1.84	0.004	1.35	0.89-2.06	0.16
Total stent length (mm)	1.13	1.04-1.23	0.005	1.18	0.93-1.51	0.18
Nr. of lesions with stenosis >50%	1.26	1.00-1.59	0.051	0.79	0.51-1.23	0.29
Syntax score (per group increase)	1.04	1.01-1.07	0.008	1.01	0.98-1.05	0.53
Number of stents implanted ±SD	1.23	1.02-1.49	0.032	0.87	0.50-1.54	0.64
Bifurcation requiring double wiring	1.37	1.03-1.84	0.033	1.07	0.75-1.52	0.71

* Per protocol definitions; ** ARC definitions; *** Not included due to colinearity problems

(OR 1.43, 95% CI 1.08 – 1.90; p=0.014) together with the presence of diabetes mellitus (OR 1.76, 95% CI 1.13 – 2.74; p=0.012).
The entire population of ARTS-II was subdivided into patients with a Syntax score <16 (n=209), >=16 and < 24 (n=199) and ≥ 24 (n=199). The Kaplan Meier estimates of MACCE free survival (Figure 4) show that the two subgroups with the highest Syntax score had significantly worse prognosis than the subgroup with the lowest Syntax score.

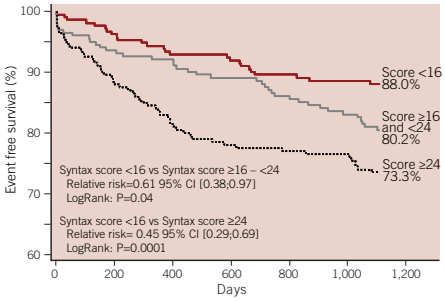

Figure 4. Kaplan-Meier curve of MACCE out to 3 years of the ARTS-II population stratified to the Syntax score: <16 (n=209), ≥ 16 and <24 (n=199) and ≥ 24 (n=199).

Quality of life

There were no differences in the quality of life as assessed by the self-rated thermometer of the EQ-5D questionnaire at three years among patients allocated to either CABG or PCI with bare-metal stents or SES (78, 76 and 76 in the ARTS-I CABG, ARTS-I PCI and ARTS-II respectively; p=0.1).

Discussion

Events per protocol

At three years, there was no significant difference in overall mortality between the ARTS-II and the ARTS-I PCI and CABG cohorts, despite a higher angiographic and clinical risk profile in the more contemporary ARTS-II cohort. Although the present study might have been underpowered to demonstrate any significant difference mortality, the findings concur with the previously published 10-year follow-up of the BARI study in which PCI was performed without coronary stents.[28]
The composite endpoint of death, CVA and MI was the lowest in the ARTS-II group and was significantly better than in the ARTS-I PCI cohort. When the MACCE rates in the three cohorts were compared, the surgical group had the lowest MACCE rate, but the actual difference in MACCE at three years between the ARTS-I CABG and the ARTS-II group was 3.2%, which did not reach statistical significance. When considering the rate of re-intervention over time it became apparent that surgical revascularisation is more durable than percutaneous revascularisation. The actual difference in MACCE between ARTS-I CABG and ARTS-II increased progressively from 4.2% at 1 year to 6.2% and 7.9% at two and three years respectively. However, it is noteworthy that the freedom from surgical or percutaneous re-intervention at three years increased from 73.7% in ARTS-I PCI BMS era to 85.7% in the ARTS-II study using SES. Furthermore, at three years, only 2.3% of patients in ARTS-II required CABG as compared to 9.2% in the ARTS-I PCI cohort treated with BMS.
A major criticism that could be levelled at the present report is that a comparison with a cohort of patients treated surgically ten years ago is inappropriate and potentially misleading considering the progress in surgical techniques and post-operative management over the past decade. The recently completed Syntax trial comparing surgery to multivessel treatment using paclitaxel-eluting stents has reported a rate of complete arterial revascularisation and use of bilateral thoracic arteries of 18.6% and 26.9%, respectively.[29] Only a true randomised comparison in all-comers can definitively address the the respective merits of surgery and PCI with a particular type of stent for multivessel treatment.[29] Nevertheless, the use of a comprehensive coronary score, recently designed and tested in a subgroup of three vessel treatment cohort in ARTS-II at one year is informative: testing this score anew on the entire population and for a period of three years confirms our initial observation that patients with a score of < 16 have a MACE-free survival rate greater than 88% when treated with the SES, while those with a score ≥ 24 may potentially have better outcomes with surgery, based on the population specifically included in ARTS-II.

Comparative assessment of MI per protocol and according to the ARC definitions

Comparing the MI rates of the ARTS-II per protocol and according to the ARC definitions revealed a difference of 5% (3.6% vs. 8.6%, respectively). In ARTS-II, the criteria for an MI according to the protocol (see methods) are those applied to ARTS-I which allows comparison with the historical PCI and CABG cohorts of ARTS-I, using less sensitive criteria for diagnosing a MI. Therefore, it may be argued that the incidence of periprocedural and spontaneous MI in ARTS-II is under-reported. However, this would likely also apply to both cohorts of patients in ARTS-I. When assessing levels of enzyme release in the peri-procedural period, it became apparent that 4.3% of the ARTS-II patients had an enzyme release > 2 x ULN, the threshold criterion used for the ARC definitions. This difference in threshold alone explains the entire difference between the variation in two incidences of MI rates at three years.

Stent thrombosis

Very late stent thrombosis, perceived as a safety issue, can potentially result in an erosion of the long-term beneficial effect of multivessel treatment with DES. ARTS-II is the first study to report the impact of stent thrombosis on the long-term outcome in a population with 2- and 3-vessel disease. The rate of stent thrombosis (definite, probable or possible) in ARTS-II was 1.5% at 30 days, 3.1% at one year, 4.4% at two years and 6.4% at three years, respectively. The rate of definite stent thrombosis in this study increased from 1.0% at 30 days to 1.6% at one year, 2.1% at 2 years and 3.5% at three years; a steady increase comparable to the rate reported in an all-comer population treated with DES.[7]

However, the rates of overall death and MI at three years are reassuring when one compares the rates of death (3.0% vs. 4.0%) and MI (3.6% vs. 6.8%) in ARTS-II and ARTS-I PCI, respectively, despite the higher baseline risk profile in ARTS-II. Despite the fact that two third of these patients sustained an MI or underwent a repeat revascularisation, none of the patients with definite angiographic stent thrombosis died up to three years. While we recognise that late and very late stent thromboses also occur with bare metal stents, we are unable to quantify the number of these events in ARTS-I PCI cohort for comparison at this time.

Figure 3 illustrates the fact that early, late and very late, as well as definite, probable or possible stent thrombosis contributed to an erosion of the treatment effect expressed as freedom from death, death/MI and death/MI/repeat revascularisation. Out of the 127 patients who had a major adverse cardiac event (ARC definitions), 21 had a definite, 11 a probable and seven a possible thrombosis (total 39 or 30.7% of adverse events). If this incidence of stent thrombosis could be reduced significantly, as a result of better stent implantation, less thrombogenic devices, and more effective antithrombotic therapy, up to 30% of the adverse events could potentially be prevented. In the early days of bare metal stenting, more than a decade ago, we suggested that bare metal stenting could reduce the impact of restenosis in angioplasty if the early phenomenon of subacute thrombosis could be adequately controlled. [30]

Limitations

First, a five year time lag exists between the groups that are being compared. Both PCI and CABG have improved with time. Second, this study is non-randomised and thus the groups are not directly comparable, precluding a formal non-inferiority comparison. Furthermore, statistical adjustment was required to correct for the differences versus the historical control group. Thirdly, while the protocol required that the lesions in ARTS-II be potentially treatable by CABG, the absence of dialogue with the surgeons prior to intervention may have caused a selection bias. However, this is not obvious considering that patients actually enrolled in ARTS-II were more complex than those enrolled in ARTS-I. Finally, the incidence and impact of stent thrombosis was not re-adjudicated according to the ARC definitions in the ARTS-I study preventing the authors to compare the results of ARTS-II to the historical PCI arm of ARTS-I.

Conclusion

At three years there was no significant difference in the incidence of the irreversible hard clinical endpoints of death, CVA and MI between the ARTS-II cohort and the ARTS-I PCI and CABG cohorts. Although CABG remained more effective in reducing the need for repeat revascularisation as compared to both PCI cohorts, the significant improvement in the reintervention rates in the ARTS-II SES cohort as compared to the bare metal ARTS-I PCI cohort resulted in a comparable MACCE rate in the ARTS-II and ARTS-I CABG cohorts at three years.

Addendum

In this study, one patient had a probable and definite stent thrombosis triggered on two consecutive days. It is clear that they may reflect the same event. As the current ARC definition does not indicate how these triggers should be reported we counted them as two separate events.

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Chapter 27

Impact of body mass index on the one-year clinical outcome of patients undergoing multivessel revascularization with sirolimus-eluting stents (from the Arterial Revascularization Therapies Study Part II)

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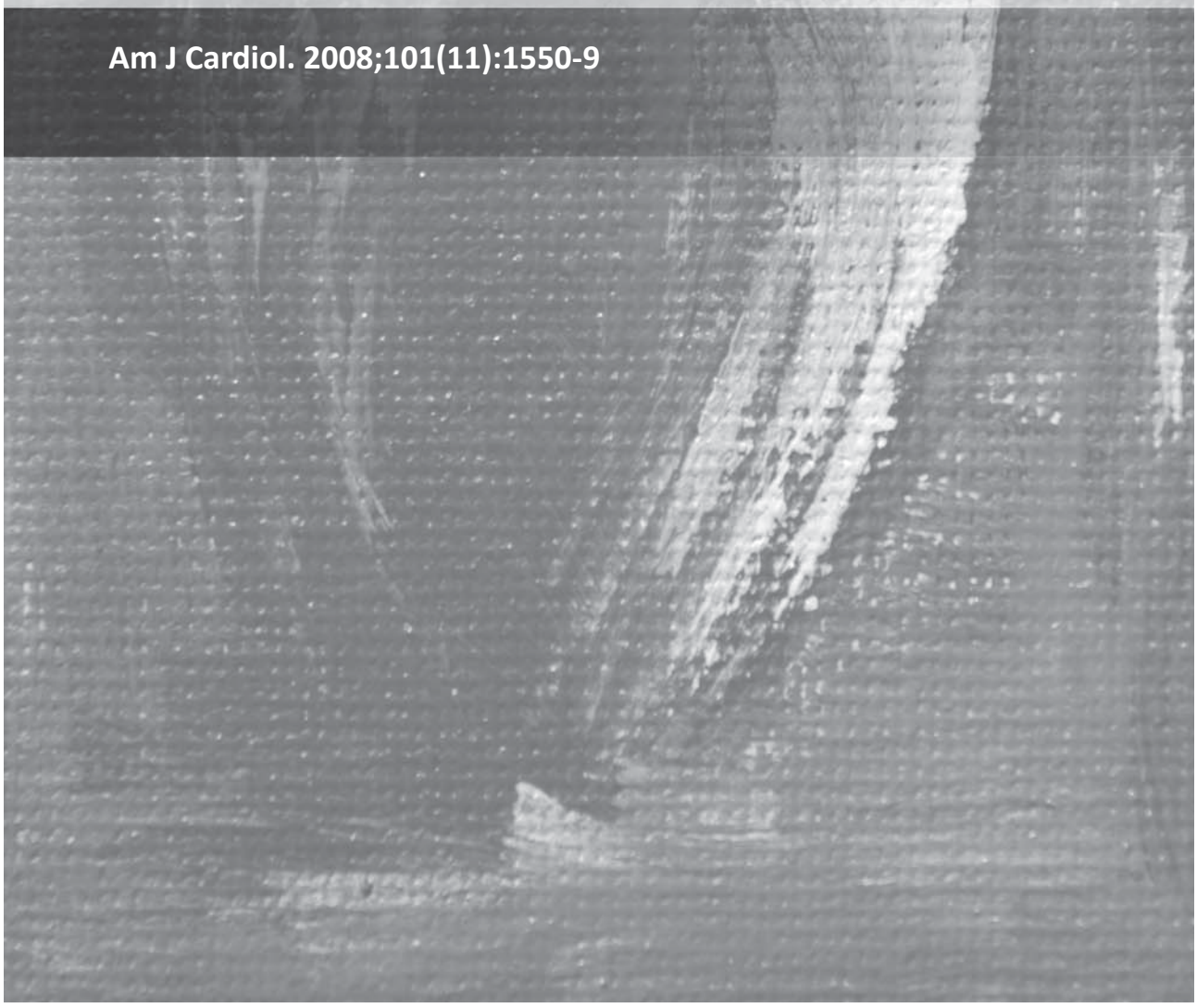

Impact of Body Mass Index on the One-Year Clinical Outcome of Patients Undergoing Multivessel Revascularization With *Sirolimus*-Eluting Stents (from the Arterial Revascularization Therapies Study Part II)†

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The differential safety and efficacy profiles of sirolimus-eluting stents when implanted in patients with multivessel coronary artery disease who have increased body mass indexes (BMIs) compared with those with normal BMIs are largely unknown. This study evaluated the impact of BMI on 1-year outcomes in patients with multivessel coronary artery disease treated with sirolimus-eluting stents as part of the Arterial Revascularization Therapies Study Part II (ARTS II). From February to November 2003, 607 patients were included at 45 centers; 176 patients had normal BMIs (<25 kg/m^2), 289 were overweight (≥25 and ≤30 kg/m^2), and 142 were obese (>30 kg/m^2). At 30 days, the cumulative incidence of the primary combined end point of death, myocardial infarction, cerebrovascular accident, and repeat revascularization (major adverse cardiac and cerebrovascular events) was 3.4% in the group with normal BMIs, 3.1% in overweight patients, and 2.8% in obese patients (p = 0.76). At 1 year, the cumulative incidence of major adverse cardiac and cerebrovascular events was 10.8%, 11.8%, and 7.0% in the normal BMI, overweight, and obese groups, respectively (p = 0.31). In conclusion, BMI had no impact on 1-year clinical outcomes in patients with multivessel coronary artery disease treated with sirolimus-eluting stents in ARTS II. **(Am J Cardiol 2008;101:1550–1559)**

The Arterial Revascularization Therapies Study Part II (ARTS II) is a multicenter, European, open-label, nonrandomized trial evaluating the safety and efficacy of sirolimus-eluting stents (SES) in patients with multivessel coronary artery disease in comparison with the randomized ARTS I trial.[1] In the overall population, ARTS II has shown a similar rate of major adverse cardiac and cerebrovascular events (MACCEs) in patients treated with SES compared with the surgical cohort of ARTS I.[2]

At present, overweight and obese individuals constitute most of the population in industrialized countries. In the United States, ≥64.5% of the population is classified as overweight, of whom 30.5% are obese.[3] Accordingly, this is a study population of particular interest. The preferred method of coronary revascularization for these patients proved to be controversial. A subgroup analysis of the ARTS I trial showed that patients treated with coronary artery bypass grafting (CABG) had significantly lower MACCE rates compared with those treated with bare-metal stents.[4] Furthermore, among patients who had been randomized to surgery, those with normal body mass indexes (BMIs) had worse outcomes than overweight or obese patients, whereas BMI did not influence the overall outcomes in patients randomized to stent implantation. This finding was confirmed in the Bypass Angioplasty Revascularization Investigation (BARI) trial and registry. However, unlike in ARTS I, an increased BMI was associated with worse long-term outcomes in patients who underwent CABG.[5]

In the present analysis, we evaluated the impact of BMI on 1-year outcomes after multivessel SES implantation in the 607 patients enrolled in ARTS II. Another objective of this analysis was to compare the overweight and obese patients in ARTS II with the respective cohorts in the 2 arms

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† Conflicts of interest: Magdaleen Pieters, Kristel Wittebols, and Hans-Peter Stoll are employees of Cordis Corporation. Joost Daemen received a consultancy fee for his scientific contribution.

Table 1
Baseline clinical characteristics of patients in the Arterial Revascularization Therapies Study Part II, stratified according to body mass index (n = 607)

Variable	BMI (kg/m^2)			p Value (Trend)
	<25 (n = 176)	25–30 (n = 289)	>30 (n = 142)	
Age (yrs)	64.2 ± 10.1 (35–80)	62.9 ± 9.3 (37–80)	61.1 ± 9.6 (36–80)	0.004
Ejection fraction (%)	59.8 ± 11.6 (35–85)	60.2 ± 11.6 (30–97)	60.4 ± 11.6 (30–88)	0.66
BMI (kg/m^2)	23.2 ± 1.6 (15–25)	27.3 ± 1.4 (25–30)	33.3 ± 2.8 (30–43)	<0.001
Men	76.1% (134/176)	84.4% (244/289)	61.3% (87/142)	0.005
Diabetes mellitus	19.9% (35/176)	22.5% (65/289)	41.5% (59/142)	<0.001
Insulin-dependent diabetics	4.5% (8/176)	2.8% (8/289)	8.5% (12/142)	0.14
Hypertension	57.4% (101/176)	70.2% (203/289)	73.2% (104/142)	0.002
Hypercholesterolemia (total cholesterol >250 mg/dl)	70.9% (124/175)	72.7% (210/289)	80.1% (113/141)	0.07
History of cerebrovascular accident	1.1% (2/176)	0.7% (2/289)	0.7% (1/141)	0.66
Family history of MI/sudden death aged <55 yrs	34.3% (60/175)	33.2% (96/289)	43.6% (61/140)	0.11
Peripheral vascular disease	11.4% (20/176)	6.6% (19/289)	2.1% (3/141)	0.001
Previous MI	37.5% (66/176)	33.2% (96/289)	33.1% (47/142)	0.39
Previous CABG	0.0% (0/176)	0.0% (0/289)	0.0% (0/142)	
Previous percutaneous coronary intervention	0.6% (1/176)	0.7% (2/289)	0.0% (0/142)	0.50
Carotid surgery	1.1% (2/176)	1.4% (4/289)	1.4% (2/141)	0.82
Chronic obstructive pulmonary disease	4.5% (8/176)	3.5% (10/289)	2.8% (4/141)	0.41
Smokers				
Previous	38.6% (68/176)	45.7% (132/289)	33.8% (48/142)	0.48
Current	22.2% (39/176)	20.1% (58/289)	14.1% (20/142)	0.08
Unstable angina pectoris	43.2% (76/176)	34.3% (99/289)	32.4% (46/142)	0.039
Stable angina pectoris	46.6% (82/176)	56.1% (162/289)	55.6% (79/142)	0.09
Silent ischemia	10.2% (18/176)	9.7% (28/289)	12.0% (17/142)	0.64
No. of narrowed coronary arteries				
1	0.0% (0/176)	0.3% (1/289)	0.7% (1/142)	0.28
2	48.3% (85/176)	43.6% (126/289)	48.6% (69/142)	0.97
3	51.7% (91/176)	56.1% (162/289)	50.7% (72/142)	0.93
Glycoprotein IIb/IIIa inhibitors	29.5% (52/176)	32.5% (94/289)	35.9% (51/142)	0.23

Data are expressed as mean ± SD (range) or as percentages.

of ARTS I, investigating treatment with CABG versus bare-metal stents.

Methods

ARTS II is a multicenter, nonrandomized, open-label trial designed to compare the safety and efficacy of SES in patients with de novo multivessel coronary artery disease, with the surgical group of ARTS I as a historical control group.[2,6] To obtain a population comparable with that of ARTS I, patients were stratified by clinical site to ensure the inclusion of ≥1/3 of patients with 3-vessel disease.

Patients were eligible for coronary revascularization if they had stable angina, unstable angina, or silent ischemia and ≥2 de novo lesions amenable to stent implantation that were located in different major epicardial vessels and/or their side branches. Patients were required to have multivessel coronary artery disease with the need for treatment of the left anterior descending artery and ≥1 other significant lesion (>50% diameter stenosis) in another major epicardial coronary artery. One totally occluded major epicardial vessel could be included. The lesion had to be amenable to stenting using a stent with a diameter of 2.5 to 3.5 mm and a length of 13 to 33 mm, without any restriction on the total stent length implanted. Patients with any previous coronary intervention, left main coronary disease, overt congestive heart failure, or left ventricular ejection fractions <30% were excluded. Additional exclusion criteria were a history of any cerebrovascular accident or ST elevation myocardial infarction (MI) in the preceding week, with persisting elevation of creatine kinase. The parameters needed to calculate BMI (weight and height) were documented, and written informed consent was obtained from each patient before enrolment. The study was approved by the ethics committee of each participating site. All interventions were performed according to current standard practice guidelines, and the final interventional strategy, including the use of glycoprotein IIb/IIIa inhibitors, was left entirely to the discretion of the operator, except for stent use. All patients were advised to maintain aspirin lifelong. Clopidogrel 300 mg as a loading dose, or ticlopidine 500 mg, was to be started ≥24 hours before the procedure. Postprocedural clopidogrel 75 mg/day or ticlopidine 250 mg twice daily was recommended for ≥2 months after revascularization.

The primary objective of this ARTS II post hoc subanalysis was to compare the safety and effectiveness of coronary stent implantation using SES in normal-weight, overweight, and obese patients. The primary outcome measure was the incidence of the combined end point MACCEs at 1 year, comprising all-cause death, any cerebrovascular event, nonfatal MI, or any repeat revascularization (contemporary comparison).

The secondary objective of this study was to compare the 1-year MACCE rate in ARTS II patients, stratified accord-

Table 2
Angiographic and procedural characteristics of patients in the Arterial Revascularization Therapies Study Part II stratified according to body mass index (n = 607 patients, n = 2,160 lesions)

Variable	BMI (kg/m^2)			p Value (Trend)
	<25 (176 patients/625 lesions)	25–30 (289 patients/1,040 lesions)	>30 (142 patients/495 lesions)	
No. of stents implanted	3.7 ± 1.4 (1–8)	3.7 ± 1.6 (1–11)	3.7 ± 1.4 (2–10)	0.93
Average stent length (mm)	19.3 ± 3.4 (11–28)	19.6 ± 3.7 (12–31)	19.7 ± 3.2 (13–30)	0.42
Total stent length (mm)	71.7 ± 30.2 (26–179)	72.9 ± 33.7 (12–253)	72.6 ± 31.3 (26–175)	0.77
Maximum dilatation pressure (atm)	16.2 ± 3.0 (8–25)	16.4 ± 2.7 (9–26)	16.6 ± 3.0 (10–24)	0.23
Days in hospital since procedure	3.3 ± 2.0 (1–18)	3.5 ± 3.1 (1–31)	3.4 ± 2.4 (1–13)	0.72
Duration of procedure (min)	84.0 ± 41.6 (16–214)	84.7 ± 42.9 (10–293)	87.4 ± 46.0 (25–252)	0.50
No. of lesions >50% DS	3.6 ± 1.3 (2–7)	3.6 ± 1.2 (2–8)	3.5 ± 1.4 (1–8)	0.69
No. of vessels with lesions >50% DS	2.5 ± 0.5 (2–3)	2.6 ± 0.5 (1–3)	2.5 ± 0.5 (1–3)	0.83
No. of treated lesions: stented lesions	3.2 ± 1.2 (1–7)	3.2 ± 1.1 (0–7)	3.2 ± 1.1 (0–8)	0.99
Coronary artery narrowed				
Right	29.8% (186/625)	28.2% (293/1,040)	30.1% (149/495)	0.96
Left main	0.0% (0/625)	0.0% (0/1,040)	0.0% (0/495)	
Left anterior descending	42.4% (265/625)	41.0% (426/1,040)	41.6% (206/495)	0.76
Left circumflex	27.8% (174/625)	30.9% (321/1,040)	28.3% (140/495)	0.78
Lesion length: diffuse >20 mm	12.6% (75/597)	11.0% (110/998)	12.7% (60/471)	1.00
Reference diameter ≥2.5 mm	91.5% (572/625)	91.0% (946/1,040)	89.5% (443/495)	0.26
Readily accessible segment	96.0% (572/596)	95.3% (948/995)	94.7% (446/471)	0.32
Ostial lesion	4.9% (29/597)	4.6% (46/997)	3.0% (14/471)	0.15
Calcification: moderate to heavy	36.2% (216/596)	28.1% (280/997)	31.3% (147/470)	0.049
Thrombus present	0.3% (2/607)	0.7% (7/1,010)	0.4% (2/482)	0.78
Total occlusion	2.7% (17/619)	2.3% (24/1,030)	2.4% (12/490)	0.73
Bifurcation requiring double guidewire	33.4% (199/596)	32.2% (321/998)	38.4% (181/471)	0.11
Type B2/C lesion	69.8% (432/619)	68.8% (709/1,030)	71.8% (352/490)	0.51

Data are expressed as mean ± SD (range) or as percentages.
DS = diameter stenosis.

ing to BMI (normal, overweight, or obese) with that of patients with similar BMI classifications who were randomized to either coronary stent implantation using bare-metal stents or CABG in the ARTS I trial (historical comparison). However, much weight cannot be given to this analysis, given differences in treatment protocols and evolution in the procedures for percutaneous coronary intervention and CABG.

The National Heart, Lung, and Blood Institute and the World Health Organization have introduced a weight classification for BMI that is calculated by dividing a patient's weight in kilograms by the patient's height in meters squared. According to this classification, a BMI of 18.5 to 24.9 kg/m^2 is considered normal, a BMI of 25 to 30 kg/m^2 is considered to represent overweight, and a BMI >30 kg/m^2 is considered to represent obesity.[7,8] Clinical and angiographic data were analyzed and adjudicated by an independent core laboratory (Cardialysis, Rotterdam, The Netherlands) and a clinical-events committee.

All-cause death was reported, and CVAs included strokes, transient ischemic attacks, and reversible ischemic neurologic deficits. In the first 7 days after the intervention, a definite diagnosis of MI was made if there was documentation of new abnormal Q waves (according to the Minnesota code) and either a ratio of serum creatine kinase-MB to total cardiac enzyme >0.1 or a creatine kinase-MB value >5 times the upper limit of normal.[1,2,9] Serum creatine kinase and creatine kinase-MB concentrations were measured 6, 12, and 18 hours after the intervention. Beginning 8 days after the intervention (the average length of hospitalization after surgery), either abnormal Q waves or enzymatic changes were sufficient for a diagnosis of MI. This 2-part method of defining MI was developed for ARTS I to address the difficulty of diagnosing MI after surgery. All repeat revascularization procedures were recorded. Events were counted from the time of the initial procedure. Thrombotic occlusions were defined by either angiographic documentation of a complete occlusion (Thrombolysis In Myocardial Infarction [TIMI] flow grade 0 or 1) or angiographic documentation of a flow-limiting thrombus (TIMI flow grade 1 or 2).

Continuous variables were compared using Student's unpaired *t* test and are expressed as mean ± SD. Categorical variables were compared using the chi-square test and are expressed as percentages. Comparisons among the 3 groups were performed using a general linear model. On the basis of a selection criterion of $p < 0.1$ when used in a univariate post hoc analysis, the following baseline and procedural variables were selected for inclusion in the multivariate model: gender, current smoking, family history, previous MI, peripheral vascular disease, diabetes mellitus, hypercholesterolemia, hypertension, unstable angina, days to procedure, number of lesions with diameter stenosis >50%, duration of procedure, number of type C lesions, number of lesions with <100% occlusion, and number of lesions with moderate to heavy calcification. For medical and statistical reasons, it was decided to include age and the left ventricular ejection fraction as binary variables, using their medi-

Table 3
Baseline characteristics of patients in the Arterial Revascularization Therapies Study Part II (n = 607) versus patients in the Arterial Revascularization Therapies Study Part I who underwent coronary artery bypass surgery (n = 604) and patients in the Arterial Revascularization Therapies Study Part I who received bare-metal stents (n = 599) (total n = 1,810)

Variable	BMI (kg/m^2)											
	<25				25–30				>30			
	ARTS II (n = 176)	ARTS I (BMS) (n = 168)	ARTS I (CABG) (n = 169)	p Value	ARTS II (n = 289)	ARTS I (BMS) (n = 307)	ARTS I (CABG) (n = 299)	p Value	ARTS II (n = 142)	ARTS I (BMS) (n = 124)	ARTS I (CABG) (n = 136)	p Value
Male gender	76.1%	70.8%	77.5%	0.33	84.4%	83.7%	76.9%	0.037	61.3%	69.4%	72.1%	0.1362
Age (yrs)	64.2 ± 10.1	61.1 ± 10.0	62.6 ± 9.7	0.016	62.9 ± 9.3	60.7 ± 9.5	61.4 ± 9.1	0.017	61.1 ± 9.6	59.8 ± 9.6	59.3 ± 9.2	0.27
Ejection fraction (%)	59.8 ± 11.6	61.3 ± 12.0	59.9 ± 13.0	0.49	60.2 ± 11.6	60.2 ± 12.3	59.8 ± 13.2	0.89	60.4 ± 11.6	62.1 ± 12.6	62.2 ± 13.6	0.47
BMI (kg/m^2)	23.2 ± 1.6	23.1 ± 1.6	23.3 ± 1.5	0.51	27.3 ± 1.4	27.2 ± 1.3	27.3 ± 1.4	0.63	33.3 ± 2.8	32.7 ± 2.4	32.5 ± 2.3	0.016
Diabetes mellitus	19.9%	8.9%	14.2%	0.015	22.5%	19.5%	15.7%	0.011	41.5%	29.8%	17.6%	<0.0001
Insulin dependent	22.9%	6.7%	25.0%	0.06	12.3%	18.3%	12.8%	0.50	20.3%	29.7%	16.7%	0.08
Hypertension	57.4%	37.5%	37.3%	<0.0001	70.2%	45.0%	44.5%	<0.0001	73.2%	53.2%	55.1%	<0.0001
Hypercholesterolemia	70.9%	52.4%	52.7%	0.0003	72.7%	58.6%	59.9%	0.0004	80.1%	63.4%	59.3%	0.0003
History of cerebrovascular accident	1.1%	1.2%	1.8%	0.90	0.7%	1.0%	1.0%	1.00	0.7%	0%	0%	1.00
Family history of MI/sudden death aged <55 yrs	34.3%	39.3%	42.6%	0.28	33.2%	36.4%	42.6%	0.06	43.6%	46.3%	40.0%	0.59
Peripheral vascular disease	11.4%	6.5%	7.1%	0.23	6.6%	4.9%	5.4%	0.66	2.1%	5.6%	2.2%	0.22
Previous MI	37.5%	47.0%	42.6%	0.21	33.2%	45.6%	40.1%	0.008	33.1%	37.9%	45.6%	0.10
Previous percutaneous coronary intervention	0.6%	1.8%	2.4%	0.37	0.7%	2.0%	2.0%	0.34	0%	0%	2.9%	0.02
Carotid surgery	1.1%	0%	0.6%	0.78	1.4%	0.7%	1.7%	0.48	1.4%	0.8%	0%	0.53
Chronic obstructive pulmonary disease	4.5%	4.2%	5.9%	0.76	3.5%	5.5%	5.4%	0.43	2.8%	4.8%	2.2%	0.53
Current smoking	22.2%	36.9%	26.6%	0.009	20.1%	24.5%	24.1%	0.36	14.1%	24.4%	28.7%	0.009
Clinical presentation												
Stable angina pectoris	46.6%	50.6%	55.0%	0.30	56.1%	56.4%	57.9%	0.89	55.6%	63.7%	61.8%	0.67
Unstable angina pectoris	43.2%	44.0%	39.6%	0.69	34.3%	37.8%	37.1%	0.64	32.4%	29.0%	34.6%	0.64
Silent ischemia	10.2%	5.4%	5.3%	0.14	9.7%	5.9%	5.0%	0.07	12.0%	7.3%	3.7%	0.032
No. of narrowed coronary arteries												
1	0%	3.7%	5.4%	0.003	0.3%	4.0%	3.4%	0.005	0.7%	4.2%	2.2%	0.16
2	48.3%	66.5%	67.5%	0.0003	43.6%	70.9%	66.3%	<0.0001	48.6%	65.3%	64.9%	0.007
3	51.7%	29.8%	27.1%	<0.0001	56.1%	25.2%	30.2%	<0.0001	50.7%	30.5%	32.8%	0.001

Data are expressed as mean ± SD or as percentages.

Table 4
Thirty-day clinical outcomes of patients in the Arterial Revascularization Therapies Study Part II stratified according to body mass index (n = 607)

Complication	BMI (kg/m^2)			P Value (Trend)
	<25 (n = 176)	25–30 (n = 289)	>30 (n = 142)	
Hierarchical complications				
MACCEs	3.4% (6/176)	3.1% (9/289)	2.8% (4/142)	0.76
Death	0.0% (0/176)	0.0% (0/289)	0.0% (0/142)	
Cerebrovascular accident without death	0.6% (1/176)	0.0% (0/289)	0.0% (0/142)	
MI without death or cerebrovascular accident	2.3% (4/176)	0.0% (0/289)	0.7% (1/142)	
Q-wave MI	2.3% (4/176)	0.0% (0/289)	0.7% (1/142)	
Non-Q-wave MI	0.0% (0/176)	0.0% (0/289)	0.0% (0/142)	
Revascularization without death or cerebrovascular accident or MI	0.6% (1/176)	3.1% (9/289)	2.1% (3/142)	
CABG without death or cerebrovascular accident or MI	0.0% (0/176)	1.7% (5/289)	1.4% (2/142)	
Repeat percutaneous coronary intervention without death or cerebrovascular accident or MI or CABG	0.6% (1/176)	1.4% (4/289)	0.7% (1/142)	
Free of MACCEs	96.6% (170/176)	96.9% (280/289)	97.2% (138/142)	0.76
Nonhierarchical complications				
Death/cerebrovascular accident/MI	2.8% (5/176)	0.0% (0/289)	0.7% (1/142)	0.037
Death	0.0% (0/176)	0.0% (0/289)	0.0% (0/142)	
Cerebrovascular accident	0.6% (1/176)	0.0% (0/289)	0.0% (0/142)	0.19
MI	2.3% (4/176)	0.0% (0/289)	0.7% (1/142)	0.09
Q-wave MI	2.3% (4/176)	0.0% (0/289)	0.7% (1/142)	0.09
Non-Q-wave MI	0.0% (0/176)	0.0% (0/289)	0.0% (0/142)	
Revascularization	1.7% (3/176)	3.1% (9/289)	2.1% (3/142)	0.76
CABG	0.6% (1/176)	1.7% (5/289)	1.4% (2/142)	0.48
Repeat percutaneous coronary intervention	1.1% (2/176)	1.4% (4/289)	0.7% (1/142)	0.75
Subacute occlusion	1.1% (2/176)	0.7% (2/289)	0.7% (1/142)	0.65

Table 5
One-year clinical outcomes of patients in the Arterial Revascularization Therapies Study Part II stratified according to body mass index (n = 607)

Complication	BMI (kg/m^2)			p Value (Trend)
	<25 (n = 176)	25–30 (n = 289)	>30 (n = 142)	
Hierarchical complications				
MACCEs	10.8% (19/176)	11.8% (34/289)	7.0% (10/142)	0.31
Death	1.1% (2/176)	0.7% (2/289)	1.4% (2/142)	
Cerebrovascular accident without death	2.3% (4/176)	0.3% (1/289)	0.0% (0/142)	
MI without death or cerebrovascular accident	2.3% (4/176)	0.7% (2/289)	0.7% (1/142)	
Q-wave MI	2.3% (4/176)	0.0% (0/289)	0.7% (1/142)	
Non-Q-wave MI	0.0% (0/176)	0.7% (2/289)	0.0% (0/142)	
Revascularization without death or cerebrovascular accident or MI	5.1% (9/176)	10.0% (29/289)	4.9% (7/142)	
CABG without death or cerebrovascular accident or MI	0.6% (1/176)	3.1% (9/289)	1.4% (2/142)	
Repeat percutaneous coronary intervention without death or cerebrovascular accident or MI or CABG	4.5% (8/176)	6.9% (20/289)	3.5% (5/142)	
Free of MACCEs				
Nonhierarchical complications				
Death/cerebrovascular accident/MI	5.7% (10/176)	1.7% (5/289)	2.1% (3/142)	0.047
Death	1.1% (2/176)	0.7% (2/289)	1.4% (2/142)	0.85
Cerebrovascular accident	2.3% (4/176)	0.3% (1/289)	0.0% (0/142)	0.021
MI	2.8% (5/176)	0.7% (2/289)	0.7% (1/142)	0.08
Q-wave MI	2.3% (4/176)	0.0% (0/289)	0.7% (1/142)	0.09
Non-Q-wave MI	0.6% (1/176)	0.7% (2/289)	0.0% (0/142)	0.50
Revascularization	7.4% (13/176)	10.4% (30/289)	5.6% (8/142)	0.66
CABG	1.1% (2/176)	3.1% (9/289)	1.4% (2/142)	0.78
Repeat percutaneous coronary intervention	6.3% (11/176)	7.6% (22/289)	4.2% (6/142)	0.52
Subacute occlusion	0.6% (1/176)	0.0% (0/289)	0.7% (1/142)	0.91

ans as cutoff (age >63 years and ejection fraction ≤59). We analyzed 3 treatment combinations: ARTS II versus ARTS I CABG, ARTS II versus ARTS I bare-metal stents, and ARTS I bare-metal stents versus CABG. In each of these treatment groups, we tested for interactions between the model parameters and the BMI groups. Survival curves were generated using the Kaplan-Meier method, and survival among groups was compared using the log-rank test.

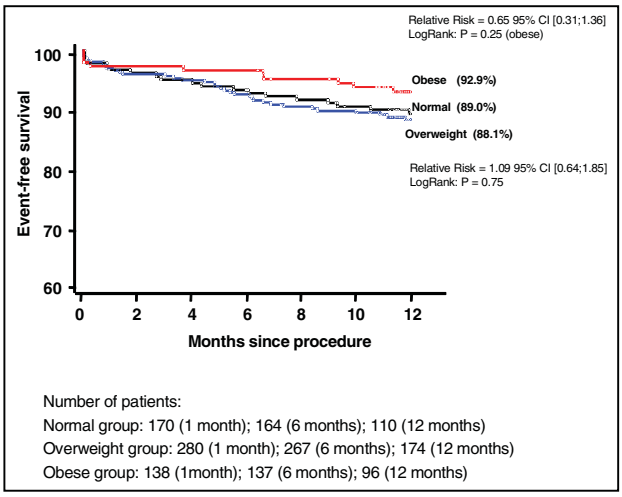

Figure 1. MACCE-free survival at 1 year for 607 patients treated with SES for multivessel coronary artery disease in ARTS II stratified according to BMI. CI = confidence interval.

Table 6
One-year clinical outcomes of patients in the Arterial Revascularization Therapies Study Part II (n = 607) versus patients in the Arterial Revascularization Therapies Study Part I who underwent coronary artery bypass surgery (n = 604) and patients in the Arterial Revascularization Therapies Study Part I who received bare-metal stents (n = 599) stratified according to body mass index (total n = 1,810)

Outcome	ARTS II	ARTS I (BMS)	RR (95% CI)	p Value	ARTS I (CABG)	RR (95% CI)	p Value
BMI <25 kg/m^2	n = 176	n = 168			n = 169		
MACCEs	11.0%	23.8%	0.45 (0.27–0.75)	0.001	15.6%	0.69 (0.40–1.20)	0.17
Death/cerebrovascular accident/MI	5.8%	7.7%	0.73 (0.33–1.63)	0.46	9.6%	0.59 (0.28–1.27)	0.17
Death	1.1%	1.8%	0.64 (0.11–3.76)	0.62	2.4%	0.47 (0.09–2.56)	0.37
Repeat revascularization	7.5%	18.6%	0.40 (0.22–0.74)	0.002	6.1%	1.23 (0.56–2.74)	0.60
BMI 25–30 kg/m^2	n = 289	n = 307			n = 299		
MACCEs	11.9%	28.3%	0.42 (0.29–0.60)	0.0001	12.1%	0.98 (0.63–1.51)	0.91
Death/cerebrovascular accident/MI	1.8%	10.4%	0.17 (0.07–0.42)	0.0001	8.0%	0.22 (0.08–0.56)	0.0005
Death	0.7%	2.9%	0.24 (0.05–1.08)	0.05	3.4%	0.21 (0.05–0.94)	0.03
Repeat revascularization	10.5%	22.8%	0.46 (0.31–0.69)	0.0001	4.7%	2.22 (1.20–4.09)	0.009
BMI >30 kg/m^2	n = 142	n = 119			n = 136		
MACCEs	7.1%	25.8%	0.27 (0.14–0.53)	0.0001	5.9%	1.19 (0.48–2.92)	0.72
Death/cerebrovascular accident/MI	2.2%	9.7%	0.22 (0.06–0.76)	0.008	5.9%	0.36 (0.10–1.32)	0.1
Death	1.5%	3.2%	0.44 (0.08–2.34)	0.32	1.5%	0.21 (0.14–6.65)	0.96
Repeat revascularization	5.7%	21.4%	0.27 (0.13–0.57)	0.0001	0.8%	7.61 (0.96–60.0)	0.03

Proportional-hazards and Weibull models were used to assess the risk reduction of adverse events. Probability was significant at a p level of <0.05. All statistical tests were 2 tailed. Statistical analysis was performed using SAS version 8.02 (SAS Institute Inc., Cary, North Carolina).

Results

From February 2003 to November 2003, 607 patients were included at 45 centers. A total of 176 patients had normal BMIs, 289 were overweight, and 142 were obese. Table 1 lists the patients' baseline demographic and clinical characteristics on the basis of their BMIs. No significant differences in angiographic and procedural characteristics were noted between the groups (Table 2). All baseline characteristics of patients in ARTS II compared with ARTS I according to BMI are listed in Table 3.

No deaths occurred in the first 30 days. There were no significant differences among patients with normal BMIs, overweight, and obesity regarding the cumulative incidence of MACCEs during the first 30 days (3.4% in patients with normal BMIs, 3.1% in overweight patients, and 2.8% in obese patients, p = 0.76). The power to detect a relative difference of 25% at 30 days was 10%. The itemized outcomes of MACCEs are listed in Table 4. A total of 5

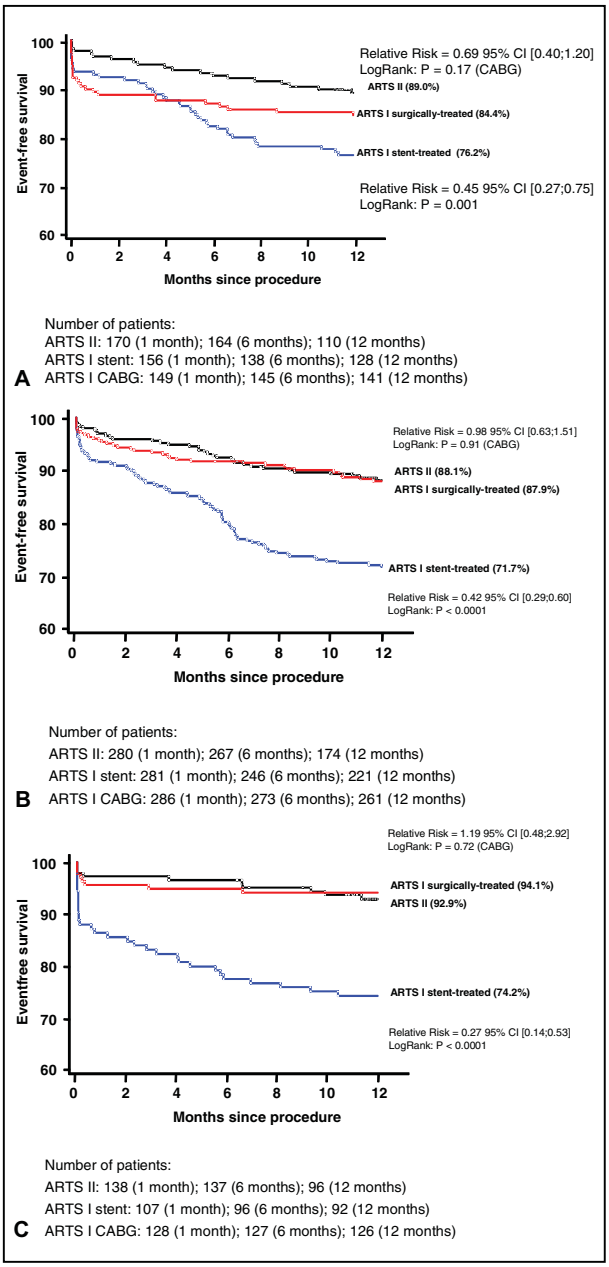

Figure 2. MACCE-free survival at 1 year for ARTS II patients compared with ARTS I CABG and bare-metal stent (BMS) patients: *(A)* patients with normal BMIs, *(B)* overweight patients, and *(C)* obese patients. CI = confidence interval.

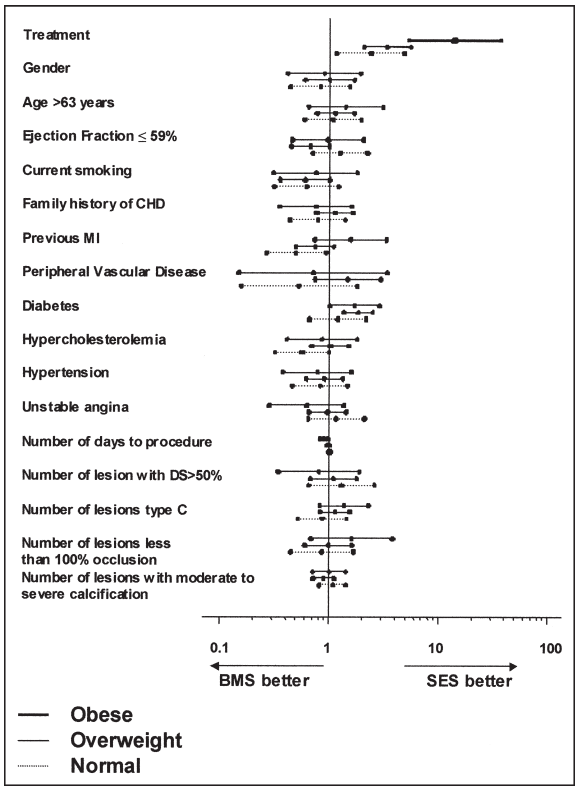

Figure 3. Heterogeneity of the treatment effect among the 3 BMI groups.

angiographically documented subacute (≥24 hours to 30 days) thrombotic occlusions were reported: 2 in the normal and overweight groups and 1 in the obese group (p = 0.65).

Clinical outcomes at 1 year are listed in Table 5. At 1 year, the incidence of MACCEs was similar in the 3 BMI groups (10.8%, 11.8%, and 7.0% in the normal, overweight, and obese groups, respectively, p = 0.31; Figure 1). The power to detect a relative difference of 45% at 1 year was 85%. Normal-weight patients were at significantly higher risk for the combined endpoint of death or cerebrovascular accident and MI compared with overweight and obese patients (5.7% vs 1.7% and 2.1%, respectively).

The outcome of each treatment arm in the 3 BMI groups is listed in Table 6 and shown in Figure 2. Compared with the ARTS I bare-metal stent patients, ARTS II patients were at significantly lower risk for MACCEs, irrespective of their BMIs. It was notable that overweight and obese patients from ARTS II were at significantly lower risk for death or cerebrovascular accident and MI than ARTS I bare-metal stent patients. The incidence of repeat revascularization was significantly lower in ARTS II patients compared with ARTS I bare-metal stent patients, a finding that was consistent among the 3 BMI groups. Compared with ARTS I CABG patients, conversely, the incidence of repeat revascularization was significantly higher in ARTS II, a finding that was mainly apparent in overweight and obese patients. In the patients with normal BMIs, the difference in repeat revascularization between ARTS II and ARTS I CABG patients did not reach a statistically significant level.

After adjusting for covariates as reported in "Methods," no statistically significant interactions between the model parameters and BMI could be detected (results of the overall likelihood-ratio tests for interaction in BMI groups: ARTS II vs ARTS I bare-metal stent p = 0.083, ARTS II vs ARTS I CABG p = 0.71). However, when examining ARTS II versus ARTS I bare-metal stent in greater detail (Figure 3), we found that the confidence intervals of treatment in the normal BMI group and the obese group were completely disjunctive. Together with a clear trend in hazard ratio over

the 3 BMI groups, an interaction between treatment and BMI group in this population is very likely.

Discussion

Several reports have suggested that patients with increased BMIs, when treated using mechanical revascularization for atherosclerotic coronary artery disease, may have different outcomes than patients with normal BMIs.[1,5,10–12] The results of these studies are mixed, however, so that no solid conclusion can be drawn with respect to the better method of revascularization for such patients. Furthermore, only very few data exist regarding the outcomes of these patients after drug-eluting stent implantation. Because the distribution of Western populations has become almost equally scattered across the different BMI classes,[3] and drug-eluting stent treatment is the most frequently applied coronary revascularization procedure, it seems more important than ever to investigate such a relation. The main finding of this analysis is that the safety and effectiveness of multivessel treatment using SES previously reported for the overall population of ARTS II at 1 year are consistent across all BMI classes. This is in concordance with ARTS I results, in which BMI did not influence long-term outcomes after multivessel percutaneous coronary intervention using bare-metal stents.[4] A subgroup analysis from TAXUS IV showed that obesity was an important risk factor for restenosis and major adverse cardiac events in patients who received bare-metal stents, whereas paclitaxel-eluting stents attenuated this increased risk so that the prognosis at 9 months was independent of body weight in these patients.[13]

Acute and late outcomes after stent treatment are greatly dependent on adequate clopidogrel therapy; this is particularly true for drug-eluting stents.[14] Ex vivo platelet aggregometry data from 2 reports[15,16] have postulated a weight adjustment of the dose of clopidogrel for percutaneous coronary intervention, with the need for higher doses in overweight and obese patients. In contrast, clinical data from >2,000 percutaneous coronary intervention patients from the Clopidogrel for Reduction of Events During Observation (CREDO) study showed that increasing BMI was associated with better efficacy and bleeding outcomes at 1 year, with the standard dose of clopidogrel given in this study.[17] Diabetes mellitus and its precursor, insulin resistance, have been repeatedly shown to be predictors of adverse events after coronary artery revascularizations.[18–22] This was also true for SES, revealing diabetes as a negative predictor of angiographic restenosis[23] and associated with higher late mortality after such treatment.[24] Manifest diabetes, undiagnosed diabetes, and insulin resistance are more common in patients with increased BMIs.[25] However, our results suggest that these considerations are probably not of clinical relevance.

Although the reduction in MACCEs in ARTS II compared with ARTS I was consistent among the 3 BMI groups, heterogeneity in the treatment effect could not be completely excluded. A clear trend was observed in a greater benefit from SES compared with bare-metal stents with increasing BMI. Compared with the ARTS I CABG cohort, SES-treated patients from ARTS II when stratified according to BMI had equivalent 1-year MACCE rates. This is in contrast to the overweight and obese patients treated with bare-metal stents from ARTS I, who had lower MACCE-free survival compared with their surgically treated counterparts, mainly because of a higher need for repeat revascularization. A final remarkable finding of this study was that overweight and obese patients from ARTS II were at significantly lower risk for the combined end point of death or cerebrovascular accident and MI compared with their counterparts in the ARTS I bare-metal stent cohort.

The obesity paradox previously described for percutaneous coronary intervention,[10,11] acute coronary syndromes,[26,27] clopidogrel safety and efficacy,[17] and CABG[4] was not observed for multivessel SES treatment in our series, with similar MACCE rates for increased BMI as for normal BMI at 1 year. However, it should be noted that the number of patients in each group was relatively small, resulting in a small number of adverse events. By its retrospective design, the present study may have suffered from a lack of power to detect statistically significant differences among the groups. Larger randomized controlled trials are needed to validate our findings. The trend toward a higher safety profile of SES use compared with CABG in overweight patients should be seen as hypothesis generating and should be confirmed by larger scale randomized controlled trials.

ARTS II should be regarded as an intermediate step before the fulfillment of the next era of randomized trials of drug-eluting stent percutaneous coronary intervention versus CABG. When ARTS II was designed, the decision was taken to use a historical control (ARTS I) to assess the improvement in clinical outcomes when SES are implanted. This decision precludes the possibility of adjusting for unmeasured confounders between the 2 groups of individuals and entails the need to use previous definitions of primary end points or patient classification. In this study, the antiplatelet regimen was different from that in ARTS I because of the recommended clopidogrel loading dose administered 24 hours before the intervention. This may have contributed, among other confounders, to the more favorable outcome of ARTS II compared with the ARTS I bare-metal stent arm. No data were available on the glycemic control of patients with diabetes in ARTS II and ARTS I. It is unknown whether this lack of information may have affected the differences among the groups. Furthermore, it must be noted that differences in MACCEs between treatments, even when broken down by BMI group, may have originated from other (possibly unknown) factors not listed here.

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Chapter 28

Three year follow up of the ARTS II Trial: Multivessel coronary revascularization in patients with and without diabetes

Daemen J, Kuck KH, Macaya C, LeGrand V, Vrolix M, Carrie D, Sheiban I, Suttorp MJ, Vranckx P, Rademaker T, Goedhart D, Schuijer M, Wittebols K, Macours N, Stoll HP, Serruys PW; on behalf of the ARTS II Investigators

J Am Coll Cardiol; in press

Three Year Follow Up of the ARTS II Trial: Multivessel Coronary Revascularization in Patients With and Without Diabetes

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J Am Coll Cardiol: in press

Objectives: To assess the 3-year relative safety and effectiveness of coronary artery bypass graft surgery (CABG) and percutaneous coronary intervention (PCI) using sirolimus-eluting stents (SES) in patients with and without diabetes with multivessel coronary artery disease.

Methods: The Arterial Revascularization Therapies Study part-II (ARTS-II) is a 45-center single-arm study (n=607) including 159 diabetics treated with SES, whose 3-year clinical outcome was compared to the historical diabetic and non-diabetic arms of the randomized ARTS-I trial (n= 1205; including 96 diabetic patients in the CABG-arm and 112 in the PCI-arm).

Results: At 3 years, in non-diabetics, the incidence of the primary composite of death, CVA, myocardial infarction (MI) and repeat revascularization (MACCE), was significantly lower in ARTS-II than in ARTS-I PCI (adjusted OR 0.41, 95% CI 0.26-0.64) and similar to ARTS-I CABG (adjusted OR 0.83, 95% CI 0.56-1.23). Additionally, ARTS-II patients were at significantly lower risk for death/CVA/MI as compared to both ARTS-I PCI (adjusted OR 0.55, 95% CI 0.34-0.91) and ARTS-I CABG (adjusted OR 0.56, 95% CI 0.35-0.92). In diabetics, the incidence of MACCE in ARTS-II was similar to both the ARTS-I PCI arm (adjusted OR 0.72, 95% CI 0.37-1.37) and ARTS-I CABG arm (adjusted OR 1.08, 95% 0.41-2.84). Conversely, the incidence of death/CVA/MI, was significantly lower in ARTS-II than in ARTS-I PCI (adjusted OR 0.67, 95% CI 0.27-1.65) and similar to ARTS-I CABG (adjusted OR 0.67, 95% CI 0.29-1.57).

Conclusion: At 3 years, PCI using SES for patients with multivessel coronary artery disease seems to be safer and more efficacious than PCI using bare metal stents, irrespective of the diabetic status of the patient. PCI using SES appears to be a valuable alternative to CABG for both diabetic and non-diabetic patients. The results of dedicated large-scale randomized trials will help to further validate our findings.

INTRODUCTION

The optimal method of revascularization for diabetic patients with concomitant multivessel coronary artery disease remains in dispute. While several randomized controlled trials have demonstrated a similar safety profile for percutaneous coronary intervention (PCI and Coronary Artery Bypass graft (CABG) surgery up to 5 years, CABG was associated with a significantly lower risk for repeat revascularizations as compared to PCI with bare metal stents (BMS), a benefit that proved to be most apparent in diabetic patients.(1-6)

However, when drug-eluting stents (DES) were shown to significantly reduce the need for repeat revascularizations, interventionalists quickly added DES treatment arms to the pivotal randomized PCI vs. CABG trials.(7,8) As a result, the 1-year results of the Arterial Revascularization Therapies Study (ARTS-II) and the Argentine randomized trial of coronary angioplasty with stenting versus coronary bypass surgery in patients with multiple vessel disease (ERACI-III) studies suggested that PCI using sirolimus-eluting stents (SES) was safe and effective and could be a viable alternative for the treatment of multivessel coronary artery disease.(7,8) Nevertheless, the higher susceptibility to repeat adverse cardiac events in diabetic patients makes extrapolation of these findings to this high-risk patient population uncertain. Diabetics are known to have an accelerated and more aggressive form of atherosclerosis with higher restenosis rates and less favourable long-term survival than non-diabetics.(9-12) Furthermore, diabetes has been a strong and consistent predictor of (late) stent thrombosis in patients treated with DES. This has raised some concerns about a potential

erosion of the initial treatment benefit due to the occurrence of stent thrombosis, a finding that only became apparent after multiple years of follow-up.(13-15)
The present study reports on the 3-year safety and effectiveness of the SES in diabetic patients with multivessel disease in ARTS-II compared to the outcomes of the historical results of the surgical and percutaneous arms of ARTS-I.

METHODS

ARTS-II STUDY DESIGN

ARTS-II is a multicenter, non-randomized, open label trial designed to compare the safety and efficacy of SES in patients with de novo multivessel coronary artery disease with the surgical group of ARTS-I as a historical control.(16) In order to obtain a population comparable to ARTS-I, patients were stratified by clinical site in order to ensure the inclusion of at least 1/3 of patients with three-vessel disease. Patients were eligible for coronary revascularization if they had either stable angina (Canadian Cardiovascular Society class I-IV), unstable angina (Braunwald class I-III B or C), or silent ischemia, and at least two lesions located in different major epicardial vessels including their sidebranches (except for the left main coronary artery) that were potentially amenable to stent implantation.(17,18) Patients were required to have multivessel disease including treatment of the left anterior descending (LAD) artery and at least one other significant lesion (>50% diameter stenosis) in another major epicardial coronary artery. The goal was to achieve complete anatomic revascularization.(19) One totally occluded major epicardial vessel or side branch could be included. The stenosis had to be amenable to stenting using a SES with a diameter of 2.5 to 3.5mm and length of 13 to 33mm, without restriction on the total implanted stent length. Decisions to place stents in lesions with bifurcations, fresh thrombus, calcification, diffuse disease, complex anatomy or stenting of side branches were left to the discretion of the operators. Patients with previous coronary intervention, left main coronary disease, overt congestive heart failure or a left ventricular ejection fraction of less than 30 percent were excluded. Additional exclusion criteria were: history of a cerebrovascular accident, transmural myocardial infarction (MI) in the preceding week, severe hepatic or renal disease, neutropenia or thrombocytopenia, an intolerance or contraindication to acetylsalicylic acid or thienopyridines, the need for concomitant major surgery and life-limiting major concomitant non-cardiac diseases. Written, informed consent was obtained from each patient prior to enrollment. The study was approved by the ethics committee of each participating site.

STUDY POPULATION

Between April 1997 and June 1998 a total of 1205 patients were randomly assigned to PCI with BMS (n=600) or CABG (n=605) in 67 participating centers in the ARTS-I trial. Diabetes was present in 112 patients in the ARTS-I BMS arm and in 96 patients in the ARTS-I CABG arm. Between February 2003 and November 2003, 607 patients, of whom 159 were diabetic, were treated at 45 participating centers in the ARTS-II study with SES.

STUDY OBJECTIVES

The primary objective of this study was to assess the safety and efficacy of SES in ARTS-II as compared to both the stent and surgical arms of ARTS-I in patients with or without diabetes. The primary safety endpoint was the composite endpoint of death, MI and CVA. The primary efficacy endpoint was MACCE, defined as the occurrence of major adverse cardiac and cerebrovascular accidents, death, stroke, MI and repeat revascularization. Secondary endpoints were the itemized outcome parameters death, CVA, MI, repeat revascularization and stent thrombosis in the ARTS-II population.

BASELINE AND ENDPOINT DEFINITIONS

Hypertension was defined as a blood pressure ≥140 systolic or ≥90 mm Hg diastolic or based on the current use of antihypertensive treatment. Dyslipidemia was classified as a total serum cholesterol level ≥6.2mmol/l or the use of lipid lowering drugs. Death was categorized

Table 1. Baseline Patient Demographics and Clinical Characteristics in non-diabetics.

Non-diabetics	ARTS II	ARTS I-CABG	ARTS I-PCI	ARTS II:I-CABG	ARTS II:I-PCI
Baseline Characteristics					
Male gender (%)	80.1	77.4	77.9	0.34	0.42
Age (years ± SD)	62.1±9.9	61.0±9.4	60.2±9.7	0.07	0.004
Body Mass Index ± SD	27.1±3.8	27.2±3.6	26.9±3.6	0.54	0.38
Risk factors					
Hypertension (%)	62.7	42.8	40.2	<0.001	<0.001
Hypercholesterolemia (%)	74.0	59.3	58.6	<0.001	<0.001
Family history of MI or sudden death < 55 (%)	36.7	43.7	38.6	0.029	0.54
Current smoker (%)	21.9	27.5	29.6	0.051	0.007
Peripheral vascular disease (%)	6.5	4.7	5.5	0.26	0.58
Previous myocardial infarction (%)	36.2	40.7	41.1	0.16	0.006
Indication for Treatment					
Stable angina (%)	53.1	57.2	55.7	0.22	0.43
Unstable angina (%)	37.9	37.9	37.7	1.00	0.95
Silent ischemia (%)	8.9	4.9	6.6	0.015	0.18
Angiographic Characteristics					
Ejection fraction (%)	60±12	60±13	61±12	0.94	0.45
No. of lesions with stenosis > 50%	3.6±1.3	2.7±1.0	2.8±0.9	<0.001	<0.001
No. of diseased vessels					
1	0.2	4.2	4.0	<0.001	<0.001
2	45.1	66.7	69.3	<0.001	<0.001
3	54.7	29.0	26.7	<0.001	<0.001
Vessel territory with stenosis (% of lesions)					
Right coronary artery	29.3	29.6	31.3	0.87	0.24
Left main	0.0	0.1	0.1	0.46	0.45
Left anterior descending	41.8	41.2	40.1	0.74	0.36
Left circumflex artery	28.9	29.2	28.5	0.90	0.84
Lesion Length (visual)					
Discrete (<10mm)	63.2	67.4	67.0	0.023	0.041
Tubular (10-20mm)	26.0	26.0	25.8	0.97	0.97
Diffuse (>20mm)	10.8	6.6	7.2	<0.001	0.001
Lesion Classification (% of lesions)					
Type A	6.9	6.8	6.5	0.88	0.65
Type B1	24.4	31.8	26.4	<0.001	0.23
Type B2	55.7	53.5	58.9	0.23	0.10
Type C	12.9	7.9	8.2	<0.001	<0.001
Procedural Characteristics					
Bifurcation requiring double wiring	34.7	30.8	35.0	0.029	0.90
Number of stents implanted ±SD	3.7±1.5	-	2.7±1.2	-	<0.001
Total stent length (mm±SD)	72.0±32.1	-	46.4±20.6	-	<0.001
Maximum dilatation pressure (Atm±SD)	16.4±2.9	-	14.6±2.8	-	<0.001
Direct stenting (% of lesions)	36.0	-	3.4	-	<0.001
Duration of procedure (mins±SD)	86±44	191±67	98±50	<0.001	<0.001
Post procedural Hospital stay (days±SD)	3.3±2.6	9.4±4.3	3.8±3.7	<0.001	0.031

Numbers are % (counts/available field sample size) or mean ± 1 Standard Deviation; SD = Standard Deviation

as cardiac or non-cardiac. Cerebrovascular events were divided into three main categories: stroke, transient ischemic attacks, and reversible ischemic neurologic deficits. All repeat revascularization procedures were recorded. In the first 7 days after the intervention, a definite diagnosis of myocardial infarction was made if there was documentation of new abnormal Q-waves and either a ratio of serum creatine kinase MB (CK-MB) isoenzyme to total cardiac enzyme that was greater than 0.1 or a CK-MB value that was 5 times the upper limit of normal.(20) Serum creatine kinase and CK-MB isoenzyme concentrations were measured 6, 12, and 18 hours after the intervention. Beginning 8 days after the intervention (the length of the hospital stay after surgery), either abnormal Q waves or enzymatic changes, as described above, were sufficient for a diagnosis of myocardial

infarction. A myocardial infarction was confirmed only after the relevant electrocardiograms had been analyzed by the core laboratory and adjudicated by the clinical-events committee. This two-part method of defining myocardial infarction was developed for ARTS-I to address the difficulty of diagnosing a myocardial infarction after surgery.(16) These definitions have been adopted by the ARC Consortium and are applied whenever a comparison between DES and surgery is performed.(21)

THREE YEAR CLINICAL FOLLOW-UP

The study protocol required all patients to have clinical follow-up including registration of an ECG at 1 month, 6 months, 1 year, and 3 years. At each visit, physical examination, anginal status, and use of medications were assessed. Additional information was obtained by telephone interview or via the referring physician when needed. An independent committee adjudicated clinical events and ECGs. Quality of life (EuroQuol/SF 36) was assessed at 1 month, 6 months, 1 year, and 3 years. Finally, complete 3-year follow-up was available for 99% of the patients in all treatment arms.

ENDPOINT MEASUREMENT

In ARTS-II, the procedure was performed within 48 hours after inclusion. In ARTS-I, patients were randomized after informed consent had been obtained and then entered onto a waiting list. Three deaths occurred in the ARTS I-CABG arm while these patients were still on the waiting list for surgery. To compensate for the temporal difference since allocation between groups, events for the present report were counted from time of procedure for all three arms and not from time of allocation as previously published.(3,22,23)

In ARTS-I and ARTS-II, only data on subacute thrombotic occlusions (<30 days) were collected in the case record form (CRF). In ARTS-II, stent thrombosis was re-adjudicated according to the ARC definitions.(24) In this process, all coronary angiograms in ARTS-II, both procedure-related (n=104) and non-procedure related (n=165) were reviewed by an independent core laboratory and adjudicated by an independent critical event committee. Thus far, no attempt has been made to assess data on stent thrombosis in ARTS-I in a similar fashion.

Statistical analysis

Demographic and procedural characteristics of diabetic patients were compared between ARTS-II and ARTS-I (CABG and PCI). A similar comparison was performed for non-diabetic patients, and for diabetics vs. non-diabetics in ARTS-II. Continuous variables are expressed as mean ± standard deviation. Binary variables are reported as percentages, and the difference between groups was presented with 95% confidence intervals. The two group T-test for continuous variables and the Fisher's exact test for categorical variables were used. (Itemized) MACCE rates at 3 years are presented as counts and percentages and were compared in terms of relative risks (ARTS-II vs. both ARTS-I arms) with 95% confidence intervals. Time-to-event variables are presented as Kaplan-Meier curves, and the overall incidence was tested using the log-rank test.

A separate multivariate regression analysis was performed to further study treatment effects, considering potential confounders listed in Table 1. Baseline and procedural characteristics listed in Table 1 were tested on a per-patient basis by univariate analysis to determine suitability for inclusion in the multivariate model. Finally, a logistic regression model was built using the statistically significant univariate predictors ($p<0.1$).

RESULTS

NON-DIABETIC PATIENTS IN ARTS I AND ARTS II

BASELINE CHARACTERISTICS

Baseline and procedural characteristics of the non-diabetic patients from ARTS-II and ARTS-I are depicted in Table 1. In brief, the ARTS-II patients had significantly more often hypertension and hypercholesterolemia as compared to both the ARTS-I CABG and ARTS-I PCI cohorts. Patients from ARTS-II presented significantly more often with 3-vessel disease and Type C lesions as compared to both ARTS-I PCI and ARTS-I CABG. Finally, as compared to ARTS-I PCI, ARTS-II patients received

Table 2. Clinical endpoints at 3 years in non-diabetics (hierarchical and non-hierarchical MACCE up to 1080 days, per patient) counted since date of procedure.

Up to 1080 days	ARTS II	ARTS I-	ARTS I-PCI	ARTS II:I-CABG	ARTS II:I-PCI
MACCE *	16.3%	15.8%	30.9%	1.03 [0.77, 1.38]	0.53 [0.41, 0.67]
Death/CVA/MI *	7.8%	10.3%	11.5%	0.76 [0.50, 1.14]	0.68 [0.46, 1.02]
Death/MI *	6.0%	8.5%	9.0%	0.71 [0.45, 1.13]	0.67 [0.42, 1.06]
Death	2.2%	4.2%	3.3%	0.54 [0.26, 1.13]	0.68 [0.31, 1.48]
- Cardiac Death	1.1%	2.4%	1.8%	0.47 [0.17, 1.33]	0.61 [0.20, 1.79]
- Non-cardiac Death	1.1%	1.8%	1.4%	0.63 [0.21, 1.86]	0.78 [0.25, 2.43]
CVA	2.5%	2.6%	2.9%	0.96 [0.43, 2.11]	0.86 [0.39, 1.87]
Myocardial Infarction	4.0%	4.9%	6.1%	0.81 [0.45, 1.47]	0.65 [0.37, 1.16]
- Q-wave	2.5%	4.5%	5.3%	0.54 [0.27, 1.10]	0.46 [0.23, 0.92]
- Non Q-wave	1.8%	0.4%	1.0%	4.52 [0.96, 21.16]	1.74 [0.57, 5.29]
Revascularization	11.8%	6.3%	23.6%	1.87 [1.23, 2.85]	0.50 [0.37, 0.68]
CABG	1.8%	1.0%	8.2%	1.81 [0.60, 5.48]	0.22 [0.10, 0.46]
- CABG TL	0.4%	0.8%	6.1%	0.56 [0.10, 3.07]	0.07 [0.02, 0.30]
- CABG non TL	1.3%	0.2%	2.0%	6.78 [0.82, 56.07]	0.65 [0.24, 1.78]
RPTCA	10.3%	5.9%	17.8%	1.73 [1.11, 2.69]	0.58 [0.41, 0.80]
- RPTCA TL	5.8%	3.8%	13.1%	1.55 [0.87, 2.75]	0.44 [0.29, 0.69]
- RPTCA non TL	5.8%	2.4%	6.4%	2.45 [1.25, 4.79]	0.91 [0.55, 1.51]

* Hierarchical; TL - target lesion; CABG - Coronary Artery Bypass Graft; RPTCA - Repeat Percutaneous Transluminal Coronary Angioplasty; MACCE - Major Adverse Cardiac Cerebrovascular Event (Death, CVA, Myocardial Infarction, Target Vessel CABG, Target Vessel RPTCA); Death, CVA and Myocardial Infarction are adjudicated by the independent Clinical Event Committee

significantly more stents, which resulted in a significantly longer total stented length.

Clinical endpoints at 3 years are depicted in Table 2. In brief, the MACCE rate in the non-diabetic patients from ARTS-II was significantly lower than in the ARTS-I PCI and similar to the ARTS-I CABG arm. [Figure 1a] Adjustment for independent predictors of the combined endpoint of MACCE resulted in an OR of 0.41 (95% CI 0.26 – 0.64) for ARTS-II vs. ARTS-I PCI and an OR of 0.83 (95% CI 0.56 – 1.23) for ARTS-II vs. ARTS-I CABG. There was a trend towards a lower incidence of the combined safety endpoint of death/CVA/MI in non-diabetic patients from ARTS-II as compared to both arms of the ARTS-I trial which reached statistical significance after adjustment for independent predictors [OR 0.56 (95% CI 0.35 – 0.92) for ARTS-II vs. ARTS-I CABG and an OR of 0.55 (95% CI 0.34 – 0.91) for ARTS-II vs. ARTS-I PCI] [Figure 1b]. The need for repeat revascularizations in ARTS-II remained significantly higher than in ARTS-I CABG but was significantly lower than in ARTS-I PCI. Adjustment for independent predictors of the combined endpoint of revascularization resulted in an OR of 1.36 (95% CI 0.80 – 2.29) for ARTS-II vs. ARTS-I CABG and an OR of 0.43 (95% CI 0.27 – 0.69) for ARTS-II vs. ARTS-I PCI.

DIABETIC PATIENTS IN ARTS I AND ARTS II

BASELINE CHARACTERISTICS

Baseline clinical and procedural characteristics of the diabetic patients are presented in Table 3. Similar to the non-diabetic population, the ARTS-II diabetic patients had a significantly higher rate of hypertension and hypercholesterolemia as compared to both the ARTS-I CABG and ARTS-I PCI cohorts. Patients from ARTS-II presented significantly more often with 3-vessel disease and Type C lesions compared to both ARTS-I PCI and ARTS-I CABG patients. Finally, as compared to ARTS-I PCI, ARTS-II patients received significantly more stents, which resulted in a significantly longer total stented length.

The 3-year results of the ARTS-II diabetic patients, compared to both arms of the randomized ARTS-I trial are depicted in Table 4. In brief, the MACCE rate in ARTS-II was significantly lower than in the ARTS-I PCI, and similar to the ARTS-I CABG arm. [Figure 2a] Adjustment for independent predictors of

Table 3. Baseline Patient Demographics and Clinical Characteristics in diabetics

Diabetics	ARTS II	ARTS I-	ARTS I-PCI	ARTS II:I-CABG	ARTS II:I-PCI
Baseline Characteristics					
Male gender (%)	66.7	68.8	73.2	0.78	0.29
Age (years ± SD)	64.5±8.	62.6±9.	62.5±9.1	0.09	0.08
Body Mass Index ± SD	28.9±4.	28.1±3.	28.7±3.7	0.16	0.78
Risk factors					
Diabetes, insulin treated (%)	17.6	16.7	20.5	1.0	0.64
Hypertension (%)	79.9	56.3	64.3	<0.001	0.005
Hypercholesterolemia (%)	74.1	49.0	55.4	<0.001	0.002
Family history of MI or sudden death < 55 (%)	33.8	32.6	41.4	0.89	0.20
Current smoker (%)	11.9	16.7	20.5	0.35	0.06
Peripheral vascular disease (%)	8.2	7.3	5.4	1.00	0.47
Previous myocardial infarction (%)	29.6	49.0	41.4	0.002	0.053
Indication for Treatment					
Stable angina (%)	53.5	62.5	58.9	0.19	0.39
Unstable angina (%)	32.1	33.3	37.5	0.89	0.37
Silent ischemia (%)	14.5	4.2	3.6	0.011	0.003
Angiographic Characteristics					
Ejection fraction (%)	60±12	60±14	61±13	0.64	0.54
No. of lesions with stenosis > 50% (n±SD)	3.6±1.3	3.0±1.1	2.9±1.2	0.001	<0.001
No. of diseased vessels					
1	0.6	1.0	3.7	1.00	0.16
2	49.1	63.5	65.4	0.028	0.012
3	50.3	35.4	30.8	0.027	0.002
Vessel territory with stenosis (% of lesions)					
Right coronary artery	28.5	29.0	30.4	0.94	0.59
Left main	0.0	0.0	0.0	-	-
Left anterior descending	40.7	40.7	36.6	1.00	0.25
Left circumflex artery	30.8	30.3	33.0	0.94	0.54
Lesion Length (visual)					
Discrete (<10mm)	54.4	71.9	59.9	<0.001	0.13
Tubular (10-20mm)	30.9	21.7	33.8	0.005	0.40
Diffuse (>20mm)	14.7	6.4	6.4	<0.001	<0.001
Lesion Classification (% of lesions)					
Type A	6.6	7.2	3.6	0.77	0.06
Type B1	20.4	29.0	26.2	0.006	0.051
Type B2	56.4	56.2	62.8	1.00	0.07
Type C	16.7	7.6	7.4	<0,001	<0.001
Procedural Characteristics					
Bifurcation requiring double wiring	31.9	36.3	32.6	0.21	0.88
Number of stents implanted ±SD	3.6±1.5	-	3.0±1.5	-	0.002
Total stent length (mm±SD)	73.9±31	-	52.7±25.6	-	<0.001
Maximum dilatation pressure (Atm±SD)	16.2±2.	-	14.9±2.9	-	<0.001
Direct stenting (% of lesions)	30.6	-	2.6	-	<0.001
Duration of procedure (mins±SD)	83±40	201±64	104±51	<0.001	<0.001
Post procedural Hospital stay (days±SD)	3.6±2.9	11.0±7.	4.6±3.4	<0.001	0.012

Numbers are % (counts/available field sample size) or mean ± 1 Standard Deviation; SD = Standard Deviation; CI = Confidence Interval

MACCE resulted in an OR of 0.72 (95% CI 0.37 – 1.37) for ARTS-II vs. ARTS-I PCI and an OR of 1.08 (95% CI 0.41 – 2.84) for ARTS-II vs. ARTS-I CABG. The incidence of death/CVA/MI was significantly lower in ARTS-II than in ARTS-I PCI, but was observed at a similar rate in the ARTS-I CABG arm [Figure 2b]. Adjustment for independent predictors of the combined endpoint of death/CVA/MI resulted in an OR of 0.67 (95% CI 0.27 – 1.65) for ARTS-II vs. ARTS-I PCI and an OR of 0.67 (95% CI 0.29 – 1.57) for ARTS-II vs. ARTS-I CABG.

As expected, there was a higher MACCE rate in the diabetic patients on insulin therapy compared to those not receiving insulin treatment.[Figure 3] The 23.6% difference in

TABLE 4. Clinical endpoints at 3 years in diabetics (hierarchical and non-hierarchical MACCE up to 1080 days, per patient) counted since date of procedure.

Up to 1080 days	ARTS II	ARTS I-CABG	ARTS I-PCI	ARTS II:I-CABG	ARTS II:I-PCI
MACCE *	27.7% (44/159)	17.7% (17/96)	47.3% (53/112)	1.56 [0.95, 2.57]	0.58 [0.43, 0.80]
Death/CVA/MI *	9.4% (15/159)	13.5% (13/96)	18.8% (21/112)	0.70 [0.35, 1.40]	0.50 [0.27, 0.93]
Death/MI *	6.9% (11/159)	9.4% (9/96)	14.3% (16/112)	0.74 [0.32, 1.72]	0.48 [0.23, 1.00]
Death	5.0% (8/159)	5.2% (5/96)	7.1% (8/112)	0.97 [0.33, 2.87]	0.70 [0.27, 1.82]
- Cardiac Death	2.5% (4/159)	4.2% (4/96)	6.3% (7/112)	0.60 [0.15, 2.36]	0.40 [0.12, 1.34]
- Non-cardiac Death	2.5% (4/159)	1.0% (1/96)	0.9% (1/112)	2.42 [0.27, 21.29]	2.82 [0.32, 24.87]
CVA	3.8% (6/159)	6.3% (6/96)	5.4% (6/112)	0.60 [0.20, 1.82]	0.70 [0.23, 2.13]
Myocardial Infarction	2.5% (4/159)	5.2% (5/96)	9.8% (11/112)	0.48 [0.13, 1.75]	0.26 [0.08, 0.78]
- Q-wave	1.3% (2/159)	4.2% (4/96)	8.0% (9/112)	0.30 [0.06, 1.62]	0.16 [0.03, 0.71]
- Non Q-wave	1.3% (2/159)	1.0% (1/96)	1.8% (2/112)	1.21 [0.11, 13.14]	0.70 [0.10, 4.93]
Revascularization	21.4% (34/159)	7.3% (7/96)	38.4% (43/112)	2.93 [1.35, 6.35]	0.56 [0.38, 0.81]
CABG	3.8% (6/159)	2.1% (2/96)	13.4% (15/112)	1.81 [0.37, 8.79]	0.28 [0.11, 0.70]
- CABG TL	1.3% (2/159)	1.0% (1/96)	8.9% (10/112)	1.21 [0.11, 13.14]	0.14 [0.03, 0.63]
- CABG non TL	2.5% (4/159)	1.0% (1/96)	4.5% (5/112)	2.42 [0.27, 21.29]	0.56 [0.15, 2.05]
RPTCA	18.2% (29/159)	6.3% (6/96)	27.7% (31/112)	2.92 [1.26, 6.77]	0.66 [0.42, 1.03]
- RPTCA TL	13.8% (22/159)	3.1% (3/96)	19.6% (22/112)	4.43 [1.36, 14.40]	0.70 [0.41, 1.21]
- RPTCA non TL	6.9% (11/159)	3.1% (3/96)	9.8% (11/112)	2.21 [0.63, 7.74]	0.70 [0.32, 1.57]

* Hierarchical; TL - target lesion; CABG - Coronary Artery Bypass Graft; RPTCA - Repeat Percutaneous Transluminal Coronary Angioplasty; MACCE - Major Adverse Cardiac Cerebrovascular Event (Death, CVA, Myocardial Infarction; Target Vessel CABG; Target Vessel RPTCA). Death, CVA and Myocardial Infarction are adjudicated by the independent Clinical Event Committee.

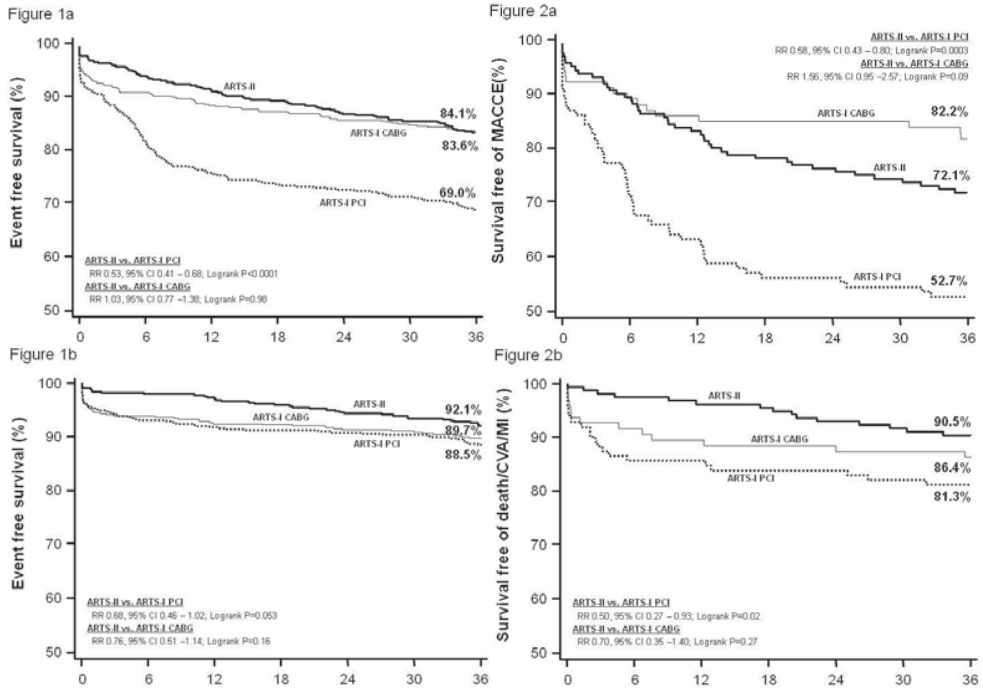

Figure 1: Kaplan-Meier curve out to 3 years in ARTS-I and ARTS-II non-diabetics patients: freedom from major adverse cardiac and cerebrovascular events (MACCE) (A), the combined endpoint of all-cause death, cerebrovascular accident (CVA), myocardial infarction and repeat revascularization and death/CVA/MI (B). **Figure 2**: Kaplan-Meier curve out to 3 years in ARTS-I and ARTS-II diabetics patients: freedom from major adverse cardiac and cerebrovascular events (MACCE) (A), the combined endpoint of all-cause death, cerebrovascular accident (CVA), myocardial infarction and repeat revascularization and death/CVA/MI (B).

TABLE 5. Clinical endpoints of diabetics and non-diabetic patients at 3 years in ARTS-II. (hierarchical and non-hierarchical MACCE up to 1080 days, per patient) counted since date of procedure.

Up to 1080 days	Diabetics	Non-diabetics	Relative Risk (95% CI)
MACCE *	27.7% (44/159)	16.3% (73/448)	1.70 [1.22, 2.36]
Death/CVA/MI *	9.4% (15/159)	7.8% (35/448)	1.21 [0.68, 2.15]
Death/MI *	6.9% (11/159)	6.0% (27/448)	1.15 [0.58, 2.26]
Death	5.0% (8/159)	2.2% (10/448)	2.25 [0.91, 5.61]
- Cardiac Death	2.5% (4/159)	1.1% (5/448)	2.25 [0.61, 8.29]
- Non-cardiac Death	2.5% (4/159)	1.1% (5/448)	2.25 [0.61, 8.29]
CVA	3.8% (6/159)	2.5% (11/448)	1.54 [0.58, 4.09]
Myocardial Infarction	2.5% (4/159)	4.0% (18/448)	0.63 [0.22, 1.82]
- Q-wave	1.3% (2/159)	2.5% (11/448)	0.51 [0.11, 2.29]
- Non Q-wave	1.3% (2/159)	1.8% (8/448)	0.70 [0.15, 3.28]
Revascularization	21.4% (34/159)	11.8% (53/448)	1.81 [1.22, 2.67]
CABG	3.8% (6/159)	1.8% (8/448)	2.11 [0.74, 6.00]
- CABG TL	1.3% (2/159)	0.4% (2/448)	2.82 [0.40, 19.84]
- CABG non TL	2.5% (4/159)	1.3% (6/448)	1.88 [0.54, 6.57]
RPTCA	18.2% (29/159)	10.3% (46/448)	1.78 [1.16, 2.73]
- RPTCA TL	13.8% (22/159)	5.8% (26/448)	2.38 [1.39, 4.08]
- RPTCA non TL	6.9% (11/159)	5.8% (26/448)	1.19 [0.60, 2.36]

* Hierarchical; TL - target lesion; CABG - Coronary Artery Bypass Graft, clinically driven; RPTCA - Repeat Percutaneous Transluminal Coronary Angioplasty, clinically driven; MACCE - Major Adverse Cardiac Cerebrovascular Event (Death, CVA, Myocardial Infarction, Target Vessel CABG, Target Vessel RPTCA); Death, CVA and Myocardial Infarction are adjudicated by the independent Clinical Event Committee.

MACCE rates between the insulin- and non-insulin treated diabetic patients in the CABG arm is worth noting. However, there were only 16 insulin- treated diabetics in the ARTS-II CABG arm, a number which precludes any definitive statement about a difference in the relative treatment effect in insulin-treated diabetics.

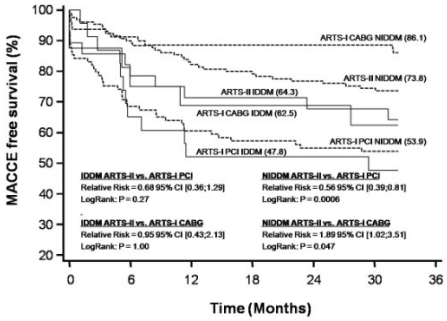

Figure 3: Kaplan-Meier curve out to 3 years in ARTS-I and ARTS-II insulin- versus non-insulin dependent diabetics patients: freedom from major adverse cardiac and cerebrovascular events (MACCE), the combined endpoint of all-cause death, cerebrovascular accident, myocardial infarction and repeat. IDDM stands for insulin-dependent diabetes mellitus; NIDDM stands for non-insulin dependent diabetes mellitus.

THE IMPACT OF DIABETES IN ARTS-II

After Adjustment for independent predictors, diabetes proved to be the strongest pre-procedural predictor of MACCE in ARTS-II (OR 1.76, 95% CI 1.13 – 2.74; p=0.012).(25) The clinical endpoints of the ARTS-II diabetics vs. non-diabetics are depicted in Table 5. In brief, the incidence of MACCE in diabetic patients was significantly higher than in non-diabetics. This difference was mainly driven by the significantly higher need for repeat revascularizations in the diabetic patients. At 3-years, the difference in the incidence of the combined safety endpoint of death/CVA/MI between diabetic and non-diabetic patients did not reach statistical significance.

Remarkably, the incidence of stent thrombosis (definite, probable or possible) at 3 years was similar in the ARTS-II diabetics as compared to the non-diabetics (6.9% (11/159) vs. 6.3% (28/448) respectively; p=0.85). Definite or probable stent thrombosis occurred in 5.0% (8/159) of the diabetics as compared to 5.4% (24/448) in the non-diabetics (p=1.00). There were no differences in the incidence of stent thrombosis between insulin and non-insulin treated diabetics. Definite or probable stent thrombosis occurred in 4.6% (6/131) of the non-insulin treated diabetics vs. 7.1% (2/28) of the insulin treated diabetics (p=0.63).

In the diabetic patients, out of the 44 patients who had a major adverse cardiac event (ARC definitions), 10 (22.7%) patients had a definite, probable or possible stent thrombosis. Out of the 83 non-diabetics patients in ARTS-II who

had a major adverse cardiac event, 28 patients (33.7%) had a definite, probable or possible stent thrombosis. More specifically, 5/26 (19.2%) of the clinically driven percutaneous target lesion revascularizations in the non-diabetics and 12/22 (54.5%) of the clinically driven percutaneous target lesion revascularizations in the diabetics were due to definite stent thrombosis.

DISCUSSION

The present study is the first to compare the long-term safety and efficacy of PCI using SES with CABG in diabetic and non-diabetic patients with multivessel coronary artery disease. In the total ARTS-II population we recently reported on the significantly lower incidence of death/CVA/MI in patients treated with SES (8.3%) as compared to the historical PCI arm of the ARTS-I (12.8%; Logrank p=0.007). Stratification of these results according to diabetic status revealed that when adjusting for independent predictors of outcome, the risk for death/CVA/MI in the non-diabetic patients was significantly lower in ARTS-II than in both arms of the ARTS-I. Conversely, in the diabetic cohort, the cumulative incidence of death/CVA/MI in ARTS-II was 9.2% lower than in the percutaneous arm of ARTS-I and 4.1% lower than in the ARTS-I CABG arm. However, these differences in the hard clinical endpoints did not reach statistical significance after adjusting for independent predictors of outcome. Thus far, no consensus has been reached about differences in hard clinical endpoints between PCI and CABG. In the pre-stent era, randomized trials and registries demonstrated higher survival rates following CABG than PCI, a difference that was most pronounced in diabetic patients.(12,26,27) Comparing PCI using BMS with CABG, a meta-analysis of the ARTS-I, SoS, ERACI-II and MASS-II trials demonstrated similar mortality rates following both treatment options in both the overall analysis as well as in the diabetic subset at 1-year.(2) We observed a clear trend towards a lower incidence of death/CVA/MI in the patients treated with DES in the ARTS-II compared to the ARTS-I PCI population. Although the present study was underpowered to make definitive statements about a better survival following PCI using DES as compared to BMS, these findings are in agreement with the 3-year results of the randomized DIABETES trial in which 6.4% of the patients treated with SES experienced an MI and/or died of a cardiac cause versus 12.6% of the patients treated with BMS.(28) Furthermore, various large-scale registries have recently shown a small, but consistent long-term survival advantage when using DES versus BMS in all-comer populations.(29-33)

CABG has been associated with a significantly lower risk for repeat revascularizations as compared to PCI with BMS, a benefit that proved to be most apparent in patients with multivessel disease often suffering from diabetes.(1-6) Although DES proved to tighten the gap between PCI and CABG, it remains unclear whether these findings can be extrapolated to diabetics. (7,8) Diabetics are known to have a smaller vessel size, longer lesion length, greater plaque burden and possibly a different restenotic cascade as compared to non-diabetics making them more susceptible to atherosclerosis and a higher need for repeat revascularizations.(9-12,34,35) This is confirmed by the 3-year revascularization rate in the ARTS-II diabetics, who had an 81% increased risk for repeat revascularization as compared to the non-diabetic patients. The use of CABG remains the most effective method for avoiding reinterventions in diabetics. When compared to the ARTS-I PCI population, the incidence of repeat revascularization was 31% lower following surgical revascularization (38.4% vs. 7.3% respectively). Although CABG remained significantly superior to PCI with DES in reducing the need for repeat revascularizations, the use of SES in this-high risk population resulted in a 44% decrease in the need for repeat revascularizations as compared to the ARTS-I PCI arm, despite the higher baseline and procedural risk profile of the ARTS-II patient population. In the non-diabetics conversely these differences were substantially smaller. The difference was 17.0% between both arms of the ARTS-I, while the difference in repeat revascularization rates between ARTS-II and ARTS-I CABG was 5.5%

confirming the more pronounced efficacy of CABG in diabetics.

Diabetes has been associated with enhanced platelet reactivity and reduced responsiveness to antiplatelet agents.(36,37) Abnormalities in neovascularization have also been recognized and are hypothesized to enhance atherosclerotic plaque destabilization.(38) The latter is reflected by the 70% higher relative risk of MACCE in diabetic as compared to non-diabetic patients in ARTS-II. However, at three years, the incidence of definite or probable stent thrombosis(21) was similar in the ARTS-II diabetic and non-diabetic patients, a finding that at first is not entirely consistent with the current literature(13-15) but may be partly explained by the relatively small and specific patient population studied. Clinical and procedural risk factors are usually worse for diabetics as compared to non-diabetics. However, in ARTS-II, clinical presentation, lesion calcification, number of stents and total stented length were similar between the diabetics and non-diabetics. As a result, the impact of ST on the 3-year MACCE-rates in ARTS-II was similar in the diabetic and non-diabetic population.

Although the present subset analysis of patients with diabetes was prespecified in the ARTS-II protocol, this non-randomized study has several limitations. First, a 5-year time lag exists between the groups that are being compared. Both PCI and CABG as well as concomitant medical therapy have improved with time. Secondly, despite the use of complex statistical adjustment methods, it remains unclear whether we were able to fully adjust for the differences between ARTS-II and ARTS-I studies. Third, while the protocol required that the lesions in ARTS II be potentially treatable by CABG, the absence of dialogue with the surgeons prior to intervention may have caused a selection bias. However, this is not obvious considering that patients actually enrolled in ARTS II were more complex than those enrolled in ARTS I. Finally, the incidence and impact of stent thrombosis was not readjudicated according to the ARC definitions in the ARTS-I study preventing the authors from comparing the results of ARTS-II to the historical PCI arm of ARTS-I. As a consequence, we were unable to verify the hypothesized increase in late stent thrombosis in diabetic patients treated with DES as compared to BMS. However, it was reassuring to note the trend towards a lower rate of death and a significantly lower rate of myocardial infarction, as well as Q-wave myocardial infarction, in the ARTS-II compared to the ARTS-I PCI population. .

Several large-scale dedicated randomized controlled trials like Syntax (using the paclitaxel-eluting stent), FREEDOM (using the PES and SES), and CARDia (comparing SES with CABG in diabetics) are ongoing to assess the relative safety and efficacy of PCI using DES and CABG.(39,40) However, until the long-term outcome data from these trials will be revealed, the results from the present study are unique in addressing the relative long-term safety and efficacy of PCI using SES for both diabetic and non-diabetic patients with multivessel coronary artery disease. The results of the randomized FREEDOM and CARDia trials are eagerly awaited to confirm the findings of this analysis.

CONCLUSION

At 3 years, PCI using SES for patients with multivessel coronary artery disease seems to be safer and more efficacious as compared to PCI using bare metal stents, irrespective of the diabetic status of the patient. Although superior to PCI with BMS, PCI using SES remains inferior to CABG in reducing the need for repeat revascularizations. However, we observed a clear trend towards a lower risk for death/CVA/MI in the ARTS-II patients as compared to both arms of the ARTS-I trial. These findings suggest that PCI using SES could be a genuine alternative to CABG. The results of dedicated large-scale randomized trials are eagerly awaited to validate our findings.

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Chapter 29

Short- and long- term health related quality-of-life and anginal status after randomisation to coronary stenting versus bypass surgery for the treatment of multivessel disease: results of the Arterial Revascularisation Therapy Study (ARTS)

van Domburg R, Daemen J, Pedersen S, Bressers M, van Herwerden L, Firth B, Unger F, Serruys PW

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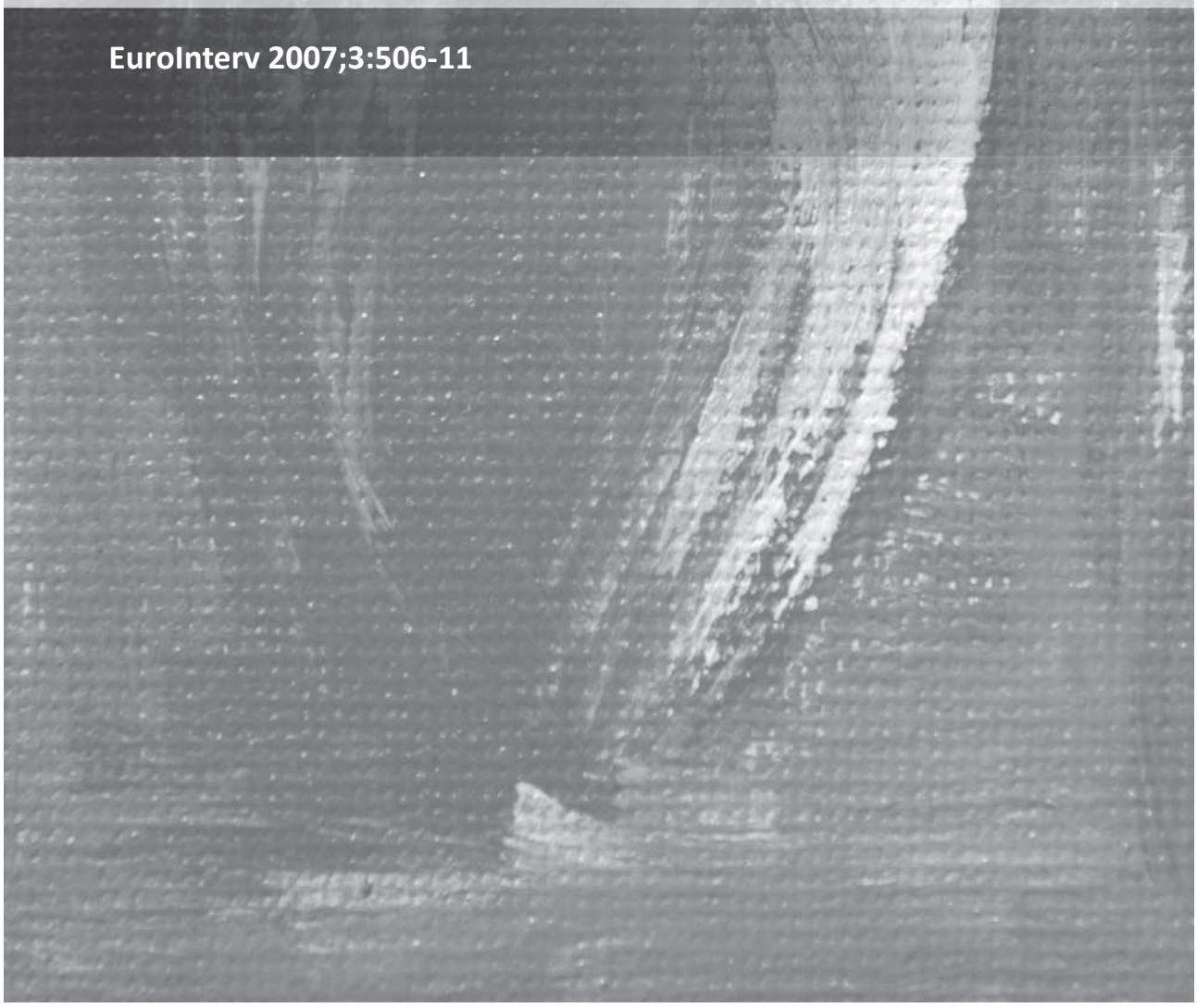

Short- and long- term health related quality-of-life and anginal status after randomisation to coronary stenting versus bypass surgery for the treatment of multivessel disease: results of the Arterial Revascularisation Therapy Study (ARTS)

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Brian Firth is an employee of Cordis, all other authors have no conflict of interest to declare.

KEYWORDS

ARTS study, quality of life, coronary stent, bypass surgery, SF 36

Abstract

Background: Health related quality-of-life (HRQL) beyond one year of treatment of multivessel coronary artery disease with stenting or coronary artery bypass grafting (CABG) is yet unknown. The Arterial Revascularisation Therapy Study (ARTS) was designed to compare CABG and stenting in multivessel disease.

Methods and results: HRQL was evaluated at baseline, at 1- month and at 6-, 12- and 36 months after revascularisation using the Short Form Health Survey (SF-36) in patients randomised to stenting (n=483) versus CABG (n=492). Both stenting and CABG resulted in significant improvement of HRQL and anginal status. Although there was a trend for better HRQL after CABG up to one year, the disparity between the two procedures decreased long-term. Most of the difference between the two procedures was attributed to repeat interventions in the stent group; at three years, 19% of stent patients versus 13% of CABG patients ($p<0.0001$) had undergone a repeat intervention. On most of the SF-36 scores, there was no difference between diabetics and non-diabetics, with diabetic patients having a worse score only on general health and physical functioning at all time points ($p<0.0001$).

Conclusions: Both stenting and CABG resulted in a significant improvement in HRQL especially up to one year, but CABG was associated with less angina at all time points. There was a trend for better HRQL after CABG, but this difference was mainly attributed to repeat revascularisation in the stent group. Based on these findings, patients should select for themselves whether or not they would prefer the improved HRQL benefits after CABG, or whether they would prefer more angina after PCI and avoid a major operation.

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Introduction

Multiple randomised studies have demonstrated similar mortality rates for percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). However, patients undergoing PCI are much more likely to have recurrent ischaemia with subsequent repeat interventions. When there is an absence of a clear advantage for either CABG or PCI, revascularisation strategies are selected based solely upon technical considerations and perceived procedural risks. Because the elimination of ischaemia is more complete with surgery, patients may derive a greater health related quality-of-life (HRQL) benefit with CABG compared with PCI. In the early 1990s, the pre-stent era, several clinical trials comparing CABG with balloon angioplasty included HRQL and showed that CABG patients had greater improvement in HRQL scores[1-3]. More recently, the AWESOME investigators reported equivalent six-months HRQL between PCI and CABG[4]. On the other hand, the Stent or Surgery (SoS) study group reported a significant improvement in angina-related health status at six months and at one year after intervention[5]. Furthermore, a few observational registries identified that over 12 months of follow-up health status was more improved after CABG than after PCI, but this was primarily driven by the adverse influence of restenosis after PCI[6,7]. However, almost no data are available to describe the HRQL recovery after revascularisation beyond one year. Only the Arterial Revascularisation Therapy Study (ARTS) reported the HRQL, assessed by the 5-item EuroQOL EQ-5D health status, at one and three years[8]. ARTS was a randomised trial comparing stenting with CABG in patients with multivessel disease[9]. At five years, there was no difference in mortality, myocardial infarction or stroke between the two procedures[10]. However, increased repeat revascularisation was needed in the stent group.

Besides the EQ-5D, ARTS also evaluated the more well-known and more detailed Short Form Healthy Survey (SF-36). The objective of this study was to evaluate the SF-36 and anginal status at baseline, at 1-month, and 6-, 12 and 36-months of patients enrolled in the ARTS trial.

Methods

Population

Between April 1997 and June 1998, 1,205 patients who had multivessel disease and considered equally treatable with the two modalities were randomised to either stent implantation (n=600) or CABG (n=605) at 67 participating centres worldwide as part of the ARTS trial. Details of this study have been described previously[11]. The indications for revascularisation included silent ischaemia, stable or unstable angina pectoris, and the presence of at least two de novo lesions located in different major epicardial coronary arteries, potentially amenable to stent implantation. For each patient, entry into the study required agreement from both the surgeon and interventional cardiologist that an equivalent degree of revascularisation could potentially be obtained using either approach. Specific exclusion criteria from the randomised trial may be summarised as follows: left ventricular ejection fraction <30%, left main stenosis, history of cerebrovascular accident, transmural myocardial infarction within the preceding week, severe hepatic or renal disease and need for concomitant major surgery. All patients gave written informed consent.

As the SF-36 questionnaire was not translated in all languages of the participating centres, of the total 1,205 patients, 1,035 patients were eligible to participate in this substudy. Of these eligible patients, 975 (94%) agreed to participate. At respectively 1-, 6-, 12- and 36 months follow-up six, 20, 24 and 43 patients had died (equally divided among both treatment groups). The corresponding participating rates were 100% at baseline and at one month, and 92% at 6-, 12- and 36 months.

Health-related quality of life and anginal status

The Short Form Health Survey (SF-36) is a generic measure of HRQL that assesses eight domains, i.e. physical functioning, role physical functioning, role emotional functioning, mental health, vitality, social functioning, bodily pain, and general health[12]. Scale scores are obtained by summing the items together within a domain, dividing this outcome by the range of scores and then transforming the raw scores to a scale from zero to 100. A higher score on the SF-36 sub domains represents a better HRQL with a high score on the bodily pain scale indicating freedom from pain. The scale has good reliability with Cronbach's alpha ranging from .65 to .96 for all subscales[12]. The SF-36 was administered at baseline, and at one, six, 12 and 36 months' post-index procedure. Anginal status was assessed by the Canadian Cardiovascular Society (CCS) classification.

Statistical analysis

Comparisons between treatment groups were analysed according to the intention-to-treat principle. Baseline characteristics were compared by unpaired Student's t test for continuous variables and Fisher exact tests for categorical variables. Health status recorded over follow-up time was analysed with repeated measures analysis of variance with Bonferroni correction. All tests of statistical significance were 2-tailed and a probability value of <0.05 was considered significant. A pre-specified subgroup analysis was performed in the stent group to investigate the effect of repeat revascularisation on HRQL. Since the BARI investigators reported better survival in diabetics after CABG, much attention has been seen in this subgroup. Therefore, also, an analysis was performed on patients with and without diabetes[3].

Results

Baseline clinical and procedural characteristics of the 975 patients who participated in this ARTS randomised HRQL substudy were similar in both treatment groups (Table 1). Mean age was 61 years and 77% were male. There were no differences in baseline characteristics between responders and non-responders on the SF-36.

The time course of recovery from the coronary intervention differed by treatment strategy (Figure 1). Patients undergoing CABG experienced a decrease in most SF-36 subscales in the first post-operative month, whereas in the group of patients undergoing PCI the HRQL immediately increased significantly. This improvement varied between 10% to 64% at one month. Between one and six

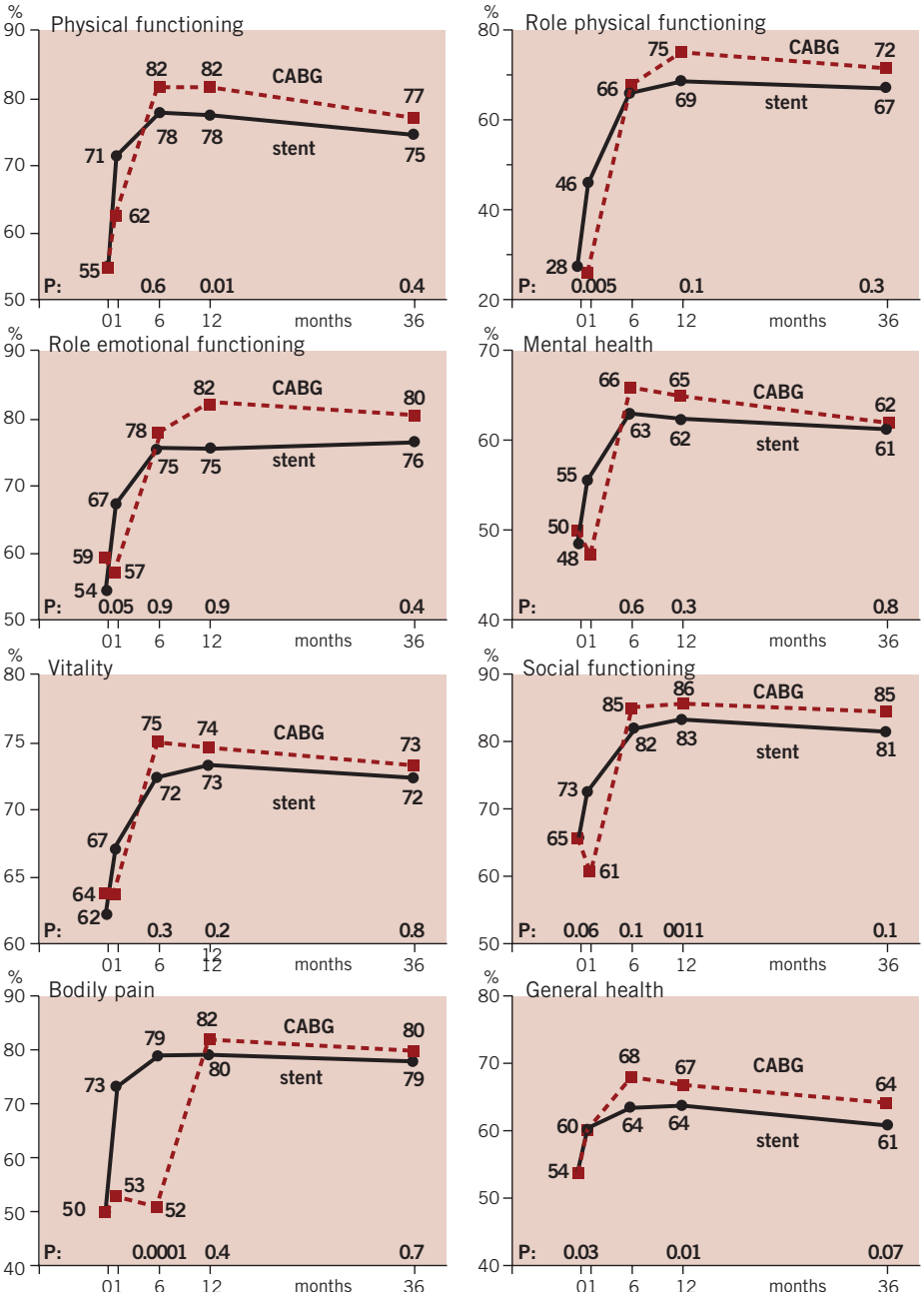

Figure 1. SF 36 subscales according to CABG and stenting at baseline, 1, 6, 12 and 36 months.

Table 1. Baseline characteristics.

	Stent (n=483)	CABG (n=492)	P
Age (years)	61	62	0.3
Range (years)	30-83	32-82	
Male (%)	77	77	0.8
Diabetes (%)	19	16	0.3
Hypertension (%)	44	44	0.9
Hypercholesterolaemia (%)	56	56	0.9
Current smoker (%)	33	26	0.2
Previous myocardial infarction (%)	54	42	0.2
Unstable angina (%)	36	35	0.7
Ejection fraction (%)	61	60	0.2
Range	30-92	30-91	
No of diseased vessels (%)			0.7
1	2	0	
2	68	67	
3	30	33	

months, most HRQL scores improved substantially, but the strongest in the CABG group up to an equal or greater level than the PCI group. Only bodily pain remained low in the first six months in patients undergoing CABG. Between six and 12 months, the HRQL sub domain scores for all stent and most CABG remained similar. Physical and emotional role functioning further increased after CABG, and bodily pain finally improved to the same stent level. Ultimately, three of the SF-36 sub domain scores (physical functioning, social functioning and general health) were significantly higher in the CABG than in the stent group. During longer follow-up up to three years, all sub-domain scores in both treatment groups slightly decreased and converged to the same level.

To better explain differences in HRQL between CABG and stenting, an additional analysis was performed to investigate the effect of repeat revascularisation on the relative benefit of CABG versus stenting. Although among those PCI patients who did not require repeat revascularisation (73% of the stent patients), average HRQL scores at six months and later were similar with the scores in the CABG patients, whether or not these CABG patients had a repeat intervention (Figure 2).

Anginal status

The incidence of angina after stenting and CABG is shown in Figure 3. At all time points, angina was more prevalent in the stent group, although the differences getting smaller with prolonged follow-up. At three years, 19% of the stent patients and 13% of the CABG patients had angina ($p<0.0001$). In the group of stent patients in whom no repeat revascularisation was needed, the prevalence of angina was lower compared with those stent patients with a repeat revascularisation, but it was still higher than the CABG group at all time points ($p<0.0001$).

Patients with diabetes

In the stent group there was no difference between diabetics and non-diabetics in most of the SF-36 scores. Only on general health, the diabetic patients scored significantly worse than the non-diabetic patients at all time points ($p<0.0001$), and physical functioning decreased gradually with longer follow-up among the diabetic stent patients. Also in the CABG group, most SF-36 scores were similar among the diabetics and non-diabetics. Only a trend in worse emotional well-being was observed in the diabetics long-term.

Discussion

The main reason for treating patients with severe ischaemia is to restore the patient to as normal a life as possible. As a consequence, evidence of a meaningful benefit from the patient's perspective is an important consideration in the comparison of treatment strategies. Both stenting and CABG resulted in significant improvements in HRQL and anginal status. Although this improvement was clear immediately following stenting, due to the major surgery, at six months HRQL after CABG was at the same level as after stenting. The first month assessment allowed us to detect both the drop in both physical and mentally function with CABG and the impact of repeat revascularisation on HRQL with stenting. Between six months and 12 months patients who underwent CABG had, in general, a better HRQL than those who underwent PCI. However, most of this difference was attributed to repeat interventions in the stent group. At one year, and up to three years, HRQL of both groups converged to each other. Furthermore, CABG surgery was associated with less angina at all time points, but again much of this difference was due to the repeat revascularisations after stenting. Therefore, with the recent introduction of the drug-eluting stents, with subsequent substantial reduction of restenosis, it is to be expected that HRQL after stenting will converge to the same as CABG.

Recently, this study reported a HRQL measurement, by means of the 5-item EuroQOL EQ-5D, beyond one year and up to three years after the procedure[8]. At one year after the intervention the stent group scored better on the subscales "mobility", "anxiety and depression" and "usual activity", but at three years all differences had diminished. However, it has been suggested that the EQ-5D is not sensitive enough as disease specific instrument and that the more well known and widely accepted 36-item SF-36 more adequately discriminates HRQL[13]. A limitation of this study is the lack of a disease-specific health status survey. Disease specific surveys have multiple advantages over generic surveys such as the SF-36, especially when comparing interventions within a disease state. A survey such as the MacNEW or SAQ would have captured domains most relevant to the question at hand, and could have added much to the results.

Multiple clinical trials have reported and demonstrated improvement in HRQL for both stenting and CABG[1-3]. However, all these studies date from the pre-stent era. Only the AWESOME and SoS investigators have reported HRQL after stenting and CABG[4,5]. The AWESOME trial found equivalent HRQL outcomes at 6-months and the SoS study reported improved HRQL up to 12 months after CABG.

In the diabetic subgroup of this study (n=208), no difference in 5-year mortality was found[10]. In general, no difference in HRQL was found between patients with and without diabetes in both the stent and CABG groups.

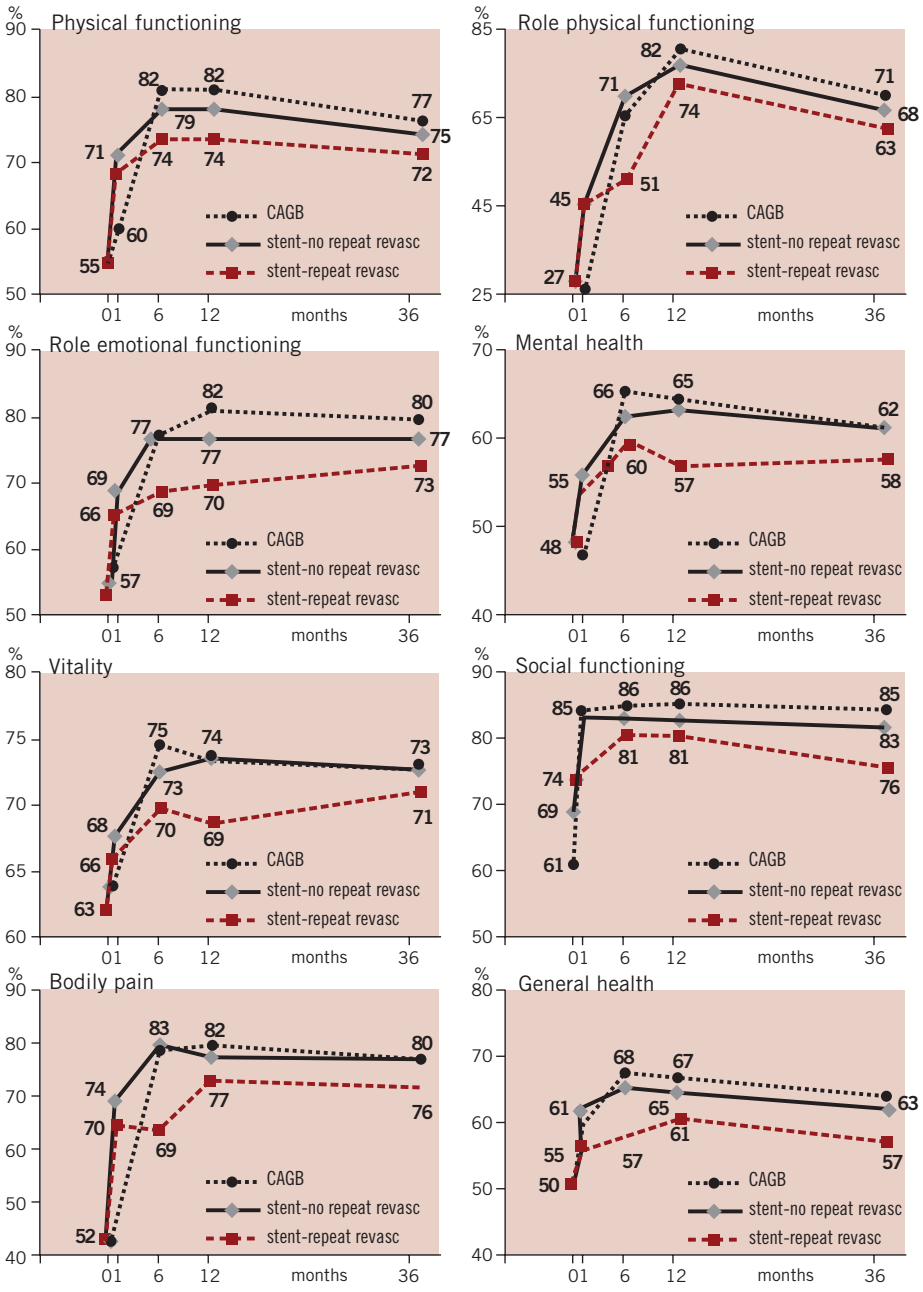

Figure 2. SF 36 subscales according to CABG and stenting with or without repeat revascularisation at baseline, 1, 6, 12 and 36 months.

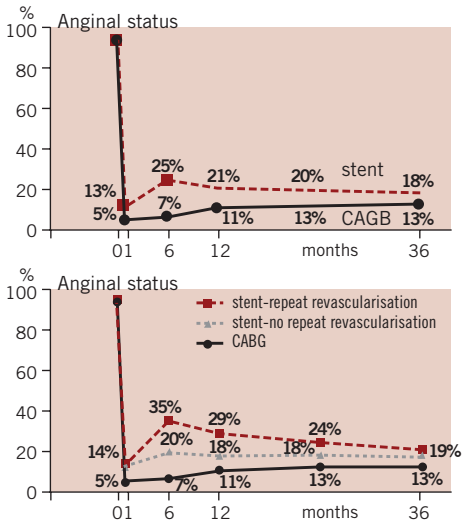

Figure 3. Anginal status according to CABG and stenting with or without repeat revascularisation at baseline, 1, 6, 12 and 36 months.

The present study has shown improved health status after either stenting or CABG, especially in the stent patients who didn't undergo a repeat intervention. Many patients may refuse to undergo the greater initial suffering of CABG compared to PCI in order to achieve only similar HRQL on the long-term. Therefore, from a HRQL point of view, there seems no reason to believe that CABG should be the first choice. All the more in this drug-eluting stent era, the need of repeat of revascularisation after stenting is decreasing rapidly.

Conclusion

Both stenting and CABG resulted in a significant improvement in HRQL especially up to one year, but CABG was associated with less angina at all time points. There was a trend for better HRQL after CABG, but this difference was mainly attributed to repeat revascularisation in the stent group. Although, based purely on HRQL outcomes, there seems little reason to prefer CABG to stenting in order to provide long-term pain relief. However, the decision should be made on an individual patient basis, including balancing the larger 'upfront' risks of CABG with the risk of repeat revascularisation and residual angina with PCI. Furthermore, based on these findings, patients should select for themselves whether or not they would prefer the improved HRQL benefits after CABG, or whether they would prefer more angina after PCI and avoid a major operation.

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Chapter 30

Cost-effectiveness of the unrestricted use of sirolimus-eluting stents vs. bare metal stents at 1 and 2-year follow-up: results from the RESEARCH Registry

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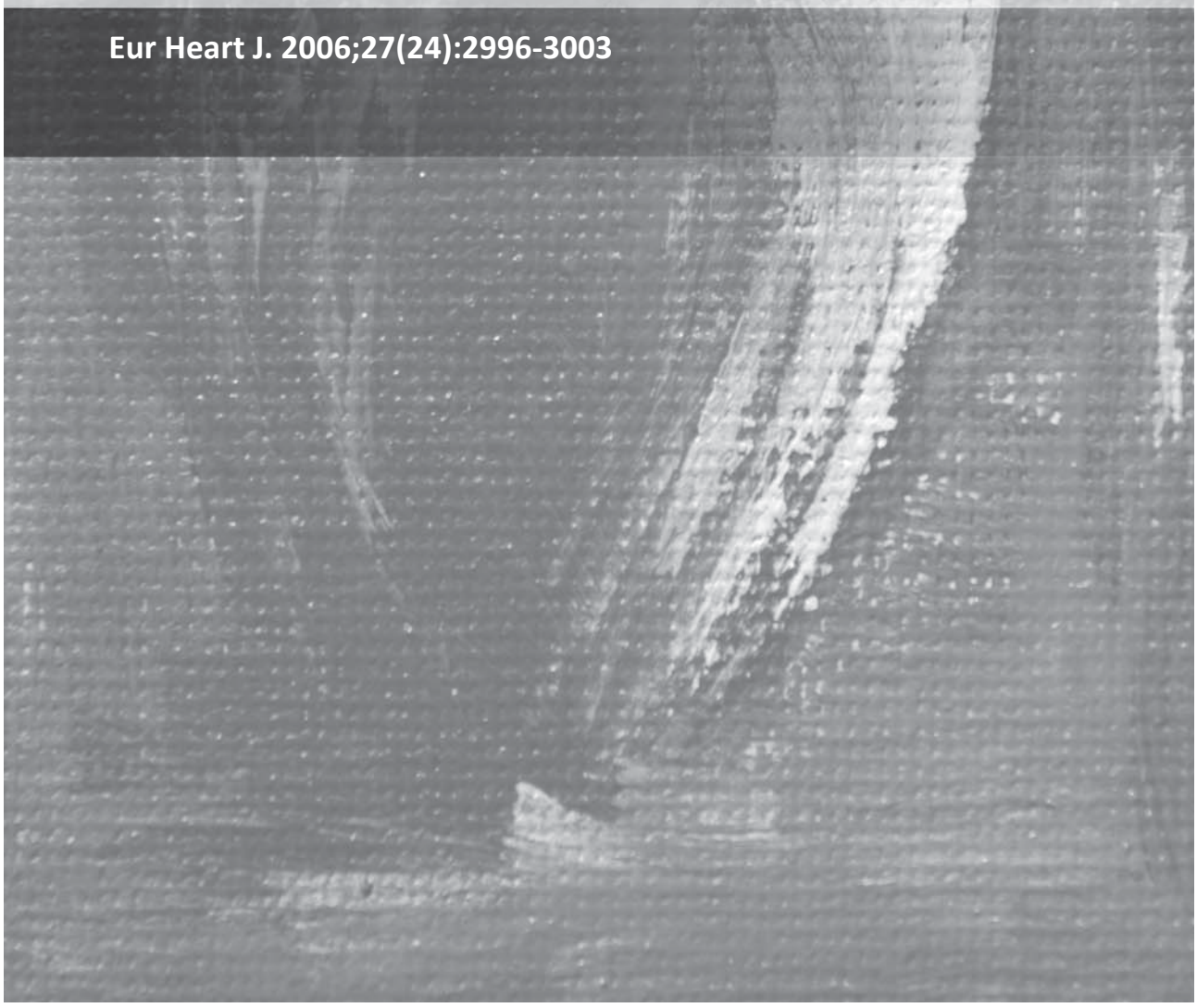

Cost-effectiveness of the unrestricted use of sirolimus-eluting stents vs. bare metal stents at 1 and 2-year follow-up: results from the RESEARCH Registry†

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KEYWORDS
Cost-effectiveness;
Drug-eluting stents;
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Registry

Aims To assess the cost-effectiveness of sirolimus-eluting stents (SESs) compared with bare metal stents (BMSs) as the default strategy in unselected patients treated in the Rapamycin Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) Registry at 1 and 2-years following the procedure.
Methods and results A total of 508 consecutive patients with *de novo* lesions exclusively treated with SES were compared with 450 patients treated with BMS from the immediate preceding period. Resource use and costs of the index procedure, and clinical outcomes were prospectively recorded over a 2-year follow-up period. Follow-up costs were measured as unit costs per patient based on the incidence of clinically driven target vessel revascularization (TVR), to obtain cumulative costs at 1 and 2-years. Cost-effectiveness was measured as the incremental cost-effectiveness ratio (ICER) per TVR avoided.
The use of SES cost €3036 more per patient at the index procedure, driven by the price of SES. Follow-up costs after 1-year were €1,089 less with SES when compared with BMS, due to less TVR, resulting in a net excess cost of €1968 per patient in the SES group, and reduced by a further €100 per patient in the second year. The incidence of death or myocardial infarction between groups was similar at 1 and 2 years. Rates of TVR in the SES and BMS groups were 3.7% vs. 10.4%, $P < 0.01$ at 1 year, respectively; and 6.4% vs. 14.7%, $P < 0.001$ at 2 years. The ICER per TVR avoided was €29 373 at 1 year, and €22 267 at 2 years.
Conclusion The use of SES, while significantly beneficial in reducing the need for repeat revascularization, was more expensive and not cost-effective in the RESEARCH registry at either 1 or 2-years when compared with BMS. On the basis of these results, in an unselected population with 1 year of follow-up, the unit price of SES would have to be €1023 in order to be cost-neutral.

Introduction

Drug-eluting stents have revolutionized the treatment of coronary artery stenosis by systemically reducing the need for re-intervention following stent implantation.[1] The pivotal European randomized trial comparing sirolimus-eluting stents (SESs) with bare metal stents (BMSs), RAVEL,[2] paved the way for the definitive trial, SIRIUS,[3] conducted in the United States. These respective trials led to its commercialization in Europe in 2002 and in the United States in 2003. Confirmation of the efficacy of SES over BMSs in a diverse unselected population was made in the Rapamycin Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) Registry with 1[4] and 2-year follow-up.[5] More recently, the randomized BASKET trial with 6 months follow-up concurred with the results of RESEARCH.[6]

The market price of drug-eluting stents has almost unanimously been perceived as the major limitation for a more widespread use of SES worldwide.[7] On the other hand, the striking decrease in the incidence of cardiac events with the use of SES is theoretically associated with a reduction in resource utilization, and therefore costs, during follow-up. In the RAVEL trial, the treatment of a single native *de novo* coronary lesion with SES was associated with an increased procedural cost of €1286 over BMS, which was reduced to an additional cost of €54 after 1 year of follow-up, mainly because of the lower frequency of repeat revascularizations among SES-treated patients.[8] Correspondingly, in the SIRIUS randomized trial, patients treated with SES cost US$2881 more than BMS patients. At 1 year, aggregate costs narrowed but were still US$ 309 higher in SES patients.[9] The incremental cost-effectiveness ratio (ICER) for SES was US$1650 per repeat revascularization avoided.

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Although the cost-effectiveness profile of SES has been assessed in the context of randomized trials,[8,9] there is limited information on the balance between costs and effects of SES in the real world. In the present study, we performed a prospective resource utilization and economic evaluation during a 2-year follow-up period of the patients treated in the RESEARCH registry.

Methods

Patient population and treatment strategy

The RESEARCH registry is a single-centre registry conducted with the main purpose of evaluating the safety and efficacy of SES implantation for patients treated in daily practice. Its study design has been previously published.[10] Briefly, since 16 April 2002, our institution has adopted a policy of using SES (Cypher; Johnson & Johnson-Cordis unit, Cordis Europa, NV, USA) as the default stent for every percutaneous coronary intervention. In the first 6 months of enrolment, 508 patients with *de novo* lesions were treated exclusively with SES (SES group) and compared with a group of 450 consecutive patients treated with BMS for *de novo* lesions in the preceding 6 months (pre-SES group). The total study population thus comprised 958 patients divided into two sequential cohorts, primarily distinguished by the interventional strategy applied (BMS or SES implantation, respectively). This protocol was approved by the hospital Ethics Committee and is in accordance with the Declaration of Helsinki. Written informed consent was obtained from every patient.

All interventions were performed according to current standard guidelines with the final interventional strategy (including use of periprocedural glycoprotein IIb/IIIa inhibitors) at the operator's discretion. All patients were advised to maintain lifelong aspirin. At least 1-month clopidogrel treatment (75 mg/d) was recommended for patients treated in the pre-SES phase. For patients treated with SES, clopidogrel was prescribed for at least 3 months, unless one of the following was present (in which case clopidogrel was maintained for at least 6 months): multiple SES implantation (>3 stents), total stented length >36 mm, chronic total occlusion, and bifurcations.

Determination of costs

For each index procedure, detailed resource use and costs were recorded on a dedicated electronic database, together with the actual costs for 2001 and 2002 and calculated on the basis of equipment opened during the angioplasty, irrespective of its actual use in the patient. With respect to costs, the analysis was limited to direct medical costs. The actual price paid for per SES was €1929 euros, while the average weighted price of a bare stent in the study period was €692. Medication costs were obtained for glycoprotein IIb/IIIa inhibitors and contrast, while for the others, a reasonable assumption of €150 per patient was made to cover the costs of other intra-procedural medications (e.g. heparin, nitrates, saline, beta-blockers, etc.). The cost of post-procedural clopidogrel in both groups was calculated on the basis of duration of prescription determined at the completion of the index procedure.

Lengths of hospital stay were calculated by querying the hospital's admission and discharge database, which records the date of admission and discharge, into and out of individual wards. Consequently, admissions to a particular type of ward are considered on a per day basis. As this hospital is a tertiary referral centre, the majority of discharges are to referring or peripheral hospitals. Length of stay was calculated from the time of the procedure up to the point of discharge from this hospital. Unit costs were estimated on the basis of detailed information from our institution following an approach similar to that reported previously.[8]

Follow-up costs were estimated according to the need for repeat revascularization. As the incidence of death and myocardial infarction (MI) between both groups did not differ, they were not costed.[4,5] A re-intervention was defined as any target-vessel revascularization (TVR) (percutaneous or surgical). Costs of re-intervention were estimated as the product of the event multiplied by the cost per event taken from the RAVEL study, adjusted for inflation.[11] The costs of outpatient visits, related work-up, and other ongoing medications were not tracked.

Determination of effectiveness and cost-effectiveness analysis

Major adverse cardiac events were defined as (1) death, (2) non-fatal MI, or (3) TVR. An MI was diagnosed by a rise in the creatine kinase-MB fraction of more than three times the upper limit of normal. A TVR was defined as a repeat intervention (surgical or percutaneous) driven by any lesion located in the same epicardial vessel(s) as the treated lesion(s). The results of both the 1 and 2-year clinical follow-up have been published.[4,5]

For the purposes of the cost-effectiveness analysis, the following assumptions were required. The incidence of repeat revascularization is given as whole numbers and the proportion estimated according to the Kaplan–Meier method. There were a disproportionate number of post-procedural coronary angiograms performed in the SES period, due to the repeat angiography mandated in 'complex' patients, typically with SES implanted in bifurcations, left main coronary, chronic total occlusions, very small vessels, long stented length (>36 mm), and acute MI.[4] Because of the well-known effect of angiographic re-evaluation in increasing the incidence of repeat revascularization,[12] all re-interventions in the first year were retrospectively adjudicated and classified as clinically driven or non-clinically driven by a group of clinicians not involved in the treatment of the particular patient analysed.[4] Clinically driven repeat revascularizations were defined as any intervention motivated by a significant luminal stenosis ($>50\%$ diameter stenosis) in the presence of anginal symptoms and/or proven myocardial ischaemia in the target-vessel territory by non-invasive testing. No mandated angiographic re-study was performed in the pre-SES group.

In order to correct for the excess additional costs related to the mandatory angiographic studies in the SES group, it was assumed that the actual number of clinically driven restudies would be proportionate to the number of clinically driven re-interventions. Therefore, the number of patients that would have had clinically driven angiography could be calculated from the figures found in the pre-SES phase. As clinically driven re-interventions in the SES phase were less frequent than in the pre-SES by a factor of 0.356, the number of patients who would have undergone clinically driven re-study in the absence of mandatory angiographic follow-up was calculated as $0.356\times$ proportion of patients in pre-SES group with angiography $\times$ number of patients in SES group. From this, it was estimated that 24 patients would have had a re-study in the SES group.

Statistical analysis

Continuous variables are presented as mean $\pm$ SD and were compared by means of the Student unpaired *t*-test. Categorical variables are presented as counts and percentages and compared by means of the Fisher exact test. Resource use is reported on a per patient basis. Cost data are reported as both mean and median values and compared by *t*-tests. All statistical and cost-effectiveness analysis were performed on an intention-to-treat principle. All statistical tests were two-tailed.

The uncertainty surrounding the differences in costs and effects were estimated using the bootstrapping technique. With bootstrapping, average costs and effects were repeated 1000 times. Each bootstrap provides a new estimate of average costs and average

effects with the resulting 1000 estimates summarized in terms of a distribution. Truncating the upper and lower 2.5% of the distribution provides the 95% confidence intervals which are then demonstrated visually. This is a useful method when the distribution cannot be obtained in a classic way.[13] Furthermore, additional graphical representation of the bootstrapping results are presented with 5%, 50%, and 95% probability ellipses, to describe their degree of uncertainty.

Cost-effectiveness was measured as the ICER per repeat revascularization avoided. It is obtained by dividing the difference in medical costs expended by our institution at the end of one and 2 years for the two treatment groups by the difference in repeat revascularization rates over the same time frames.[9]

Results

Baseline and procedural characteristics

The RESEARCH registry was a real-world study into drug-eluting stent use, and enrolled all-comers. The baseline and procedural characteristics in *Table 1* reflect the complex patient demographics typically seen in a tertiary referral centre for PCI. Both groups were reasonably well matched for baseline characteristics, with the exception of previous MI being more common in the pre-SES group. Over half of the patients presented with an acute coronary syndrome, and an acute MI was the reason for intervention in 18% of patients.

Major adverse cardiac events

The 1 and 2-year results of the RESEARCH registry have been published.[4,5] Briefly, the combined outcome of death or MI was similar and the difference in major adverse cardiac events was driven by the reduction in the need for repeat revascularization, defined as TVR in the SES group. Similarly, at 2 years, the reduction in major adverse cardiac events was again due to the reduction in TVR in the SES group.

At the end of 1 year, less patients underwent a re-intervention procedure in the SES group (3.65% in the SES group as compared with 10.4% in the pre-SES group, $P < 0.001$; *Table 4*, *Figure 1*). During the first year of follow-up, because of mandated angiographic re-study, significantly more patients underwent coronary angiography in the SES period compared with the BMS period, 175 vs. 59, $P < 0.001$). At 2 years, the difference in re-intervention

Table 1 Baseline and procedural characteristics

	Pre-SES group ($n = 450$)	SES group ($n = 508$)	*P*-value
Male, *n* (%)	317 (72)	345 (68)	0.4
Age, years ± SD	61 ± 11	61 ± 11	0.7
Diabetes, *n* (%)	67 (15)	90 (18)	0.3
Non-insulin-dependent, *n* (%)	49 (11)	60 (12)	0.7
Insulin-dependent, *n* (%)	18 (4)	30 (6)	0.2
Hypertension, *n* (%)	169 (48)	210 (41)	0.2
Hypercholesterolaemia, *n* (%)	249 (55)	282 (56)	1.0
Current smoking, *n* (%)	153 (34)	156 (31)	0.3
Previous MI, *n* (%)	176 (40)	152 (30)	0.002
Previous angioplasty, *n* (%)	81 (18)	95 (19)	0.8
Previous coronary bypass surgery, *n* (%)	36 (8)	47 (9)	0.5
Single-vessel disease, *n* (%)	235 (52)	232 (46)	0.05
Multivessel disease, *n* (%)	215 (48)	275 (54)	0.05
Clinical presentation	—	—	0.8
Stable angina, *n* (%)	214 (48)	227 (45)	—
Unstable angina, *n* (%)	156 (35)	189 (37)	—
Acute MI, *n* (%)	80 (18)	92 (18)	—
Cardiogenic shock, *n* (%)[a]	9 (12)	9 (10)	0.7
Treated vessel			
Left anterior descending, *n* (%)	267 (59)	298 (59)	0.8
Left circumflex, *n* (%)	149 (33)	161 (32)	0.7
Right coronary artery, *n* (%)	153 (34)	196 (39)	0.2
Left main coronary, *n* (%)	10 (2)	15 (3)	0.6
Bypass graft, *n* (%)	9 (2)	17 (3)	0.2
Lesion type			
Type A, *n* (%)	88 (20)	111 (22)	0.4
Type B1, *n* (%)	143 (32)	156 (31)	0.7
Type B2, *n* (%)	223 (50)	247 (49)	0.8
Type C, *n* (%)	134 (30)	216 (43)	0.000
Bifurcation stenting, *n* (%)	35 (8)	80 (16)	0.000
Number of stented segments ± SD	1.8 ± 0.9	2.0 ± 1.0	0.000
Individual stent length ≥33 mm, *n* (%)	44 (10)	178 (35)	0.000
Total stented length per patient, mm ± SD	30.1 ± 19.6	38.7 ± 28.7	0.000
Nominal stent diameter ≤2.5 mm, *n* (%)	102 (23)	183 (36)	0.000
Post-dilatation with a balloon ≥0.5 mm larger, *n* (%)	85 (19)	249 (49)	0.000
Angiographic success of all lesions, *n* (%)	438 (97)	494 (97)	1.0

[a]Relative to acute MI.

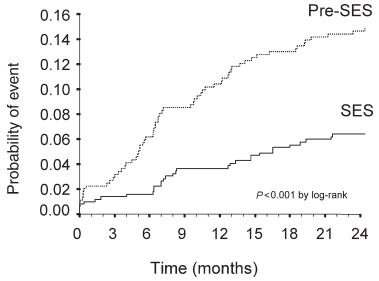

Figure 1 Clinically driven re-intervention (TVR) in the RESEARCH Registry at 2-year follow-up.

rates widened from 6.75 to 8.3%. (a cumulative incidence of 6.4 vs. 14.7% respectively, $P < 0.001$).

Resource use at index procedure

The procedural equipment use is listed in *Table 2* with the results expressed as mean number of items consumed per patient. On a per patient basis, significantly more guiding catheters, coronary wires, balloons, and contrast were used, and more stents were implanted resulting in a longer procedural time in the SES phase compared with the pre-SES phase. This reflects the increased complexity of cases seen in the SES phase. Post-procedurally, total in-hospital stay at our institution was similar, 2.6 days in the pre-SES phase and 2.0 days in the SES group, $P = 0.15$.

Costs of index procedure

The overall average per patient cost of the index procedure was €6887 in the pre-SES group and €9924 in the SES group, an excess of €3036 in the SES group (*Table 3*), driven by the difference of €2925 due to the price premium of SES.

Costs at follow-up

At 1-year follow-up, the difference in costs had narrowed from €3036 to €1968 due to the reduction in re-interventions (*Table 4*). At the end of 2 years following the index procedure, this difference further narrowed to €1869, due to a non-significantly fewer number of events in the SES group in the second year of follow-up.

Cost effectiveness

Figures 2 and *3* depict the estimated differences in costs and effectiveness of SES vs. BMS, at 1 and 2 years. All estimates lie in the right-upper quadrant, indicating that SES are clearly more effective but also more costly than BMS. Note that the ellipse in *Figure 4* is shifted downwards and outwards in the 2-year follow-up, as compared with the 1-year follow-up, although not significantly.

On the basis of costs and results obtained from the RESEARCH registry, the ICER was then calculated. In the 1-year analysis, the ICER for SES was calculated at €29 373 per repeat revascularization avoided; while at the end of 2 years, this number had decreased to €22 627 per repeat revascularization avoided (*Table 4*).

From this ratio, a straight-line relationship exists between the unit price of a new device vs. the ICER at a given unit price of the old device (*Figure 4*). Thus, at a price of €692 per bare stent for the bare stent group (the actual average weighted price of BMSs in this registry), the calculated cost neutral price for the DES would be €1023 with the 1-year result of this registry, while at the maximum acceptable threshold of €10 000 per repeat revascularization avoided,[9] the highest price would be €1336 per DES. At 2 years, the cost neutral price and the cost at the €10 000 threshold declined slightly (€1069 and €1452, respectively) due to the non-significant reduction in events in the second year.

Discussion

The primary finding of this analysis of the RESEARCH registry is that based on the price of €1929 per SES paid by our institution in April 2002, the unrestricted use of SES was not cost-effective to our institution, at either 1 or 2 years, using the acceptable maximum threshold of €10 000 per repeat revascularization avoided. Using 1-year costs and effects, the calculated cost-neutral price for SES was €1023; while at the acceptable threshold of €10 000 per repeat revascularization avoided, the calculated price was €1336 per SES. With the inclusion of second year costs, in association with a further non-significant reduction in events in the second year, the cost neutral price was €1069 or €1452 at the €10 000 threshold.

Specific features of this study

As a tertiary referral centre with a feeder population of 14 peripheral hospitals, our institution has a policy of returning stable patients to their referral hospital or to the hospital in their catchment area. Unstable patients and patients from our catchment area are treated at our institution until such time that they are suitable for discharge home or discharge to their local hospital. In the combined population, only 4.1% of patients were admitted for longer than 10 days at our institution.

The introduction of SES in the second period of the RESEARCH registry created a real-world imbalance. Despite similar presenting symptoms and clinical characteristics, more segments were treated, resulting in longer stented lengths and the use of more stents. Although this resulted in higher costs to the SES group, it reflects daily practice outside of clinical trials, where the introduction of DES has resulted in the implantation of more stents. Furthermore, the ongoing use of DES at our institution resulted in the treatment of more complex patients, with even longer stented lengths implanted in the following year.[14]

Costs outside randomized trials

Cost-effectiveness studies from the randomized RAVEL and SIRIUS trials have been published. In both these studies, use of SES resulted in additional 1-year costs of €166 and US$309 in the SES groups, respectively (NB €1 ~ US$1.30 April 2005). The additional cost of DES was effectively negated by the decreased follow-up costs resulting from a decrease in the need for repeat intervention. In this present study, the reduction in follow-up costs were insufficient to compensate for the elevated index cost, when

Table 2 Resource use at index procedure

Index procedure	BMS ($n = 450$)	SES ($n = 508$)	Difference (95% CI)	*P*-value
Equipment use during the index procedure, expressed as units used per patient unless stated otherwise				
Basic diagnostic packet (includes 0.035 in. wire)	1.00	1.01	0.00 (−0.01; 0.01)	0.5
Diagnostic catheter, *n*	0.63	0.50	0.13 (0.01; 0.25)	0.03
Guiding catheter, *n*	1.43	1.59	−0.16 (−0.27; −0.05)	0.003
Additional 0.035 in. wire, *n*	0.16	0.19	−0.03 (−0.09; 0.03)	0.3
0.014 in. coronary wire, *n*	1.62	2.07	−0.45 (−0.63; −0.28)	<0.001
Coronary balloon, *n*	1.30	1.81	−0.50 (−0.68; −0.32)	<0.001
Multifunctional probing catheter, *n*	0.08	0.06	0.02 (−0.01; 0.05)	0.3
Pressure/Flow/Doppler wire, *n*	0.08	0.07	0.10 (−0.03; 0.05)	0.6
IVUS catheter, *n*	0.15	0.18	−0.02 (−0.08; 0.03)	0.4
Atherectomy catheter, *n*	0.01	0.01	0.00 (−0.01; 0.01)	0.9
Cutting balloon, *n*	0.03	0.02	0.01 (−0.01; 0.03)	0.3
Thrombectomy catheter, *n*	0.00	0.01	−0.01 (−0.02; 0.01)	0.4
Distal protection device, *n*	0.01	0.01	0.00 (−0.02; 0.01)	0.5
Swan Ganz catheter, *n*	0.02	0.04	−0.01 (−0.03; 0.01)	0.3
Temporary pacing wire, *n*	0.02	0.02	−0.01 (−0.02; 0.01)	0.5
Intra-aortic balloon pump, *n*	0.02	0.02	0.01 (−0.01; 0.02)	0.5
Femoral artery closure device, *n*	0.47	0.53	−0.06 (−0.13; 0.01)	0.08
Bare stent, *n*	1.81	–		
Covered stent, *n*	0.01	–		
Drug-eluting stent, *n*	–	2.16		
Contrast volume, mL ± SD	253 ± 118	284 ± 137	−31 (−49; −12)	0.001
Abciximab use, %	33	19	14 (8; 20)	<0.001
Clopidogrel prescription, months ±SD	2.9 ± 2.0	4.0 ± 2.0	−1.1 (−1.4; 1.0)	<0.01
Procedure time, mins ± SD	92 ± 43	107 ± 48	−15 (−21; −9)	<0.001
Post-procedural hospital stay				
ICU, days	0.06 ± 0.75	0.01 ± 0.11	0.05 (−0.01;0.12)	0.12
CCU, days	0.56 ± 1.87	0.54 ± 2.14	0.02 (−0.24;0.28)	0.9
General ward, days	2.27 ± 4.76	1.56 ± 4.1	0.71 (0.15;1.27)	0.01

Table 3 Costs at index procedure, expressed on a per patient basis

Index procedure	BMS	SES	Difference (95% CI of the difference)	*P*-value
Cost of stents, € ± SD	1266 ± 771	4192 ± 2791	−2925 (−3192; −2659)	0.000
Cost of consumables (excluding stents), € ± SD	1575 ± 772	1819 ± 938	−244 (−353; −134)	0.000
Medication, € ± SD	765 ± 529	685 ± 473	79 (15; 143)	0.015
Laboratory cost, € ± SD	1790 ± 841	2078 ± 937	−288 (−401; −174)	0.000
Post-procedural hospital stay, € ± SD	1491 ± 3323	1150 ± 3350	341 (−83; −765)	0.11
Total cost at index, € ± SD	6887 ± 3962	9924 ± 5734	−3036 (−3669; −2403)	0.000

measured at the end of either 1 or 2 years. The respective excess cost in the SES group were €1968 and €1869, respectively, much higher than that reported from the randomized trials. This reflects the results of DES use outside of trials.

Acceptable cost of DES outside randomized trials

The results of RAVEL and SIRIUS would suggest that the prices of DES of €2000 and US$2900 are reasonably cost-effective. At the time this registry was conducted, the price of DES paid for by our institution was €1929 while the price of bare stents was €692, reflecting the prices of April 2002. Since that time, paclitaxel-eluting stents (Boston Scientific Corporation) have been introduced, and zotarolimus-eluting stents (Medtronic Corporation) have recently received CE mark certification. This increased competition, together with an increasing market share of DES, will serve to bring down prices of DES to that judged as cost-effective in our model. Correspondingly, as the market share of BMSs shrink, their prices will also fall, thus necessitating that the price of DES fall even further than that predicted. Given a not unreasonable bare stent price of €400 today, a DES would have to fall to €779 to be cost-neutral within the framework of the model presented here.

Comparison with other 'real-world' trials

The BASKET 'real-world' randomized study demonstrated that at 6 months, DES were on average, €905 more

Table 4 Costs, effectiveness, differences in costs and effectiveness at the end of 1 and 2 years, expressed on a per patient basis

Follow-up events	BMS events, *n*	BMS events, %	BMS cost, €	SES events, *n*	SES events, %	SES cost, €	Difference, (95% CI)[a]
First year of follow-up							
Clinically driven repeat revascularization	45	10.4[b]		18	3.65[b]		6.75 (3.0;9.4)
Re-PCI	35	8.1	695	16	3.3	279	
CABG	10	2.3	393	2	0.4	69	
Total coronary angiography	59	13.1	506	175	3.45	177	
Total follow-up cost			1594			525[c]	
Total cost at 1 year			8481			10 449	−€1968 (−€2854; −€1212) ICER = 29 373 (14 659; 83 884)
Second year of follow-up							
Repeat revascularization	18	4.3		13	2.75		8.3 (3.8;11.4)
Re-PCI	16	3.8	331	11	2.3	203	
CABG	2	0.5	82	2	0.4	73	
Coronary angiography	17	3.8	148	24	4.7	185	
Total follow-up cost			561			461	
Total cost at 2 years			9042			10 911	−€1869 (€2796; €1080) ICER = 22 627 (10 737; 65 978)

[a]95% confidence intervals calculated using the bootstrap method. The comparison of costs and effectiveness are presented in *Figures 3* and *4*.
[b]Event rate derived from Kaplan–Meier estimates.
[c]Correction factor of 0.35 applied to coronary angiograms in the SES phase relative to the BMS phase.

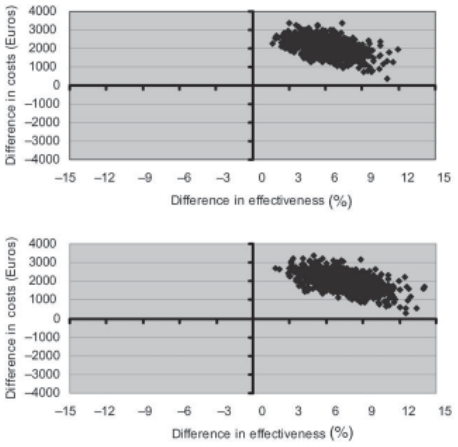

Figure 2 Estimates of differences in cost and effects after bootstrapping analysis based on the normal distributions surrounding the estimates of the relative risks at one (top panel) and 2 years (bottom panel), respectively. All points reside in the top-right quadrant, signifying that SESs are more effective, but more expensive than BMSs, both at 1 and at 2 years following implantation.

expensive per patient when compared with BMS. In that study, the price difference between DES and BMS were considerably less than in this study, resulting in a calculated ICER of less than €20 000 per major event avoided, as opposed to the €29 373 at 1 year, and €22 627 at 2 years per repeat revascularization avoided in our series. Despite the smaller difference, the results of the present study are in concordance with their findings, and has the advantage of extended follow-up out to 2 years.

Implications of prolonged follow-up

A specific feature of this report is the prolonged follow-up out to 2 years. The non-significant widening of the treatment effect from the first to the second year resulted in lowering of the ICER by almost €7000, but not sufficient to make the finding cost-effective. It remains to be seen if prolonged follow-up out to 5 years will equalize the groups, however, most cost-effectiveness studies are generally limited to short-term follow-ups of 1 year.

Applicability to other drug-eluting stent systems and to newer bare-stent systems

This study was a specific comparison between SES and BMS, and since both pricing and efficacy of the different DES systems in the market today vary, the results of this study may not be totally generalizable to other systems. However, given the ongoing price premium and better outcomes of DES, this study may therefore be used as a guide. Similarly, there are now newer generation BMS, such as those incorporating non-drug-eluting coatings (e.g. carbon-, titanium oxide-, and CD34 antibody-coated stents),[15,16] which have demonstrated better restenosis rates than conventional BMS used in this study and consequently, the possibility exists that the differential benefit of DES may be reduced when compared against these newer BMS devices.

Limitations

By design, the costs in this study specifically reflect procedural and follow-up costs directly impacting on our institution. It is therefore an institutional as opposed to a

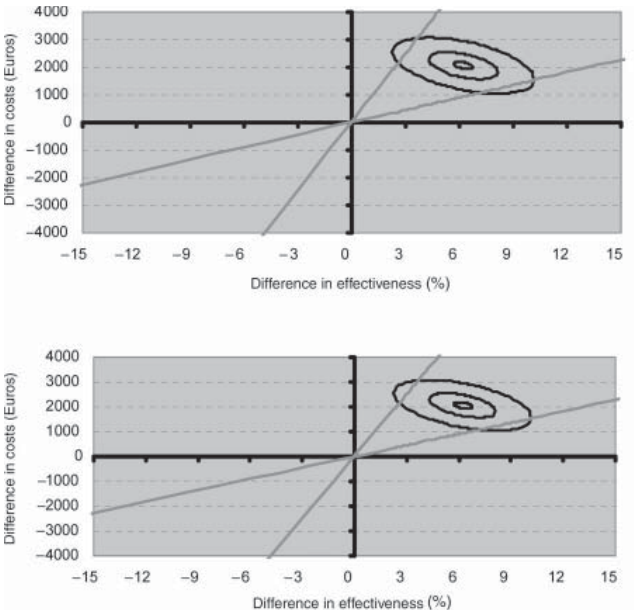

Figure 3 Estimates of differences in costs and effects following bootstrapping, with associated probability ellipses of 5, 50, and 95% (from innermost to outermost ellipse) at one (top panel) and 2 years (bottom panel), respectively. Note that the probability ellipses reside in the top-right quadrant, signifying that SESs are more effective, but more expensive than BMSs, both at 1 and at 2 years following implantation. Note also that the ellipses marginally move outwards and downwards slightly due to the non-significant further reduction in events in the second year.

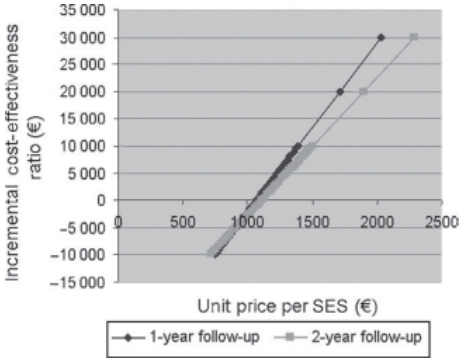

Figure 4 Graph depicting the relationship between the ICER and the unit price per SES in the RESEARCH registry at both 1 and 2-year follow-up.

societal analysis, and therefore underestimates the true overall societal cost by not accounting for total length of stay in other hospitals nor costs associated with follow-up visits and work-up for recurrent symptoms. This was a necessary limitation, given the tertiary referral nature of our practice and the multiple complex co-morbidities seen in this 'real-world' population.

Conclusion

The lower differential effect in real-world outcomes, together with increased material use compared with randomized trials combine to reduce the cost-effectiveness of SESs compared with BMSs. On the basis of our findings, prices of SES need to be further reduced in order to become cost-effective.

Acknowledgements

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Conflict of interest: no conflict of interest.

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Chapter 31

Type-D personality exerts a stable, adverse effect on vital exhaustion in PCI patients treated with paclitaxel-eluting stents

Pedersen SS, Daemen J, van de Sande M, Sonnenschein K, Serruys PW, Erdman RA, van Domburg RT

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Type-D personality exerts a stable, adverse effect on vital exhaustion in PCI patients treated with paclitaxel-eluting stents

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Abstract

Objective: Vital exhaustion is associated with the pathogenesis of cardiovascular disease (CVD), but its prevalence after percutaneous coronary intervention (PCI) with drug-eluting stent implantation, as well as the impact of personality on exhaustion, is not known. In PCI patients, we examined (a) the prevalence of exhaustion, (b) the impact of type-D personality on exhaustion over time, and (c) the clinical significance of type-D personality compared with gender and age as predictors of exhaustion. **Methods:** Consecutive patients (n=419) with stable or unstable angina treated with PCI with drug-eluting stent implantation completed the Type-D Scale (DS14) at baseline and the Maastricht Questionnaire (which assesses exhaustion) at baseline and at 1 year. **Results:** Of all patients, 53% were exhausted at baseline and at 1 year, with 41% experiencing chronic symptoms. Type-D patients [F(1, 417)=98.688; P<.001] had significantly higher exhaustion levels than non type-D patients both at the time of the index PCI and at 1 year. There was a general improvement in symptoms of exhaustion over time [F(1, 417)=5.005; P=.03], but type-D exerted a stable effect on exhaustion (P=.06). In multivariable analysis, type-D (OR=3.53; 95% CI=1.88–6.64) remained an independent predictor of exhaustion at 1 year, adjusting for demographic and clinical risk factors and exhaustion at baseline. The impact of type-D on exhaustion was large compared with a small effect for gender and age, as measured by Cohen's effect size index. **Conclusions:** Symptoms of exhaustion were still highly prevalent in PCI patients 1 year post-PCI despite treatment with the latest technique in interventional cardiology. Type-D exerted a large and stable effect on exhaustion compared with that of gender and age. CVD research and clinical practice may benefit by adopting a personality approach in order to identify high-risk patients.

Keywords: Cardiovascular disease; Drug-eluting stent; Revascularization; Type-D personality; Vital exhaustion

Introduction

Vital exhaustion is a mental state characterized by unusual fatigue, demoralization, and increased irritability [1]. Exhaustion is an etiological risk factor for ischemic heart disease and all-cause mortality in healthy individuals [2] and a prognostic risk factor for adverse health outcomes in patients following percutaneous coronary intervention (PCI) and myocardial infarction (MI) [3–6]. The risk associated with exhaustion in patients with established cardiovascular disease (CVD) ranges from two- to three-fold [3,5], making it a risk factor on par with traditional biomedical risk factors [6,7]. Of note, exhaustion is not merely a marker of subclinical CVD but a risk factor in its own right [3].

Symptoms of exhaustion have been linked to inflammation [8,9], cytomegalovirus, *Chlamydia pneumoniae* [9,10], lower levels of cortisol and adrenocorticotropic hormones [11,12], impaired fibrinolysis [13], and low vagal tone [14],

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all of which have been associated with the pathogenesis of CVD. Conceptually, exhaustion shares several features with depression, and results are conflicting as to their independence [15,16]. Hence, this is the subject of an ongoing debate. To fuel the debate, a recent study found that exhaustion and self-rated health, but not depression, were associated with increased inflammation in women with CVD [17].

The recent Exhaustion Intervention Trial (EXIT) showed that although symptoms of exhaustion were reduced by 55% following a behavioral intervention, this benefit was only seen in patients without a previous history of CVD [18]. Similarly, only patients without a previous history of CVD experienced a 60% reduction in the risk of adverse health outcomes, whereas the intervention did not lead to overall enhanced survival at 2 years follow-up [18].

Although the EXIT increases our knowledge of factors that may impede changes in exhaustion and subsequent benefits to survival, little is known about the impact of personality on exhaustion. Knowledge of the predictors of exhaustion may lead to more successful intervention trials in the future. In addition, focus on patient-centered outcomes, such as exhaustion and its determinants, may bridge the gap between research and clinical practice [19].

In a previous study conducted in the pre-drug-eluting stent era, we identified type-D personality as a predictor of exhaustion in a mixed group of cardiac patients pre- and post-treatment with PCI, coronary artery bypass graft (CABG) surgery, or conservative treatment [20]. Type-D is defined as the tendency to experience increased negative emotions paired with the non-expression of these emotions in social interactions [21]. Type-D is an emerging risk factor in CVD that has been associated with an increased risk of adverse prognosis [22–26]. However, given that the use of drug-eluting stents has been associated with a significant decrease in the risk of restenosis and the need for repeat revascularization [27] and that exhaustion plays a role in the etiology of restenosis post-PCI, it is not clear whether exhaustion remains a problem in the drug-eluting stent era.

The current study was conducted in a series of consecutive PCI patients treated with the paclitaxel-eluting stent (PES) as the default stent. The aims were to (a) evaluate the prevalence of symptoms of exhaustion, (b) examine the impact of type-D personality on exhaustion at the time of the index PCI and at 1 year, and (c) compare the clinical significance of type-D personality with gender and age as predictors of exhaustion.

Materials and methods

Study design and participants

Consecutive patients with stable or unstable angina, treated with PCI at the Erasmus Medical Center Rotterdam using PES as the default strategy between July 1, 2003, and July 1, 2004, qualified for inclusion in the current study. Of the 845 patients treated during this period, 19 patients died within the first month and 116 were excluded due to insufficient knowledge of the Dutch language. The remaining 710 patients were approached and asked to complete a number of psychological questionnaires 4 weeks post-PCI, of whom 536 (75%) agreed. In the remainder of the article, we will refer to this assessment as baseline. Although assessment at 4 weeks was adapted for logistic reasons, preliminary evidence suggests that psychological assessment at the time of PCI may be less optimal than 1 month post-procedure [28].

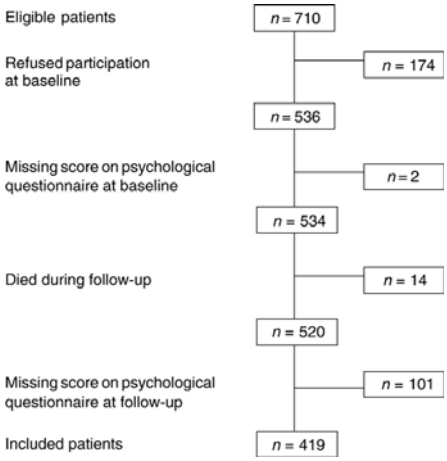

Fig. 1. Flowchart of patient selection.

Given that we used a prospective design, analyses are based on 419 patients, who had a score on the relevant psychological questionnaires both at baseline and at follow-up. See Fig. 1 for a flowchart of the patient selection for the current study.

The study was approved by the local medical ethics committee and conducted in accordance with the Helsinki Declaration. Written informed consent was provided by all patients.

Materials

Socio-demographic and clinical variables

Socio-demographic variables included gender and age. Information on clinical variables, that is, indication for PCI (stable or unstable angina), stent type (PES, sirolimus-eluting stent, or other), multivessel disease, previous cardiac history (i.e., MI, PCI, or CABG prior to the index PCI), hypertension, dyslipidemia, diabetes mellitus, smoking, and cardiac medication (aspirin, beta-blockers, diuretics, ACE inhibitors, and statins), was obtained from the patients' medical records.

Type-D personality

We used the Type-D Scale (DS14) to assess the *distressed* (type-D) personality [21]. The scale consists of 14 items that are answered on a five-point Likert scale from 0 (*false*) to 4 (*true*). Seven items tap negative affectivity, and seven items tap social inhibition (score range, 0–28 for each subscale). Type-D caseness is defined by a high score on both subscales, as determined by a standardized cut-off score ≥10 [21]. The DS14 is a valid and reliable scale with Cronbach's α=.88/.86 and 3-month test–retest reliability (*r*)=.72/.82 for the negative affectivity and social inhibition subscales, respectively [21]. Type-D personality is more than negative affect, as it also takes into account how patients deal with this affect through the inclusion of the social inhibition component [21,22]. The DS14 was administered at baseline.

Vital exhaustion

The Maastricht Questionnaire (MQ) was used to assess symptoms of exhaustion [1]. The questionnaire consists of 21 items that are answered on a three-point scale (0=*no*; 1=*?*; 2=*yes*), with a score range of 0–42. We used a standardized cutoff score ≥14 to identify patients who were exhausted [18,29]. The reliability of the scale, as measured by Cronbach's α, is .89 [1]. The MQ was administered both at baseline and at 1 year post-PCI. Patients were asked to complete the MQ items with regard to how they felt at the time of completing the questionnaire; hence, answers were not prone to recall bias.

Statistical analyses

Discrete variables were compared with the chi-square test (Fisher's exact test when appropriate), whereas continuous variables were compared with Student's *t* test for independent samples. Analysis of variance (ANOVA) for repeated measures was used to examine whether the impact of type-D was stable over time. Univariable and multivariable logistic regression analyses were used to examine the impact of type-D personality on exhaustion at 1 year. Prior to analyses, we dichotomized vital exhaustion using a standardized cutoff, with a score ≥14 indicating those who are exhausted [18,28]. Exhaustion scores were dichotomized to be able to compare results with previous research and to enhance clinical interpretability, as advocated by others [30,31]. In multivariable analyses, we entered type-D personality, baseline exhaustion, gender, age, indication for PCI, stent type, multivessel disease, previous cardiac history (defined as MI, PCI, or CABG prior to the index PCI), hypertension, dyslipidemia, diabetes, and smoking. Cohen's effect size index was used to evaluate the clinical significance of type-D personality compared with gender and age as predictors of exhaustion [32]. An effect size of 0.20, 0.50, and ≥0.80 is considered small, moderate, and large, respectively. We used a *P* value <.05 to indicate statistical significance. Odds ratios (ORs) with 95% confidence intervals (CIs) are reported. All statistical analyses were performed using SPSS 12.0.1 for Windows (SPSS, Chicago, IL, USA).

Results

Differences between responders and non-responders on baseline characteristics

Excluded patients and non-responders on psychological questionnaires were more likely to smoke (22% vs. 14%; *P*=.003) but less likely to suffer from dyslipidemia (63% vs. 74%; *P*=.001) than responders. No other differences were found between excluded patients/non-responders and responders on baseline characteristics, including cardiac medication.

Patient baseline characteristics stratified by personality

Of the 419 patients, 104 (25%) had a type-D personality. Baseline characteristics stratified by personality type are shown in Table 1. Except for type-D patients being more likely to be prescribed diuretics compared with non type-D patients (5% vs. 1%; *P*=.02), no differences were found on baseline characteristics between the two personality types.

Both at baseline and at 1 year post-PCI, 53% of the patients were exhausted according to the predetermined cut-off score ≥14. Of the 419 patients, 173 (41%) experienced chronic symptoms, that is, a score ≥14 on the MQ both at baseline and at 1 year. Exhaustion at 1 year could not be

Table 1
Baseline characteristics stratified by personality type

	Type-D (*n*=104)	Non type-D (*n*=315)	*P*
Demographics			
Males	79 (76)	235 (75)	.88
Age, mean (S.D.)	62 (10)	63 (11)	.30
Indication for PCI			
Unstable angina	55 (53)	137 (44)	.12
Stent type			
PES	91 (88)	284 (90)	.56
Clinical variables			
Multivessel disease	58 (56)	193 (61)	.38
Previous cardiac history[a]	55 (53)	174 (55)	.76
Hypertension	51 (49)	151 (48)	.94
Dyslipidemia	82 (79)	237 (75)	.54
Diabetes mellitus	23 (22)	57 (18)	.45
Current smoking	12 (12)	39 (12)	.96
Cardiac medication			
Aspirin	100 (96)	302 (96)	1.00
Beta-blockers	23 (22)	71 (23)	1.00
Diuretics	5 (5)	2 (1)	.02*
ACE inhibitors	13 (13)	25 (8)	.23
Statins	74 (71)	239 (76)	.41

Values are expressed as *n* (%) unless otherwise specified.
[a] MI, PCI, or CABG prior to the index PCI.
* *P*<.05.

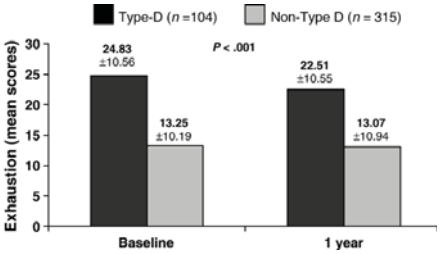

Fig. 2. Exhaustion (mean scores) stratified by type-D personality at baseline and at 1 year post-PCI. Mean scores (± standard deviations) are presented on top of bars.

attributed to a cardiac event (i.e., MI, PCI, or CABG) during follow-up (12% vs. 7%; P=.07).

Impact of type-D personality on exhaustion

As indicated in Fig. 2, ANOVA for repeated measures showed that type-D patients [F(1, 417)=98.688; P<.001] had significantly higher mean exhaustion scores compared with non type-D patients both at the time of the index PCI and at 1 year. The within-subjects effect for time was also significant [F(1, 417)=5.005; P=.03], indicating a general decline in symptoms of exhaustion over time. The type-D×time interaction effect was not significant [F(1, 417)=3.702; P=.06], showing that type-D exerted a stable effect on exhaustion over time.

Patients with chronic exhaustion, defined as exhaustion both at baseline and at 1 year, were more likely to have a type-D personality compared with patients with exhaustion at either baseline or follow-up alone or exhaustion at neither time points, with patients in the no-exhaustion group having the lowest prevalence of type-D [χ^2(3, N=419)=58.822; P<.001] (Fig. 3).

In univariable analyses, type-D was associated with a five-fold increased risk of exhaustion at 1 year post-PCI (OR=5.53; 95% CI=3.23–9.45; P<.001).

Independent predictors of exhaustion at 1 year

In multivariable analysis, type-D (OR=3.53; 95% CI= 1.88–6.64; P<.001) remained an independent predictor of exhaustion at 1 year with a three-fold increased risk, adjusting for demographic (gender and age) and clinical risk factors (unstable angina, stent type, multi-vessel disease, cardiac history, hypertension, dyslipidemia, diabetes, and smoking) and exhaustion at baseline (Table 2). Exhaustion at baseline (OR=9.33; 95% CI=5.73–15.19; P<.001) was also an independent predictor of exhaustion at follow-up.

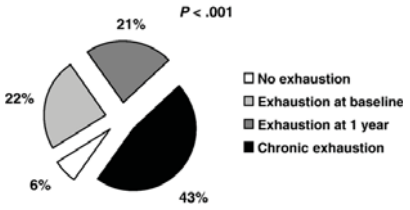

Fig. 3. Prevalence of type-D personality stratified by chronicity of exhaustion.

Table 2
Predictors of exhaustion at 1 year (multivariable analysis)

	OR	95% CI	P
Type-D personality	3.53	1.88–6.64	<.001*
Exhaustion at baseline	9.33	5.73–15.19	<.001*
Males	0.81	0.45–1.43	.46
Age	1.01	0.99–1.04	.39
Unstable angina	0.96	0.59–1.56	.86
PES	2.12	0.94–4.76	.07
Multivessel disease	0.97	0.58–1.62	.92
Previous cardiac history[a]	1.48	0.90–2.43	.13
Hypertension	0.66	0.40–1.10	.11
Dyslipidemia	0.72	0.41–1.28	.26
Diabetes mellitus	1.64	0.87–3.11	.13
Current smoking	0.78	0.36–1.69	.53

[a] Previous MI, PCI, or CABG.
* P<.001.

Clinical significance of type-D personality versus gender and age

Given that gender and age are individual difference variables routinely included in CVD research, we wanted to evaluate the clinical significance of type-D compared with gender and age ≥60 in relation to exhaustion, using Cohen's effect size index. We found that the effect of type-D on symptoms of exhaustion was large both at baseline and at 1 year, whereas the effect of gender was small and that of age was negligible at both time points (Fig. 4). In other words, although the effects of gender, age, and type-D on exhaustion were stable over the 1-year period, they had a significantly differential effect on exhaustion.

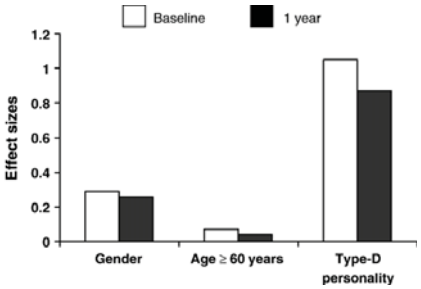

Fig. 4. Clinical relevance of type-D personality versus age and gender as determinants of exhaustion at baseline and at 1 year.

Discussion

This is the first study to examine levels of exhaustion and the impact of personality on exhaustion in PCI patients treated in the drug-eluting stent era. The prevalence of exhaustion at the time of the index procedure and at 1 year was 53%, with 41% experiencing chronic symptoms. This indicates that exhaustion is also highly prevalent in the drug-eluting stent era. Patients with a type-D personality experienced significantly higher levels of exhaustion both at baseline and at 1 year, with type-D exerting a stable effect over time. Type-D was also an independent predictor of exhaustion 1 year post-PCI and was associated with a three-fold increased risk, adjusting for demographic and clinical baseline characteristics and exhaustion at baseline.

Despite treatment with PCI with drug-eluting stents, we found that exhaustion is still highly prevalent, with 41% being exhausted at both time points and, hence, experiencing chronic, persistent exhaustion. This suggests that, once present, exhaustion remains relatively stable and may not abate with time. Similar prevalence rates have been found in studies conducted in the pre-drug-eluting stent era in PCI patients [29] and mixed cardiac patients [20]. In the latter study, the prevalence of exhausted patients decreased from 75% at baseline to 59% following treatment [20]. However, it should be noted that the baseline assessment took place prior to PCI, CABG, or conservative treatment and that these prevalences were point prevalence rates and do not reflect levels of chronic symptoms.

Type-D personality was shown to exert a stable effect on exhaustion during the 1-year follow-up period. In addition, type-D was an independent predictor of exhaustion at 1 year post-PCI, even when adjusting for demographic and clinical characteristics and exhaustion at baseline, with the risk being three-fold. This finding is at odds with a prospective study on personality predictors of chronic fatigue in a sample of working men and women, which found that the impact of personality is negligible when adjusting for baseline fatigue [33]. However, the latter study investigated the impact of single personality traits rather than the combination of traits, used fatigue as the outcome measure rather than the broader construct of exhaustion, and was conducted in a healthy population rather than in CVD patients. In a previous study of a mixed group of cardiac patients in the pre-drug-eluting stent era, we also found that type-D personality was an independent predictor of exhaustion at baseline and at follow-up, but in this study, we did not adjust for baseline scores of exhaustion [20].

The results of the current study have implications for research and clinical practice. Symptoms of exhaustion are still highly prevalent in the drug-eluting stent era, with future studies needing to investigate whether exhaustion is also related to adverse clinical outcome in this era. More importantly, these symptoms persisted over time, which has also been shown by others, both in CVD patients [18,20] and in a healthy sample [34]. Although the EXIT trial demonstrated that a behavioral intervention can successfully alleviate symptoms of exhaustion leading to improved prognosis, this benefit was only seen in patients without a previous cardiac history [18]. In other words, we still have no means by which to reduce exhaustion in patients with a previous cardiac history and enhance their survival, although several suggestions have been put forward in a recent substudy of the EXIT trial that examined the impact of the intervention on quality of life and other secondary outcomes [35]. These suggestions comprise the targeting of inhibition and hostility in future intervention trials and to be aware of potential limiting factors, such as chronic, painful comorbidities (e.g., rheumatism).

Future studies also need to examine the potential interrelationship between exhaustion and depression. Exhaustion and depression conceptually share several features, and to date, results as to their independence have been conflicting [15,16]. This knowledge is important to reduce the burden to patients and for epidemiological research, given the limited number of questionnaires that can usually be included in a study design.

The current study pointed to type-D personality as an important predictor of exhaustion, with type-D exerting a stable and clinically significant effect compared with the effect of gender and age. Gender and age are routinely included in CVD research, whereas, to a large extent, a personality approach has been abandoned since inconsistent results in relation to the type-A Behavior Pattern were reported [36]. The findings of the current study and other studies [23–26] indicate that a personality approach may be advantageous in terms of identifying high-risk patients. However, the ensuing question is that if type-D personality is an all-important predictor of exhaustion, how do we modify its impact on exhaustion and other health outcomes? Undoubtedly, it will be important to teach type-D patients to cope with stress in a different way, which can be done by means of a combination of cognitive behavioral therapy, psychotherapy, and relaxation therapy. However, designing an intervention trial targeting type-D at this point in time is somewhat premature, as we know very little about the moderators and mechanisms that may relate type-D to adverse health outcome, be they physiological or behavioral or a combination thereof. In other words, attention should now be focused on research into these moderators and mechanisms, which may, on the long term, lead to the designing of more successful intervention trials.

The results of the current study should be interpreted with some caution. First, the response rate was 75%, with non-responders/excluded patients being more likely to smoke but less likely to suffer from dyslipidemia than responders. Second, we only included patients with stable or unstable angina, and the results may not generalize to patients, who had an acute MI as indication for PCI. Nevertheless, the studying of patients with angina is important since psychosocial factors have also been shown to predict mortality in these patients [37]. Third, we had no

information on participation in cardiac rehabilitation and the use of psychotropic medication, such as antidepressants, which could potentially influence levels of exhaustion. Fourth, there is evidence to suggest that the Maastricht Interview for Vital Exhaustion may have better predictive validity concerning future cardiac events than the self-report MQ [38], which was used in the current study. However, the MQ has also been shown to predict future adverse clinical events [3,5] and is a more feasible instrument to use in clinical research and practice. An advantage of the current study was its prospective design with the assessment of exhaustion at two time points.

In conclusion, the results of the current study show that exhaustion is still highly prevalent in PCI patients treated in the drug-eluting stent era and that symptoms remain relatively stable over a 1-year period. Type-D personality exerted a three-fold increased risk even when adjusting for baseline exhaustion in addition to demographic and clinical characteristics. When comparing the clinical relevance of type-D with gender and age, two characteristics that are routinely included in CVD research, a large effect was found for type-D, whereas small effects were found for gender and age. CVD research and clinical practice may benefit by adopting a personality approach in order to identify high-risk patients.

Acknowledgments

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Chapter 32

Fatigue, depressive symptoms, and hopelessness as predictors of clinical events following percutaneous coronary intervention with paclitaxel-eluting stents

Pedersen SS, Denollet J, Daemen J, van de Sande M, de Jaegere PT, Serruys PW, Erdman RA, van Domburg RT

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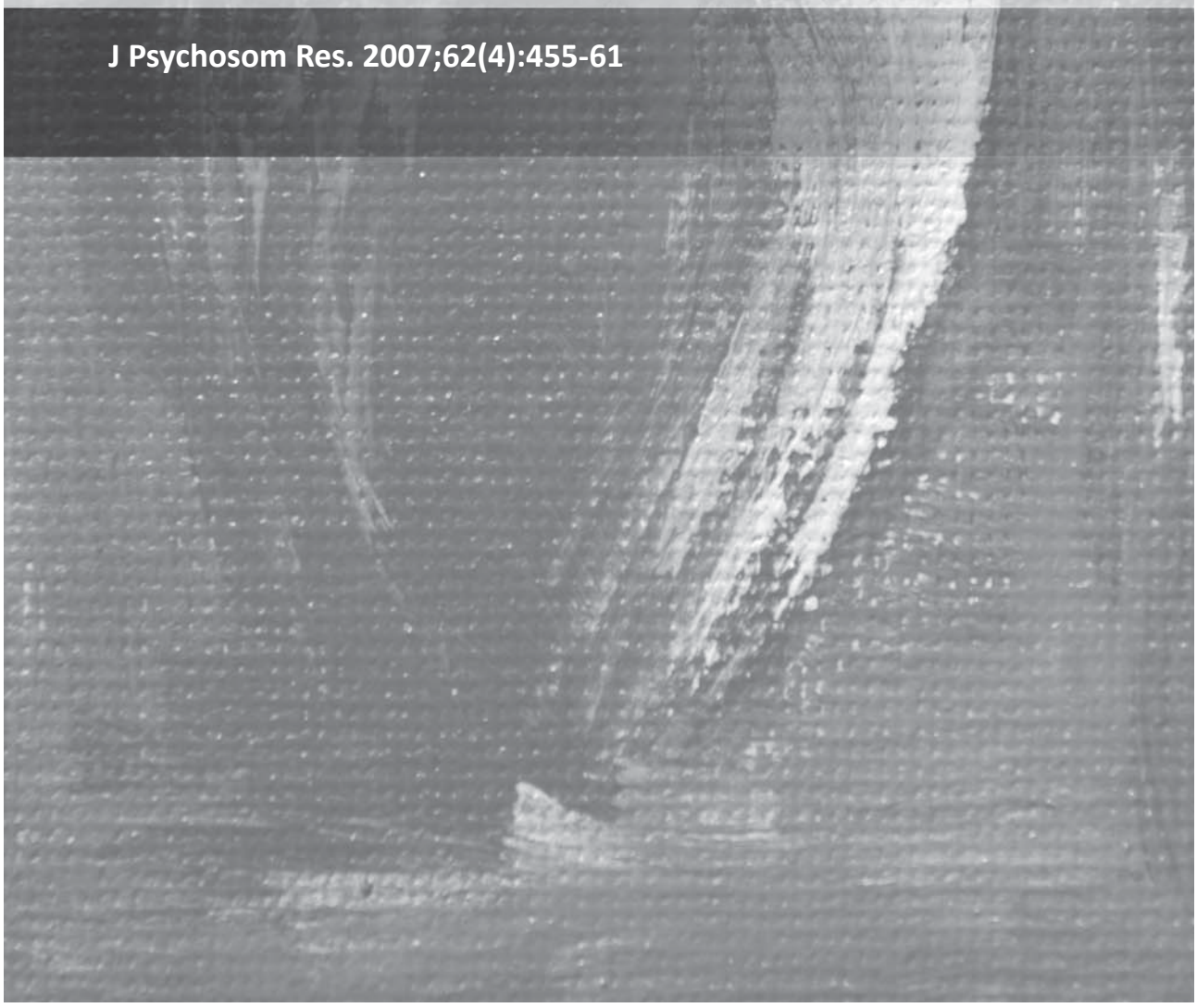

Fatigue, depressive symptoms, and hopelessness as predictors of adverse clinical events following percutaneous coronary intervention with paclitaxel-eluting stents☆

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Abstract

Objective: We investigated the relative effects of fatigue, depressive symptoms, and hopelessness on prognosis at 2-year follow-up in percutaneous coronary intervention (PCI) patients. **Methods:** Consecutively admitted PCI patients (n=534) treated with paclitaxel-eluting stent as the default strategy completed the Maastricht Questionnaire (MQ) at baseline. Apart from an overall vital exhaustion score, the MQ also assesses fatigue (seven items; Cronbach's α=.87) and depressive symptoms (seven items; Cronbach's α=.83), with hopelessness (one item) comprised in the depressive symptom items. Patients were followed up for adverse clinical events (mortality and nonfatal myocardial infarction) at 2 years. **Results:** At 2-year follow-up, there were 31 clinical events. In univariable analyses, overall vital exhaustion and depressive symptoms, but not fatigue, were associated with adverse prognosis; in multivariable analysis, depressive symptoms [hazard ratio (HR)=2.69; 95% confidence interval (95% CI)=1.31–5.55] remained the only predictor of clinical outcome. Among the depressive symptoms, hopelessness (HR=3.44; 95% CI=1.65–7.19) was the most cardiotoxic symptom. The incidence of clinical events was higher in the high-hopelessness patients (11% vs. 3%; P=.001) than in the low-hopelessness patients. Hopelessness (HR=3.36; 95% CI=1.58–7.14; P=.002) remained an independent predictor of clinical outcome at 2 years in adjusted analysis. **Conclusion:** Symptoms of depression, but not fatigue, predicted adverse clinical events. Hopelessness was the most cardiotoxic symptom, associated with a more than three-fold risk of clinical events 2 years post-PCI. Screening for hopelessness may lead to the identification of high-risk patients.

Keywords: Coronary artery disease; Depressive symptoms; Fatigue; Hopelessness; Percutaneous coronary intervention; Prognosis

Introduction

In the context of coronary artery disease (CAD), there is an ongoing debate as to whether depressive symptoms reflect actual depression or symptoms of underlying disease, given the overlap between depression and somatic symptoms, such as fatigue, trouble sleeping, and so on [1,2]. Fatigue [3–6], depression [1], and hopelessness [7,8] have all been associated with CAD. Fatigue is a frequently reported symptom in patients with cardiac conditions, with prevalence rates ranging from 59% to 75% [9]. Fatigue has been shown to precede the onset of myocardial infarction (MI) [3] and to be a risk factor for ischemic heart disease and mortality in healthy individuals [4]. In CAD patients, fatigue or exhaustion confers a two-fold to three-fold increased risk of morbidity and mortality, adjusting for clinical risk factors including disease severity [5,6].

☆ No conflict of interest exists.

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Fatigue in patients with cardiac conditions has primarily been assessed with the Maastricht Questionnaire (MQ), which taps symptoms of exhaustion, demoralization, and increased irritability [10]. However, evidence suggests that the MQ assesses not only symptoms of fatigue but also symptoms of depression [11,12]. Given that depression is a risk factor for adverse clinical outcome in CAD [1,2,13], it is possible that depressive symptoms, as assessed by the MQ, may predict prognosis above and beyond fatigue. Previous attempts addressing this issue have primarily been performed at a conceptual level and have yielded inconsistent results [11,12,14–16].

Knowledge of the nature of depressive symptoms is important for secondary prevention in order to optimize risk stratification in clinical practice. Hence, there is a quest for the identification of the core and most cardiotoxic depressive symptoms. In epidemiological studies, hopelessness has been associated with the progression of carotid atherosclerosis [17,18], risk of mortality, and incidence of MI and cancer [7,19]. Although hopelessness may be considered a feature of depression, the strength of association with established depression scales is weak, suggesting that this psychological symptom should be studied in its own right [19]. To our knowledge, only one study has examined the role of hopelessness in the clinical course of CAD in patients with established disease and has found hopelessness to be associated with reduced survival [8]. However, this study did not compare the influence of fatigue relative to the influence of depressive symptoms and hopelessness.

Hence, in the current study, we investigated the relative effect of fatigue, depressive symptoms, and hopelessness on prognosis in patients treated with percutaneous coronary intervention (PCI).

Materials and methods

Participants and study design

Consecutively admitted patients presenting with stable or unstable angina, treated with PCI at the Erasmus Medical Center Rotterdam (Rotterdam, The Netherlands) between July 1, 2003, and July 1, 2004, qualified for inclusion in the current study. Implantation with paclitaxel-eluting stent comprised the default strategy. During this period, 845 patients were treated; patients who died within the first 4 weeks after the index procedure (n=19) or who were not sufficiently proficient in the Dutch language to complete a psychological questionnaire (n=116) were excluded. The remaining surviving patients (n=710) were approached in writing and asked to complete the MQ 4 weeks post-PCI, which, in the remainder of the article, will be referred to as baseline; 536 (response rate, 75%) agreed to participate. Patients were followed up for clinical adverse events for 2 years.

Excluded patients and nonresponders on the MQ were more likely to smoke (22% vs. 14%; P=.003) but were less likely to suffer from dyslipidemia (63% vs. 74%; P=.001) than responders. No other differences were found between excluded/nonresponders and responders on baseline characteristics, including cardiac medication.

The hospital medical ethics committee approved the protocol. All patients provided written informed consent, and the study was carried out to conform with the Helsinki Declaration.

Demographic and clinical variables

Demographic variables comprised sex and age. Information on clinical variables, [i.e., indication for PCI (stable or unstable angina), previous MI, previous coronary artery bypass graft (CABG) surgery, previous PCI, stent type (paclitaxel-eluting stent or other), multivessel disease, hypertension, dyslipidemia, diabetes mellitus, smoking, and cardiac medications such as aspirin, angiotensin-converting enzyme (ACE) inhibitors, β-blockers, diuretics, and statins] was obtained from medical records.

Fatigue, depressive symptoms, and hopelessness

The 21-item MQ, administered at baseline, was used to evaluate overall vital exhaustion and symptoms of fatigue, depression, and hopelessness [10]. Items were answered on a 3-point scale (0=*no*, 1=*?*, 2=*yes*), with the total score ranging from 0 to 42. The reliability of the total scale is good (Cronbach's α=.89) [5]. Research suggests that the MQ predominantly assesses two symptom dimensions: fatigue and depression [11]. We could replicate these findings in the current study (Table 1). A principal components analysis (varimax rotation with scree plot criterion to determine the number of factors to extract) indicated two dominant dimensions, and both scales had good internal consistency, as measured by Cronbach's α: (I) fatigue (seven items; Cronbach's α=.87; variance=36.4%) and (II) depressive symptoms (seven items; Cronbach's α=.83; variance=8.0%). Hopelessness was assessed with Item 10 of the MQ (i.e., "Have you experienced a feeling of hopelessness recently?"). Previous studies have also used one or two items to assess hopelessness as a risk factor for the onset of CAD [7,8,17,18].

Clinical end point

The end point was defined as a clinical adverse event (all-cause mortality or nonfatal MI) 2 years post-PCI.

Statistical analysis

Comparisons of baseline characteristics stratified by hopelessness (using the highest tertile to indicate a high score) were performed using chi-square test (Fisher's exact test, when appropriate) for nominal variables and Student's t test for independent samples for continuous variables.

Table 1
Symptoms of fatigue and depression, as assessed by the MQ

Item	Factor analysis	Reliability[a]	MQ item number
Fatigue (Factor I)			
1. Do you often feel tired?	*.76*	0.69	1
2. Do you have a feeling that you have not been accomplishing much lately?	*.75*	0.69	5
3. Do you feel weak all over?	*.71*	0.69	4
4. I feel fine (reverse).	*.71*	0.68	14
5. Do you feel more listless lately than before?	*.68*	0.67	8
6. Do you have a feeling these days that you just do not have what it takes any more?	*.65*	0.58	17
7. Do you sometimes feel that your body is like a battery that is losing its power?	*.63*	0.58	15
		Cronbach's α=.87	
Depressive symptoms (Factor II)			
1. Would you want to be dead at times?	*.76*	0.57	16
2. Do you feel you want to give up trying?	*.72*	0.59	13
3. Do you feel dejected?	*.68*	0.66	18
4. Do you believe that you have come to a "dead end"?	*.66*	0.66	7
5. Do you feel like crying sometimes?	*.60*	0.50	19
6. Have you experienced a feeling of hopelessness recently?	*.56*	0.57	10
7. Do you ever wake up with feelings of exhaustion and fatigue?	*.49*	0.46	20
		Cronbach's α=.83	

Factor loadings are presented in italics.
[a] Corrected item–total correlations (Cronbach's α=estimate of internal consistency).

Univariable and multivariable Cox regression analyses were used to examine the predictive value of the total MQ scale (21 items) and the MQ subscales fatigue (seven items) and depressive symptoms (seven items), using both continuous and dichotomized scores. When using dichotomized scores, we used the standardized cutoff of ≥14 for the total MQ [20] and the highest tertile to indicate clinically manifest symptoms on the separate fatigue and depressive symptom dimensions, respectively. In all multivariable analyses, we adjusted for sex, age, multivessel disease, previous cardiac history, hypertension, dyslipidemia, diabetes, and smoking. Hazard ratios (HRs) with 95% confidence intervals (CIs) are reported. $P<.05$ was used to indicate statistical significance. All tests were two-tailed. All analyses were performed using SPSS 12.0.1.

Results

Of the 536 patients, two patients did not have a score on the hopelessness item of the MQ and were therefore excluded from further analyses.

Baseline characteristics

Baseline characteristics stratified by hopelessness are shown in Table 2. Patients who scored high on hopelessness were younger, were more likely to have had a previous cardiac history, and were more likely to have been prescribed ACE inhibitors. No other differences on demographic and clinical characteristics were found between high-hopelessness patients and low-hopelessness patients.

Fatigue, depressive symptoms, and clinical events

At 2-year follow-up, there were 31 (21 deaths and 10 nonfatal MIs) clinical events.

In univariable analyses using dichotomized scores, depressive symptoms, but not fatigue, were significantly associated with the incidence of death and nonfatal MI at 2-year follow-up (Fig. 1). Subjecting these subscales and the original MQ scale (assessing vital exhaustion, cutoff of ≥14) to a multivariable Cox regression analysis using a stepwise procedure, depressive symptoms (HR=2.69; 95% CI=1.31–5.55; $P=.007$), but not fatigue and vital exhaustion, were associated with clinical outcome (Table 3). A stepwise procedure was chosen in order to extract the component(s) that exerted the most toxic influence on prognosis.

Table 2
Baseline characteristics stratified by hopelessness

	High hopelessness (n=187)	Low hopelessness (n=347)	P
Demographic characteristics			
Male (%)	68	74	.20
Age in years [mean (S.D.)]	61 (11)	64 (11)	.002**
Married/partner (%)	81	81	1.00
Clinical variables (%)			
Paclitaxel-eluting stent[a]	90	88	.53
Multivessel disease	60	60	1.00
Cardiac history[b]	62	52	.04*
Hypertension	45	50	.35
Dyslipidemia	73	74	.87
Diabetes mellitus	24	18	.12
Smoking	18	12	.06
Cardiac medication (%)			
Aspirin	93	96	.15
ACE inhibitors	16	6	<.001***
β-Blockers	25	21	.26
Diuretics	2	1	.81
Statins	77	73	.39

[a] Paclitaxel-eluting stent was used as the default stent (i.e., in 89% of the total sample). The other stents used were sirolimus-eluting stent (4%), both paclitaxel-eluting stent and sirolimus-eluting stent (1%), or bare-metal stent/balloon dilation (6%).
[b] MI, PCI, or CABG prior to the index event.
* $P<.05$.
** $P<.01$.
*** $P<.001$.

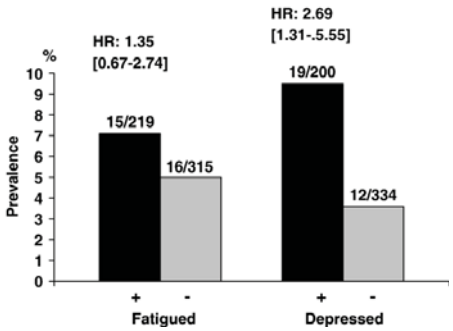

Fig. 1. Death/MI stratified by fatigue and depressive symptoms. *Numbers are presented on top of bars.

Hopelessness and clinical events

Given the possibility that the predictive value of depressive symptomatology might be attributed to specific symptoms such as hopelessness, we performed a series of univariable analyses using continuous scores of the items. Only the symptoms "hopelessness" and "wanting to be dead" were significant predictors of death/MI (Table 4). In a multivariable analysis with a stepwise procedure subjecting all depressive symptom items as continuous scores, the only symptom that was retained was "hopelessness" (MQ 10; HR=1.93; 95% CI=1.33–2.80; *P*=.001). Since "hopelessness" and "wanting to be dead" (i.e., the only two items that were significant predictors in univariable analyses) could potentially be equally important cardiotoxic depressive symptoms, we entered both in a multivariable analysis, together with baseline characteristics. However, only hopelessness (HR=1.91; 95% CI=1.28–2.86; *P*=.02), but not "wanting to be dead" (HR=0.97; 95% CI=0.62–1.48; *P*=.88), was associated with adverse clinical events

Table 3
Baseline symptoms and death/MI (31 events) at 2 years post-PCI

	HR [95% CI]	*P*
(A) Univariable analysis		
Subscale scores		
Fatigue	1.35 [0.67–2.74]	.40
Depressive symptoms	2.69 [1.31–5.55]	.007**
Total MQ score		
Vital exhaustion	2.73 [1.17–6.33]	.02*
(B) Multivariable analysis[a]		
Significant		
Depressive symptoms	2.69 [1.31–5.55]	.007**
Nonsignificant		
Fatigue		.42
Vital exhaustion		.29

[a] Stepwise procedure.
* *P*<.05.
** *P*<.01.

Table 4
Predictive value of specific depressive items in relation to death/MI at 2 years post-PCI[a]

	HR [95% CI]	*P*
1. Hopelessness (MQ 10)	1.89 [1.31–2.74]	.001**
2. Wanting to be dead (MQ 16)	1.59 [1.07–2.37]	.02*
3. Feeling dejected (MQ 18)	1.24 [0.83–1.85]	.30
4. Feeling like crying (MQ 19)	1.19 [0.81–1.75]	.38
5. Waking up exhausted (MQ 20)	1.16 [0.80–1.69]	.43
6. Wanting to give up trying (MQ 13)	1.15 [0.77–1.71]	.50
7. Coming to a "dead end" (MQ 7)	1.07 [0.71–1.62]	.75

[a] Univariable analyses, using continuous scores for depressive items.
* *P*<.05.
** *P*<.01.

on follow-up. After dichotomizing the hopelessness symptom, with the highest tertile representing clinically manifest symptomatology, the incidence of clinical events was 11% (20 of 187) in high-hopelessness patients versus 3% (11 of 347) in low-hopelessness patients (*P*=.001). Hopelessness was associated with a more than three-fold risk (HR=3.44; 95% CI=1.65–7.19; *P*=.001) of adverse clinical outcome in univariable analysis (Fig. 2).

Entering the hopelessness symptom together with the rest of the subscale comprising the six other depression symptoms showed that hopelessness was an independent predictor of clinical events (HR=4.07; 95% CI=1.76–9.43; *P*=.001), whereas the six-item depression score was no longer associated with death/MI (HR=0.73; 95% CI=0.32–1.63; *P*=.44). In multivariable analysis, hopelessness (HR=3.36; 95% CI=1.58–7.14; *P*=.002) remained an independent predictor of death/MI and was associated with a more than three-fold increased risk, adjusting for sex, age, multivessel disease, previous cardiac history, hypertension, dyslipidemia, diabetes, and smoking.

In the final analysis, we investigated whether the addition of hopelessness to a multivariable model, comprising demographic and clinical baseline characteristics, improved the level of prediction of death and MI on follow-up. As indicated by the −2 log likelihood function, the level of

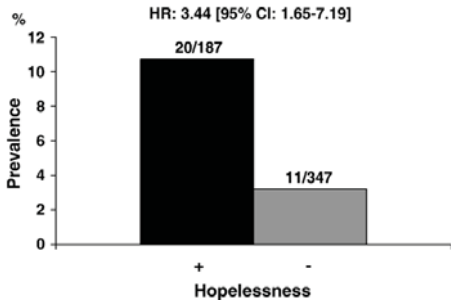

Fig. 2. Death/MI stratified by hopelessness. *Numbers are presented on top of bars.

prediction of the model improved with the addition of hopelessness [χ^2=10.420 (*df*=1), *P*=.001].

Discussion

To our knowledge, this is one of the first studies to have examined the relative effects of fatigue, depressive symptoms, and hopelessness on clinical events in patients with established CAD. In PCI patients treated with paclitaxel-eluting stents, we found that depressive symptoms, but not fatigue, were associated with adverse clinical outcomes, with the most cardiotoxic depressive symptom being hopelessness. Hopelessness was associated with a three-fold increased risk of death/nonfatal MI at 2 years in adjusted analyses.

The last decade has witnessed a surge in research on depression as a risk factor for CAD, leading to a call for the recognition of depression as an established risk factor [13]. Despite extensive research, we still know little about the nature of depressive symptoms and those that are most toxic in terms of predicting clinical outcomes. Hence, identification of the core and most toxic symptoms of depression is now receiving increased attention [1,2,21]. However, studies to date have been rather heterogeneous in their focus, ranging from deriving subscales from the Beck Depression Inventory (BDI) and relating them to clinical outcome [1], to comparing the predictive validity of instruments (BDI vs. the depression subscale of the Hospital Anxiety and Depression Scale) [2], to assessing whether depressive cognitions comprise an underpinning of depression in post-MI patients [21].

In the current study, we identified hopelessness as the depressive symptom that was most salient in predicting prognosis. PCI patients who scored high on hopelessness, as measured by one item on the MQ, had a more than three-fold increased risk of mortality and nonfatal MI 2 years postprocedure, independent of baseline demographic and clinical characteristics. Previous epidemiological studies also found that hopelessness was associated with the progression of carotid atherosclerosis [17,18], morbidity, and mortality [7,19], but to our knowledge, only one study has examined the impact of hopelessness as a risk factor in patients with established CAD [8]. In the latter study, hopelessness was also associated with decreased survival and was shown to exert an independent effect on prognosis relative to depressive symptoms. However, the study did not compare the influence of fatigue relative to depressive symptoms and hopelessness.

Physiological pathways through which hopelessness may exert its deleterious effect on health include decreased heart rate variability (particularly reduced vagal tone or parasympathetic activity) [22], impaired fibrinolysis [23], and inflammation [17]. In the latter study, plasma fibrinogen, a marker of systemic inflammation, was shown to mediate the relationship between hopelessness and progression of carotid atherosclerosis. Compliance may comprise a behavioral pathway, given that depression has been shown to have a negative influence on adherence to cardiac rehabilitation [24] and medication [25]. However, whether these results extend to hopelessness needs to be confirmed in future studies.

Given the relatively high prevalence of fatigue and its deleterious effects on health [3–5,9], it is surprising that fatigue has not received more attention in the cardiovascular literature. Although we were not able to confirm that fatigue was associated with adverse prognosis in the current study, it is too premature to write off fatigue as a risk factor in CAD. The reason for the nonsignificant result may be due to the relatively small number of events in the current study, as the incidence of death and nonfatal MI was larger in fatigued patients than in nonfatigued patients. As voiced by others, there is an urgent need to develop measures of fatigue that tap these symptoms in patients with cardiac conditions without the confounding of related symptomatology [11]. With the availability of such measures, it will be possible to establish the salience of fatigue as a predictor of clinical events in CAD.

The findings of the current study have implications for research and clinical practice. Given that there is an inverse relationship between the length of a questionnaire and the response rate [26], when collating a test battery, it may be important to prioritize the inclusion of a measure of hopelessness if there is no room for a more lengthy measure of depressive symptoms. A two-item measure of depressive symptoms [i.e., the Patient Health Questionnaire (PHQ-2)], which includes hopelessness, has previously been shown to have good sensitivity and specificity, compared with the gold standard of a clinical diagnosis of depression, and to be sensitive to change [27]. The recent four-item Symptoms of mixed Anxiety–Depression Index (SAD_4) also includes hopelessness [28] and has been shown to predict a clinical diagnosis of depression even when adjusting for depressive symptomatology, as measured by the BDI. However, neither the PHQ-2 nor the SAD_4 has yet been used as a potential predictor of clinical outcome in CAD. In terms of clinical practice, screening for hopelessness is feasible and can be incorporated into the daily routine of practicing cardiologists. PCI patients suffering from hopelessness need to be identified early on and to be followed more closely throughout in order to motivate them to participate in cardiac rehabilitation, as they may be more inclined to refuse participation or to drop out from rehabilitation programs [24]. In terms of intervention, it may be possible to reduce feelings of hopelessness using a cognitive–behavioral approach either on its own or in combination with pharmacotherapy, as hopelessness is predominantly considered a cognitive symptom of depression [29,30].

The current study has some limitations. First, for 42% of the patients, we had no information on left ventricular ejection fraction; therefore, in multivariable analyses, we were not able to adjust for measures of disease severity

but only for a measure of the extent of disease, as assessed by multivessel disease. Second, results may not be generalizable to MI patients, since only patients with stable or unstable angina as an indication for PCI were included. Nevertheless, the results of this study show that the assessment of psychosocial risk factors is also important in more low-risk patients, such as patients with angina, given their impact on adverse clinical events. Third, 25% of patients declined to participate. However, nonresponders and excluded patients (excluded due to lack of language proficiency) did not differ from responders on demographic and clinical baseline characteristics, except for nonresponders/excluded patients being more likely to smoke and less likely to suffer from dyslipidemia. Fourth, our multivariable model was overfitted given the number of adverse clinical events. Fifth, hopelessness was assessed by one item, but other studies have also used a one-item measure of hopelessness and have shown that hopelessness is a predictor of adverse clinical outcome [8]. Finally, although it may seem contrary to expectations that the item "Do you ever wake up with a feeling of exhaustion and fatigue?" loaded on the depression factor rather than on the fatigue factor, insomnia and fatigue both form part of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnostic criteria for a major depressive disorder.

In conclusion, we found that depressive symptoms, but not fatigue, were associated with adverse clinical outcome in PCI patients treated with paclitaxel-eluting stents. More specifically, hopelessness proved to be the most cardiotoxic component and was associated with a more than three-fold increased risk of death and nonfatal MI at 2 years, after adjusting for demographic and clinical baseline characteristics. It is feasible to include the assessment of hopelessness in research protocols and clinical practice. Future studies that replicate these findings are warranted, given that few studies have examined the impact of hopelessness on patients with established CAD.

Acknowledgments

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Chapter 33

Reduced positive affect (anhedonia) predicts major clinical events following implantation of coronary-artery stents

Denollet J, Pedersen SS, Daemen J, de Jaegere P, Serruys PW, van Domburg RT

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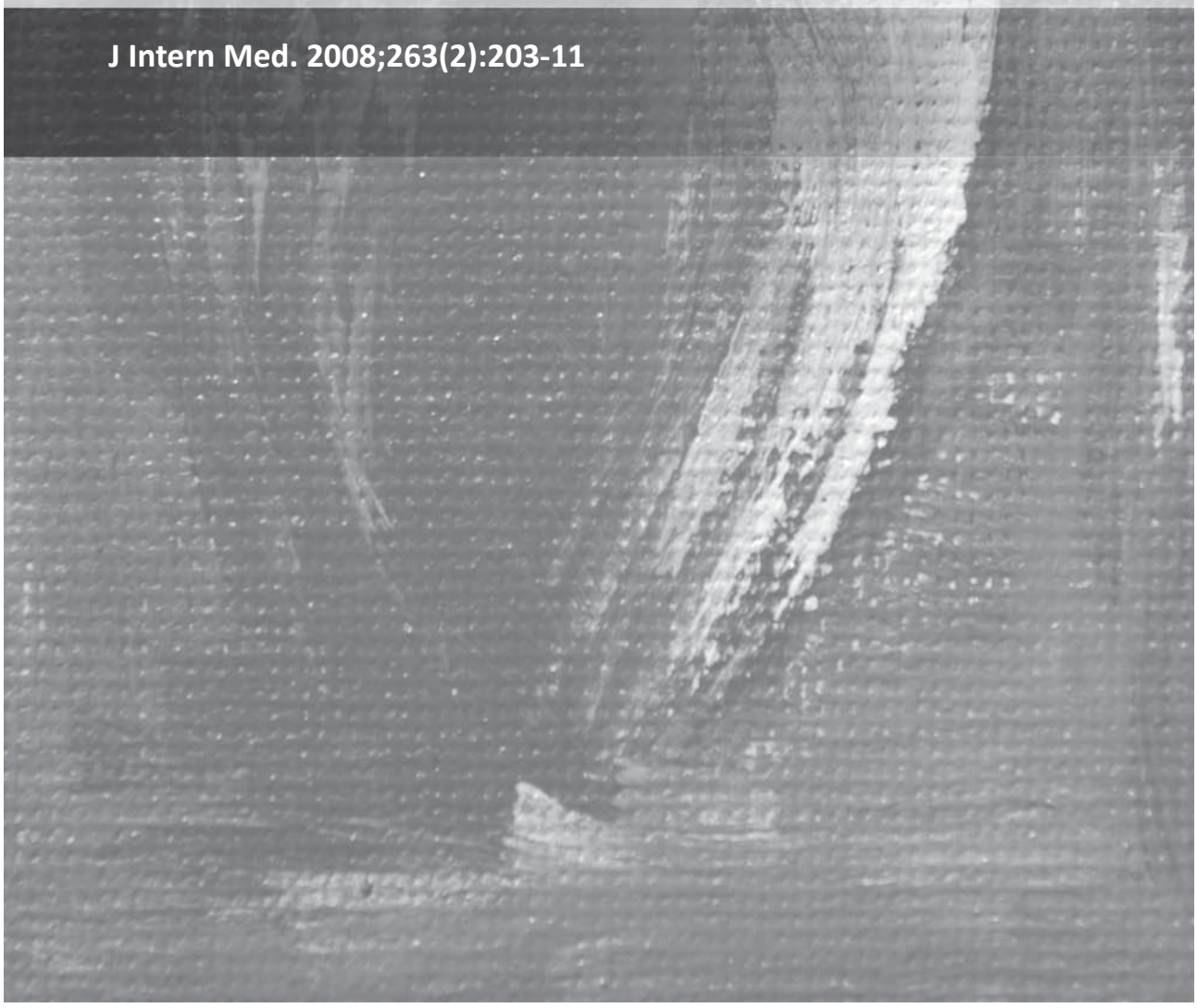

Reduced positive affect (anhedonia) predicts major clinical events following implantation of coronary-artery stents

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Abstract. Denollet J, Pedersen SS, Daemen J, de Jaegere P, Serruys PW, van Domburg RT (Tilburg University, Tilburg; and Erasmus Medical Center, Rotterdam; The Netherlands). Reduced positive affect (anhedonia) predicts major clinical events following implantation of coronary-artery stents. *J Intern Med* 2008; **263**: 203–211.

Objective. Emotional distress has been related to clinical events in patients with coronary artery disease, but the influence of positive affect (i.e. mood states such as activity, joy and cheerfulness) has received little attention. Therefore, we wanted to investigate the role of positive affect on clinical outcome after percutaneous coronary intervention (PCI) with stent implantation in these patients.

Design. Prospective follow-up study. At baseline, patients from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry completed measures of positive affect, depression and anxiety post-PCI. Patients with reduced positive affect scored 1 SD below the mean score.

Setting. University Hospital; Thoraxcenter of the Department of Cardiology.

Subjects. 874 patients (72% men; 62.2 ± 10.9 years) from the RESEARCH registry.

Main outcome measure. Death or myocardial infarction (MI) 2 years post-PCI.

Results. At follow-up, there were 52 clinical events (deaths $n = 27$, MIs $n = 25$). Reduced positive affect and depression/anxiety were associated with poor prognosis, but reduced positive affect was the only independent predictor of events. The incidence of death/MI in adequate versus reduced positive affect patients was 4% (29/663) vs. 11% (23/211); HR = 2.55 (95% CI 1.46–4.34, $P = 0.001$), adjusting for clinical variables. Reduced positive affect and diabetes were independent prognostic factors, and patients with one (HR = 2.84, 95% CI 1.58–5.10) or both (HR = 5.61, 95% CI 2.25–13.99) of these factors had a higher risk when compared with nondiabetic patients with adequate positive affect, $P \leq 0.003$.

Conclusions. Reduced positive affect independently predicted death/MI following stent implantation, and improved risk stratification above and beyond diabetes.

Keywords: coronary artery disease, diabetes, depression, positive affect, anhedonia.

Introduction

Symptoms of psychosocial distress have been associated with an increased risk of cardiac events [1–4]. However, little is known about the impact of positive affect. Positive affect refers to mood states such as joy, activity and cheerfulness [5]. Positive affect is not merely the opposite of negative affect [6], as

people can experience positive and negative emotions at the same time [7]. Epidemiological research in middle-aged adults [8] and patients with coronary artery disease (CAD) [9] has confirmed that these emotions are relatively independent mood dimensions.

Positive affect may enhance immune function [10] and one's ability to achieve successful outcomes in life [11], and dampen physiologic reactivity to stress [12]. Reduced positive affect has also been associated with an increased risk of mortality [13] and stroke [14] in community-based studies of older adults. By contrast, there is a paucity of research on the role of positive affect in surviving serious illness [5]. Positive affect may benefit survival in AIDS [15] and surgery [16] patients, but more research is needed on the effect of adequate versus reduced positive affect in cardiac patients. An advantage of studying positive affect is that CAD patients are not likely to describe themselves in terms of negative emotions alone. Accordingly, positive affect scales may be especially responsive to the effect of intervention [17].

The current study investigated the role of positive affect in the clinical course of CAD patients who received percutaneous coronary intervention (PCI) with either a sirolimus-eluting stent (SES) or a bare metal stent (BMS) implantation, as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry [18]. The aim of this study was to compare the impact of positive versus negative affect on the risk of clinical events at 2-year follow-up of these patients.

Methods

Participants

The RESEARCH registry population comprised consecutive patients with CAD treated with PCI with either SES or BMS implantation between October 2001 and October 2002 [18]. This registry was designed to evaluate the efficacy and safety of SES implantation in patients treated with PCI in the 'real world' of interventional cardiology; no patients were excluded based on anatomical/clinical presentations, and 68% of the RESEARCH registry patients would not qualify for inclusion in clinical trials [19]. At 6 months post-PCI, all living patients were asked to complete a psychological questionnaire; 874 (71%) returned this questionnaire [20]. Nonresponders were younger, more likely to have a history of MI, to have diabetes and to be treated with ACE inhibitors, but less likely to have renal impairment or to be treated with β-blockers and aspirin than responders (all $P < 0.05$). The mean age of the present sample of 875 patients was 62.2 ± 10.9 years, and 72% ($n = 629$) were men; 41% ($n = 358$) were treated with SES. The study was approved by the local hospital ethics committee, and every patient provided written informed consent.

Symptoms of anxiety and depression

The two seven-item scales of the Hospital Anxiety and Depression Scale (HADS) were administered 6 months post-PCI to assess anxiety and depression symptoms [21].

The HADS has been related to mortality in patients referred for exercise testing; a cut-off score ≥8 yields a good balance between sensitivity and specificity for both scales and was used to indicate probable anxiety and depression caseness [22, 23].

Assessment of positive affect

Self-report depression/anxiety scales not only tap a broad range of negative affects in CAD patients but also (the absence of) positive affect [9]. Previous research in myocardial infarction patients showed that the HADS comprised three distinct factors, and found support for the use of a subscale to assess (the absence of) positive affect [24]. Accordingly, we also used exploratory factor analysis (i.e. principal components analysis with varimax rotation) to examine the notion that positive affect was distinctly different from negative affect in the present study. The scree-plot was used as a criterion for the number of underlying factors to extract.

This analysis yielded two dominant affect factors that were assessed by the HADS measure, and a third, smaller factor. Four items of the HADS reflected a positive affect dimension as indicated by high loadings on factor I; i.e. *being cheerful*, *looking forward with enjoyment to things*, *being still able to enjoy things* and *seeing funny side of things* (Table 1). Corrected item–total correlations ranging between 0.69/0.72 and Cronbach's $\alpha = 0.86$ indicated a high internal consistency of this four-item factor. Previous research supports the use of a factor analytically derived HADS subscale to assess positive affect [24]; by analogy, these four items were summed to comprise a Positive Affect score (range 0–12, mean 9.4, SD 2.9) in this study.

Factor II represented the negative affect dimensions of mood, and was also defined by four items: i.e. *fears something awful will happen* (item 3; factor loading 0.84), *feelings of panic* (item 13; loading 0.83), *frequently worries* (item 5; loading 0.75) and *feels tense* (item 1; loading 0.62). Factor III comprised three items reflecting relaxation; i.e. *not bothered by restlessness* (item 11; loading 0.80), *feels relaxed* (item 7; loading 0.69) and *enjoys a good book or radio/TV program* (item 14; loading 0.67). These items were summed to comprise Negative Affect (mean 3.1 ± 2.8; $\alpha = 0.85$) and Relaxed Affect (mean 6.5 ± 2.1; $\alpha = 0.69$) scores respectively.

Table 1 Positive affect scale ($n = 874$)

Item no.	Factor analysis factor I	Reliability[a] Cronbach's $\alpha = 0.86$	HADS item
1. Looks forward with enjoyment to things	**0.80**	0.69	HADS #12
2. Still enjoys things he/she used to enjoy	**0.79**	0.72	HADS #2
3. He/she can laugh and see funny side	**0.77**	0.72	HADS #4
4. Feels cheerful	**0.74**	0.69	HADS #6

HADS, Hospital Anxiety and Depression Scale [21–23]. Factor loadings are presented in bold.
[a]Corrected item–total correlations; Cronbach's α = estimate of internal consistency.

Two of the three remaining HADS items loaded on the Positive Affect (items 8 and 10) and one on the Negative Affect (item 9) factor. These items had relatively lower item–total correlations, did not add significantly to the internal consistency of the corresponding scales and therefore were not included in the new affect subscales. Overall, we replicated the three-factor model of the HADS, but the Positive Affect subscale that we derived included four items, and not seven as previously described [24].

Endpoint

The endpoint was a composite of death and MI 2 years post-PCI. Events occurring between PCI and psychological assessment were excluded as an endpoint from analyses. MI was diagnosed by a rise in the creatine kinase-MB level to more than three times the upper normal limit [25].

Demographic, clinical variables and medication

Demographic variables included age and sex. Information on clinical variables was obtained from the patients' medical records at the time of psychological assessment. Clinical variables included stent type, multi-vessel disease (52%, $n = 458$), MI (37%, $n = 327$), coronary artery bypass graft (CABG) surgery (12%, $n = 101$) or PCI (25%, $n = 219$) prior to index event, hypercholesterolaemia (81%, $n = 709$), hypertension (39%, $n = 339$), smoking (31%, $n = 273$), renal impairment (creatinine ≤60 ml/min, 30%, $n = 265$) and diabetes (15%, $n = 127$). More than 95% of the patients were treated with β-blockers ($n = 856$), aspirin ($n = 840$) and clopidogrel ($n = 830$); statins (67%), calcium antagonists (47%) and ACE-inhibitors (26%) were also included.

Statistical analyses

Cox regression analyses were performed to investigate continuous scores on the positive affect, negative

affect, depression and anxiety scales as predictors of clinical events. To enhance the clinical interpretability of findings on the role of affect measures in prognosis, similar analyses were used to examine the effect of a 1 SD decrease in positive affect on the clinical course following implantation of coronary stents. Hence, a score ≤7 (i.e. 1 SD below the mean Positive Affect score) was used to identify patients with anhedonia, which refers to markedly reduced positive affect [24]. In multivariable analyses, we adjusted for age, gender and clinical variables. All variables, including reduced positive affect, were entered simultaneously in the multivariable models. In *post hoc* analyses, diabetes and reduced positive affect were used to stratify patients by four risk groups. All statistical tests were two-tailed; $P < 0.05$ was used to indicate statistical significance. Hazard ratios (HR) with 95% confidence intervals (CI) are reported. Analyses were performed using SPSS (SPSS Inc., Chicago, IL, USA) for Windows version 12.0.

Results

Positive affect, depression, anxiety and clinical events

At 2-year follow-up, there were 52 clinical events (death $n = 27$, MI $n = 25$). In univariable analyses, higher scores of positive affect and relaxed affect were associated with a lower risk of clinical events (HR = 0.86 and 0.87 respectively), while higher scores of negative affect (HR = 1.14), depression (HR = 1.10) and anxiety (HR = 1.10) were associated with a higher risk of events (Table 2, top). However, a multivariable regression analysis indicated that positive affect (HR = 0.85), older age (HR = 1.94) and male sex (HR = 2.81) were the only independent predictors of clinical events, and that symptoms of depression, anxiety or other affect measures did not add significantly to this prediction model (Table 2, bottom).

Table 2 Baseline emotions and death/MI post-PCI ($n = 52/874$)

	Hazard ratio [95% CI]	*P*
Univariable analysis		
Affect measures		
Positive affect	0.86 [0.79–0.93]	0.0001
Relaxed affect	0.87 [0.77–0.98]	0.021
Negative affect	1.14 [1.05–1.24]	0.002
HADS Scales		
Depression	1.10 [1.04–1.17]	0.001
Anxiety	1.10 [1.04–1.18]	0.002
Multivariable analysis		
Significant		
Positive affect	0.85 [0.78–0.92]	0.0001
Age ≥60 years	1.94 [1.07–3.54]	0.03
Male sex	2.81 [1.33–5.91]	0.007
Not significant		
Relaxed affect		0.54
Negative affect		0.06
Depression		0.81
Anxiety		0.06

MI, myocardial infarction; PCI, percutaneous coronary intervention.

Individual positive affect items and clinical events

To better understand which characteristics of positive affect were responsible for the observed health effect, we examined the relation between individual items and prognosis. The items *being still able to enjoy things* (HR = 0.51, 95% CI 0.40–0.66, $P < 0.0001$), *being cheerful* (HR = 0.62, 95% CI 0.47–0.80, $P < 0.0001$) and *looking forward with enjoyment to things* (HR = 0.66, 95% CI 0.51–0.86, $P = 0.002$) were significantly related to prognosis, adjusting for age and sex. There was a trend for the item *seeing funny side of things* (HR = 0.74, 95% CI 0.55–1.00, $P = 0.053$).

Reduced positive affect and clinical events

Using a score ≤7 (i.e. 1 SD below the mean) as a cut-off, 211 patients (24%) were classified as experiencing reduced positive affect. These patients had a significantly increased rate of 2-year clinical events (23/211 = 11%) when compared with patients with an adequate positive affect (29/663 = 4%); OR=2.84, 95% CI 1.59–5.07, $P < 0.0001$, adjusted for age and sex. Conversely, a high positive affect score (i.e. 1 SD above the mean) was associated with a decreased risk of clinical events (OR = 0.33, 95% CI 0.15–0.72, $P = 0.005$). However, a multivariable model only retained reduced positive affect as

independent predictor of events ($P < 0.0001$). There was a trend for high positive affect ($P = 0.064$).

Demographic and clinical predictors

In univariable analysis, multi-vessel disease ($P = 0.045$), previous CABG ($P = 0.005$), diabetes mellitus ($P = 0.008$) and ACE-inhibitor therapy ($P = 0.032$) were significantly related to an increased risk of death/MI at 2-years follow-up (Table 3, top). There was also a trend for age ≥60 years ($P = 0.055$), male sex ($P = 0.069$) and previous MI ($P = 0.069$). In multivariable analysis, diabetes mellitus (HR = 2.42), previous CABG (HR = 2.36), male sex (HR = 2.28) and age ≥60 (HR = 2.03) emerged as independent predictors of prognosis (Table 3, bottom); there was a trend for smoking ($P = 0.057$). These variables were included in the following analyses.

The prevalence of reduced positive affect was different as a function of demographic characteristics; i.e. this prevalence was significantly lower in men when compared with women (Table 4). There was also a trend for older age to be associated with reduced positive affect ($P = 0.081$). However, reduced positive affect was not significantly associated with smoking, previous CABG or diabetes.

Independent predictors of cardiac events

To determine whether reduced positive affect and the clinical variables that emerged from previous analyses were independent predictors of prognosis, we entered these factors in a multivariable regression model. The final Cox regression model indicated that reduced positive affect was associated with a more than 150% increase in risk of clinical events, adjusting for clinical and demographic variables (Table 5). Diabetes, previous CABG, male sex and older age (all with an increase in risk >100%) were also independent predictors of events in this regression model.

Diabetes and reduced positive affect subgroups

Because diabetes and reduced positive affect emerged as two independent predictors of clinical

Table 3 Baseline characteristics and death/MI post-PCI (n = 52/874)

	Hazard ratio [95% CI]	*P*
(a) **Univariable analysis**		
Demographics		
Age ≥60 years	1.78 [0.99–3.21]	0.055
Male sex	1.95 [0.95–4.00]	0.069
Clinical factors		
Sirolimus-eluting stent	1.50 [0.83–2.70]	0.18
Multi-vessel disease	1.80 [1.01–3.18]	0.045
Previous MI	1.66 [0.96–2.85]	0.069
Previous CABG	2.54 [1.33–4.83]	0.005
Previous PCI	1.55 [0.87–2.77]	0.014
Hypercholesterolemia	0.84 [0.43–1.63]	0.60
Hypertension	1.17 [0.68–2.03]	0.58
Smoking	1.38 [0.79–2.41]	0.26
Diabetes mellitus	2.29 [1.24–4.24]	0.008
Renal impairment	1.22 [0.69–2.14]	0.50
Beta-blockers	1.10 [0.15–7.96]	0.93
Aspirin	1.04 [0.25–4.29]	0.95
Clopidogrel	2.92 [0.40–21.09]	0.29
Statins	1.06 [0.59–1.92]	0.84
Calcium antagonists	1.28 [0.74–2.22]	0.37
ACE-inhibitors	1.85 [1.06–3.23]	0.032
(b) **Multivariable analysis**		
Age ≥60 years	2.03 [1.10–3.78]	0.024
Male sex	2.28 [1.10–4.73]	0.027
Previous CABG	2.36 [1.21–4.58]	0.011
Smoking	1.76 [0.98–3.15]	0.057
Diabetes mellitus	2.42 [1.31–4.49]	0.005

Previous, prior to index event; MI, myocardial infarction; CABG, coronary artery bypass surgery; PCI, percutaneous coronary intervention.

Table 4 Association between baseline characteristics and reduced positive affect

	Adequate positive affect (n = 663)	Reduced positive affect (n = 211)	*P*-value
Age ≥60 years	54% (360)	61% (129)	0.081
Male sex	74% (490)	66% (139)	0.024
Previous CABG	11% (72)	14% (29)	0.25
Smoking	30% (199)	35% (74)	0.17
Diabetes mellitus	14% (91)	17% (36)	0.23

Number of subjects appears within parentheses.

events, we examined the combination of these factors in relation to prognosis in *post hoc* analyses. Patients were stratified by four subgroups: no diabetes and adequate positive affect (n = 572), diabetes but adequate positive affect (n = 91), reduced positive affect but no diabetes (n = 175) and both diabetes and reduced positive affect (n = 36). Patients with no diabetes but reduced positive affect had a similar risk of clinical events when compared with patients with diabetes but adequate positive affect (P = 0.81); the effect of reduced positive affect on prognosis was equal to that of diabetes (Fig. 1). Patients with either diabetes or reduced positive affect had a higher risk when compared with nondiabetic patients with adequate positive affect (HR = 2.84, 95% CI 1.58–5.10). Those with both diabetes and reduced positive affect were in the highest risk group (HR = 5.61, 95% CI 2.25–13.99).

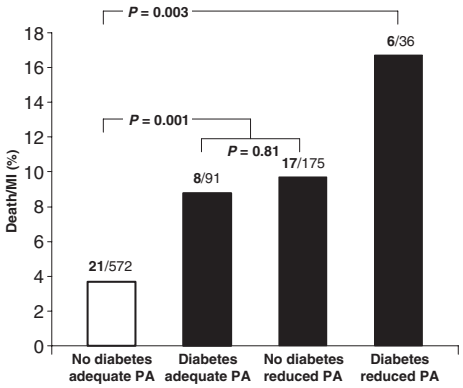

Fig. 1 Clinical events stratified by diabetes/reduced positive affect subgroups. Number of clinical events (bold) and patients are presented on top of each bar. PA: positive affect; adequate PA: score ≥8 on the Positive Affect Scale; reduced PA: score ≤7 on the Positive Affect Scale.

Discussion

The impact of negative emotions has been studied extensively in the context of CAD. By contrast, the potential role of positive emotions on clinical outcome has been neglected. In the current study, we found that the incidence of death/MI 2-year post-PCI was significantly higher in patients with reduced positive affect, with the risk being more than twofold adjusting for demographic and clinical factors. Of note, reduced positive affect was a risk factor on par with diabetes, an established, biomedical risk factor. Stratification of patients by reduced positive affect and diabetes showed that patients with both risk factors had a significantly higher risk compared with the presence of one or neither of these risk factors.

Table 5 Multivariable predictors of death/MI post-PCI (n = 52/874)

	Hazard ratio [95% CI]	P
Demographics		
Age ≥60 years	2.04 [1.09–3.82]	0.026
Male sex	2.53 [1.21–5.30]	0.014
Clinical factors		
Previous CABG	2.15 [1.11–4.19]	0.024
Smoking	1.62 [0.90–2.91]	0.11
Diabetes mellitus	2.32 [1.25–4.30]	0.008
Psychological status		
Reduced positive affect[a]	2.55 [1.46–4.34]	0.001

Previous, prior to index event; MI, myocardial infarction; CABG, coronary artery bypass surgery; PCI, percutaneous coronary intervention.
[a]Score ≤7 on the Positive Affect Scale coded as 1.

Unresolved issues in coronary-artery stenting include the adverse effect of diabetes on the clinical course post-PCI [26]. The present findings confirm this, but also suggest that markedly reduced positive affect may have an adverse effect as well. Constructs that are related to positive affect such as positive self-perceptions [27] and emotional well-being [28] have previously been associated with increased longevity in older community-dwelling individuals, and optimism has been related to a significantly reduced risk for cardiac events [29]. There is also some evidence to suggest that the relative lack of positive emotions may be a better predictor of clinical outcomes than negative emotions [13, 14, 28]. Accordingly, we also found that the presence of negative emotions, in addition to reduced positive affect,

did not increase the level of prediction of clinical events. These findings suggest that future research should focus more on the role of anhedonia, as indicated by the relative inability to enjoy things or to be cheerful, in the prognosis of CAD patients.

CAD patients may be more likely to recognize themselves by means of a combination of negative and positive emotions rather than negative emotions alone. Positive affect is not merely the opposite of negative affect [6]; rather there seems to be a relative independence of positive and negative affect in CAD patients [8, 10], which the factor analysis of the HADS in the present study also confirmed. Hence, positive affect needs to be assessed in its own right. For example, future randomized trials may benefit from the assessment of basal positive affect levels.

There are several potential pathways through which positive affect could influence health, although at this point they remain speculative as they are yet to be tested empirically. One pathway is health-related behaviours, that is the adoption of more health-promoting practices, such as exercising or getting sufficient sleep [5]. The autonomic nervous system comprises another mechanism, with positive affect probably altering the activity of the sympathetic nervous system in turn leading to decreases in heart rate and blood pressure [5, 12]. The hypothalamus–pituitary–adrenal axis may also be involved, as induction of positive mood states has been shown to lead to reduction in cortisol levels [5]. In turn, cortisol regulation is important in immune functioning. In a recent study, Steptoe *et al.* showed that happiness was inversely related to inflammation, heart rate (although in men only) and cortisol levels [10]. These factors have all been associated with cardiovascular prognosis.

This study has several limitations regarding the causality and conclusiveness of its findings. First, the psychological questionnaires were administered 6 months after stenting because of logistic reasons [20]. This may have biased our results; i.e. there may have been a number of high positive affect individuals who died in the first months post-PCI, before the assessment of positive affect took place. It is also possible that patients who reported more positive affect at this time point were doing so because they had less recurrence of angina or other health problems following successful PCI. However, the study did not include a measure of symptoms at 6 months after stenting, making it impossible to control for the effect of cardiac symptoms at this point in time. Secondly, nonresponders differed from responders on baseline characteristics, and therefore the results may not be generalizable to the total sample. Thirdly, we did not have information on the cause of death, and the combined endpoint included MI as well as all types of death. Fourthly, we had no information on health-related behaviours, apart from smoking, that potentially may explain the relation between affect and health outcome.

Finally, the scale used in this study may not be a typical measure of positive affect; i.e. it includes one affective item (cheerful), two items reflecting the ability to enjoy things (or lack of anhedonia) and one on humour. Nevertheless, the technique that we used to construct a positive affect measure has also been used by others in studies that have factor analysed the Center for Epidemiologic Studies Depression Scale (CES-D) to derive a positive affect component.

This study also has a number of strengths, including its prospective design and use of psychometrically sound measures of self-reported symptoms of depression and anxiety. Moreover, this study was conducted in the 'real world' of interventional cardiology, representing patients seen in daily clinical practice [19]. Research conducted in the 'real world' has been proposed as a means by which to close the gap between research and clinical practice [30]. Finally, given the paucity of research on positive affect and coronary health, the findings of the present study add to our understanding of the influence of emotions on cardiovascular health.

In conclusion, we found that reduced positive affect was a significant independent predictor of adverse clinical events, adjusting for demographic and clinical risk factors. Of note, negative emotions did not

add to the level of prediction of clinical events above and beyond positive emotions and demographic and clinical risk factors. In addition, reduced positive affect was a risk factor on par with diabetes, with patients with both risk factors forming a high-risk group. The present results highlight the importance of looking beyond depression and other negative emotions and also focusing on the relative lack of positive emotions in CAD research and clinical practice. The results also suggest that subgroups of patients, such as those with diabetes and reduced positive affect, may not benefit from coronary-artery stent implantation on par with other patients. Finally, this points to a new target for behavioural interventions, namely focusing on enhancing positive affect.

Conflict of interest statement

No conflict of interest was declared.

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Part IX

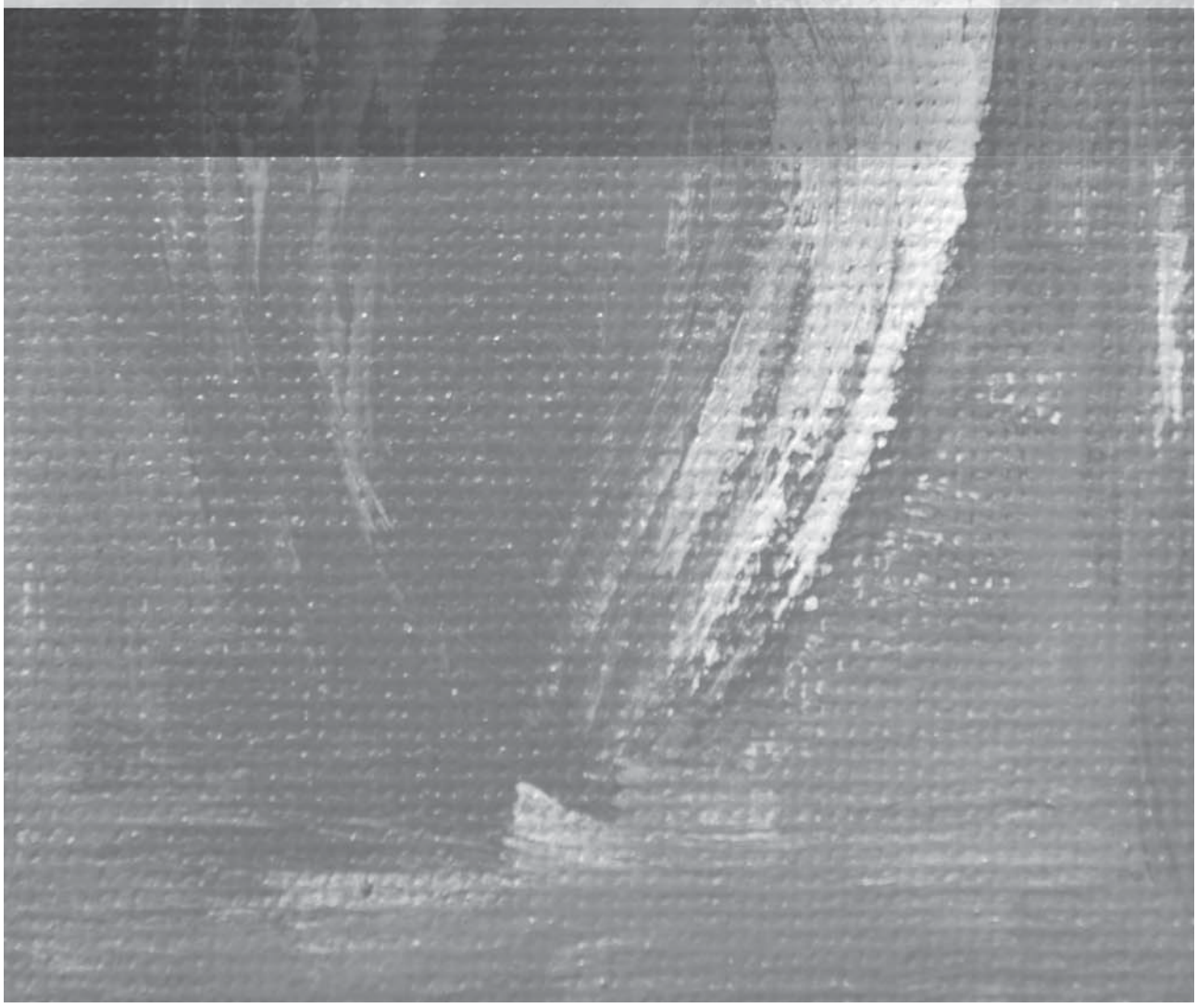
Summary and conclusions

Samenvatting en conclusies

Acknowledgements

Curriculum Vitae

List of Publications



Summary and Conclusions

Pivotal randomized controlled trials and registries showed that both sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) proved to be superior to bare metal stents (BMS) at 1-year of follow-up in selected patients. The present thesis aims to provide insights into the long-term safety, efficacy and caveats of drug-eluting stents (DES).

The all-comer population

The Thoraxcenter was one of the few centers worldwide that pursued an unrestricted DES use from the moment of the commercial introduction of the Cypher stent in April 2002. By extending the follow-up of the RESEARCH and T-SEARCH registries (in which SES and PES respectively were used in an unrestricted manner), we were the first to demonstrate that SES remained significantly superior to BMS at 2, 3 and 4 years of follow-up (Chapters 5 and 6). The use of SES proved to decrease major adverse cardiac event rates with 27% and 43% at 3 and 4 years respectively as compared to BMS. These lower event rates were mainly due to a persistent and significant decrease in target vessel revascularization rates along with similar rates of death and myocardial infarction. Additionally, we demonstrated that there was no statistically significant difference in safety and efficacy endpoints between SES and PES (Chapter 4).

The performance of DES in specific patient and lesion subsets

Following all patients treated in our center between January 2000 and December 2005 allowed us to assess the particular performance of DES in high-risk patient and lesion subsets. Recognizing the detrimental impact of renal impairment on the long-term outcome of patients treated with PCI, we demonstrated that in a cohort of 10 patients on haemodialysis, no cases of death, myocardial infarction or target lesion revascularization occurred up to 1 year (Chapter 7). In Chapter 8, we looked for the performance of DES in patients presenting with acute myocardial infarction, a subset of patients that had been rarely studied in randomized controlled trials. While the use of SES proved to be superior to BMS at 1 year in reducing repeat revascularization, we demonstrated that at 3-years, the use of both SES and PES was no longer superior to BMS in reducing major adverse cardiac events in patients presenting with ST-segment elevation myocardial infarction. Additionally, we demonstrated that PES were not superior to BMS in reducing the incidence of adverse cardiac events at 1-, 2- and 3 years of follow-up. Chapter 8 demonstrates that this latter finding could be due to the increased rates of stent thrombosis in both DES groups as compared to the BMS group.

Moreover, the growing subset of patients from diabetics was studied. With an accelerated and more aggressive form of atherosclerosis and subsequently higher rates of restenosis as compared with non-diabetics, diabetes is inherently linked to a smaller vessel size, longer lesion length, greater plaque burden and a possibly differently acting restenotic cascade as compared to non-diabetics. Given their superior antirestenotic properties, DES were hypothesized to be a particular interesting option in these high-risk patients. In Chapters 9 we demonstrate that in 708 consecutive diabetic patients, at 2 years, there was a trend towards a more favorable outcome associated with the use of PES over BMS. There was no significant difference between SES and PES in each of the clinical endpoints, and neither in the NIDDM patients, which are hypothesized to be better off with PES. After propensity analyses we found that none of the differences in any of the clinical endpoints in SES or PES as compared to BMS reached statistical significance. We hypothesized that part of this non-superiority was due to the high rate of stent thrombosis in both DES cohorts (4.4% in the SES group vs. 2.4% in the PES group) as compared to the BMS group (0.8%). Following these patients for another more year (Chapter 10) revealed that the trend toward a superior outcome with PES became statistically significant, whereas the differences between SES and BMS did not. After multivariate adjustment, risks of TVR and MACE (all-cause mortality, any myocardial infarction or TVR) in PES were lower than in BMS (Hazard ratio [HR] 0.50 [95%CI: 0.33-0.75] for TVR, HR 0.65 [95%CI: 0.48-0.87] for MACE), but these risks in SES were comparable with BMS (HR 0.75 [95%CI:

0.46-1.24] for TVR, HR 0.77 [95%CI: 0.52-1.13] for MACE).

Focussing more specifically on the performance of DES in specific lesion types, we started by evaluating the long-term safety and efficacy of DES in bifurcations lesions. SES proved to be safe and efficacious despite the challenging clinical setting of the bifurcation lesion by using either the Crush or Culotte technique (Chapter 11). With the growing confidence in the superiority of DES, the clinical indications for their use expanded despite the lack of long-term data. Physicians started to stent smaller vessels, longer lesions and used more stents. In Chapter 12 we assessed the relatively efficacy of SES and PES in vessels with a diameter of 2.25mm or less, a clinical setting which would have resulted in exclusion of the patient in pivotal randomized controlled trials. At 2 years, the cumulative incidence of major adverse cardiac events (MACE) in the SES group was significantly lower than in the PES group (10.3% vs. 23.3%, P = 0.02). Another challenging clinical setting which would without any doubt have been treated with bypass surgery several years ago is the chronic total occlusions. In Chapter 13 we demonstrated that SES where associated with a similar safety profile as compared to BMS up to 3 years of follow-up. However, the crude difference in TVR was only 3.5% (12.7% in the BMS group vs. 9.2% in the SES group). Respecting the limited size of the study population (n=147), we concluded that the use of SES in patients with chronic total occlusions did not appear to be significantly superior to BMS at 3 years of follow-up.

Percutaneous treatment of stenoses involving aorto-ostial lesions is a technically demanding procedure for interventionalists and has been associated with lower procedural success, and poorer clinical and angiographic outcomes when compared with treatment of non-ostial lesion, however data on the efficacy of DES for ostial lesions are still limited. In Chapter 14 we examined the 7-months angiographic and 2-year clinical outcome of 76 consecutive patients treated with PES for aorto-ostial lesions. At 7-months the late lumen loss was 0.48mm, which resulted in a TVR rate of 14.5% along with a total MACE rate of 31.6% at 2 years. We concluded that although the use of PES was feasible, the gradual increase in late adverse events makes that PCI for aorta-ostial lesions remains problematic.

Finally, we analyzed the 4-year outcome of SES and PES versus BMS after concerns were raised on the long-term safety of DES for saphenous vein graft disease. In a cohort of 250 patients with vein graft disease, the cumulative survival rate in the DES group was 80.5% versus 77.5% in the BMS group (adjusted HR 1.09; 95% CI 0.63 – 1.90) along with a higher event free survival of clinically driven target vessel revascularization in the DES group as compared to the BMS group (81.6% vs. 69.0%; adjusted HR 0.53; 95% CI 0.27 – 1.05).

Disputing the safety concerns

In September 2006, several proceedings from the European Society and world congress of Cardiology tempered the success of DES (Chapter 16). As compared to BMS, DES would be associated with a higher rate of late stent thrombosis as compared to BMS. A concern that had already been acknowledged for several high-risk patient subsets (Chapter 8,9 and 10) was hypothesized to be also associated with a detrimental effect on the long-term hard clinical safety endpoints. By having followed a cohort of more than 4000 patients treated with DES, we decided to test and strengthen our observations by pooling our data with the data collected by the University medical center of Bern Switzerland, at which a similar unrestricted use of DES was applied from the moment of the commercial introduction of the SES in April 2002. Scrutinizing the 3-year follow-up of over 8000 patients treated with either SES or PES demonstrated that stent thrombosis (>30 days) occurred with an incidence of 0.6%/year (Chapter 17), a rate that had never been published before. Additionally, we were the first to report the cumulative incidence of angiographic stent thrombosis in an all-comer patient population up to 3 years, which appeared to be 2.9%. In Chapter 18 we verified these findings by analyzing the 4-year data of this cohort and found that the incidence of stent thrombosis steadily accrued instead of decreasing after 3 years. In Chapter 19 we assessed the impact of thrombus burden on the clinical outcome of 812 consecutive patients presenting with STEMI treated with DES. Intracoronary thrombus burden was

angiographically estimated and categorized as large thrombus burden (LTB), defined as thrombus burden ≥2 vessel diameters, and small thrombus burden (STB) to predict clinical outcomes. At a mean follow-up of 18 months, we demonstrated that LTB was an independent predictor of mortality (hazard ratio [HR] 1.76, p= 0.023) and MACE (HR 1.88, p<0.001). The cumulative angiographic infarct related artery stent thrombosis was 1.1% at 30 days and 3.2% at 2 years, and continued to augment beyond 2 years. It was significantly higher in the LTB compared with the STB group (8.2% vs. 1.3% at 2 years, respectively, p<0.001). Significant independent predictors for infarct related artery stent thrombosis were LTB (HR 8.73, p<0.001), stent thrombosis at presentation (HR 6.24, p<0.001), bifurcation stenting (HR 4.06, p=0.002), age (HR 0.55, p=0.003), and rheolytic thrombectomy (HR 0.11, p=0.03).

Following the worrying findings presented at the European Society of Cardiology conference in Barcelona 2006, physicians were challenged by reports showing a detrimental effect on long-term outcome in patients treated with DES. In brief, DES would increase the risk of death and myocardial infarction as compared to BMS. As a reaction to these accusations, we pooled the individual patient level data from the pivotal randomized controlled Cypher and Taxus trials to specifically assess the long-term safety of DES. In Chapters 20 and 21 we demonstrate that, at least for on-label indications, there are no significant differences in the rates of death, myocardial infarction and stent thrombosis in DES as compared to BMS. However, the highly selected patients in these pivotal randomized trials constitute only ~25% of the daily clinical practice. For this reason the board of directors of the Erasmus Medical Center requested a reassessment of the Thoraxcenter policy of an unrestricted DES use, and more specifically, that the extensive analysis of the RESEARCH and T-SEARCH registries be complemented by a retrospective analysis of an equally sized cohort of patients treated with BMS. Therefore, the long-term survival of 3 sequential cohorts of all-comers treated with either BMS, SES and PES in our center was analyzed by our cardiovascular epidemiological department. In this real world patient population, after 4 years, the overall use of DES was associated with similar all-cause mortality rates and a significantly reduced risk for post-operative MI and TVR as compared to BMS (Chapter 22).

As together with our data more reports were published on the long-term safety and efficacy of DES, the European Society of Cardiology got triggered and felt responsible for bringing out a European consensus on the use of DES in daily clinical practice. Chapter 23 contains the official meeting report of the ESC forum on DES.

DES for multivessel coronary artery disease

The superior antirestenotic properties of DES suddenly made PCI a more appealing option for patients with multivessel coronary artery disease (MVD). While coronary artery bypass surgery (CABG) proved to be superior to PCI with BMS in avoiding repeat revascularizations, the introduction of DES changed the efficacy equation. At first, we were able to demonstrate in a patient level based data meta-analysis that PCI with BMS resulted in similar rates of death, stroke and myocardial infarction as compared to CABG. An important conclusion that could thus far not be drawn based on the individual trials randomizing patients to either PCI with BMS or CABG (Chapter 25). Following the interest in the long-term safety and efficacy of DES as compared to CABG, we used the data from the Arterial Revascularization Therapies Study part II (ARTS-II) and showed that at 3 years, the use of SES was associated with a survival free of death/Cerebrovascular accident CVA/MI of 91.7%, versus 89.1% (p=0.1) and 87.2% (p=0.007) in ARTS-I CABG and PCI cohorts, respectively. Freedom from revascularization in ARTS-II was 85.5%, lower than in ARTS-I CABG (93.4%; p<0.001) but higher than in ARTS-I PCI (73.7%; p<0.001) cohorts. In addition we specifically studied the performance of overweight (BMI ≥25 and ≤30kg/m^2)and obese (BMI >30kg/m^2) patients (Chapter 27) with MVD who make up the majority of the population in industrialized countries (in the United States, at least 64.5% is classified as overweight, versus 40% in the Netherlands). The preferred method of coronary revascularization for these patients proved to be controversial. At first, we demonstrated that BMI had no impact on the 1-year clinical outcome

in patients with multivessel CAD treated with SES in ARTS II. Additionally, as compared to the ARTS-I CABG cohort, SES treated patients from ARTS II when stratified according to their BMI had equivalent 1-year MACCE rates. This is in contrast to the BMS treated overweight and obese patients from ARTS I who had a lower MACCE-free survival as compared to their surgically treated counterparts, mainly due to a higher need for repeat revascularization. In Chapter 28 we studied the efficacy of PCI with SES in diabetics with concomitant multivessel coronary artery disease in which the optimal method of revascularization remains in dispute. At 3 years, PCI using SES for patients with multivessel coronary artery disease seems to be safer and more efficacious than PCI using BMS, irrespective of the diabetic status of the patient. PCI using SES appears to be a valuable alternative to CABG for both diabetic and non-diabetic patients. Of note, in the diabetic cohort, the cumulative incidence of death/CVA/MI in ARTS-II was 9.2% lower than in the percutaneous arm of ARTS-I and 4.1% lower than in the ARTS-I CABG arm. Finally, we used the ARTS-II data to assess the short- and long-term health related quality of life and anginal status in patients treated for of multivessel coronary artery disease in ARTS-II. At 3 years, both stenting and CABG resulted in a significant improvement in HRQL and angina. HRQL after SES was significantly improved as compared with BMS and was similar to CABG.

Cost-effectiveness of DES

In Chapter 31 we assessed the cost-effectiveness of DES based on the 2-year follow-up of the RESEARCH registry. The use of SES cost €3,036 more per patient at the index procedure, driven by the price of SES. Follow-up costs after 1-year were €1,089 less with SES when compared with BMS, due to less TVR, resulting in a net excess cost of €1,968 per patient in the SES group, and reduced by a further €100 per patient in the second year. The ICER (calculated as the difference in costs devided by the difference in effectiveness) per TVR avoided was €29 373 at 1 year, and €22,267 at 2 years.

Beyond the conventional riskfactors

Type-D is defined as the tendency to experience increased negative emotions paired with the non-expression of these emotions in social interactions. Type-D is an emerging risk factor in cardiovascular disease that has been associated with an increased risk of adverse prognosis. However, given that the use of DES has been associated with a significant decrease in the risk of restenosis and the need for repeat revascularization and that exhaustion plays a role in the etiology of restenosis post-PCI, it is not clear whether exhaustion remains a problem in the DES era. In Chapter 31 we demonstrated that Type-D personality was an independent predictor of exhaustion at 1 year. The impact of type-D on exhaustion was large compared with a small effect for gender and age. CVD research and clinical practice may benefit by adopting a personality approach in order to identify high-risk patients. In addition to these findings we addressed the relative effects of fatigue, depressive symptoms and hopelessness on the 2-year outcome of patients treated with DES. Correcting for independent predictors, depressive symptoms appeared to have a negative effect on the 2-year outcome following PCI. Moreover, hopelessness was associated with a more than 3-fold higher risk for clinical events. Finally, we assessed the role of positive affect on clinical outcome after PCI with DES implantation. The incidence of death⁄MI in adequate versus reduced positive affect patients was 4% vs. 11% (HR 2.55; 95% CI 1.46–4.34, P = 0.001), adjusting for clinical variables. Reduced positive affect and diabetes were independent prognostic factors, and patients with one (HR 2.84, 95% CI 1.58–5.10) or both (HR 5.61, 95% CI 2.25–13.99) of these factors had a higher risk when compared with nondiabetic patients with adequate positive affect, P < 0.003.

Conclusion

Probably the most important finding of this thesis was that both SES and PES were associated with a similar risk of death and myocardial infarction as compared to BMS up to 4 years, irrespective of the baseline or procedural characteristics of the patient. This latter finding remained valid despite the higher risk for late stent thrombosis following SES and PES implantation. A second important observation was that when looking at the long-term efficacy of both DES, baseline and procedural patient characteristics did seem to be of particular importance. We demonstrated that

in several high risk patient subsets, there was no more than a persistent trend towards lower repeat revascularization rates. However, if the price of DES would lower, little to no contraindications would remain to restrict their use. Finally, given their emerging role in predicting adverse events, psychological risk factors will become of particular interest in future studies.

Samenvatting en conclusies

Initiële gerandomiseerde studies en registraties toonden dat zowel sirolimus-eluting stents (SES) als paclitaxel-eluting stents (PES) superieur waren ten opzichte van niet gecoate bare-metal stents (BMS) 1 jaar na stent implantatie in strict geselecteerde patiënten. Dit proefschrift heeft als doel inzicht te verschaffen in de lange termijn resultaten alsmede de valkuilen te belichten van het ongelimiteerde gebruik van drug-eluting stents (DES).

Een studiegroep zonder exclusie criteria

Het Thoraxcentrum was een van de eerste centra wereldwijd dat vanaf het moment van de commercialisering van de Cypher stent in April 2002 een ongelimiteerd drug-eluting stent beleid voerde. Door de follow-up van de RESEARCH en T-SEARCH registraties (in welke zowel SES als PES ongelimiteerd gebruikt werden) uit te breiden, waren wij een van de eerste die konden aantonen dat het gebruik van SES tot significant betere resultaten leidde in vergelijking tot BMS na 2, 3, en 4 jaar follow-up (Hoofdstuk 5 en 6). Het gebruikt van SES resulteerde in een vermindering van de incidentie van het gecombineerde eindpunt dood, myocard infarct en herinterventie van het initieel behandelde bloedvat (MACE), van respectievelijk 27% en 43% op 3 en 4 jaar in vergelijking tot BMS. Deze significante reductie was met name het gevolg van de significant lagere revascularizaties van het tijdens de index procedure behandelde bloedvat, zonder verschillen in de incidentie van dood of myocard infarct. Aanvullend vonden wij geen verschillen in de relatieve veiligheid en effectiviteit van SES in vergelijking tot PES (Hoofdstuk 4).

De veiligheid en effectiviteit van drug-eluting stents in specifieke patiënten en laesies

Door alle patiënten die tussen 2000 en 2005 in ons centrum behandeld waren te volgen waren we in staat om de prestaties van DES in specifieke patiënten en laesies te bestuderen. Nierinsufficiëntie staat reeds lang bekend als een factor die de lange termijn resultaten van PTCA negatief kan beïnvloeden. Om deze reden analyseerden wij de uitkomsten van 10 dialysepatiënten behandeld met DES. Een jaar na follow-up waren allen nog in leven, en waren er geen myocard infarcten danwel nieuwe revascularizaties gerapporteerd (Hoofdstuk 7). In Hoofdstuk 8 keken we naar de effectiviteit van DES in patiënten die zich presenteerde met een acuut myocard infarct, een subgroep van patiënten die slechts in zeer beperkte mate door gerandomiseerde studies was bestudeerd. Ondanks dat het gebruik van SES tot een significant lager aantal revascularizaties leidde op 1-jaar na implantatie, lieten wij zien dat na 3 jaar, zowel SES als PES niet in staat waren het aantal cardiale events (inclusief revascularizaties) te verminderen in vergelijking tot BMS in patiënten die zich presenteerden met een acuut myocard infarct. Bovendien lieten we zien dat PES-gebruik in deze populatie niet tot significant betere resultaten leidde in vergelijking tot BMS op zowel 1, 2 als 3 jaar. Hoofdstuk 8 laat zien dat dit gebrek aan superioriteit gedeeltelijk verklaard kan worden door de verhoogde incidentie van late stent trombose in beide DES groepen. Vervolgens werd de alsmaar groter wordende groep van diabeten bestudeerd. Met een versnelde en agressievere atherosclerose progressie en als gevolg meer restenose in vergelijking tot niet-diabeten, is diabetes onlosmakelijk verbonden met een kleine coronaire diameter, langere laesies, een grotere plaque belasting en een restenose cascade die mogelijk anders werkt dan bij niet-diabeten. Gezien hun superieure anti-restenotische eigenschappen werden DES als snel geacht bij uitstek geschikt te zijn in deze hoog-risico patiënten. In Hoofdstuk 9 lieten wij zien dat na 2 jaar, in 708 opeenvolgende patiënten met diabetes er een trend was naar een betere uitkomst in de met PES behandelde groep in vergelijking tot de BMS groep. Verder werd er geen verschil gevonden tussen de relatieve effectiviteit van SES en PES in elk van de individuele eindpunten (dood, myocard infarct, revascularizatie van het initieel behandelde vat), alsmede in niet insuline afhankelijke diabeten die geacht werden een betere prognose te hebben wanneer ze behandeld werden met PES. Na propensity analyse vonden we dat geen van de verschillen in elk van de klinische eindpunten na SES of PES in vergelijking tot BMS statistisch significant bleken te zijn. We maakten de

hypothese dat ook hier een deel van deze niet superioriteit verklaard kon worden door de hogere incidentie van stent trombose in beide DES groepen (4.4% in de SES groep versus 2.4% in de PES groep) in vergelijking tot de BMS groep (0.8%). Wanneer we deze patiënten nog een jaar langer volgden (Hoofdstuk 10) bleek dat de trend tot een betere uitkomst met PES statistisch significant werd, terwijl SES niet significant beter was dan BMS. Na multivariate analyse waren de risico?s voor revascularizatie van het initieel behandelde bloedvat (TVR) en het gecombineerde eindpunt van dood, infarct en revascularisatie (MACE) in patiënten behandeld met PES lager dan na BMS (Hazard ratio [HR] 0.50 [95%CI: 0.33-0.75] voor TVR, HR 0.65 [95%CI: 0.48-0.87] voor MACE). De risico?s in patiënten behandeld met SES waren vergelijkbaar met (HR 0.75 [95%CI: 0.46-1.24] voor TVR, HR 0.77 [95%CI: 0.52-1.13] voor MACE).

Vervolgens richtten wij ons meer specifiek op de prestaties van DES in specifieke laesies. Als een van de eerste bekeken wij de lange termijn veiligheid en effectiviteit van DES in bifurcatie laesies. Het gebruik van SES bleek veilig en effectief ondanks deze klinische uitdagende setting waarin zowel de Crush als de Culotte techniek gebruikt werden (Hoofdstuk 11). Met het groeiende enthousiasme in de superioriteit van DES groeiden ondanks het gebrek aan lange termijn resultaten, het aantal klinische indicaties . Interventie cardiologen gingen kleinere en langere laesies stenten en gebruikten meer en meer stents. In Hoofdstuk 12 bekeken we de relatieve effectiviteit van SES en PES in vaten met een diameter van ≤2.25mm, een klinische setting welke zeker zou geleid hebben tot exclusie in gerandomiseerde studies. Na 2 jaar, was de cumulatieve incidentie van MACE in de SES groep significant lager dan in de PES groep (10.3% vs. 23.3%, p=0.02). Vervolgens keken we naar de effectiviteit van DES in chronisch totale occlusies, een klinische setting die tot dusver vaak leidde tot een chirurgische interventie. In Hoofdstuk 13 toonden we dat na 2 jaar, SES even veilig waren als BMS. Het verschil in TVR bleek echter niet meer te zijn 3.5% (12.7% in de BMS groep vs. 9.2% in de SES groep). Ondanks het beperkt aantal studiepatiënten (147), concludeerden we dat het gebruik van SES en patiënten met chronisch total occlusies niet tot significant betere resultaten leidde van BMS na 3 jaar van follow-up.

De percutane behandeling van stenoses in aorta-ostiale laesies is een technisch ingewikkelde procedure en wordt gekenmerkt door lagere procedurele succes percentages en een slechtere klinische en angiografische prognose in vergelijking tot laesies verder van het ostium. Tot dusver waren de gegevens over de effectiviteit van DES in deze laesies echter zeer beperkt. In Hoofdstuk 14 analyseerden we de 7-maanden angiografische en 2-jaar klinische uitkomsten van 76 opeenvolgende patiënten behandeld met PES voor aorta-ostiale laesies. Na 7 maanden bleek de late lumen loss 0.48mm te zijn, wat resulteerde in een TVR incidentie van 14.5% met een incidentie van MACE van 31.6% na 2 jaar. We concludeerden dat ondanks dat het gebruik van PES zeer wel mogelijk was, PTCA van aorta-ostiale laesies problematisch blijft dankzij het lineair toenemende risico op MACE.

Tot slot analyseerden we de 4-jaar resultaten van het gebruik van SES en PES in vergelijking tot BMS in veneuze bypass grafts waar recent ernstige waarschuwingen voor waren uitgesproken met betrekking tot hun veiligheid. In een cohort van 250 post-bypass chirurgie patiënten met stenoses in veneuze bypass grafts, was de cumulatieve overleving in de DES groep 80.5% in vergelijking tot 77.5% in de BMS groep (adjusted HR 1.09; 95% CI 0.63-1.90) in combinatie met een hogere TVR vrije overleving in de DES groep in vergelijking tot de BMS groep (81.6% vs. 69.0%, adjusted HR 0.53; 95% CI 0.27 - 1.05).

De waarschuwingen omtrent veiligheid aan de tand gevoeld

In September 2006, werd het succes van DES bruusk de kop ingedrukt door een trio van presentaties op het congres van de European Society and World Congres of Cardiology (Hoofdstuk 16). In vergelijking tot BMS, zouden DES geassocieerd zijn met hogere incidentie van late stent trombose in vergelijking tot BMS. Een zorg die reeds eerder geopperd was in hoog-risico patiënten (Hoofdstuk 8, 9 en 10) bleek mogelijk te leiden tot hogere incidentie van sterfte en myocard infarct. Doordat we een cohort van meer dan 4000 DES patiënten hadden gevolgd, besloten we onze bevindingen te testen en te versterken door onze data te poolen met vergelijkbare data die was verzameld door het Universitair Medisch Centrum in Bern, Zwitserland alwaar een vergelijkbaar

ongelimiteerd DES beleid was gevoerd vanaf het moment van de commerciële introductie van de SES in april 2002. We onderzochten in groot detail de 3-jaar follow-up van meer dan 8000 patiënten behandeld met SES en PES en vonden dat de incidentie van late stent trombose (>30 dagen na implantatie) 0.6% per jaar bedroeg (Hoofdstuk 17). Een incidentie die nooit eerder gepubliceerd was. Bovendien waren we de eerste die rapporteerden dat 3 jaar na implantatie, de totale incidentie van agiografisch bewezen stent trombose in een all-comer patiënten populatie 2.9% bleek te zijn. In Hoofdstuk 18 verifieerden we deze bevindingen door ook de 4-jaar follow-up van dit cohort te bestuderen en vonden dat de incidentie van stent trombose langzaam met dezelfde trend verder steeg in plaats van af te nemen na 3 jaar. In Hoofdstuk 19 keken we meer specifiek naar de impact van trombus last op de klinische uitkomsten van 812 opeenvolgende patiënten behandeld met DES in de setting van een ST-elevatie myocard infarct. Intracoronaire trombus last was angiografisch geschat en gecategoriseerd als grote trombus last (LTB) en was gedefinieerd als een trombus last van ≥2x de coronair diameter en kleine trombus last (STB) om klinische uitkomsten te voorspellen. Na 18 maanden van follow-up toonden we aan dat LTB een onafhankelijke voorspeller bleek te zijn van mortaliteit (HR 1.76, p=0.023) en MACE (HR 1.88, p<0.001). De cumulatieve incidentie van angiografische infarct arterie gerelateerde stent trombose was 1.1% na 30 dagen en 3.2% na 2 jaar, en liep nog verder op na 2 jaar. Deze incidentie bleek significant hoger in de LTB groep dan in de STB groep (respectievelijk 8.2% vs. 1.3% na 2 jaar, p<0.001). Significante onafhankelijke voorspellers van infarct arterie gerelateerde stent trombose waren LTB (HR 8.73, p<0.001), presentatie met stent trombose (HR 6.24, p<0.001), bifurcatie stenten (HR 4.06, p=0.002), leeftijd (HR 0.55, p=0.003) en rheolytic trombectomie (HR 0.11, p=0.03).

In navolging van de verontrustende bevindingen die werden gepresenteerd op het European Society of Cardiology congres in Barcelona 2006 werden artsen geconfronteerd met tal van waarschuwingen omtrent veiligheid jaren na DES implantatie. Vergeleken met BMS zouden DES het risico op dood en myocard infarct vergroten. Als reactie hierop besloten we de individuele patiënten data uit de initiële gerandomiseerde Cypher en TAXUS studies te poolen om specifiek te kijken naar de lange-termijn veiligheid van DES. In Hoofdstuk 20 en 21 toonden we aan dat, ten minste voor on-label indicaties, er geen verschillen was in de incidentie van dood, myocard infarct en stent trombose in patiënten behandeld met DES in vergelijking tot BMS. Een kanttekening moet gemaakt worden over het feit dat deze patiënten slechts representatief zijn voor zo□n 25% van de dagelijkse populatie in een modern cathlab. Om deze reden werden we door de raad van bestuur van het Erasmus MC dringen verzocht het ongelimiteerde DES beleid van het Thoraxcentrum opnieuw te beoordelen en meer specifiek, de RESEARCH en T-SEARCH populaties te vergelijken met een retrospectieve analyse van een qua grootte vergelijkbaar cohort van BMS patiënten. Statistische analyses werden uitgevoerd door de afdeling klinische epidemiologie van het Thoraxcentrum. Vier jaar na implantatie bleek het ongelimiteerd gebruik van DES niet te leidden tot een verhoogd risico op sterfte maar wel te resulteren in een significant lager risico op post-operatief myocard infarct en TVR in vergelijking tot BMS (Hoofdstuk 22).

In dezelfde tijd werden meerdere vergelijkbare studies gedaan en gepubliceerd en de European Society of Cardiologie voelden zich geroepen een Europees consensus paper uit te brengen over het gebruik van DES in de dagelijkse klinische praktijk. Hoofdstuk 23 bevat het officiële meeting rapport van het ESC forum over DES.

DES voor meervatslijden

Door de significant lagere behoefte aan nieuwe revascularizaties werd PTCA plots een interessante optie voor patiënten met meervatslijden. Ondanks dat coronaire bypass chirurgie (CABG) bewezen had effectiever te zijn dan PTCA met BMS gebruik veranderde DES deze effectiviteitverhouding. Om te beginnen toonden we in een meta-analyse aan dat PTCA met BMS resulteerde in dezelfde incidentie van dood, beroertes en myocard infarct in vergelijking tot CABG. Een belangrijke bevinding die tot dusver niet met zekerheid gesteld kon worden gezien de beperkte statische power van de individuele gerandomiseerde PTCA (met BMS) vs. CABG studies (Hoofdstuk 25). In navolging aan de interesse in de lange termijn veiligheid van DES in vergelijking tot CABG gebruikten we de data van de Arterial Revascularization Therapies Study part II (ARTS-II) studie en toonden aan dat na 3 jaar, het gebruik

van SES geassocieerd was met een overleving vrij van dood, beroerte of myocard infarct van 91.7%, versus 89.1 (p=0.1) en 87.2% (p=0.007) in respectievelijk de ARTS-I CABG en PTCA cohorten. Overleving vrij van nieuwe revascularizatie in ARTS-II was 85.5%, welke lager bleek dan in ARTS-I CABG (93.4%; p<0.001) maar hoger dan in het ARTS-I PTCA cohort (73.7%; o<0.001). Bovendien bestudeerden we meer specifiek de uitkomsten van patiënten met overgewicht (BMI ≥25 and ≤30kg/m^2) en obesitas (BMI >30kg/m^2) die in de geïndustrialiseerde landen de meerderheid van de populatie bedragen (in de VS lijdt >64.5% aan overgewicht versus 40% in NL). De optimale revascularizatie methode voor deze patiënten blijft echter controversieel. We vonden dat BMI geen impact had op de 1-jaar klinische prognose in patiënten behandeld met SES voor meervatslijden in ARTS-II. In vergelijking tot het ARTS-I CABG cohort waren er geen significante verschillen in patiënten behandeld met SES in ARTS-II gestratificeerd naar hun BMI in de incidentie van het gecombineerde eindpunt dood, infarct, beroerte en revascularizatie. Dit laatste gold niet voor patiënten met overgewicht en obesitas die behandeld waren met BMS in ARTS-I. Deze patiënten hadden een significant hogere incidentie van het gecombineerde eindpunt in vergelijking tot de ARTS-I CABG patiënten, met name door het significant hoger aantal revascularizaties. In Hoofdstuk 28 bestudeerden we de effectiviteit van PTCA met SES in diabeten met meervatslijden, een cohort van patiënten waarin de optimale behandelingsmethode controversieel blijft. Drie jaar na stent implantatie bleek PTCA met DES veiliger en effectiever in vergelijking tot PTCA met BMS, onafhankelijk van het hebben van diabetes. Vervolgens bleek PTCA met SES een waardevol alternatief voor CABG in zowel diabeten als niet diabeten. De cumulatieve incidentie van dood, beroerte of myocard infarct in ARTS-II was 9.2% lager dan in de percutane arm van ARTS-I en 4.1% lager dan in de ARTS-I CABG arm. Tot slot gebruikten we de ARTS-II data om de korte- en lange-termijn gezondheid gerelateerde kwaliteit van leven en angina status te onderzoeken in patiënten met meervatslijden. Na 3 jaar bleken zowel PTCA als CABG tot een significante verbeteringen te leiden in kwaliteit van leven en angina pectoris klachten. Kwaliteit van leven na SES bleek significant beter dan na BMS en vergelijkbaar met CABG.

De kosteneffectiviteit van DES

In Hoofdstuk 33 beoordeelden we de kosteneffectiviteit van DES gebaseerd op de 2-jaar follow-up van de RESEARCH registratie. Het gebruik van SES was €3036,- duurder dan het gebruik van BMS tijdens de indexprocedure, bepaald door de hogere prijs van SES. Follow-up kosten 1 jaar na implantatie waren €1089,- minder in de SES groep dan in de BMS groep door de lagere incidentie van herinterventie, wat resulteerde in een netto kosten overschot van €1968,- per patiënt in de SES groep. Deze kosten verminderde met €100,- in het tweede jaar. We berekenden dat de ICER (uitgedrukt in het verschil in kosten gedeeld door het verschil in effectiviteit) per te vermijden TVR €29373,- was na 1 jaar, en €22267,- euro na 2 jaar.

De conventionele risicofactoren voorbij

Type-D persoonlijkheid is gedefinieerd als de neiging tot het overmatig ervaren van negatieve emoties tezamen met het niet in staat zijn deze emoties tot expressie te brengen tijdens sociale contacten. Type-D is een opkomende risicofactor in cardiovasculaire ziekte waarvan is aangetoond te leiden tot een slechtere prognose. Gezien het gebruik van DES leidt tot een significante reductie van restenose en de noodzaak tot herinterventie, tezamen met het feit dat uitputting een rol speelt in de etiologie van restenose na PTCA, blijft het onduidelijk of uitputting een probleem blijft in de DES periode. In Hoofdstuk 31 tonen we aan dat een Type-D persoonlijkheid een onafhankelijk voorspeller is van uitputting 1 jaar na stent implantatie. De impact van Type-D op uitputting bleek groot in vergelijking tot de relatief kleine impact van leeftijd en geslacht. Cardiovasculair onderzoek alsmede de klinische praktijk zouden kunnen profiteren van een psychologische benadering om patiënten met een slechtere prognose te identificeren. Bovenop deze bevindingen keken we naar de relatieve effecten van uitputting, depressieve symptomen en hulpeloosheid 2 jaar na DES implantatie. Wanneer we corrigeerden voor onafhankelijke voorspellers, bleken depressieve symptomen een negatief effect te hebben op de 2-jaar uitkomsten na PTCA. Hulpeloosheid bleek te leiden tot een 3x verhoogd risico op klinische events. Tot slot bestudeerden we de rol van verminderd positief affect op de klinische uitkomsten na PTCA met DES gebruik. De incidentie van dood en myocard

infarct in patiënten met een adequaat versus een verminderd positief affect waren respectievelijk 4% en 11% (HR 2.55; 95% CI 1.46-4.34, P = 0.001), gecorrigeerd voor klinische variabelen. Verminderd positief affect en diabetes waren onafhankelijke prognostische factoren en patiënten met 1 (HR = 2.84, 95% CI 1.58-5.10) of beide (HR = 5.61, 95% CI 2.25-13.99) risico factoren hadden een verhoogd risico in vergelijking tot niet diabetisch patiënten met een adequaat positief affect (p<0.003).

Conclusie

Misschien wel de belangrijkste bevinding van dit proefschrift is dat zowel SES als PES geassocieerd zijn met een vergelijkbaar risico op dood en infarct in vergelijking tot BMS tot 4 jaar na implantatie, onafhankelijk van de klinische of procedurele patiënten karakteristieken. Deze bevinding bleef geldig ondanks het verhoogd risico op late stent trombose na zowel SES als PES implantatie. Een tweede belangrijke bevinding was dat als we keken naar de lange termijn effectiviteit van beide DES, klinische en procedurele patiënten karakteristieken wel degelijk van invloed bleken. We toonden aan dat in multipele hoog risico cohorten, enkel een persisterende trend werd gezien richting een lagere herinterventie incidentie. Desalniettemin, als de prijs van de DES zou zakken, zouden er weinig tot geen contra-indicaties zijn welke hun gebruik zouden limiteren. Tot slot, gegeven hun opkomende prognostische waarde, zullen psychologische risicofactoren meer een meer een rol gaan spelen in toekomstige studies.

Ackowledgements

It must have been somewhere at the end of 2002 when I started looking for a research topic to finalize my doctoral exam in medicine. Thinking about the future and my personal interests I decided to contact the head of the surgical cardiothoracic department. Having seen several presentations on minimal invasive cardiothoracic surgery I applied for a research position on the topic. Merely one week later, my request was turned down. Although they were interested in my request, there was nobody who had the time to supervise me. I had to say, I was disappointed. Nevertheless, a few days later I told a fellow student about what happened. Without arguing he directed me to "somebody on the fourth floor who was quit successful in doing something with new metal tubes called stents". Being a complete lay in the field of interventional cardiology I started looking for some background information. Soon I found out, the person upstairs was called prof. Patrick Serruys who just started a novel project on the use of sirolimus-eluting stents. Having caught my attention I decided to send a letter. A couple of weeks later I was invited for an interview. Tuesday January 2003, 4pm. Nicely on time I knocked the door on the fourth floor where a secretary told me he was still in "the lab". After having been waiting for more than an hour I decided to ask a guy in the room next to the lab whether he could tell me where prof. Serruys was and whether there was a chance I was going to meet him. The guy couldn't help me but reassured me that professor would show up soon. Another hour later a man stepped outside the lab, completely ignoring the young guy sitting on the chair in front of the door. Although I had no idea whether this man was prof. Serruys, I approached him and told him who I was. I was lucky! He took me to his office where he told me he was tired from a day in the lab and that he just came back from a trip to the US. The interview took no more than 2 minutes, however, I was welcome and a guy called Pedro (apparently the guy in the room next to the lab I spoke to a little bit earlier) would take care of me. From that moment on things changed. I had just entered the rollercoaster called "Thoraxcenter". Although I was still a 4th year med-school student, from July until November 2003 I learned incredibly lot on many things going on in the Thoraxcenter. Being embraced by the ongoing RESEARCH study project I left the Thoraxcenter in November 2003 for two years to do my rotations with already a few small publications. From that moment on I was sure about my future plans. It had to be cardiology with a particular interest in the field of interventional cardiology. No more than 1 year later I applied for an official PhD position in the group of prof. Serruys. However, this would have never happened without the supervision of Pedro Lemos, a fellow from Brazil who appeared to be one of the most intelligent and friendly people I have ever met. Pedro, I'm still convinced that I would have never come this far without the enormous amount of time you invested to help me, teach me, and involve me in many projects going on during the time I spent in the Thoraxcenter as a student. It's a true honour to have you in my PhD committee! The second person I have to thank in particular at this moment is Ron van Domburg, my co-promoter. Ron, your enthusiasm and help in working with the databases, your lessons in statistics, data collection and management, clinical follow-up and writing were of exceptional value. I will never forget the many moments we spent together from the first day as a student in July 2003. Completing the rest of my training in the Thoraxcenter, I look forward to continue working with you.

In November 2005 when I started my PhD project it had already been two and a half years since the first drug-eluting stent was introduced. For this reason we decided to start focussing on the long-term follow-up of the drug-eluting stent. When I started, the group of international fellows I was used to work with had changed. Pedro had left the Thoraxcenter in 2003, and was followed-up by Andrew Ong, an Australian fellow, with Malaysian roots. To be honest, I was afraid when I started in November 2005 and was supposed to follow-up Andrew, who was finishing his thesis. Both Andrew and Pedro had left enormous footprints in the Thoraxcenter. Andrew, each time we meet again during international conferences I need to think about the moments you thought me many tips and tricks to survive in the Thoraxcenter jungle. Thereby, your lessons in how to manage the database, contact journals and industry partners, and most importantly, how to survive under the 24hour non-stop pressure of the department were unforgettable. From the moment you left I

tried to handle things without your continuous supervision. At the same time it was Ron who introduced me to a variety of medical students who were all interested in helping us to complete the follow-up. What Ron discovered already way earlier was that without them, we would have never come this far. Although many students came and left, I have to thank two people in particular. At first Giulio Stefanini, an Italian student who appeared when I just started. Giulio, I'm grateful for all your help and I will never forget the headache I had after having finished a full bottle of your homemade limoncello. Secondly, Piet Hein van Twisk, the tall guy. Piet Hein, your incredible enthusiasm and understanding for everything going on was unforgettable. The many evenings and weekends we spent together on the 14th floor were definitely worth the effort. I'm confident you both will have a fantastic future ahead of you.

At this moment I also have to mention all the many fellows from all over the world I worked with during the past years. Francesco Saia, Marco Valgimigli, Muzaffer Degertekin, Angela Hoye, Neville Kukreja, Yoshi Onuma, Keiichi Tsuchida, Shuzou Tanimoto, Jiro Aoki, Masato Otsuka, Steve Ramcharitar, Emanuel Meliga, Sophia Vaina, Hector Garcia-Garcia, Nieves Gonzalo. It was a great pleasure to work with each of you! I truly hope we can keep in contact in the future.

The longer I worked in the Thoraxcenter I started recognizing the importance of the people in the lab. Not a single paper would have been published without the marvelous activities of the interventional cardiologists; Evelyn Regar, Erik Duckers, Robert Jan van Geuns, Georgios Sianos, Carlos van Mieghem, Martin vd Ent, Prof. Wim vd Giessen, Prof. Pim de Feyter. In particular I have to name and thank Peter de Jaegere, an incredibly smart and friendly person. Peter, I have to be honest. In the beginning when I asked you to review a manuscript, I could hardly recognize my work due to all the corrections you made. However, it was a great pleasure working with you and very soon I realized that your clear and concise way of writing impacted my skills in a positive way. Finally, Prof. Maarten Simoons, head of the department. Although we had little contact in the beginning of the PhD project, it was a great honor to accept your invitation to participate in the ESC DES Taskforce meeting in Nice 2007 and to work with you on the meeting report - a task which finally proved to be one of the most challenging ever. Only several months after having started my PhD project I experienced that 36 hour working weeks belonged to the past. Weekly working hours quickly increased to up to 60 hours per week. At the same time I realized that the people I worked with became more than colleagues. At first Bob Meijboom, who was doing a PhD at the cardiovascular imaging department. While not working together on a regular basis, we went to many conferences together. In particular the weeks in Barcelona 2006 and Florida early 2007 I will never forget. Although I could write a full acknowledgement on our adventures, I believe it's better for the both of us to keep this between you and me. Nevertheless, it's a great pleasure to continue the cardiology training in parallel with you and it's an honor to have you as a paranymf. A special thanks as well to Gerrit-Anne, Marie-Angele, Marco, Dick, Tessa and the other people from Cardialysis. Thanks to the many meetings in your office I started appreciating the many aspects of a core-lab which turned out to be of crucial importance while raising the quality level of a study.

When long-term safety and efficacy data of the drug-eluting stent became available, several caveats emerged. As a consequence, single center experiences were no longer sufficient and our network of fellow researchers expanded beyond the Dutch borders. A fantastic collaboration arose with Stephan Windecker, Peter Wenaweser and Peter Jüni from the University Hospital Medical Center in Bern, Switzerland. Dear all, I enjoyed every minute we worked together on the Bern Rotterdam study! I truly hope we can continue our collaboration in the future. Finally, Stephan, it's a great honor to have you as a member of the PhD committee. A second collaboration I will never forget is with Christian Spaulding from Cochin Hospital in Paris, France. Christian, the memorable moments we spent together discussing with the editors form the New England Journal of Medicine and the meeting with John Jarcho were unforgettable. It was only after these experiences that I started to recognize the true and exceptionally high level of such a Journal. Besides that, it was a great pleasure working with you and many thanks for being a member of the PhD committee. Another word of thanks goes to Susanne Pedersen, with whom I got in contact as early as 2004. Although I have to admit I was somewhat skeptical in accepting the psychological aspects in PCI studies, your persistent enthusiasm about the topic made that I got more and

more interested in these new risk factors in cardiovascular disease. It was a great pleasure working with you in the many psychological studies we did. Finally, Paul Cummins. Paul, I learned to know you as probably the most colorful guy in the Thoraxcenter. Your humor and enthusiasm made my long working hours and evening activities during international conferences a lot more fun. Furthermore, it was a great pleasure to accept the invitation to become an associate editor for Euro Intervention, the journal that is still growing thanks to all your work as a managing editor.

At this moment, it´s time to thank the man who made it all happen, my boss, my promotor, my mentor, Prof.dr. Patrick W. Serruys. The enthusiasm with which you launched new projects and ideas on a daily basis and the millions of opportunities you offered me are unforgettable. The difficulties I experienced in the beginning soon belonged to the past when I figured out Andrew and Pedro were right. The wide diversity of projects in which you involved your fellows were overwhelming and there was no way to manage or to stay involved in all of them. Instead, I had to learn to make choices and priorities. This resulted in many phone calls during the day (please note, day means 24hours), evenings and weekends in your house. Arriving in the attic, after having been welcomed by you incredible wife, I have to think back on the many anecdotes you told me. More importantly, you taught me how to write, and whereas it took months to finalize my first manuscripts, it was incredible to see that at the end, we wrote editorials in merely 2 evenings. You gave me the opportunity to get in contact with people from all over the world, ranging from the editorial board of EuroIntervention, the people from Cardialysis, Stephan Windecker, Christian Spaulding, and even Eugene Braunwald (the legend). In a certain way I always felt proud to be one of your fellows whenever you received a new international Award and the longer worked with you, the more I understood why. Given your habit of carefully selecting top clinical and research fellows from all over the world, recommended by key-opinion leaders in the field, I'm still curious to see what drove you to accept a 24 year student with a zero knowledge of cardiology for a PhD position at the end of 2005?! I hope I didn't disappoint you and regret that I will probably not be able to do my clinical training under your supervision. Instead I hope that we will keep in close contact in the years your still in the Thoraxcenter. Thanks for everything!

Dan miscchien wel de belangrijkste mensen in mijn leven, mijn familie en vrienden. Mijn ouders, papa en mama, en mijn zusje Francine, zonder jullie oneindige steun en liefde zou ik nooit zover zijn gekomen. Jullie leerden mij zaken in perspectief te plaatsen en te genieten van de vele mooie dingen van het leven die alleen nog maar mooier bleken nadat er hard gewerkt was. En dan Lisanne, alles verandere toen jij je in mijn leven nestelde. Ondanks dat mijn werktijden er zeker in het begin niet langer op werden werkte ik in de resterende tijd met nog meer plezier. Jouw onophoudelijke vrolijkheid en enthousiasme gaven mijn leven meer kleur. Ik wil je nooit meer kwijt! Vervolgens mijn vrienden: Vincent, Ly, Sebastiaan, Guido, Emiel, Britta, Jan Jaap, Oscar, Elisa, Hans, Annefloor, Marc, Bart, John, Robert Jan en Anouk. Zonder jullie zou mijn leven er zeker weten anders uit hebben gezien. Ondanks dat de frequentie van onze talrijke etentjes en stapavonden zeker is afgenomen dankzij onze hectische levens weet ik zeker dat we nog vele mooie jaren tegemoet gaan. In het bijzonder Henk-Jan, mijn paranymf. Bedant voor al je hulp om van 14 november een onvergetelijke dag te maken!

Curriculum Vitae

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Opleiding

1993-1999:	College Heilig Kruis Sint Ursula, Maaseik (België) VWO gymnasium (Highschool) Latijn – Wetenschappen - Wiskunde
1999-2003 (jul):	Geneeskunde aan de Erasmus Universiteit Rotterdam Doctoraal examen Geneeskunde juli 2003
2003 (jul-nov):	Extra klinisch onderzoek in het Thoraxcentrum, Erasmus MC Onderwerp: “Drug-Eluting Stents”, “Quality of Life and Type D personality following coronary interventions”, “Stent-techniques”, “Drug-Eluting Stents in renal impaired patients” en “Drug-eluting stents in acute myocardial infarction patients”
2003-2005:	Co-schappen
21 okt 2005:	Artsexamen Erasmus Universiteit Rotterdam
2005 (okt)-2007:	Promotieonderzoek Erasmus MC, Thoraxcentrum Promotor: Prof. Dr. P.W. Serruys
2008 tot heden:	Start cardiologie vooropleiding interne geneeskunde in het St. Franciscus Gasthuis Rotterdam

List of publications

Journals

1. Editor EuroIntervention Suppelement “A Critical appraisal of the safety contcerns tempering the success of drug-eluting stents”

Published manuscripts

1. **Daemen J**, Lemos PA, Serruys PW. Multi-lesion culotte and crush bifurcation stenting with sirolimus-eluting stents: long-term angiographic outcome. J Invasive Cardiol. 2003;15(11):653-6.
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