The Unrestricted Use of Paclitaxel-Eluting Stents and Sirolimus-Eluting Stents in the Rotterdam T-SEARCH and RESEARCH Registries:

Studies on Efficacy, Safety, Stent Thrombosis, Cost Effectiveness and the Future

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Onbeperkt gebruik van de met paclitaxel- en sirolimus gecoate stents in de Rotterdamse RESEARCH en T-SEARCH registraties:

Studies over effectiviteit, veiligheid, stent trombose, kosteneffectiviteit en de toekomst

Thesis

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and in accordance with the decision of the Doctorate Board
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by

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Born in Melaka, Malaysia

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For May Yee

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CHAPTER 1:

GENERAL INTRODUCTION AND OUTLINE OF THESIS

This year, 2007, marks the 30th anniversary of the first percutaneous coronary intervention, in the form of a percutaneous transluminal coronary angioplasty (PTCA) or balloon angioplasty, by Andreas Gruentzig.[1] It is also the 20th anniversary of the first report of the use of a stent to maintain vessel patency following balloon angioplasty.[2]

Up until recently, the major limitation to stent implantation was restenosis, or renarrowing, at the site of stent implantation, leading to recurrence of angina. This occurred in between 10 to 50% of patients. In 2000, the first reports of a revolutionary new stent, the drug-eluting stent began to emerge, with early promises of zero restenosis.[3] In 2003, the first drug-eluting stent was commercialised, coated with the immunosuppressive agent sirolimus, leading to the sirolimus-eluting stent, and followed in 2004 by the paclitaxel-eluting stent.

The trials performed that led to the commercialisation of drug-eluting stents were in simple lesions, to reduce the number of confounding factors.[4] The patients studied in these trials make up only 25% of the typical patient population seen in a cardiac catheterisation laboratory. For the remaining 75%, it was extrapolated that these drug-eluting stents would be safe and efficacious, but that assumption required proving.

At the Thoraxcentre, a decision was made to implant these drug-eluting stents in all patients suitable for stent implantation, irrespective of clinical or angiographic findings, and to research the efficacy and safety of these stents in these untested patient populations.[5] All patients receiving drug-eluting stents were thus enrolled into the RESEARCH registry (which enrolled from April 2002 to February 2003), and the T-SEARCH registry (from February 2003 onwards).[6]

The aims of this thesis are multiple: (1) firstly, to consolidate the research that emanated from the RESEARCH and T-SEARCH registries, by providing an independent assessment of the efficacy, safety and cost-effectiveness of drug-eluting stents as used in the real-world; (2) to provide the setting for coronary artery stenting as a viable alternative to bypass surgery, and finally; (3) to provide some insights into newer second generation agents.

Part 1 introduces the reader to percutaneous coronary intervention by providing a historical and scientific account of coronary artery stenting and drug-eluting stents in Chapters 2 and 3 respectively. In **Part 2**, the overall one-year results comparing paclitaxel- and sirolimus-eluting stents are presented, as well as longer term results comparing sirolimus-eluting stents to bare metal stents. Importantly, these are the overall results of the T-SEARCH and RESEARCH registries respectively. We then go into detail and study specific subgroups of patients and lesions, in particular, those patients and lesions that were not studied in the initial randomized controlled trials that led to the approval of the device. It was important

to be able to provide early and timely data to reassure the interventional community regarding the safety of these new devices.

Part 3 has now become an extremely important topic. As we write in Chapter 2, the initial period of overblown enthusiasm with new technologies is quickly followed by a period of intellectual reproach. Within the RESEARCH registry initially, then with the T-SEARCH registry, we began to see a peculiar late complication of drug-eluting stents, namely late stent thrombosis. We also saw early stent thrombosis, which we reported as occurring with the same incidence as in bare metal stents. But it was the late thrombosis that has now become a highly important topic, and recognised as occurring more commonly with drug-eluting stents. We were able to first report its occurrence (Chapter 16) and to provide an incidence (Chapters 15 and 17) to go along with it from our data.

Part 4, which although only consists of one chapter, is also highly important as it explores the cost-effectiveness of drug-eluting stents with respect to bare metal stents. Contrary to the findings of company sponsored studies, we demonstrated that at the prices we paid, drug-eluting stents were not cost effective. We then, in a proactive and provocative paper propose a cost-effective unit price, the first manuscript to do so with real-world data.

Part 5 consolidates the knowledge obtained from the ARTS I and II trials, comparing surgery versus stenting in multivessel disease and utilises it to go forward in the design of the most advanced trial, the SYNTAX trial, comparing surgery versus drug-eluting stenting in left main and /or triple vessel disease. A section emphasising the need for complete revascularisation is included in this section.

The final section of the main body of this thesis (**Part 6**) deals with new challengers to the established first generation eluting stents. Everolimus is an analogue of sirolimus used as an immunosuppressive agent following kidney transplantation. The result of the first randomized trial of everolimus with a durable polymer constitutes Chapter 26. Lastly, the one-year result of a novel paclitaxel-eluting stent with drug- reservoirs is presented. This chapter is important because it demonstrates the relationship between drug pharmacokinetics (i.e. duration of drug delivery) and clinical outcome.

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PART I.

PREFACE: A HISTORY OF CORONARY ARTERY STENTING AND AN OVERVIEW OF DRUG-ELUTING STENTS

Chapter 2

Coronary Artery Stents

Patrick W. Serruys, Michael J. Kutryk, and Andrew T. L. Ong.
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DRUG THERAPY

Coronary-Artery Stents

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N Engl J Med 2006;354:483-95.

The use of percutaneously introduced prosthetic devices to maintain the luminal integrity of diseased blood vessels was proposed by Dotter and Judkins in 1964,[1] well before the introduction of coronary angioplasty by Grüntzig et al. in 1977.[2] Palmaz et al. introduced the use of balloon-mounted stents (as used in coronary arteries today) in peripheral arteries in 1985.[3] Schatz et al. subsequently modified the Palmaz stent, which led to the development of the first commercially successful stent, the Palmaz–Schatz stent.[4] Puel and Sigwart were the first to implant a stent in humans in March 1986; they used a self-expanding mesh device. Sigwart and colleagues were also the first to describe the use of this stent in 1987 for emergency vessel closure during balloon angioplasty,[5] on the basis of the ability of the device to act as a scaffold to move intimal and medial flaps away from the lumen and maintain radial support to offset elastic recoil.[6] Early observational trials highlighted problems associated with the use of stents, in particular, a high incidence of subacute occlusion, despite aggressive anticoagulation regimens that prolonged hospital stays and were also associated with bleeding complications that were difficult to control and occasionally led to serious events.[7] Subsequent reports involving larger numbers of patients confirmed the utility and efficacy of stenting as a means to avoid emergency bypass surgery.[8]

In 1993, two important randomized clinical trials compared the Palmaz–Schatz stent with balloon angioplasty, establishing the elective placement of coronary stents as a standard treatment. The 520-patient Belgium Netherlands Stent (BENESTENT) study[9] and the 410-patient North American Stent Restenosis Study (STRESS)[10] separately demonstrated that intracoronary stents significantly reduced the incidence of angiographic restenosis (defined as more than 50 percent narrowing of a previously stented site, as measured by quantitative coronary angiography) and repeated angioplasty in patients with discrete, new lesions in large target vessels, leading to the era of elective stent implantation. By 1999, stenting comprised 84.2 percent of percutaneous coronary interventions.[11] Although the implantation of an intracoronary stent prevents the acute recoil and postinjury arterial shrinkage (constrictive remodeling) associated with balloon angioplasty, it increases the risk of subacute thrombosis and, more important, replaces atherosclerotic coronary disease with the more severe iatrogenic condition of in-stent neointimal hyperplasia — that is, the growth of scar tissue inside the stent through the cell-cycle pathway and as a result of the proliferation and migration of vascular smooth-muscle cells (Fig. 1).

At the time of the STRESS and BENESTENT trials, despite the use of an intensive anticoagulation regimen, subacute occlusion occurred in 3.7 percent of patients, a value higher than that seen with balloon angioplasty alone. The use of high balloon pressures to optimize apposition of the stent strut to the vessel wall, together with dual antiplatelet therapy with aspirin and ticlopidine (a thienopyridine) rather than anticoagulation resulted in a dramatic reduction in the rates of stent thrombosis.[12] Currently, clopidogrel is the more popular thienopyridine, owing to its bet-

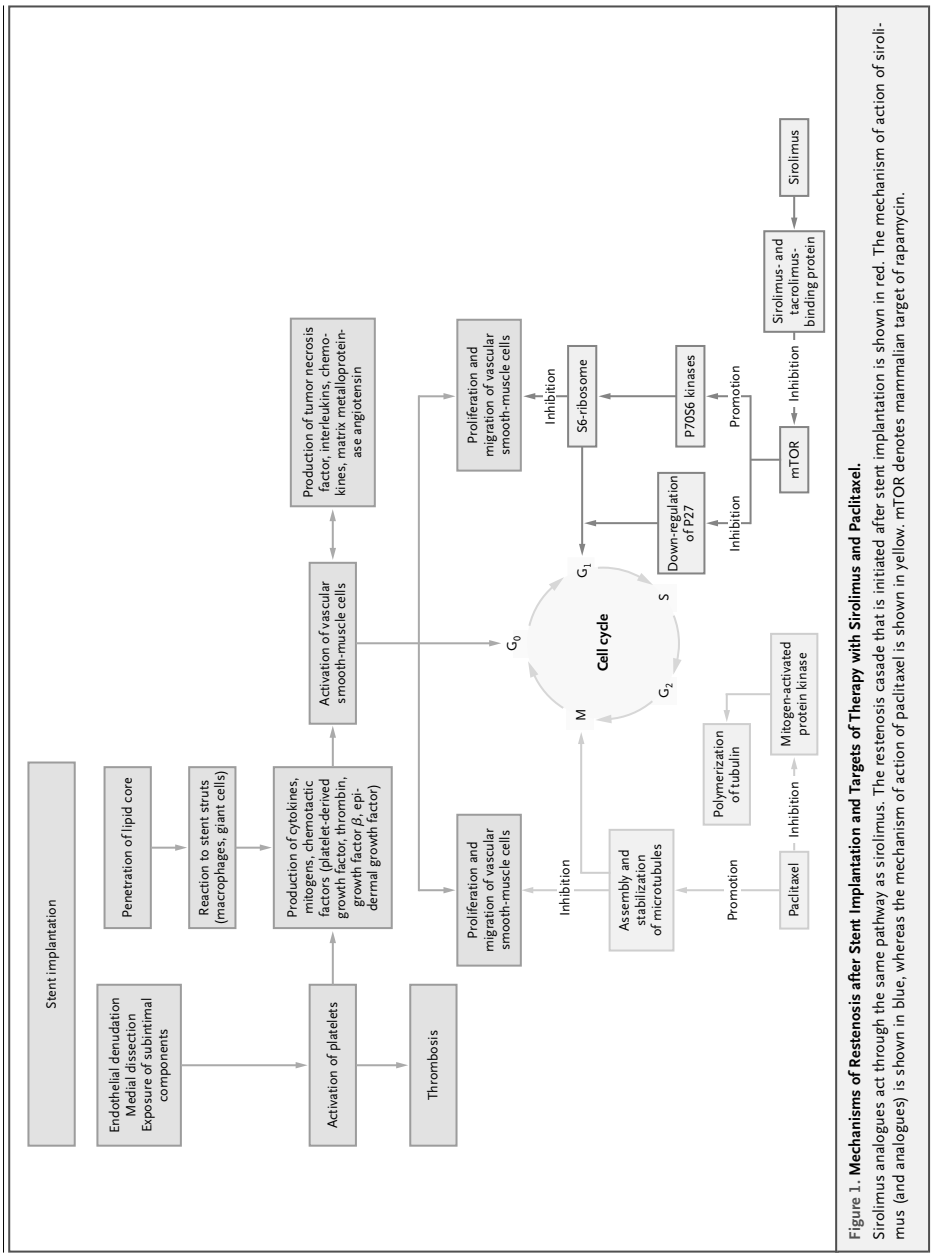

Figure 1. **Mechanisms of Restenosis after Stent Implantation and Targets of Therapy with Sirolimus and Paclitaxel.**
Sirolimus analogues act through the same pathway as sirolimus. The restenosis casade that is initiated after stent implantation is shown in red. The mechanism of action of sirolimus (and analogues) is shown in blue, whereas the mechanism of action of paclitaxel is shown in yellow. mTOR denotes mammalian target of rapamycin.

ter safety profile, with a lower incidence of rash and neutropenia.[13] A recent meta-analysis of 29 published, randomized studies involving 9918 patients and comparing balloon angioplasty with routine coronary stenting with bare stents confirmed that stenting reduces restenosis and repeated intervention, but does not reduce mortality or myocardial infarction.[14] Once a role for elective stent implantation was established, the next goal was to overcome the complications of subacute stent thrombosis and neointimal hyperplasia through pharmacologic and physical means.

BARRIER AND BIOACTIVE STENT COATINGS

BARRIER STENT COATINGS

Stent implantation, inherently a thrombogenic procedure, initiates a complex interaction between the blood components and the metal surface of the stent, which includes the deposition of protein; the activation of platelets, the complement system, and coagulation factors; and the eventual propagation of thrombi over the surface of the stent[15] and the establishment of a confluent endothelial monolayer. Various biologically inert surface coatings, such as carbon, platinum, phosphorylcholine, and gold, have been applied to stainless-steel stents in an attempt to reduce thrombosis and restenosis, but the effectiveness of these strategies has not been proven in clinical trials. Indeed, gold coatings result in increased rates of restenosis.[16]

ACTIVE STENT COATING TO PREVENT THROMBOSIS

In contrast to barrier laminates, heparin coatings provide a biologically active surface that interacts with circulating blood. The BENESTENT II randomized trial demonstrated that heparin-coated stents resulted in a lower rate of adverse events at one year than did balloon angioplasty (11 percent vs. 21 percent, $P=0.004$).[17] Analysis of data from a large, single-center registry demonstrated that, as compared with bare-metal stents, heparin-coated stents significantly reduced the rate of stent thrombosis.[18]

DRUG-ELUTING STENTS

Considerable efforts have gone into the development of stents with an active coating to inhibit in-stent restenosis — the drug-eluting stent. The components of a drug-eluting stent can be divided into a platform (the stent), a carrier (usually a polymer), and an agent (a drug) to prevent restenosis. Stents are ideal delivery systems because they allow the local delivery of the active agent to the area of vascular injury, averting the need to deliver high doses systemically. The development of a suitable carrier to transport an appropriate agent has been challenging, since it must have mechanical resistance to abrasion during implantation, be suitable for sterilization, allow time- and dose-controlled drug release, and not promote thrombogenesis and inflammation of the vessel wall and tissue.[19] Various coatings have been developed, including phosphorylcholine; biocompatible nonerodable, biodegradable, or bioabsorbable polymers; and ceramic layers.[20-25] Polymers are the most commonly used carriers. A drug that is successfully eluted should inhibit the complex cascade of events that leads to neointimal formation after stent implantation (Fig. 1). The inflammatory and proliferative mechanisms of the general tissue-healing response and specific blood and vessel-wall components of the vascular reparative processes are potential targets for therapeutic approaches aimed at reducing neointimal proliferation.

The success of eluting devices is highly dependent on each component of the complex, as well as on the interactions among these elements. It is therefore unlikely that drug-eluting stents have a class effect, since there are myriad possible therapeutic combinations. Different drug-eluting stents vary in their ability to inhibit neointimal growth.[26] Finally, because the results of experiments in animal models cannot be directly translated to humans, specific clinical trials of safety and efficacy are required for each device.[27]

SUCCESSFUL DRUG-ELUTING STENTS

Sirolimus-Eluting Stents

The first positive clinical data on drug-eluting stents came from trials examining sirolimus-coated stents. Sirolimus, a natural macrocyclic lactone with potent antiproliferative, antiinflammatory, and immunosuppressive effects, acts by inhibiting the activation of the mammalian target of rapamycin (mTOR), ultimately causing arrest of the cell cycle (Fig. 1).[28,29]

The Cypher sirolimus-eluting stent (Cordis, Johnson & Johnson) is produced by coating a stainless-steel stent with a thin layer of a nonerodable

polymer containing sirolimus. The seminal first implantations of slow- and fast-release sirolimus-eluting stents, in the First in Man (FIM) clinical study, were performed in São Paulo, Brazil,[20] and Rotterdam, the Netherlands.[30] Four months after implantation, both types of stents were associated with minimal neointimal hyperplasia, as measured by intravascular ultrasonography and quantitative coronary angiography. The slow-release formulation was subsequently used. In the Brazilian study, intravascular ultrasonography at four years revealed continued suppression of intimal hyperplasia in the group of 30 patients with the slow-release sirolimus-eluting stent, with an event-free survival rate of 87 percent.[20]

The results of four randomized trials involving sirolimus-eluting stents have been published and are summarized in Figures 2 and 3 and in Table 1 of the Supplementary Appendix (available with the full text of this article at www.nejm.org). The Randomized Study with the Sirolimus-eluting Bx Velocity Balloon Expandable Stent (RAVEL) demonstrated a remarkable 0 percent rate of restenosis and complete inhibition of neointimal hyperplasia in the group that received a sirolimus-eluting stent, as measured by angiography, and led to the approval of the device in Europe.[31] Percutaneous revascularization of the treated lesion was required in 0 percent of the group that received a sirolimus-eluting stent group, as compared with 23 percent of the control group at one year. The results of the randomized, double-blind Sirolimus Eluting Stent in de Novo Coronary Lesions (SIRIUS) trial, involving 1055 patients, were used to gain approval of the device by the Food and Drug Administration (FDA) in the United States in 2003.[32] The SIRIUS trial confirmed the safety and efficacy of the sirolimus-eluting stent in single, previously untreated coronary artery lesions, with a lower rate of in-stent restenosis than found with otherwise identical bare-metal stents (3.2 percent vs. 35.4 percent, P<0.001). The smaller European and Latin American (E-SIRIUS)[33] and Canadian (C-SIRIUS)[34] multicenter SIRIUS trials confirmed the results of the SIRIUS trial. Most recently, the single-group Arterial Revascularization Therapies Study Part II (ARTS II), involving a cohort of patients with highly complex conditions who received an average of 3.7 sirolimus-eluting stents, reported low rates of repeated intervention rates — 8.5 percent — at one year, with an event-free survival rate of 89.5 percent.[35]

Polymeric Paclitaxel–Eluting Stents

Paclitaxel is a potent antiproliferative agent that inhibits the disassembly of microtubules (Fig. 1). A series of studies — the Randomized, Double-Blind Trial of a Slow-Release Paclitaxel-Eluting Stent for de Novo Coronary Lesions (TAXUS) studies — were conducted to collect data on two paclitaxel-eluting stents, the NIR stent and the Express stent (Boston Scientific). A copolymer coating (Translute, Angiotech) is used for the biphasic release of paclitaxel, with an initial burst in the first 2 days, followed by lower-level release for 10 days. Three randomized trials of this device have been published (Fig. 2 and 3, and Table 1 of the Supplementary Appendix). TAXUS-I evaluated the feasibility and safety of paclitaxel-eluting stents as compared with bare-metal stents and found similar six-month rates of restenosis of 0 and 10 percent, respectively.[21]

TAXUS-II investigated two formulations of paclitaxel-eluting stents: slow- and moderate-release.[36] Although both devices carry the same total dose of medication, drug release from the moderate-release device is eight times as high in the first 10 days. Excellent results were achieved with both formulations; only the slow-release formulation was readied for commercial use and received European approval partly on the basis of the results of this trial. The randomized, double-blind TAXUS-IV, involving 1314 patients, assessed the safety and efficacy of the slow-release paclitaxel-eluting stent in single, previously untreated lesions and led to FDA approval in 2004.[37] Nine months after stenting, the need for a repeated procedure in the treated vessel was 4.7 percent in the group that received paclitaxel-eluting stents, as compared with 12.0 percent in the groups that received bare-metal stents (P<0.001). TAXUS-V and TAXUS-VI subsequently confirmed the efficacy of this stent in small vessels (less than 2.5 mm in diameter) and long lesions and the safety of procedures involving overlapping paclitaxel-eluting stents (Table 2 of the Supplementary Appendix).

REAL-WORLD EXPERIENCE

Concern that the results of the clinical trials might not translate into daily practice were addressed in the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) sequential registry.[38] A total of 508 consecutive patients with previously untreated coronary lesions exclu-

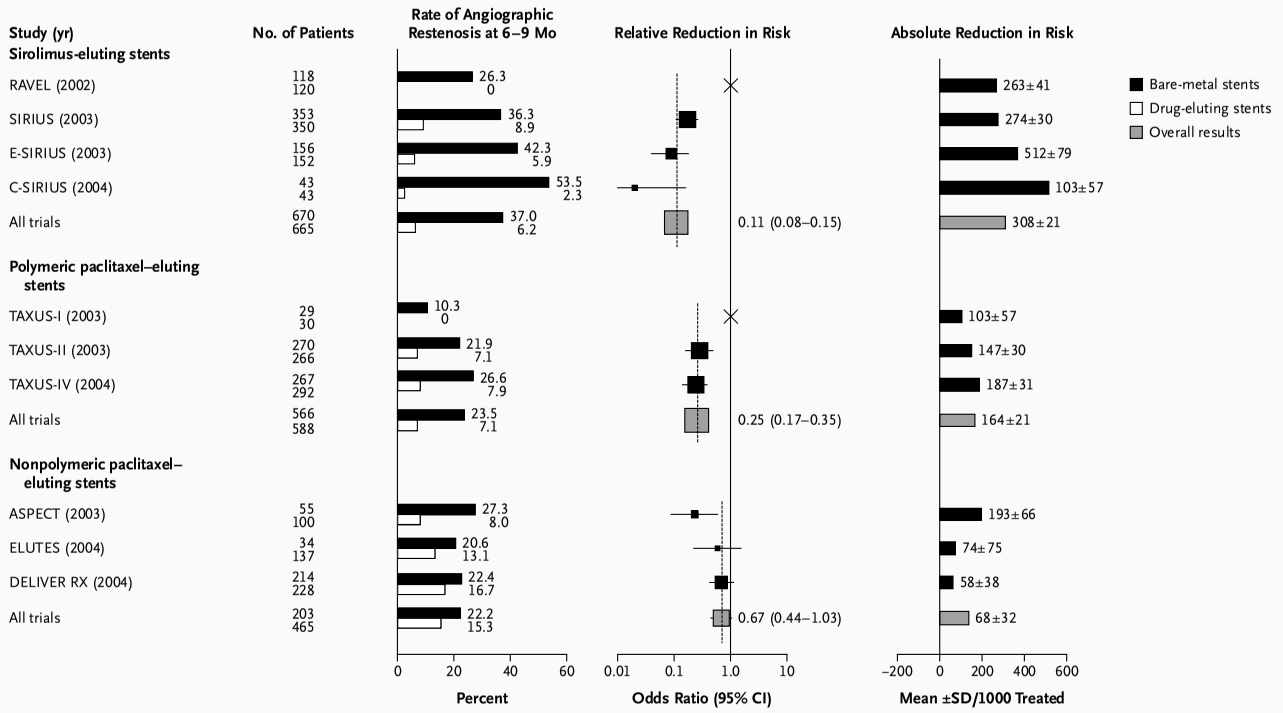

Figure 2. Rates of Angiographic Restenosis and the Relative and Absolute Reduction in the Risk of Angiographic Restenosis among Patients Given Drug-Eluting Stents, as Compared with Those Given Bare-Metal Stents, at Six to Nine Months.

The analysis was confined to patients who underwent follow-up angiography after receiving a stent. RAVEL denotes Randomized Study with the Sirolimus-eluting Bx Velocity Balloon Expandable Stent, SIRIUS Sirolimus Eluting Stent in de Novo Coronary Lesions, E-SIRIUS European and Latin American SIRIUS, C-SIRIUS Canadian SIRIUS, TAXUS Randomized, Double-Blind Trial of a Slow-Release Paclitaxel-Eluting Stent for de Novo Coronary Lesions, ASPECT Asian Paclitaxel-Coated Stent Clinical Trial, ELUTES European Evaluation of Paclitaxel Eluting Stent, and DELIVER RX Achieve Drug-Eluting Coronary Stent System in the Treatment of Patients with De Novo Native Coronary Lesions.

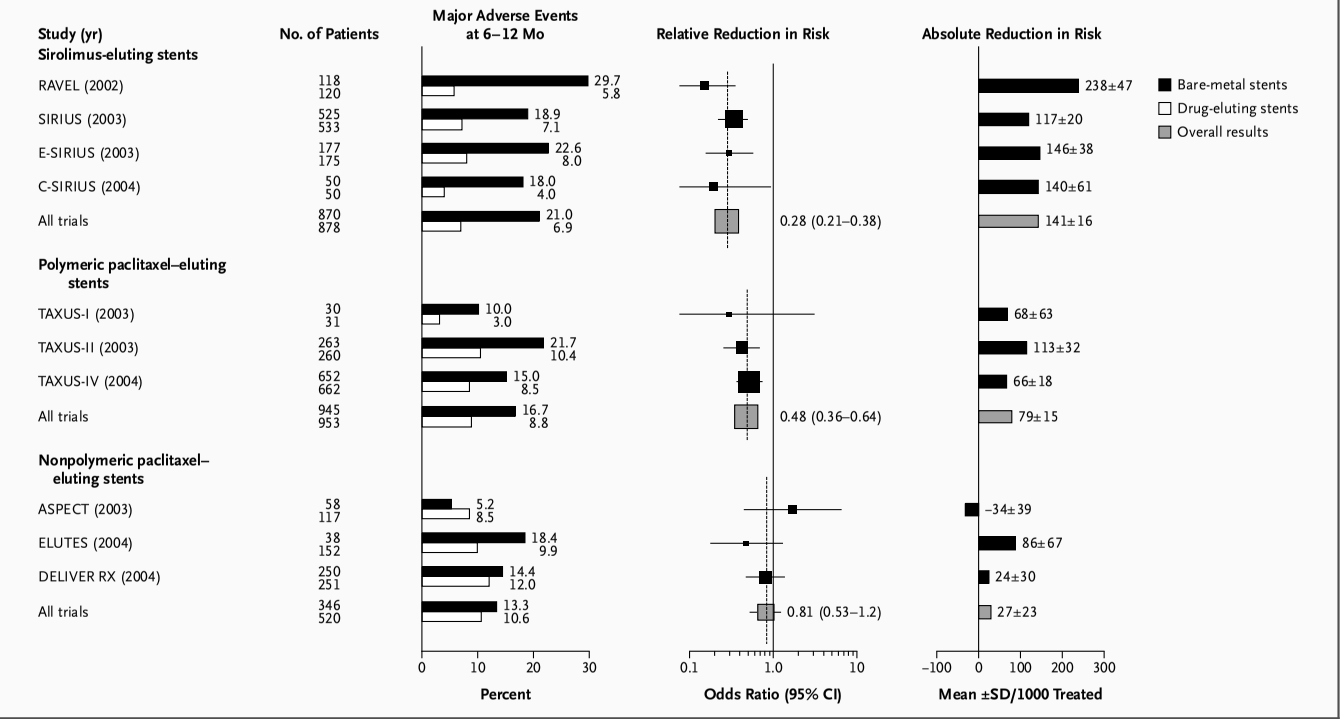

Figure 3. Plots of Major Adverse Cardiac Events and the Relative and Absolute Reduction in the Risk of Such Events among Patients Given Drug-Eluting Stents, as Compared with Those Given Bare-Metal Stents, up to One Year.

RAVEL denotes Randomized Study with the Sirolimus-eluting Bx Velocity Balloon Expandable Stent, SIRIUS Sirolimus Eluting Stent in de Novo Coronary Lesions, E-SIRIUS European and Latin American SIRIUS, C-SIRIUS Canadian SIRIUS, TAXUS Randomized, Double-Blind Trial of a Slow-Release Paclitaxel-Eluting Stent for de Novo Coronary Lesions, ASPECT Asian Paclitaxel-Coated Stent Clinical Trial, ELUTES European Evaluation of Paclitaxel Eluting Stent, and DELIVER RX Achieve Drug-Eluting Coronary Stent System in the Treatment of Patients with de Novo Native Coronary Lesions.

sively treated with sirolimus-eluting stents were compared with a control group of 450 patients who had received bare-metal stents in the period immediately preceding the introduction of drug-eluting stents. Patients who received sirolimus-eluting stents had a lower rate of adverse events at one year (9.7 percent vs. 14.8 percent, P=0.008), with the difference largely accounted for by a reduction in the rate of clinically driven reinterventions (3.7 percent vs. 10.9 percent, P<0.001). The two-year results of this study confirmed the durability of this device, with rates of adverse events of 15.4 percent in the group given sirolimus-eluting stents, as compared with 22.0 percent in the group given bare-metal stents (P<0.01).[39] The randomized Basel Stent Kosten Effektivitäts Trial (BASKET) confirmed the superiority of drug-eluting stents over bare-metal stents at six months.[40]

COMPARATIVE TRIALS

The Prospective, Randomized, Multi-Center Comparison Study of the Cypher Sirolimus-Eluting and TAXUS Paclitaxel-Eluting Stent Systems (REALITY) compared sirolimus-eluting stents and paclitaxel-eluting stents.[26] The rate of late loss (a measure of neointimal hyperplasia assessed by means of quantitative coronary angiography) was lower with sirolimus-eluting stents than with paclitaxel-eluting stents, but the rates of angiographic restenosis and, more important, the need for reintervention in the treated lesion did not differ significantly between groups (5.0 percent vs. 5.4 percent, P=0.8). The two-center Randomized Comparison of Sirolimus with Paclitaxel Eluting Stents for Coronary Revascularization of All Comers (SIRTAX)[41] reported better outcomes with sirolimus-eluting stents than with paclitaxel-eluting stents. The single-center Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) study, a sequential monocentric registry of patients who received drug-eluting stents without any restrictions, reported no significant difference in the incidence of adverse cardiac events between the two devices.[42] Two smaller randomized trials demonstrated that sirolimus-eluting stents were more efficacious than paclitaxel-eluting stents in specific types of patients: those with restenosis in bare-metal stents (the Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for In-Stent Restenosis [ISAR-DESIRE] study) and those with diabetes (the ISAR: Do Diabetic Patients Derive Similar Benefit from Paclitaxel-Eluting and Sirolimus-Eluting Stents [ISAR-DIABETES] study).[43,44]

INVESTIGATIVE AGENTS

Zotarolimus

Zotarolimus is a sirolimus analogue that blocks the function of mTOR and is currently being investigated (Fig. 1, and Table 2 of the Supplementary Appendix). A series of clinical trials — Trial to Evaluate the Safety and Efficacy of the Medtronic AVE ABT-578 Eluting Driver Coronary Stent in de Novo Native Coronary Artery Lesions (ENDEAVOR) — have been designed to examine the safety and efficacy of zotarolimus released from a phosphorylcholine-delivery matrix on the cobalt-based alloy Driver stent (Medtronic).[22] The single-group ENDEAVOR-I safety study was followed by the randomized, multicenter ENDEAVOR-II trial, involving 1197 patients, which confirmed the efficacy of this device, with restenosis rates of 9.5 percent, as compared with 32.7 percent for bare-metal stents (P<0.001).[45] The implications of a mean in-stent late loss of 0.62 mm, which was consistently seen in both trials and is higher than that reported in trials of sirolimus-eluting and paclitaxel-eluting stents, are unknown.

The Zomaxx stent (Abbott) contains zotarolimus on a low-profile, trilayer stent composed of tantalum and stainless steel (TriMaxx), with a modified phosphorylcholine coating to allow slower drug release than afforded by the Medtronic device. The first of Abbott's clinical trials has completed enrollment, and a second is under way (Table 2 of the Supplementary Appendix).

Everolimus

As a sirolimus analogue, everolimus inhibits mTOR (Fig. 1). Trials involving everolimus-coated stents are split into two: the First Use to Underscore Restenosis Reduction with Everolimus (FUTURE) and A Randomized Comparison of a Durable Polymer Everolimus-Eluting Stent with a Bare-Metal Coronary Stent (SPIRIT) studies (Tables 1 and 2 of the Supplementary Appendix). The small FUTURE-I study was a prospective, randomized, single-blind trial that evaluated the safety of an everolimus-eluting stent with an ultrathin coating of a polyhydroxyacid bioabsorbable polymer used for drug delivery (Biosensors International). As compared with bare-metal stents in previously untreated lesions, everolimus-eluting stents sig-

nificantly reduced the extent of late loss (0.11 mm vs. 0.85 mm, P<0.001).[23] The results of the FUTURE-II trial have yet to be published. The SPIRIT FIRST trial confirmed the safety and efficacy of everolimus coupled with a durable polymer on a chromium–cobalt stent and has led to the initiation of SPIRIT-II outside and SPIRIT-III within the United States.[24]

Other Agents

Other agents that appear promising and are currently undergoing safety and efficacy trials include biolimus A9 (a sirolimus analogue),[25] tacrolimus (a sirolimus analogue), and paclitaxel contained in reservoirs within the stent. If shown to be successful, they will then undergo larger comparative trials, most likely with one or more of the established devices used as a benchmark.

INDICATIONS FOR THE USE OF CORONARY STENTS

Currently, better equipment and drug-eluting stents have changed percutaneous coronary intervention so that 90 to 95 percent involve stent implantation. However, most published data originated in the era of bare-metal stents. Given the lack of long-term follow-up with drug-eluting stents, careful scrutiny of the literature is necessary before convincing recommendations can be made.

PRIMARY REVASCULARIZATION AFTER MYOCARDIAL INFARCTION INVOLVING ST-SEGMENT ELEVATION

Randomized trials have compared stent implantation with balloon angioplasty as the primary revascularization strategy for myocardial infarction involving ST-segment elevation,[46-48] with meta-analyses reporting the superiority of stenting, as reflected by a reduced need for reintervention in the treated vessel for up to 12 months.[49] More recently, two major studies, Danish Multicenter Randomized Study of Fibrinolytic Therapy vs. Acute Coronary Angioplasty in Acute Myocardial Infarction 2 (DANAMI-2)[50] and Primary Angioplasty in Patients Transferred from General Community Hospitals to Specialized Percutaneous Transluminal Coronary Angioplasty (PTCA) Units with or without Emergency Thrombolysis 2 (PRAGUE-2),[51] have indicated the superiority of stenting over thrombolytic therapy, primarily as a result of the ability of stenting to reduce reinfarction rates. Drug-eluting stents are superior to bare-metal stents because they further reduce the need for reintervention in the treated vessel.[52]

Focal Lesions in Vessels 3.0 mm or More in Diameter

The trials comparing balloon angioplasty with stent implantation have been confined to patients with vessels with diameters of 3.0 mm or greater on visual assessment (smaller-diameter stents were not available in the past). Results of such trials have consistently shown a reduction in adverse events with the use of stenting.[9,10,17] A notable finding is that a sizable number of patients who received stents had vessel diameters smaller than 3.0 mm when later measured with the use of quantitative coronary angiography.

Focal Lesions in Saphenous-Vein Grafts

Both observational and randomized trials have indicated a high rate of procedural success with vein-graft stenting, improved clinical outcomes during hospitalization, and improved long-term graft patency.[53] The Randomized Evaluation of Polytetrafluoroethylene Covered Stents in Saphenous Vein Grafts (RECOVERS) study[54] demonstrated that stents covered with a polytetrafluoroethylene membrane conferred no advantage over bare-metal stents for the treatment of vein-graft disease. Distal embolization is a major problem in old and friable vein grafts, and the use of devices placed downstream of the treated area to catch vascular debris has improved the safety of vein-graft interventions.[55,56]

Treatment of Chronic Total Occlusions

Various trials comparing stenting with balloon angioplasty for coronary-artery occlusions have reported that stenting reduces the rate of angiographic and clinical restenosis and reocclusion.[57] More recently, registry series comparing drug-eluting stents with bare-metal stents have confirmed the superior efficacy of the former.[58]

Treatment of Restenosis after Balloon Angioplasty

The randomized Restenosis Stent Trial (REST) demonstrated that in patients with restenosis after balloon angioplasty, the implantation of a stent was associated with a lower rate of angiographic restenosis and repeated intervention than was balloon angioplasty.[59]

SEGMENTAL LESIONS FOR WHICH CORONARY STENTING IS PROBABLY BENEFICIAL

Although stents are used for long lesions, vessels that are less than 3.0 mm in diameter, and lesions at bifurcations, there is less evidence to support their use.

Long Lesions

The length of the stented segment is a recognized independent risk factor for restenosis.[60] In a nonrandomized comparison, balloon angioplasty with intravascular-ultrasound–guided placement of multiple small stents to cover stenoses along vessel lesions ("spot" stenting) had a better long-term outcome than stenting the entire portion of a diseased vessel.[61] One randomized trial compared the use of stents with balloon angioplasty for long lesions and found lower rates of angiographic restenosis in the stent group than in the angioplasty group at six months (27 percent vs. 42 percent, $P<0.05$) but no significant difference in clinical benefit at nine months.[62] Placing sequential overlapping stents in long lesions increases the length of the stented area within the vessel and is associated with increased rates of restenosis. Evidence to date indicates that drug-eluting stents may be safely used in this manner and are seemingly associated with markedly reduced rates of restenosis. Thus, drug-eluting stents appear to be associated with a substantially smaller risk of restenosis than bare-metal stents, especially in long lesions.[63]

Small Vessels

The benefit of stenting vessels smaller than 3.0 mm in diameter is unclear; a meta-analysis indicated that stenting significantly reduced the rates of repeated revascularization, as compared with balloon angioplasty, with similar rates of adverse events.[64] The recent subgroup analyses of TAXUS-V and TAXUS-VI suggest that drug-eluting stents reduce the rate of restenosis in small vessels, without associated side effects.

Lesions at Bifurcations

Different stenting techniques, each with their own advantages and indications, have been used to treat lesions at bifurcations.[65] Observational studies have suggested that stenting both branches of bifurcated lesions confers no advantage over stenting one branch and performing balloon angioplasty on the other.[66] Currently, the most appropriate technique for treating lesions at bifurcations remains to be determined. As compared with historical results with bare-metal stents, drug-eluting stents are associated with a lower overall rate of restenosis, although the rates remain higher in side branches than in the main vessel.[67]

UNRESOLVED ISSUES

Stenosis of an Unprotected Left Main Coronary Artery

Safety studies and early efficacy studies have shown that stenting of a previously ungrafted stenosis in the left main stem may be a promising alternative to bypass surgery in selected patients.[68,69] Analysis of recent registries suggests a potential role for drug-eluting stents in left main lesions,[70,71] with the ongoing Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) Study designed to address the role of drug-eluting stents as compared with bypass surgery in a randomized manner.[72]

Multivessel Disease

Long-term follow-up of patients with multivessel disease in the ARTS trial found no significant difference in mortality rates between patients treated with bare-metal stents and those treated with bypass surgery, but the former group had a higher rate of repeated procedures.[73] The SYNTAX study will address the role of drug-eluting stents, as compared with bypass surgery, in three-vessel disease.[72]

Diabetes Mellitus

Diabetes has repeatedly been shown to confer an independent risk of restenosis and adverse clinical events after stent implantation in multiple trials of bare-metal and drug-eluting stents.[32,37] Although as compared with bare-metal stents, drug-eluting stents appear to reduce the reintervention rate by up to two thirds among patients with diabetes with bare stents, the reintervention rate in this subgroup remains up to twice as frequent as that among patients without diabetes who receive stents.[35] A randomized trial is under way — the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) study — that specifically compares drug-eluting stents with bypass surgery in patients with diabetes who have multivessel disease.

In-Stent Restenosis

Both sirolimus-eluting stents[74] and paclitaxel-eluting stents[75] have been examined as treatments for restenosis. Although definitively better than balloon angioplasty in reducing the rate of recurrent restenosis,[43] they appear similar to conventional intracoronary brachytherapy (radiation delivered intravascularly through a catheter within the stent borders).[76] The TAXUS-V–In-Stent Restenosis randomized trial is comparing drug-eluting stents with brachytherapy for in-stent restenosis to confirm these results.

Biodegradable Stents

The development of biodegradable stents has been hampered by difficulties in replicating the properties of stainless-steel stents. There has been a revival of interest in developing a fully biodegradable stent that has pharmacologically active agents incorporated into the polymeric matrix. An effective drug-releasing, biodegradable stent must not cause an inflammatory reaction or release toxic breakdown products. The release of the drug from the stent must be safe and reliable, and the stent must have high radial strength similar to that of metal. Biodegradation should occur within a reasonable period (12 to 24 months). The Duke biodegradable stent[77] and the Igaki–Tamai biodegradable stent[78] are made from a special form of poly-L-lactide and are capable of incorporating pharmacologically active agents. The Igaki–Tamai stent has been successfully loaded with tranilast, a drug that inhibits the migration and proliferation of vascular smooth-muscle cells.[79] This type of stent has also been loaded with paclitaxel, and although effective in reducing the rate of restenosis in an animal model, it incites a considerable inflammatory response.[80] Another promising degradable stent undergoing clinical evaluation is made from magnesium alloy.[81]

CAVEATS AND CONCLUSIONS

The three major milestones in the evolution of interventional cardiology were the development of the angioplasty balloon by Andreas Grüntzig, the introduction of the coronary-artery stent, and most recently, the development of drug-eluting stents. In the past three years, the use of drug-eluting stents has had an unprecedented effect on the practice of interventional cardiology. The acceptance of drug-eluting stents has followed the same course as all newly introduced techniques, with the initial period of overblown enthusiasm quickly followed by a period of intellectual reproach.

Recent results of longer-term studies in broader patient populations have highlighted troubling clinical issues. In studies in animals, the presence of fibrin, inflammatory cells, and incomplete endothelialization has been noted and at three months, when the drug has been completely eluted from the stent, neointimal growth at levels similar to those for bare-metal stents,[27] arousing concern about the possibility of late restenosis.[82] Delayed endothelialization has been seen in human arteries treated with drug-eluting stents[83]; this complete inhibition of healing may prevent encapsulation of the stent but, in one study, did not translate into adverse events at one year.[84] There have been rare instances of hypersensitivity reactions to the polymer, which can be fatal.[85]

The consequences of these findings have been clinically observed as stent thrombosis, a potentially fatal complication of stent implantation. Thrombosis within the stent may occur early, within the first 30 days after implantation, or late, if after this period, with differing causes. The most common cause of early stent thrombosis is mechanical (unrecognized dissection or underexpansion of the stent), whereas late stent thrombosis is potentially due to a mismatch between the stent and the vessel (stent malapposition), hypersensitivity,[85] or abnormal reendothelialization. A recently recognized potential predisposing factor for stent thrombosis is resistance to aspirin and clopidogrel; this association requires more investigation. The rates of early stent thrombosis probably do not differ significantly between drug-eluting and bare-metal stents, occurring in 1.0 to 1.5 percent of patients.[86,87] Whether this is also true for late stent thrombosis is unclear; however, caution must be exercised, given the lack of comparative data and the difference in the duration of dual antiplatelet therapy between devices (one month for bare-metal stents and three to six months for drug-eluting stents).[88]

Most important, after the implantation of a drug-eluting stent, patients must strictly adhere to their regimen of dual antiplatelet therapy and, on completion, take aspirin monotherapy.[89] Patients with drug-eluting stents who require surgery, elective or otherwise, irrespective of the time since implantation, must continue to take aspirin

perioperatively unless it is absolutely contraindicated, since cessation of antiplatelet therapy, even if it occurs long after the implantation of the stent, may precipitate stent thrombosis, which carries a high risk of death or myocardial infarction.

As a solution, coatings that are more biologically friendly and promote rather than inhibit natural healing processes are rapidly being developed.[90,91] One example is the use of immobilized antibodies against circulating endothelial progenitor cells as a means of "self-seeding" intravascular devices.[90] Such techniques show promise for use in combination with drug-eluting stents and may provide a more physiologic alternative. With the development of better devices, uniquely engineered to be specific for each subgroup of lesions, the treatment of coronary artery disease will improve.

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Chapter 3

Technology Insight: An Overview of Research in Drug-Eluting Stents.

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Technology Insight: an overview of research in drug-eluting stents

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SUMMARY

Drug-eluting stents (DESs) have revolutionized interventional cardiology over the past few years to the extent that balloon angioplasty and bare stents did in the 1980s and 1990s. The first DESs became commercially available in Europe in 2002 and in the US in 2003, and it is estimated that up to 80% of patients who undergo stent implantation in the US now receive a DES. Two devices, Cypher® sirolimus-eluting stents (Cordis Corporation, Miami Lakes, FL) and Taxus® paclitaxel-eluting stents (Boston Scientific Corporation, Natick, MN), are currently licensed for sale in both regions. Multiple new devices using different drugs, carriers and stents are currently undergoing clinical trials to establish their efficacy and obtain approval for commercialization. While the remarkable reduction of restenosis has accounted for the success of DESs, concerns remain regarding long-term follow-up; published 3-year follow-up results are available for fewer than 200 patients overall. Reports of late stent thrombosis have emerged, particularly in relation to discontinuation of antiplatelet therapy. In patients treated with DESs, long-term administration of at least one antiplatelet agent must be continued following completion of the mandatory dual antiplatelet regimen. In this review, we summarize the findings available for DESs so far, discuss emerging safety and efficacy data, and look at the future directions for these devices.

KEYWORDS angioplasty, drug-eluting stent, paclitaxel, sirolimus, thrombosis

REVIEW CRITERIA

Manuscripts and references selected for this review were identified through a relevant search of the literature on PubMed and conference presentations published within the last 2 years, and from the authors' own collection of materials. Multiple search terms were used as follows: "stents", "drug-eluting", "sirolimus", "paclitaxel", "everolimus" and "thrombosis".

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INTRODUCTION

Following the commercialization of drug-eluting stents (DESs) in April 2002 in Europe, and in March 2003 in the US, there has been a rapid uptake of this new technology—more than 2.5 million stents had been implanted worldwide up to February 2005.[1,2] In Europe, DESs are currently estimated to account for 40% of all stent sales, and in the US the market penetration has reached 80%. Two devices are currently commercially available in both continents, with others at various stages of product development. In this review, we discuss the data available so far for the two commercially available devices, summarize the findings for other DESs being tested or developed, and look at the possible future applications for these devices.

DRUG-ELUTING-STENT COMPONENTS

The components of a DES are the platform (the stent itself), the carrier (usually a polymer) and the agent (a drug that prevents restenosis). Metallic coronary stents alleviate coronary obstructions and preserve the luminal area by providing a mechanical scaffold to prevent the elastic recoil seen with balloon angioplasty. The structure provides an ideal way to locally deliver the active agent to the area of vascular injury, thus avoiding the need for high systemic doses.

The development of a suitable carrier for the agent has been challenging.[3] Prerequisites include suitability for sterilization, mechanical resistance to abrasion during the laborious process of stent implantation, controllable drug release (both in concentration and time), and no thrombogenic or inflammatory effects on the vessel wall and tissue. Different agents might require different delivery vehicles. Most commonly, this vehicle has been a polymer coating. Various coatings have been developed, including phosphorylcholine, biocompatible nonerodible, biodegradable or bioabsorbable polymers and ceramic layers.

A successful agent should inhibit the complex cascade of events that leads to neointimal

Table 1 In-stent late loss and restenosis outcomes from company-sponsored, randomized, double-blind, placebo-controlled, multicenter trials comparing polymer-coated sirolimus-eluting or paclitaxel-eluting stents with bare-metal stents.

Study (inclusion criteria)	Stent platform and carrier[a]	Mean (SD) in-stent late loss (mm) and *P* value	Proportion of in-stent binary restenosis (%)	Angiographic/ clinical follow-up (months)
Sirolimus				
RAVEL[8,12] (one *de novo* native coronary lesion <18 mm, single-stent, vessel diameter 3.0–3.5 mm)	Bx Velocity™ with 140 μg/cm^2 slow-release sirolimus; Cypher® stent	–0.01 (0.33) vs 0.80 (0.53), *P* <0.001	0 vs 26.2, *P* <0.001	6/36
SIRIUS[9,63] (one *de novo* native coronary lesion 15–30 mm, up to two stents, vessel diameter 2.5–3.5 mm)	Bx Velocity™ with 140 μg/cm^2 slow-release sirolimus; Cypher® stent	0.17 (0.45) vs 1.00 (0.70), *P* <0.001	3.2 vs 35.4, *P* <0.001	8/12
E-SIRIUS[10] (one *de novo* native coronary lesion 15–32 mm, up to two stents, vessel diameter 2.5–3.0 mm)	Bx Velocity™ with 140 μg/cm^2 slow-release sirolimus; Cypher® stent	0.20 (0.38) vs 1.05 (0.61), *P* <0.0001	3.9 vs 41.7, *P* <0.0001	8/9
C-SIRIUS[11] (one *de novo* native coronary lesion 15–32 mm, up to two stents, vessel diameter 2.5–3.0 mm)	Bx Velocity™ with 140 μg/cm^2 slow-release sirolimus; Cypher® stent	0.12 (0.37) vs 1.02 (0.69), *P* <0.001	0 vs 45.5, *P* <0.001	8/9
Paclitaxel				
TAXUS I[15] (one restenotic or *de novo* native coronary lesion ≤12 mm, one stent, vessel diameter 3.0–3.5 mm)	NIRx with 1 μg/mm^2 slow-release paclitaxel	0.36 (0.48) vs 0.71 (0.47), *P* = 0.008	0 vs 10, *P* = NS	6/12
TAXUS II[16] (one de *novo* native coronary lesion ≤12 mm, one stent, vessel diameter 3.0–3.5 mm)	NIRx with 1 μg/mm^2 slow-release and moderate-release paclitaxel	Slow release 0.31 (0.38) vs 0.79 (0.45), *P* <0.0001; moderate release 0.30 (0.39) vs 0.77 (0.50), *P* <0.0001	Slow release 2.3 vs 17.9, *P* <0.0001; moderate release 4.7 vs 20.2, *P* = 0.0002	6/12
TAXUS IV[17,64] (one *de novo* native coronary lesions 10–28 mm, one stent, vessel diameter 2.5–3.75 mm)	Taxus® Express^{2}™ with 1 μg/mm^2 slow-release paclitaxel	0.39 (0.50) vs 0.92 (0.58), *P* <0.001	5.5 vs 24.4, *P* <0.001	9/12
TAXUS V[18] (One *de novo* native coronary lesions 10–46 mm, multiple stents allowed, vessel diameter 2.25–4.0 mm)	Taxus® Express^{2}™ with 1 μg/mm^2 slow-release paclitaxel	0.49 (0.61) vs 0.90 (0.62), *P* <0.0001	13.7 vs 31.9, *P* <0.0001	9/9
TAXUS VI[19] (*de novo* native coronary lesions 18–40 mm, multiple stents allowed, vessel diameter 2.5–3.75 mm)	Taxus® Express^{2}™ with 1 μg/mm^2 moderate-release paclitaxel	0.39 (0.56) vs 0.99 (0.59), *P* <0.0001	9.1 vs 32.9, *P* <0.0001	9/9

[a]All drugs in nonerodible polymer matrix. C-SIRIUS, Canadian SIRolImUS-Eluting Bx Velocity™ Balloon-Expandable Stent trial; E-SIRIUS, European SIRolImUS-Eluting Bx Velocity™ Balloon-Expandable Stent trial; RAVEL, Randomized Study with the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with De Novo Native Coronary Artery Lesions trial.

formation after stent implantation. The inflammatory and proliferative mechanisms of the general tissue-healing response, and the specific role of blood and vessel-wall components in the vascular-reparative processes, are potential targets for therapeutic approaches aimed at reducing neointimal proliferation. The clinical effect of DESs is highly dependent on each individual component, as well as on the interactions between these elements. A class effect of DESs is therefore unlikely, because of the myriad of possible therapeutic combinations. Different DESs vary, for example, in their ability to inhibit neointimal growth.[4]

AVAILABLE DRUG-ELUTING STENTS

Polymer-coated sirolimus-eluting stents

The Cypher® sirolimus-eluting stent (SES; Cordis Corporation, Miami Lakes, FL) has had the longest follow-up of the available DES systems. It is produced by coating a stainless steel stent with a thin layer of a nonerodible methacrylate

Table 2 Revascularization and major adverse coronary events outcomes from company-sponsored, randomized, double-blind, placebo-controlled, multicenter trials comparing polymer-coated sirolimus-eluting or paclitaxel-eluting stents with bare-metal stents.

Study	TLR (%)	TVR (%)	MACE (%)
Sirolimus			
RAVEL[8,12]	5.3 vs 15.0, $P=0.02$ (clinically driven); 6.1 vs 25.7, $P<0.001$ (all TLR)	0.8 vs 23.7, $P<0.001$[a]	10.5 vs 23.9, $P=0.008$ (death, MI, clinically driven TVR); 11.4 vs 33.6, $P<0.001$ (death, MI, TVR)
SIRIUS[9,63]	4.9 vs 20.0, $P<0.001$	N/A	9.8 vs 24.8, $P<0.001$ (cardiac death, MI, TVR); 8.3 vs 22.3, $P<0.001$ (death, MI, TLR)
E-SIRIUS[10]	4.0 vs 20.9, $P<0.0001$	N/A	8.0 vs 22.6, $P=0.002$ (death, MI, TLR)
C-SIRIUS[11]	4.0 vs 18.0, $P=0.05$	N/A	4.0 vs 18.0, $P=0.05$ (death, MI, clinically driven TLR)
Paclitaxel			
TAXUS I[15]	0 vs 10, $P=0.2$	3 vs 10, $P=0.6$	3 vs 10, $P=0.6$ (death, MI TVR)
TAXUS II[16]	Slow release 4.7 vs 12.9, $P=0.03$; moderate release 3.8 vs 16.0, $P=0.002$	Slow release 10.1 vs 15.9, $P=0.2$; moderate release 6.9 vs 19.1, $P=0.005$	Slow release 10.9 vs 22.0, $P=0.02$ (cardiac death, MI, TVR); moderate release 9.9 vs 21.4, $P=0.02$ (cardiac death, MI, TVR)
TAXUS IV[17,64]	4.4 vs 15.1, $P<0.0001$	7.1 vs 17.1, $P<0.0001$	10.8 vs 20.0, $P<0.0001$ (cardiac death, MI, ischemia-driven TVR)
TAXUS V[18]	8.6 vs 15.7, $P=0.0003$	12.1 vs 17.3, $P=0.02$	15.0 vs 21.2, $P=0.008$ (cardiac death, MI, TVR)
TAXUS VI[19]	6.8 vs 18.9, $P=0.0001$	9.1 vs 19.4, $P=0.003$	16.4 vs 22.5, $P=0.12$ (cardiac death, MI, TVR)

C-SIRIUS, Canadian SIRolImUS-Eluting Bx Velocity™ Balloon-Expandable Stent trial; E-SIRIUS, European SIRolImUS-Eluting Bx Velocity™ Balloon-Expandable Stent trial; MACE, major adverse coronary events; MI, myocardial infarction; N/A, not available; RAVEL, Randomized Study with the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with De Novo Native Coronary Artery Lesions trial; TLR, target-lesion revascularization; TVR target-vessel revascularization.

and a mixture of 50% polyethylenevinyl acetate and 50% poly(*n*-butyl methacrylate) polymer containing sirolimus. This stent was first implanted in December 1999, as part of a first-in-man study in 45 patients with non-complex *de novo* lesions treated in São Paulo, Brazil, and Rotterdam, The Netherlands.[5,6] The 4-year results for the 30 São Paulo patients showed persistent suppression of intimal hyperplasia (mean in-stent late loss 0.09 mm for slow-release stents and 0.41 mm for fast-release stents), confirmed by intravascular ultrasonography; event-free survival was 87%.[7]

Four randomized trials comparing the outcomes in patients treated with SESs and those who received conventional bare-metal stents (BMSs) have been published (Tables 1 and 2).[8–11] The positive results of the Randomized Study with the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with De Novo Native Coronary Artery Lesions (RAVEL) trial,[8] with no restenosis detected in any patient at 6 months, led to SESs being approved for commercialization in Europe. The 3-year follow-up data demonstrate the continued benefit of reduced target-lesion revascularization in the SES group compared with the BMS group (95.0% versus 85.6%, $P=0.01$).[12]

The pivotal SIRolImUS-Eluting Bx Velocity™ Balloon-Expandable Stent (SIRIUS) trial randomized 1,101 patients with *de novo* lesions to SESs or BMSs. The findings confirmed the clinical efficacy of the SES and led to FDA approval of the device in the US in 2003. Long-term follow-up data of up to 3 years from the SIRIUS trial have also confirmed the sustained benefit. Two smaller SIRIUS trials in Europe[10] and Canada[11] further reinforced the efficacy of SESs. The Canadian study reported no harmful effects with direct stenting.

The Rapamycin Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) study[13] was a single-center registry with a non-restrictive inclusion criterion into which patients treated with SESs were enrolled. At 1 year, SESs reduced clinically driven repeat intervention by 65% compared with BMSs (3.7% versus 10.9%, $P<0.01$), thus reducing the 1-year risk of major cardiac events by 38% (9.7% versus 14.8%, $P<0.01$). This beneficial effect was maintained at 2 years, with a major adverse cardiac event rate of 15.4% for SESs compared with 22.0% for BMSs ($P=0.01$).[14] Importantly, these patients were

Table 3 Clinical studies with new drug-eluting stents.

Trial name	Inclusion criteria	Stent platform and carrier	In-stent late-loss (mm)	Binary restenosis (%)	Duration of angiographic/ clinical follow-up (months)	TLR (%)	TVR (%)	MACE (%)
Zotarolimus (ABT-578)								
ENDEAVOR I[20]	Single *de novo* native coronary lesions, lesion length <15 mm, vessel diameter 3.0–3.5 mm	Endeavor® phosphorylcholine-coated, ABT-578-eluting Driver® cobalt alloy stent	~0.60	5.4	12/12	1	1	2
ENDEAVOR II[21]	Single *de novo* native coronary lesions, lesion length 14–27 mm, vessel diameter 2.25–3.5 mm	Endeavor® phosphorylcholine-coated, ABT-578-eluting Driver® cobalt alloy stent	0.62 vs 1.03, $P<0.0001$	9.5 vs 32.7, $P<0.0001$	8/9	4.6 vs 12.1, $P<0.0001$	5.7 vs 12.8, $P<0.0001$	8.1 vs 15.4, $P<0.0005$ (cardiac death, MI, TVR)
Everolimus								
FUTURE I[25]	Single *de novo* lesions, lesion length <18 mm, vessel diameter 2.75–4.0 mm	Bioabsorbable, polymer-coated, everolimus-eluting S-Stent (197 μg everolimus/mm^2)	0.11 (0.23) vs 0.85 (0.32), $P<0.0001$	0 vs 9.1, $P=$NS	6/6	3.8 vs 7.1, $P=$NS	3.8 vs 7.1, $P=$NS	7.7 vs 7.1, $P=$NS (death, MI, TLR, TVR-CABG)
FUTURE II[65]	Single *de novo* lesions, lesion length <18 mm, vessel diameter 2.75–4.0 mm	Bioabsorbable, polymer-coated, everolimus-eluting S-Stent (197 μg everolimus/mm^2)	0.12 vs 0.85, $P<0.0001$	N/A	6/12	4.8 vs 14.0, $P=$N/A	N/A	4.8 vs 18.6, $P=$N/A (death, MI, TLR, TVR-CABG)
SPIRIT FIRST[23]	Single *de novo* native coronary lesions, lesion length <18 mm, vessel diameter 3.0 mm	Xience® V durable, polymer-coated, everolimus-eluting Vision® chromium–cobalt stent	0.10 (0.21) vs 0.87 (0.37), $P<0.001$	0 vs 25.9, $P=0.01$	6/6	3.8 vs 21.4, $P=$NS	3.8 vs 21.4, $P=$NS	7.7 vs 21.4, $P=$NS (death, MI, TVR)
Biolimus A9®								
STEALTH[24]	*De novo* native coronary lesion, lesion length <24 mm, vessel diameter 2.75–4.0 mm	Biolimus A9® in a biodegradable polymer coated stainless steel S-Stent (15.6 μg/mm stent length)	0.26 (0.43) vs 0.74 (0.45), $P<0.001$	3.9 vs 7.7, $P=0.4$	6/6	1.3 vs 0, $P=0.99$	1.3 vs 0, $P=0.99$	3.8 vs 2.5, $P=0.99$ (death, MI, TLR, TVR CABG)
Nitric-oxide-drug-elution								
TiNOx[61]	Single *de novo* native coronary lesions, lesion length <15 mm, vessel diameter 2.5–3.5 mm	Titanium, nitric-oxide-coated stainless steel stent	0.55 (0.63) vs 0.90 (0.76), $P=0.03$	15 vs 33, $P=0.07$	6/6	7 vs 23, $P=0.07$	N/A	7 vs 27, $P=0.02$ (death, MI, clinically driven TLR)
17β-estradiol								
EASTER trial[66]	Single *de novo* lesions, lesion length <18 mm, vessel size 2.5–3.5 mm	Phosphorylcholine-coated, 17β-estradiol-eluting stent (2.54 μg/ mm^2)	0.31 (0.38)	6.6	6/12	3.3	3.3	3.3
Dexamethasone								
STRIDE[67]	Single *de novo* lesions, lesion length <15 mm, vessel diameter 2.75–4.0 mm	Phosphorylcholine-coated stent immersed in dexamethasone solution (0.5 μg/mm^2 stent)	0.47 (0.47)	13.3	6/6	2.8	N/A	5.6 (death, MI, TLR)

CABG, coronary-artery-bypass grafting; EASTER, Estrogen And Stents To Eliminate Restenosis trial; FUTURE, First Use To Underscore restenosis Reduction with Everolimus trial; MACE, major adverse coronary events; MI, myocardial infarction; STEALTH, Stent Eluting A9 BioLimus Trial in Humans; STRIDE, Study of antirestenosis with the BiodivYsio dexamethasone-eluting stent; TiNOx, The Randomized Comparison of a Titanium-Nitride-Oxide-Coated Stent With a Stainless Steel Stent for Coronary Revascularization Trial; TLR, target-lesion revascularization; TVR, target-vessel revascularization.

representative of those seen in daily practice, with approximately 68% of those in the registry not meeting the inclusion criteria of earlier clinical trials (e.g. previous coronary surgery, acute myocardial infarction and multivessel stenting).

Polymer-coated paclitaxel-eluting stents

Randomized clinical studies of a durable polymer-coated paclitaxel-eluting stent (PES; Taxus®, Boston Scientific Corporation, Natick, MN) have consistently demonstrated better outcomes than those of BMSs (Tables 1 and 2). This stainless steel stent is coated with a durable copolymer (Translute®, Boston Scientific Corporation, Natick, MN) to provide biphasic paclitaxel release, with an initial burst in the first 2 days, followed by lower-level release sustained over 10 days. In total, more than 3,500 patients with *de novo* lesions have been randomized in the TAXUS I,[15] II,[16] IV,[17] V[18] and VI[19] trials. The TAXUS program commenced in October 2000, with TAXUS I[15] (a safety study) followed by TAXUS II,[16] which tested two different release formulations: slow release and moderate release. The moderate-release formulation released eight times more paclitaxel in the first 10 days than the slow-release formulation, and the slow-release formulation was commercialized as it was the lowest effective dose required; based on this trial, European approval of the slow-release formulation was obtained. The 2-year follow-up data from TAXUS II have confirmed the safety profile of the PES.

The pivotal trial that led to FDA approval for the PES was the TAXUS IV trial conducted in the US,[17] in which 1,314 patients were randomized to PESs or BMSs with a different platform (Express™ stent, Boston Scientific Corporation, Natick, MN) and confirmed the angiographic and clinical efficacy of the Taxus® device. Subsequently, TAXUS V,[18] which studied the moderate-release formulation, and TAXUS VI,[19] which studied the slow-release formulation, were initiated to expand the clinical indication for PESs. These studies were primarily designed to confirm the efficacy of PESs in small vessels (2.25–2.50 mm) and in long lesions (up to 46 mm).

DRUG-ELUTING STENTS COMING TO THE MARKET

Zotarolimus

The DES that is currently most advanced in phase III clinical trials is the zotarolimus-coated stent (Table 3). Zotarolimus, previously called ABT-578, is a sirolimus analog developed by Abbott Pharmaceuticals (Abbott Park, IL) and licensed to two companies: its own subsidiary, Abbott Vascular (Redwood City, CA), and Medtronic (Minneapolis, MN). Medtronic have actively pursued the development of this agent through its ENDEAVOR series of trials, using the Endeavor® device, which consists of a cobalt chromium stent, zotarolimus and a phosphorylcholine polymer coating (Table 3). ENDEAVOR I[20] was a safety study conducted in Australia and New Zealand, and was followed by the ENDEAVOR II[21] multicenter, randomized trial in countries other than the US. In this study, the Endeavor® device was better than BMSs (8.1 versus 15.4%, $P<0.0005$ for major adverse cardiovascular events), and the device was granted European approval in July 2005. Results of the non-inferiority ENDEAVOR III trial are expected to be announced at the Transcatheter Cardiovascular Therapeutics (TCT) meeting in October 2005 (Table 4), and ENDEAVOR IV is currently enrolling participants.

Abbott Vascular, the colicensee of zotarolimus, has also started clinical trials with the Zomaxx® stent (Abbott Park, IL), which comprises zotarolimus on a low-profile, tri-layer, tantalum and stainless steel stent (TriMaxx™), with an additional phosphorylcholine polymer coating (Pharmacoat®, Biocompatibles International Plc., Farnham, UK) for drug elution, differentiating it from the Endeavor® device. Abbott Vascular's clinical trials are Zomaxx I and II (Table 4); enrolment is complete for Zomaxx I but is still in progress for Zomaxx II.

Everolimus

The immunosuppressant everolimus has been tested in two sets of trials: First Use To Underscore restenosis Reduction with Everolimus (FUTURE) and SPIRIT. FUTURE I[22] was a first-in-man study that evaluated the safety and efficacy of everolimus-eluting stents coated with a bioabsorbable polymer compared with BMSs. The findings from FUTURE I and II are detailed in Table 3. More trials were initially planned for the FUTURE series, but the company has chosen to suspend further investment on this set of studies and, instead, to focus on their second arm, the SPIRIT trials, using the Xience® V stent (Advanced Cardiovascular Systems, Inc., Santa Clara, CA), which employs everolimus on a chromium–cobalt alloy stent (Vision®, Guidant, Indianapolis, IN) with a durable polymer as carrier. The SPIRIT FIRST[23] safety and efficacy trial demonstrated

Table 4 Major randomized multicenter clinical trials currently being planned or in progress.

Trial name	Trial description	Stent and drug	Control	Location	Number of patients/ centers	Primary endpoint
COSTAR II	Randomized (3:2) non-inferiority trial in *de novo* lesions	CoStar® biodegradable polymer and paclitaxel in reservoirs	Taxus® PES	US, outside US[a]	1,700/90	8-month major adverse cardiac events
ENDEAVOR III	Randomized (3:1) non-inferiority trial in *de novo* lesions	Endeavor® phosphorylcholine-coated ABT-578-eluting	Cypher® SES	US	436/30	8-month late loss
ENDEAVOR IV	Randomized non-inferiority trial in *de novo* lesions	Endeavor® phosphorylcholine-coated ABT-578-eluting	Taxus® PES	US	1,548/80	9-month target-vessel failure
FREEDOM	Randomized nested-registries non-inferiority trial in *de novo* lesions, two-or three-vessel disease in diabetic patients	Cypher® durable polymeric SES; Taxus® durable polymeric PES	CABG	US, Europe	2,400 randomized, 2,000 registries/100	5-year mortality
NOBORI	Randomized non-inferiority trial in *de novo* lesions	Nobori™ biodegradable polymer-coated Biolimus A9®-eluting	Taxus® PES	Outside US[a]	400/30	9-month in-stent late loss
SPIRIT II	Randomized non-inferiority trial in *de novo* lesions	Xience® V durable polymer-coated everolimus-eluting	Taxus® PES	Outside US[a]	300/32	6-month in-stent late loss
SPIRIT III	Randomized non-inferiority trial in *de novo* lesions	Xience® V durable polymer-coated everolimus-eluting	Taxus® PES	US, Japan	1,380/92	9-month in-segment late loss
SYNTAX[58]	Randomized nested-registries non-inferiority trial in *de novo* lesions, two-or three-vessel disease in diabetic patients	Taxus® durable polymeric PES	CABG	US, Europe	1,500 randomized, 2,800 registries/90	12-month major adverse cardiac and cerebrovascular events
TAXUS V-ISR	Randomized trial in bare stent in-stent restenosis	Taxus® durable polymeric PES	Brachytherapy	US	488/40	9-month target-vessel revascularization
ZOMAXX I	Randomized non-inferiority trial in *de novo* lesions	Zomaxx® phosphorylcholine-coated with extra cap, ABT-578-eluting	Taxus® PES	Outside US[a]	400/30	9-month in-segment late loss
ZOMAXX II	Randomized non-inferiority trial in *de novo* lesions	Zomaxx® phosphorylcholine-coated with extra cap, ABT-578-eluting	Taxus® PES	US	1,670/80	9-month target-vessel revascularization

[a]Typically Europe, Australia and New Zealand. CABG, coronary-artery-bypass grafting; COSTAR, CObalt chromium STent with Antiproliferative for Restenosis; FREEDOM, Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; SYNTAX, Synergy between Taxus™ PCI and Bypass Surgery trial.

superiority with the primary endpoint of in-stent late loss at 6 months. SPIRIT II will begin enrollment soon, and SPIRIT III has received FDA approval to begin. The impending commercial acquisition of Guidant Corporation by Johnson & Johnson (the parent company of Cordis Corporation, which manufactures Cypher® stents) has created uncertainty in the future development of the everolimus-based stent.

IN THE PIPELINE

Biolimus

The Stent Eluting A9 BioLimus Trial in Humans (STEALTH) trial of Biolimus A9® (Biosensors International, Newport Beach, CA), a sirolimus analog coupled to a BMS on a bioabsorbable polymer, demonstrated superiority of the device over BMSs (Table 3).[24] Biosensors International has a joint marketing and development

Table 5 Stent devices that have proved unsuccessful in trials.

Trial	Agent	Vehicle	Stent platform	Reason for clinical failure
SCORE[49]	Taxol derivative QP2 (4,000 μg)	Polymer sleeves	QuaDS-QP2 stent	Excessive stent thrombosis and myocardial infarction due to the polymer sleeves and high dose
ACTION[50]	Actinomycin-D (10 and 2.5 μg/mm^2)	Polymeric coating	Multilink tetra	Lack of efficacy
BRILLIANT-EU	Batimastat	Phosphorylcholine coating	BiodivYsio® stent	Lack of efficacy
PRESENT I, II and PRESET	Tacrolimus (60 and 230 μg)	Nanoporous ceramic coating	FlexMaster ceramic stent	Lack of efficacy
EVIDENT	Tacrolimus (352 g)	PTFE	PTFE-covered graft stent	Lack of efficacy
DELIVER I[53]	Paclitaxel (3 μg/mm^2)	Direct binding	Multilink penta	Lack of efficacy

ACTION, ACTinomycin eluting stent Improves Outcomes by reducing Neointimal Hyperplasia trial; BRILLIANT-EU, Batimastat (BB-94) antiRestenosis trIaL utiLizIng the Bio*divYsio* local drug delivery PC stent; DELIVER-I, Drug-Eluting Coronary Stent System In the Treatment of Patients With De NoVo NativE CoronaRy Lesions study; EVIDENT, Endo-Vascular Investigation Determining the Safety of a New Tacrolimus Eluting Stent Graft; PRESENT, PREliminary Safety Evaluation of Nanoporous Tacrolimus eluting stents; SCORE, Study to COmpare REstenosis rate between QueST and QuaDS-QP2; PTFE, polytetrafluoroethylene.

agreement with Terumo Corporation, Japan, and the NOBORI1 randomized non-inferiority trial is the first collaboration (Table 4).

Paclitaxel-eluting stents with bioabsorbable polymer reservoirs

Conor Medsystems (Menlo Park, CA) uses a unique technology in which the stent is punctured with holes throughout, into which drugs and a carrier can be loaded, like a reservoir. Development of this system began with the PISCES (Paclitaxel In-Stent Controlled Elution Study),[25] SCEPTER (Study of Controlled Elution of Paclitaxel for the Elimination of Restenosis) (paclitaxel in a resorbable polymer in BMSs) and COSTAR I (paclitaxel in a resorbable polymer on a CoStar™ cobalt chromium stent) dose-finding safety studies. Based on the results of PISCES, The European Cobalt Chromium Stent with Antiproliferative for Restenosis Trial (EUROSTAR)[26] was started. This two-dose multicenter registry investigates the CoStar® stent, containing paclitaxel within a resorbable polymer set in holes within a chromium–cobalt stent. A 12-month target lesion revascularization rate of 3.5% has so far been reported in the low-dose study group. COSTAR II, a 1,700-patient multicenter, randomized, non-inferiority trial, will compare the CoStar® stent with the Taxus® stent (Table 4).

Tacrolimus

The Sorin Group (Milan, Italy) have begun clinical trials with tacrolimus-coated stents, but their results have been neither published nor presented as final results to date. Whether any clinical success has been achieved with this device is unclear. Previous trials with tacrolimus have been unsuccessful (Table 5).

Preliminary studies

Pimecrolimus is a sirolimus analog currently used in dermatology.[27] Several companies have begun preliminary animal experiments to assess its suitability for use in DESs.

COMPARATIVE TRIALS

The most notable comparative trials so far have compared SESs with PESs (Table 6). In the REALITY trial,[4] the only true multicenter comparative randomized trial yet done, 1,386 patients with one or two *de novo* lesions were randomized to SESs or PESs.[4] The primary endpoint of this superiority trial, binary restenosis at 9 months, was not met because no significant differences were observed between the two devices (7.0 versus 8.3%, $P=0.3$). The rate of late loss, an angiographic secondary endpoint surrogate for neointimal inhibition, was lower in the sirolimus than in the paclitaxel group (0.09 mm versus 0.31 mm, $P<0.001$).

The SirTax (A Randomized Comparison of SIRolimus With PacliTAXel Eluting Stents for Coronary Revascularization of All Comers) trial,[28] a two-center trial enrolling nonselected individuals, reported that patients randomized to SESs had lower 9-month rates of major adverse coronary events than those assigned

Table 6 Comparative trials of sirolimus-eluting and polymeric paclitaxel-eluting stents.

Study (study type)	Number of centers (country)	Population	Number of patients	Duration and type of follow-up	Angiographic outcome (binary restenosis)	MACE
TAXI[68] (randomized)	1 (Switzerland)	In practice, ~50% of treated patients randomized	202	6 months clinical	—	No difference (underpowered)
T-SEARCH[29] (registry)	1 (The Netherlands)	Nonselected patients with *de novo* lesions	1,024	12 months clinical	—	No difference
REALITY[4] (randomized)	88 (European)	Patients with ≤2 lesions	1,353	8 months angiographic, 9 months clinical	No difference	No difference
SirTax[28] (randomized)	2 (Switzerland)	Nonselected patients	1,012	9 months clinical	Sirolimus better	Sirolimus better
ISAR-DESIRE[30] (randomized)	1 (Germany)	Bare-stent restenosis	300	6–8 months angiographic, 12 months clinical	No difference	Sirolimus better
ISAR-DIABETES[31] (randomized)	1 (Germany)	Patients with diabetes	250	6–8 months angiographic, 9 months clinical	Sirolimus better	No difference (underpowered)

ISAR-DESIRE, Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for In-Stent Restenosis; ISAR-DIABETES, the Intracoronary Stenting and Angiographic Results: Do Diabetic Patients Derive Similar Benefit from Paclitaxel-Eluting and Sirolimus-Eluting Stent; MACE, major adverse cardiac events; SIRTAX, A Randomized Comparison of SIRolimus With PacliTAXel Eluting Stents for Coronary Revascularization of All Comers; TAXI, A Prospective Randomized Comparison Between Paclitaxel and Sirolimus Stents in the Real World of Interventional Cardiology; T-SEARCH, Taxus-Stent Evaluated At Rotterdam Cardiology Hospital.

to PESs (6.2% versus 10.8%, $P=0.009$). The T-SEARCH (Taxus-Stent Evaluated at Rotterdam Cardiology Hospital) single-center registry[29] compared PESs with SESs in an unselected population and reported no differences between stent types (adjusted hazard ratio 1.16, $P=0.4$). Other single-center, randomized studies have compared the two devices in selected populations (ISAR DESIRE [Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for In-Stent Restenosis][30] for patients with in-stent restenosis and ISAR-DIABETES [the Intracoronary Stenting and Angiographic Results: Do Diabetic Patients Derive Similar Benefit from Paclitaxel- Eluting and Sirolimus-Eluting Stent][31] in diabetic patients) and demonstrated better results with SESs than with PESs. For the DESs that are yet to be approved, the previously prerequisite comparison trials with BMS are thought to be unethical because of the consistently superior results with existing DESs compared with BMSs. The upcoming phase III trials are predominantly non-inferiority studies comparing the new device with an incumbent (usually Taxus®), and are conducted with the approval of the FDA. In the future, numerous comparative trials between different DESs will emerge (Table 4).

CELLULAR INSIGHTS INTO SIROLIMUS AND PACLITAXEL

At a cellular level, restenosis occurs through a complex interaction within the vessel wall involving endothelial cells, smooth-muscle cells, fibroblasts, lymphocytes and macrophages.[32] Following stenting, endothelial cells are damaged, and the underlying extracellular matrix is exposed. Sirolimus and paclitaxel have been the most extensively studied drugs in this setting.[33] Sirolimus has been found to inhibit smooth-muscle-cell proliferation and migration, and endothelial-cell proliferation, but not migration, via a complicated sirolimus–FK-binding protein–mammalian target of rapamycin complex. The different 'limus' analogs might vary in their potency and effect, and this issue needs further investigation.[34] Paclitaxel nonselectively stabilizes microtubules, and inhibits smooth-muscle-cell proliferation and migration, as well as endothelial-cell migration, but not proliferation. Computational mathematics has been used to model achievable effects of DES use. In one study, such modeling has demonstrated that the presence of thrombus can influence drug uptake; it might either act as a barrier, thereby decreasing drug availability, or prevent washout of drug, thus increasing local drug concentrations.[35]

Although necessary for the preclinical safety evaluation and understanding of the pharmacokinetics of different drug-eluting devices, results from preclinical studies on DESs might not be completely transferable to human studies.[36] For example, porcine models of sirolimus stents demonstrated a late catch-up phase whereby neointimal growth was suppressed in the short term. In long-term models, however, growth was similar to that for BMSs, a finding that has not been observed in human trials.[37] This disparity emphasizes the need for separate safety and efficacy human studies for each particular device.

PITFALLS WITH DRUG-ELUTING STENTS

Stent thrombosis

Stent thrombosis can be classified as early (within the first 30 days after stent implantation) or late (longer than 30 days after implantation). Early stent thrombosis is most commonly due to a mechanical factor (underexpansion or unrecognized intimal dissection), whereas late stent thrombosis is thought to be due to an abnormality in re-endothelialization after stenting, particularly following DES implantation given the actions of the agents used, as described above. Late angiographic stent thrombosis was initially reported with brachytherapy[38] and resulted in long-term prescription of dual antiplatelet therapy. Early stent thrombosis appears to occur with similar frequency with DESs and BMSs in randomized trials and in practice.[39] The rate is reported to be between 1% and 2%, with allowance for a wide confidence interval, and varies depending on the definition (angiographic only, or including clinically suspected cases).[4,28,39,40] Late angiographic stent thrombosis has led to concern over the potent effects of DESs on the cell cycle—and, therefore, on endothelial cells—and over hypersensitivity reactions to the polymer.[41] Comparative studies of the incidence of late angiographic stent thrombosis with BMSs and DESs are lacking, but the frequency for the latter is probably below 1%,[40,42] which is similar to that in historical reports for the former.[43,44] The duration of antiplatelet therapy differs, however, between groups: 1 month with BMSs versus 3–6 months with DESs. More investigation is required to elicit the true etiology of late angiographic stent thrombosis. We reported late angiographic stent thrombosis in DES in four patients who suddenly stopped antiplatelet therapy 11–14.5 months after implantation; provocatively, BMSs implanted at a similar time in two of the four patients were widely patent.[45] Physicians should endeavor to ensure, therefore, that all patients treated with a DES fully adhere to long-term antiplatelet therapy. Periprocedural administration of antiplatelet therapy is also essential in all surgery patients—elective or otherwise and regardless of time since stent implantation—because of the risk of potentially fatal early or late angiographic stent thrombosis.

Incomplete stent apposition

In the RAVEL trial, incomplete stent apposition, as seen by intravascular ultrasound, was more frequent at 6 months in patients who received SESs than in controls.[46] In TAXUS II,[16] however, patients treated with BMSs or PESs had similar rates of late-acquired malapposition. Nevertheless, these intravascular ultrasound observations have not been associated with any adverse events throughout the follow-up period in these studies.[47,48]

Unsuccessful programs

Not all DES programs have worked. Multiple attempts with different carriers and agents have been unsuccessful (Table 6). With the exception of the Study to COmpare REstenosis rate between QueST and QuaDS-QP2 (SCORE),[49] and the ACTinomycin eluting stent Improves Outcomes by reducing Neointimal Hyperplasia (ACTION) trial,[50] many of the negative trials have not been published. The failed QP2 stent (Boston Scientific) used a high-dose paclitaxel derivative loaded onto polymer ribbons placed circumferentially around the stent. Use of this device was associated with an excess of myocardial infarctions, and early and late stent thrombosis, resulting in the device being abandoned.[49] Similarly, Guidant's failed actinomycin-coated stent was studied in the first-in-humans randomized ACTION trial.[50] Patients treated with the DESs underwent more target-lesion revascularization, and further development was halted.

Clinical trials with non-polymeric-bonded paclitaxel on stainless steel stents have not demonstrated consistent clinical efficacy.[51–53] The European Evaluation of Paclitaxel Eluting Stent (ELUTES) trial[51] and the ASian Paclitaxel-Eluting stent Clinical Trial (ASPECT)[52] showed a significant, dose-dependent reduction in restenosis, but the larger RX Achieve™ Drug-Eluting Coronary Stent System In the Treatment of Patients With De NoVo NativE CoronaRy Lesions (DELIVER-I) study[53] demonstrated no beneficial effect of these devices.

COST-EFFECTIVENESS

The costs of the currently marketed DESs have been perceived as a major limitation for the more widespread use of these devices. In an analysis from the RAVEL trial,[54] based on costs in the Netherlands the use of an SES resulted in a mean additional procedural cost of €1,286, on top of therapy costs, in the control group. The decrease in reinterventions attributable to the SES at the end of the first year of follow-up, however, led to the estimated cost difference being only €54; in other words, the reduction of major event risk from 28.8% to 5.8% after SES implantation was accomplished at an extra cost of €54 per patient. Moreover, data from the SIRIUS trial[55] have shown that at 1 year the costs of SES implantation were approximately US$300 higher per patient than those for treatment of controls, with an incremental cost-effectiveness ratio of approximately $1,650 per repeat revascularization avoided. This finding compares favorably with other medical treatments for patients with cardiovascular disease. Cost-and-effect estimations derived from the RAVEL and SIRIUS trials cannot be extrapolated to daily practice. Data have been presented from the RESEARCH registry and demonstrate that in real-world practice, DESs are not cost-effective at 1 or 2 years on the basis of the actual prices paid.[56] This finding was confirmed by the randomized Basel Stent Cost-effectiveness (BASKET) trial,[57] albeit with only 6 months of follow-up. To achieve cost-effectiveness with DESs requires further significant price reductions in the devices.[56]

THE FUTURE

New indications

In a scientific attempt to expand the indications, two new trials—Synergy between Taxus™ PCI and Bypass Surgery (SYNTAX),[58] and Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM)—will address the role of DESs for three-vessel and left-main disease, and in diabetic patients with multivessel disease, respectively. Coronary-artery-bypass surgery is the gold standard for the treatment of both these conditions,[59] and these two trials will randomize eligible patients to either DES implantation or coronary-artery-bypass grafting.

New agents

Parallel to the development of new drugs and optimization of carriers, other methods are currently being investigated to treat the injured vessel wall locally. An appealing method to contain the harmful effects of vessel-wall injury after percutaneous intervention is to restore the integrity of the endothelial cell lining as soon as possible. In this way, the attraction of inflammatory cytokines, as well as activated platelets and macrophages, can be limited. In the Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth-First In Man (HEALING-FIM) registry,[60] antibodies to CD34 receptors, surface-cell receptors found on endothelial progenitor cells, were used to coat metal stents. The aim was to capture circulating endothelial progenitor cells from the circulation to allow local differentiation into endothelial-like cells and provide early re-endothelialization on the stent surface. This study has been followed by the HEALING II registry, which is in progress. The Randomized Comparison of a Titanium-Nitride-Oxide-Coated Stent With a Stainless Steel Stent for Coronary Revascularization (TiNOX) Trial[61] has demonstrated that nitric-oxide-coated stents have significantly lower late loss than BMSs. Finally, in animal models, local delivery via gene-eluting stent of naked plasmid DNA encoding human vascular endothelial growth factor-2 has been successfully shown to reduce neointima formation while accelerating re-endothelialization compared with BMSs.[62]

CONCLUSIONS

The final frontier remains the long-term viability of all devices, whether already commercially available or impending, as demonstrated by long-term safety results. From the multiple studies with results published for follow-up of longer than 1 year, the beneficial effects of these devices occurred in the first year after implantation.[7,12,14] Mandatory extended follow-up of 5–10 years is required to confirm the safety profile for the agent and carrier components in terms of late thrombosis, acquired malapposition and changes to the vessel wall. Given the potentially fatal complication of in-stent thrombosis, it is imperative that DES-treated patients strictly adhere to their mandatory dual-antiplatelet-therapy regimen and, following completion, continue to take aspirin long term. Finally, the results of numerous clinically and commercially unsuccessful devices and trials have not been published, which precludes a thorough critique of the data.

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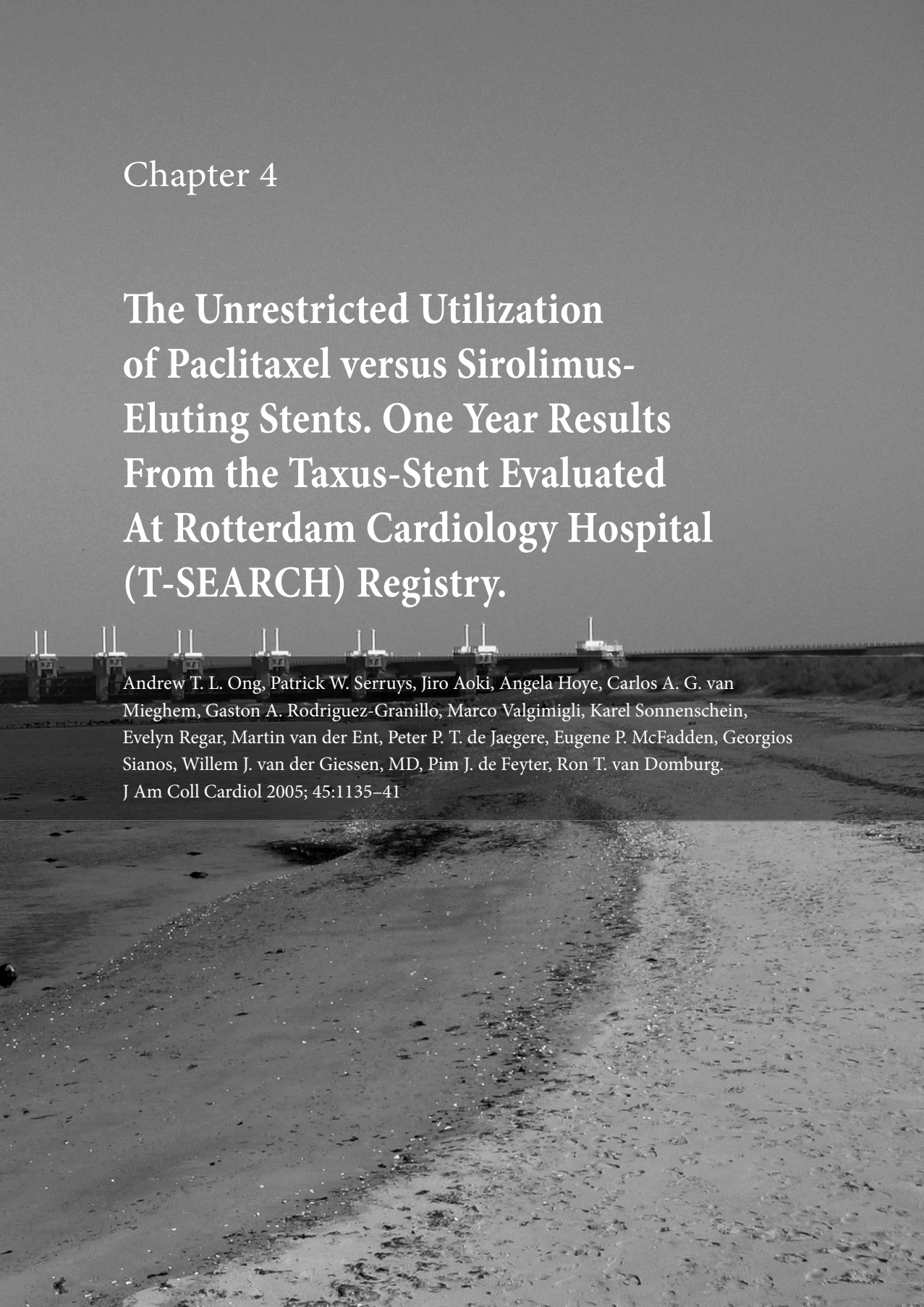
PART II.

THE ROTTERDAM T-SEARCH AND RESEARCH REGISTRIES

II.I PACLITAXEL-ELUTING STENTS COMPARED TO SIROLIMUS-ELUTING STENTS: 1-YEAR FOLLOW-UP OF T-SEARCH

Chapter 4

The Unrestricted Utilization of Paclitaxel versus Sirolimus-Eluting Stents. One Year Results From the Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) Registry.



Andrew T. L. Ong, Patrick W. Serruys, Jiro Aoki, Angela Hoye, Carlos A. G. van Mieghem, Gaston A. Rodriguez-Granillo, Marco Valgimigli, Karel Sonnenschein, Evelyn Regar, Martin van der Ent, Peter P. T. de Jaegere, Eugene P. McFadden, Georgios Sianos, Willem J. van der Giessen, MD, Pim J. de Feyter, Ron T. van Domburg.
J Am Coll Cardiol 2005; 45:1135–41

The Unrestricted Use of Paclitaxel- Versus Sirolimus-Eluting Stents for Coronary Artery Disease in an Unselected Population

One-Year Results of the Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) Registry

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OBJECTIVES We investigated the efficacy of paclitaxel-eluting stents (PES) compared to sirolimus-eluting stents (SES) when used without restriction in unselected patients.

BACKGROUND Both SES and PES have been separately shown to be efficacious when compared to bare stents. In unselected patients, no direct comparison between the two devices has been performed.

METHODS Paclitaxel-eluting stents have been used as the stent of choice for all percutaneous coronary interventions in the prospective Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registry. A total of 576 consecutive patients with de novo coronary artery disease exclusively treated with PES were compared with 508 patients treated with SES from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry.

RESULTS The PES patients were more frequently male, more frequently treated for acute myocardial infarction, had longer total stent lengths, and more frequently received glycoprotein IIb/IIIa inhibitors. At one year, the raw cumulative incidence of major adverse cardiac events was 13.9% in the PES group and 10.5% in the SES group (unadjusted hazard ratio [HR] 1.33, 95% confidence interval [CI] 0.95 to 1.88, $p = 0.1$). Correction for differences in the two groups resulted in an adjusted HR of 1.16 (95% CI 0.81 to 1.64, $p = 0.4$, using significant univariate variables) and an adjusted HR of 1.20 (95% CI 0.85 to 1.70, $p = 0.3$, using independent predictors). The one-year cumulative incidence of clinically driven target vessel revascularization was 5.4% versus 3.7%, respectively (HR 1.38, 95% CI 0.79 to 2.43, $p = 0.3$).

CONCLUSIONS The universal use of PES in an unrestricted setting is safe and is associated with a similar adjusted outcome compared to SES. The inferior trend in crude outcome seen in PES was due to its higher-risk population. A larger, randomized study enrolling an unselected population may assist in determining the relative superiority of either device. (J Am Coll Cardiol 2005;45:1135–41) © 2005 by the American College of Cardiology Foundation

Sirolimus-eluting stents (SES, Cypher, Cordis, Johnson and Johnson, Miami Lakes, Florida) (1) and paclitaxel-eluting stents (PES, TAXUS, Boston Scientific Corp., Natick, Massachusetts) (2) have both been independently shown to reduce the need for repeat intervention when compared to bare-metal stents (BMS) in separate randomized clinical trials. The Food and Drug Administration approvals for these devices were granted in 2003 and 2004, respectively, and it is estimated that drug-eluting stents (DES) currently comprise 70% of the stent market in the U.S. The randomized controlled trials on which approval was granted enrolled highly selected patients with single lesions that could be covered with one DES and were compared against BMS which is not representative of daily clinical practice.

Our group has previously published the results of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry, which demonstrated that routine implantation of SES resulted in a reduction in major adverse cardiac events (MACE), principally driven by a reduction in target vessel revascularization (TVR) when compared with a historical BMS control group (3). The PES were commercialized subsequent to SES, based

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Abbreviations and Acronyms

BMS	= bare-metal stent
CI	= confidence interval
CK-MB	= creatine kinase-MB
DES	= drug-eluting stent
HR	= hazard ratio
MACE	= major adverse cardiac event
MI	= myocardial infarction
PES	= paclitaxel-eluting stent
RESEARCH	= Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital
SES	= sirolimus-eluting stent
TIMI	= Thrombolysis In Myocardial Infarction
T-SEARCH	= Taxus-Stent Evaluated At Rotterdam Cardiology Hospital
TVR	= target vessel revascularization

on the results of randomized controlled trials (4,5). The beneficial effect of PES in patients treated in daily practice remains to be defined. The aim of this study was to report the one-year outcomes of unrestricted/universal use of PES in patients with de novo coronary artery lesions and to compare its efficacy against our historical SES cohort (3).

METHODS

Study design and patient population. The Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registry is a prospective single-center registry with the main purpose of evaluating the safety and efficacy of PES implantation for consecutive unselected patients treated in daily practice. Its conceptual design and methodology are similar to that of the RESEARCH registry (6) and follows the dynamic registry design described by Rothman and Greenland (7).

Since February 16, 2003, when PES was granted Conformité Européenne approval, it replaced SES as the default stent for every percutaneous coronary intervention. Up until 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). This comprised 83.7% of all patients with de novo disease who received coronary stents. In this period, only 12 patients received BMS exclusively (11 were due to requirement for stents >3.5mm, 1 patient had elevated liver enzymes that precluded long-term clopidogrel therapy). Patients treated with PES and BMS in the same procedure (20 patients), those treated with PES and SES (20 patients), those treated with SES only (15 patients), and patients enrolled in other drug-eluting trials (44 patients) were not included in the present report. The PES are available in diameters of 2.25 mm, 2.5 mm, 3.0 mm, and 3.5 mm and in lengths of 8 to 32 mm in 4-mm increments for each available diameter.

This PES group was compared with a control group that comprised the active arm of the RESEARCH registry, that is the 508 patients with de novo disease treated solely with SES (SES group). Thus, the report consists of 1,084 patients treated with DES, differentiated by the type of drug coating on the stent, either sirolimus or paclitaxel.

Procedures and postintervention medications. Interventions were performed according to current standard procedures, with the final interventional strategy (including direct stenting, postdilation, periprocedural glycoprotein IIb/IIIa inhibitor, and use of intravascular ultrasound) left entirely up to the operator's discretion (6). Angiographic success was defined as residual stenosis ≤30% by visual analysis in the presence of Thrombolysis In Myocardial Infarction (TIMI) flow grade 3. Patients were advised to maintain lifelong aspirin (at least 80 mg/day) and were pretreated with 300 mg clopidogrel. Postprocedural clopidogrel treatment differed between the two groups. Patients treated with PES were prescribed at least six months of clopidogrel (75 mg/day), based on existing data from randomized, controlled trials (5). For patients treated with SES, clopidogrel was prescribed for at least three months, unless one of the following was present (in which case clopidogrel was maintained for at least six months): multiple SES implantation (≥3 stents), total stent length ≥36 mm, chronic total occlusion, and bifurcations.

End point definitions and clinical follow-up. The primary outcome was the occurrence of MACE, defined as a composite of: 1) all cause death, 2) nonfatal myocardial infarction (MI), or 3) TVR. Myocardial infarction 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 American Heart Association/American College of Cardiology guidelines (8). In patients who underwent coronary artery bypass surgery during the follow-up period, a periprocedural MI was diagnosed by a rise in the CK-MB level of five times the upper limit of normal (9). For patients who presented with an acute MI, a diagnosis of re-MI in the acute phase required a fall and rise of CK-MB of 50% above the previous level (10). Target lesion revascularization 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. Target vessel revascularization was defined as a re-intervention driven by any lesion located in the same epicardial vessel. Thrombotic stent occlusion 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 successfully treated artery. A committee of three cardiologists (A.O., J.A., and E.M.F.) reviewed all MACE.

All patients underwent clinical follow-up. Information about the in-hospital outcomes was obtained from our institutional electronic clinical database and by review of the hospital records for those discharged to referring hospitals (patients were referred from a total of 14 local hospitals). Postdischarge survival status was obtained from the Municipal Civil Registries at 1, 6, and 12 months. All repeat interventions (surgical and percutaneous) and re-hospitalizations were prospectively collected during the

follow-up. Questionnaires regarding adverse events, anginal status, and medication use were sent to all living patients at 6 and 12 months. Referring physicians and institutions were contacted for additional information if required.

In both groups, follow-up coronary angiography was clinically driven by symptoms or signs suggestive of myocardial ischemia or mandated by the operator at the end of the index procedure predominantly for complex procedures. In the PES group, three specific subgroups were restudied: left main stem stenting, crush-bifurcation procedures, and patients who were concomitantly in a vulnerable plaque study involving non-treated vessels (in total, 27% [n = 154] of PES patients underwent re-study during follow-up, including 14% [n = 81] that were clinically driven). In the SES group, the following "complex patient" subgroups were re-studied: bifurcation lesions, left main stem stenting, chronic total occlusions, very small vessels, long stent length (36 mm), and acute MI (in total, 40% [n = 204] of SES patients were re-studied, including 8% [n = 40] that were clinically driven). Because of the well-known effect of angiographic re-evaluation in increasing the incidence of repeat revascularization (11), all re-interventions were retrospectively adjudicated and classified as either clinically driven or non-clinically driven. Clinically driven repeat revascularization was defined as any intervention motivated by a significant luminal stenosis (≥50% diameter stenosis) in the presence of anginal symptoms and/or proven myocardial ischemia in the target vessel territory by noninvasive testing.

Statistical analysis. Continuous variables are presented as mean ± standard deviation, and were compared using the Student unpaired *t* test. Categorical variables are presented as counts and percentages and compared by means of the Fisher exact test. All statistical tests were two-tailed. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. 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. Separate Cox regression analyses 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 adjusted hazard ratios (HRs).

RESULTS

Baseline and procedural characteristics. The PES patients were more often male, had more MI as their presenting symptom, more cardiogenic shock, more complex lesions treated, longer total stent lengths, and more frequently received glycoprotein IIb/IIIa inhibitors (Tables 1 and 2). Fewer PES patients had a history of previous bypass surgery, and fewer segments per patient were stented, although the number of vessels treated per patient was identical. Other baseline and procedural characteristics were similar.

Table 1. Baseline Characteristics

	SES Group (n = 508)	PES Group (n = 576)	p Value
Male, %	68	74	0.04
Age, yrs ± SD	61 ± 11	62 ± 11	0.4
Diabetes, %	18	18	0.8
Non–insulin-dependent, %	12	13	0.5
Insulin-dependent, %	6	5	0.7
Hypertension, %	41	42	0.9
Hypercholesterolemia, %	56	62	0.03
Current smoking, %	31	29	0.6
Previous myocardial infarction, %	30	35	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.
PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent.

Clinical outcome. FIRST 30 DAYS. No significant differences were noted between groups with respect to the incidences of death, death or MI, TVR, or MACE in the first month (Table 3). Mortality in the first 30 days was 2.1% in the PES group and 1.6% in the SES group (p = 0.7). In both groups, most deaths occurred in patients with cardiogenic shock. Angiographically proven stent thrombosis occurred in six patients in the PES group, four of whom were treated for AMI, the other two presented with unstable angina. Two patients with AMI also underwent bifurcation stenting, as did one with unstable angina. In total, three patients with bifurcation stenting experienced stent thrombosis. In the SES group, two patients were diagnosed with stent thrombosis. One patient died as a result of stent thrombosis in the PES group.

ONE YEAR. The MACE components are presented in Figures 1 and 2. At one year, 5.3% of patients in the PES group and 3.4% in the SES group had died (HR 1.69, 95% confidence interval [CI] 0.93 to 3.00, p = 0.08). In total, 8.8% of patients in the PES group versus 7.0% in the SES group had either died or suffered a nonfatal re-MI (HR 1.28, 95% CI 0.84 to 1.95, p = 0.3). The incidence of TVR was similar in the SES and PES groups: 7.3% versus 5.1% (HR 1.31, 95% CI 0.81 to 2.13, p = 0.3). Clinically driven TVR was reduced by a similar magnitude in both groups, specifically 3.7% versus 5.4%, respectively (HR 1.38, 95% CI 0.79 to 2.43, p = 0.3). Post-hoc analysis of clinically driven TVR demonstrates that confidence limits crossed unity, with point estimates close to unity in the subgroups

Table 2. Procedural Characteristics

	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 artery, %	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	4.0 ± 2.0	6 ± 0	< 0.05
Bifurcation stenting, %	16	16	0.9
No. of stented segments ± SD	2.0 ± 1.0	1.7 ± 0.9	< 0.001
No. of stented vessels ± SD	1.3 ± 0.6	1.3 ± 0.6	0.8
No. 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 stent length >33 mm, %	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.
Abbreviations as in Table 1.

analyzed (Fig. 3). Regarding the primary end point of MACE (the composite of death, MI, or TVR), Kaplan-Meier estimates were 13.9% in the PES group versus 10.5% in the SES group (unadjusted HR 1.33, 95% CI 0.95 to 1.88, p = 0.10).

There were two cases of late (>6 months to 1 year) stent thrombosis documented angiographically in the PES group. In one, it occurred eight months after the index procedure while the patient was on antiplatelet monotherapy with aspirin. The second occurred 11 months after the index procedure after the patient had temporarily suspended antiplatelet therapy (aspirin) for noncardiac surgery.

Predictors of adverse events. To assess the independent predictors of MACE at one year, two separate multivariate analyses were performed. First, a model was built using all baseline and procedural characteristics shown in Tables 1 and 2. Forward stepwise regression was performed with entry and stay criteria of 0.05 and 0.10, respectively. The following variables were significant: cardiogenic shock, female gender, multivessel disease, diabetes mellitus, left main stenting, bifurcation stenting, and lesion type B2/C (Table 4). A second model built using the same variables with the end point of TVR at one year revealed bifurcation stenting was the only significant independent predictor of TVR.

Adjustment for differences between groups. The Cox regression models were 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 from Table 4 (see Table 5). All previously significant variables remained significant except for lesion type B2/C. The adjusted HR for use of PES became even less significant, decreasing from 1.33 (95% CI 0.95 to 1.88, p = 0.10) to 1.20 (95% CI 0.85 to 1.70, p = 0.3), after controlling for the increased complexity in the PES group.

A second model was then built forcing stent type and significant univariate variables (independent predictors plus total stent length and number of stents), and the adjusted outcome of MACE at one year was similar between SES and PES (adjusted HR 1.16, 95% CI 0.81 to 1.64, p = 0.4).

Finally, stent type was also not a significant predictor of TVR when adjusted for bifurcation stenting (adjusted HR 1.33, 95% CI 0.82 to 2.15, p = 0.25).

Table 3. Major Adverse Cardiac Events in the First Month Following Stent Implantation

0 to 1 Month	SES Group (n = 508)	PES Group (n = 576)	p Value*
Death, n (%)	8 (1.6)	12 (2.1)	0.7
Nonfatal myocardial infarction, n (%)	12 (2.4)	17 (3.0)	0.6
Target lesion revascularization, n (%)	6 (1.2)	7 (1.2)	1.0
Target vessel revascularization, n (%)†	6 (1.2)	13 (2.3)	0.2
Any event, n (%)	23 (4.5)	34 (5.9)	0.3
Stent thrombosis, n (%)‡	2 (0.4)	6 (1.0)	0.3

*By Fisher exact test. †Includes target lesion revascularization. ‡Angiographically documented stent thrombosis requiring repeat intervention.
Abbreviations as in Table 1.

DISCUSSION

The major finding of this report is that the unrestricted use of PES in de novo lesions is associated with a nonsignificant difference in outcome compared to SES, both unadjusted and when controlled for significant baseline and procedural characteristics. The trend toward an inferior crude outcome

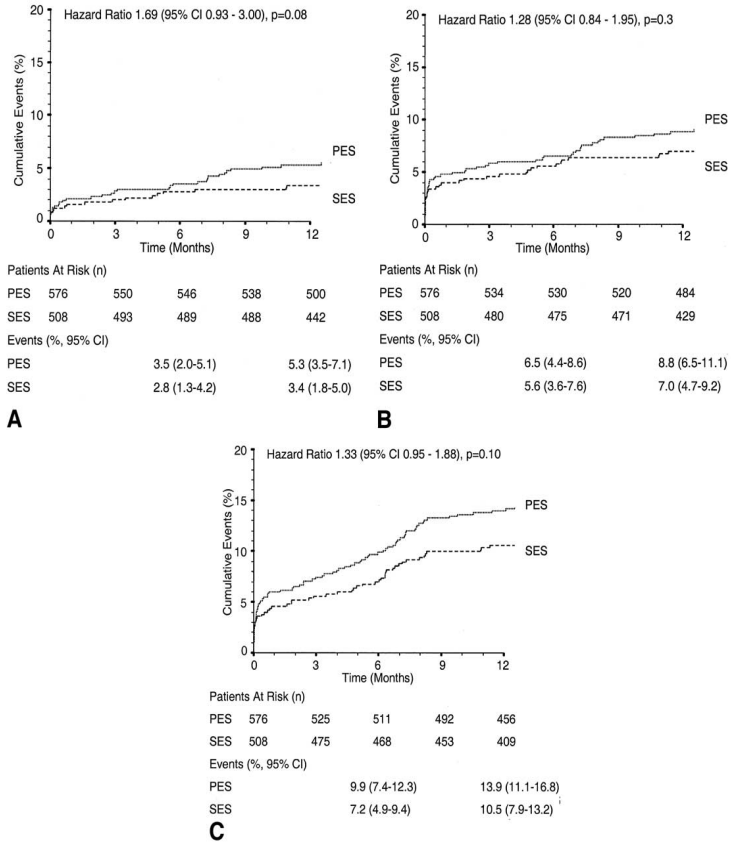

Figure 1. Unadjusted Kaplan-Meier event curves at one year. **(A)** Cumulative risk of death. **(B)** Cumulative risk of death or myocardial infarction. **(C)** Cumulative risk of death, myocardial infarction, or target vessel revascularization. CI = confidence interval; PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent.

with PES was due to the more complex characteristics of the group.

The two sequential registries were separated by a four-month interval. Several differences in baseline characteristics were noted. More MIs including patients in cardiogenic shock were treated in the T-SEARCH registry because of the implementation of a local pre-hospital protocol that triaged more patients to primary percutaneous coronary intervention. More complex lesions were treated in the T-SEARCH registry, with a shift from type A/B1 to B2/C lesions, with more stents being implanted in the T-SEARCH registry. This in part reflects the increased complexity of cases being performed with time and as operators and referring physicians becoming more aware and familiar with DES.

The primary end point of this trial was overall MACE, and the results for this comparison are presented both unadjusted and following adjustment for significant predictive variables (Table 5). With the commercialization of PES, our institution switched completely from SES to PES, precluding randomization. Therefore, it was intuitive to present the data as such and imperative to statistically correct by using significant predictive variables to account for the increased complexity seen in the PES group. To preserve the prospective, consecutive, and unselected nature of both registries, and the requirement to control for multiple significant variables, the Cox regression model was used. Our results demonstrate that, following adjustment, the HR was closer to unity compared to the crude result, further confirming the increased complexity in the PES group.

The multivariate analysis (Table 4) for independent predictors of MACE is unique as it is an analysis of 1,084 DES patients treated in an unrestricted setting. In a total cohort of DES patients, cardiogenic shock, female gender, multivessel disease, diabetes mellitus, left main stenting,

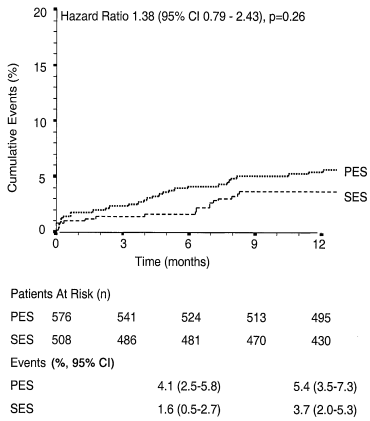

Figure 2. Unadjusted one-year cumulative risk of clinically driven target vessel revascularization. Abbreviations as in Figure 1.

bifurcation stenting, and treatment of a complex lesion significantly predicted an adverse outcome. From this list, patients who possess these characteristics should undergo more regular clinical surveillance.

The major advantage of DES has been to reduce the need for repeat revascularization (1–3). In our study, the incidence TVR at one year with PES was not significantly different from the results obtained with SES. Furthermore, when the adjusted end point of clinically driven TVR was used (Fig. 2), similar outcomes were reproduced, thus confirming that both drug-eluting systems serve to reduce clinical restenosis in an unselected population.

A nonsignificantly higher incidence of angiographic stent thrombosis in the first 30 days was noted in the PES cohort (1.0% in SES vs. 0.4% in PES, p = 0.3). However, it is important to emphasize that, owing to the infrequent occurrence of this event, large numbers of patients are required to assess this complication properly. We have

Table 4. Multivariate Predictors of Major Adverse Cardiac Events at One Year (Cox Proportional Hazards Model)

	HR	95% CI	p Value
Major adverse cardiac events*			
Cardiogenic shock (stable angina as reference variable)	4.54	2.44–8.48	< 0.001
Female gender	1.72	1.22–2.43	0.002
Multivessel disease	1.74	1.19–2.55	0.005
Diabetes mellitus	1.65	1.12–2.42	0.01
Left main stenting	1.96	1.10–3.48	0.02
Bifurcation stenting	1.59	1.06–2.38	0.03
Lesion type B2 or C	1.85	1.01–3.40	0.047
Target vessel revascularization			
Bifurcation stenting	2.77	1.68–4.57	< 0.001

*Major adverse cardiac events: death, myocardial infarction, or target vessel revascularization.
CI = confidence interval; HR = hazard ratio.

shown that in a larger population, the incidence rates in both DES were in the same range: 1.0% (95% CI 0.6% to 1.9%) in PES and 1.0% (95% CI 0.5% to 1.8%) in SES (12).

At the time the T-SEARCH registry was conducted, TAXUS II (5) and the Randomized Comparison of a Sirolimus-Eluting Stent with a Standard Stent for Coronary Revascularization (RAVEL) (13) were the two published trials available with one-year MACE results from the eluting stent arms of 10.9% (slow-release arm) and 5.8%, respectively. Based on those results, the group sample sizes of our study would have been adequately powered to show a difference.

Subsequent to that, the results of larger trials of both devices—TAXUS IV and Sirolimus-Eluting Stent in Coronary Lesions (SIRIUS)—were published and demonstrated a smaller difference (8.4% vs. 7.1%, respectively). The population of this registry is an all-inclusive unrestricted one, a sample that is representative of the population seen in a tertiary catheterization laboratory. Therefore, this population is directly comparable to daily practice and the results do not require extrapolation as for randomized trials. The results of this registry complement published randomized trials.

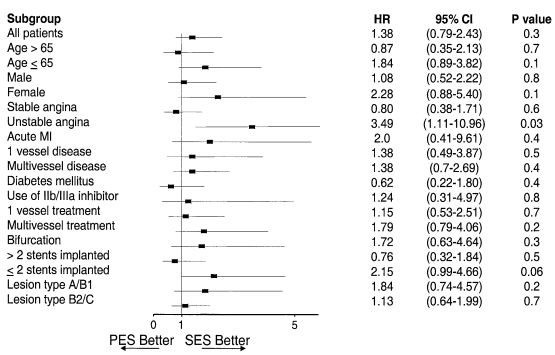

Figure 3. Hazard ratios (HR) of stent type at one-year follow-up for clinically driven target vessel revascularization in subgroups of patients according to baseline and procedural characteristics. MI = myocardial infarction; other abbreviations as in Figure 1.

Table 5. Hazard Ratios by Stent Type of Major Adverse Cardiac Events After Adjustment*

	HR	95% CI	p Value
MACE†			
Unadjusted	1.33	0.95–1.88	0.10
Adjusted for significant predictors of MACE	1.20	0.85–1.70	0.3
Adjusted for significant univariate variables‡	1.16	0.81–1.64	0.4
TVR			
Unadjusted	1.31	0.81–2.13	0.26
Adjusted for significant predictors of TVR	1.33	0.82–2.15	0.25

*Stent type coded as: 0 = sirolimus-eluting stent, 1 = paclitaxel eluting stent. †Major adverse cardiac events: death, myocardial infarction, or target vessel revascularization (TVR). ‡Significant univariate variables for major adverse cardiac event (MACE) were the significant predictors plus total stent length and number of stents implanted. Abbreviations as in Table 4.

CONCLUSIONS

The universal use of PES in an unrestricted setting is safe, and associated with a non-significant adjusted difference in outcome at one year compared to SES, with a trend toward worse outcomes in the PES cohort, in part owing to its higher-risk profile. Both DES reduce the need for repeat intervention in the real world setting of complex patient and procedural characteristics.

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PART II.

THE ROTTERDAM T-SEARCH AND RESEARCH REGISTRIES

II.II MEDIUM-TERM FOLLOW-UP OF SIROLIMUS-ELUTING STENTS: 2 AND 3-YEAR FOLLOW-UP OF RESEARCH

Chapter 5

Sirolimus-Eluting Stents Remain Superior to Bare Metal Stents at 2 years – Medium-Term Results From the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) Registry.

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Sirolimus-Eluting Stents Remain Superior to Bare-Metal Stents at Two Years

Medium-Term Results From the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) Registry

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OBJECTIVES The purpose of this study was to investigate the medium-term (two year) outcome of the unrestricted utilization of sirolimus-eluting stents (SES) in an all-comer population.

BACKGROUND Despite the implantation of SES in over a million patients to date, limited data exist on long-term outcomes.

METHODS Sirolimus-eluting stents were used as the default strategy as part of the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry. A total of 508 consecutive patients with de novo lesions exclusively treated with SES were compared with 450 patients who received bare stents in the immediately preceding period (pre-SES group).

RESULTS Patients in the SES group more frequently had multivessel disease, more type C lesions, received more stents, and had more bifurcation stenting. At two years, the cumulative rate of major adverse cardiac events (death, myocardial infarction, or target vessel revascularization) was 15.4% in the SES group and 22.0% in the pre-SES group (hazard ratio [HR] 0.68, 95% confidence interval [CI] 0.50 to 0.91; p = 0.01). The two-year risk of target vessel revascularization in the SES group and in the pre-SES group was 8.2% and 14.8%, respectively (HR 0.53, 95% CI 0.36 to 0.79; p = 0.002).

CONCLUSIONS In an unrestricted population, the beneficial effects of sirolimus-eluting stent implantation extend out to two years compared with bare-metal stents, driven by a reduction in re-intervention rates. These findings should be confirmed by the results of the large randomized trials. (J Am Coll Cardiol 2006;47:1356–60) © 2006 by the American College of Cardiology Foundation

In the two years since the introduction of drug-eluting stents worldwide, the take-up has been astounding. Drug-eluting stents now comprise at least 70% of the stent market in the U.S. and 40% in Europe, and they are increasing with time. To date, over 1 million patients have received 1.5 million sirolimus-eluting stents (SES) worldwide despite a paucity of long-term follow-up data (1). For simple lesions, encouraging two-year results were reported by the first investigations in humans (2,3), as was the recent publication of the three-year results in the Randomized Study With the Sirolimus-Eluting Velocity Balloon-Expandable Stent in the Treatment of Patients With de Novo Native Coronary Artery Lesions (RAVEL), the first randomized trial on SES (4). However, fewer than 200 patients with simple lesions treated with a single 18-mm SES were studied in both trials combined.

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In porcine models, there have been some concerns regarding a late catch-up phenomenon whereby the initial benefits of SES disappear with time (5). Furthermore, initial attempts at developing an antirestenosis device using a radioactive stent demonstrated that in humans restenosis and neointimal hyperplasia were delayed but not prevented (6). Late "unpredictable" events have been anecdotally reported with drug-eluting stents (7,8).

In the treatment of unselected "all-comer" patients with complex disease, our group has previously reported on the intermediate results of the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry, demonstrating that the use of SES is associated with significantly lower incidence of major adverse cardiac events (MACE) and target vessel revascularization (TVR) when compared with bare-metal stents (BMS) at one year in patients with de novo coronary artery lesions (9). The purpose of this report is to investigate whether the beneficial effects of SES extend beyond one year and to detail the major adverse cardiac events that have occurred between one and two years.

METHODS

Study design and patient population. The methodology of the RESEARCH registry has been reported previously (10). Briefly, RESEARCH is a single-center registry conducted with the main purpose of evaluating the safety and efficacy of SES implantation for patients treated in daily practice. Since April 16, 2002, our institution adopted a

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Abbreviations and Acronyms

BMS	= bare-metal stent
CI	= confidence interval
HR	= hazard ratio
MACE	= major adverse cardiac event
MI	= myocardial infarction
RAVEL	= Randomized Study With the Sirolimus-Eluting Velocity Balloon-Expandable Stent in the Treatment of Patients With de Novo Native Coronary Artery Lesions
RESEARCH	= Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital
SES	= sirolimus-eluting stent
TLR	= target lesion revascularization
TVR	= target vessel revascularization

policy of using SES (Cypher; Johnson & Johnson-Cordis unit, Cordis Europa, Roden, the Netherlands) as the default strategy for every percutaneous coronary intervention. In the first six months of enrollment, 508 patients with de novo lesions were treated exclusively with SES (SES group) and compared with a group of 450 consecutive patients treated with bare stents for de novo lesions in the preceding six 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) (9). 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.

Procedures and postintervention medications. 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. Angiographic success was defined as residual stenosis <30% by visual analysis in the presence of Thrombolysis In Myocardial Infarction (TIMI) flow grade 3. All patients were advised to maintain lifelong aspirin. At least one-month clopidogrel treatment (75 mg/day) was recommended for patients treated in the pre-SES phase. For patients treated with SES, clopidogrel was prescribed for at least three 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.

Definition of major adverse cardiac events. Major adverse cardiac events were defined as: 1) death; 2) nonfatal myocardial infarction (MI); or 3) TVR. Myocardial infarction was diagnosed by a rise in the creatine kinase-MB fraction of more than three times the upper limit of normal (11). Target lesion revascularization (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. Target vessel revascularization was defined as a re-intervention driven by any lesion located in the same epicardial vessel.

Two-year follow-up data. For the two-year follow-up, survival data for all patients were obtained from municipal civil registries. A health questionnaire was sent to all living patients with specific questions on rehospitalization and major adverse cardiac events. As the principal referral center within the region, repeat procedures (percutaneous and 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 summaries from the other institutions were systematically reviewed. General practitioners, referring cardiologists, and patients were contacted as necessary if further information was required.

Statistical analysis. Continuous variables are presented as mean ± 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. All statistical tests were two tailed. The cumulative incidence of adverse events was estimated according to the Kaplan-Meier method, and Cox proportional hazards models were used to assess risk reduction of adverse events. 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 1 and 2.

Table 1. Baseline Characteristics of Patients Treated With Conventional Bare-Metal Stents Before the Introduction of SES (Pre-SES Group) and Patients Treated Exclusively With SES Implantation (SES Group)

	Pre-SES Group (n = 450)	SES Group (n = 508)	p Value
Male, %	72	68	0.4
Age, yrs ± SD	61 ± 11	61 ± 11	0.7
Diabetes, %	15	18	0.3
Non–insulin-dependent, %	11	12	0.7
Insulin-dependent, %	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, %	48	45	—
Unstable angina, %	35	37	—
Acute myocardial infarction, %	18	18	—
Cardiogenic shock, %*	12	10	0.7

*Relative to patients with acute myocardial infarction.
SES = sirolimus-eluting stent.

Table 2. Angiographic and Procedural Characteristics of Patients Treated With Conventional Bare-Metal Stents Before the Introduction of SES (Pre-SES Group) and Patients Treated Exclusively With SES Implantation (SES Group)

	Pre-SES Group (n = 450)	SES Group (n = 508)	p Value
Treated vessel			
Left anterior descending, %	59	59	0.8
Left circumflex, %	33	32	0.7
Right coronary artery, %	34	39	0.2
Left main coronary, %	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, months ± SD	2.9 ± 2.0	4.0 ± 2.0	<0.01
Bifurcation stenting, %	8	16	<0.01
Number of stented segments ± SD	1.8 ± 0.9	2.0 ± 1.0	<0.01
Number of implanted stents ± SD	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 ± SD	30.1 ± 19.6	38.7 ± 28.7	<0.01
Nominal stent diameter ≤2.5 mm, %	23	36	<0.01
Post-dilation with a balloon ≥0.5 mm larger, %	19	55	<0.01
Angiographic success of all lesions, %	97	97	1.0

SES = sirolimus-eluting stent.

RESULTS

Baseline and procedural characteristics. The baseline and procedural characteristics have been previously described and are included in Tables 1 and 2 for reference. Briefly, approximately half of the patients in both groups were admitted with acute coronary syndromes, and diabetes was present in 16% of cases. Patients treated with SES had significantly more multivessel disease, more type C lesions, more bifurcation stenting, more segments stented, and more stents used. Also, 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 both groups.

One-year follow-up. At one year, the cumulative incidence of death and death or myocardial infarction was similar between groups. Patients treated with SES had significantly less death, MI, or TLR at one year than patients treated in the pre-SES phase (8.8% vs. 12.6%, respectively; hazard ratio [HR] 0.66, 95% confidence interval [CI] 0.45 to 0.97; $p = 0.03$). Similarly, the one-year cumulative risk of MACE (death, MI, or TVR) was significantly reduced in the SES group (9.7% vs. 14.8% in the pre-SES group; HR 0.62, 95% CI 0.44 to 0.89; $p = 0.008$). The difference in outcomes between groups was mainly due to a decrease in the need for TVR in the SES group (5.1% vs. 10.9% in the pre-SES group; HR 0.49, 95% CI 0.29 to 0.82; $p = 0.007$).

Two-year follow-up. Follow-up information was obtained in 97.7% of patients. At two years, there were no significant differences in mortality between the SES and pre-SES groups, (5.8% vs. 6.3%; HR 0.92, 95% CI 0.55 to 1.54; $p = 0.7$)

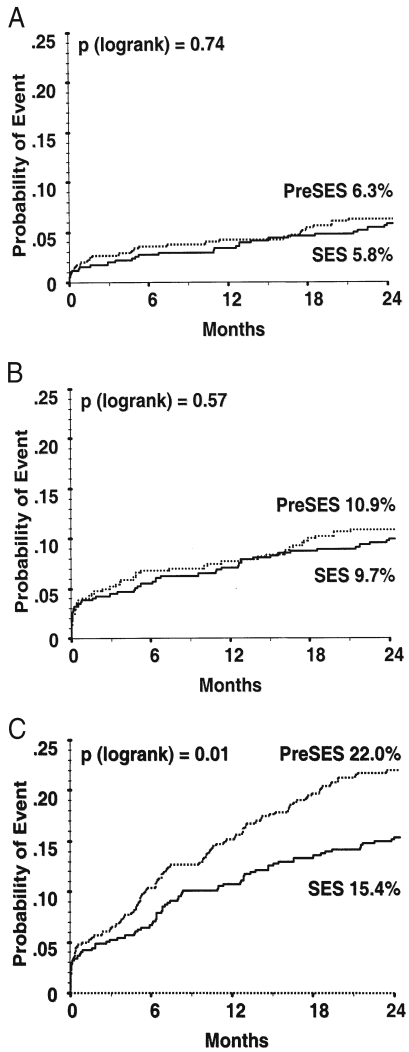

Figure 1. Two-year adverse events in patients treated with bare stents before the introduction of sirolimus-eluting stents (SES) (pre-SES group) and in patients treated exclusively with SES implantation (SES group). **(A)** Cumulative risk of death. **(B)** Death or myocardial infarction. **(C)** Death, myocardial infarction, or target vessel revascularization.

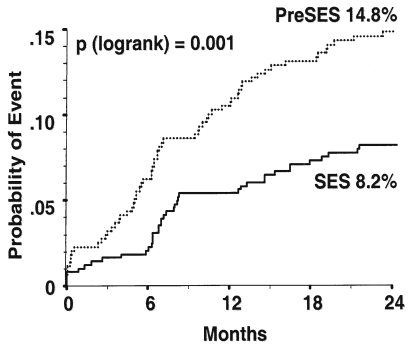

Figure 2. Two-year cumulative risk of target vessel revascularization in patients treated with bare stents before the introduction of sirolimus-eluting stents (SES) (pre-SES group) and in patients treated exclusively with SES implantation (SES group).

(Fig. 1A). The combined end point of death or MI were also similar (9.7% vs. 10.9%, respectively; HR 0.89, 95% CI 0.60 to 1.33; p = 0.6) (Fig. 1B). The two-year incidence of the combined end point of MACE was lower in the SES group than in the pre-SES group (15.4% vs. 22.0%; HR 0.68, 95% CI 0.50 to 0.91; p = 0.01) (Fig. 1C), driven by a significantly lower incidence of TVR in the SES group (8.2% vs. 14.8%, respectively; HR 0.53, 95% CI 0.36 to 0.79; p = 0.002) (Fig. 2).

Events from one to two years. Between one and two years, 53 events occurred (Table 3). There were 12 deaths in the SES group and 9 deaths in the pre-SES group. Two MIs occurred in the SES group compared with five in the pre-SES group (p = 0.3). Target lesion revascularizations were infrequent in both the SES group (n = 11) and the pre-SES group (n = 14) (p = 0.4). Including TLRs, there were 13 TVRs in the SES group versus 18 in the pre-SES group (p = 0.3). Overall MACE occurred in 23 patients in the SES phase and 30 in the pre-SES phase (p = 0.16). In this RESEARCH registry cohort of 958 patients, no patient in either group experienced late angiographic stent thrombosis out to 24 months. Between one and two years, a further five patients in the SES group and six in the pre-SES group required a repeat intervention for a lesion in a different vessel (p = 1.0).

Table 3. Number of Events Between One and Two Years

Events Between 1 and 2 Years	Pre-SES Group (n = 450)	SES Group (n = 508)	p Value
Death, n (%)	9 (2.0)	12 (2.4)	0.8
MI, n (%)	5 (1.1)	2 (0.4)	0.3
TLR, n (%)	14 (3.1)	11 (2.2)	0.4
TVR (includes TLR), n (%)	18 (4.0)	13 (2.6)	0.3
Non-TVR, n (%)	5 (1.1)	6 (1.2)	1.0
Total MACE, n (%)	30 (6.7)	23 (4.5)	0.16

MACE = major adverse cardiac event; MI = myocardial infarction; SES = sirolimus-eluting stent; TLR = target lesion revascularization; TVR = target vessel revascularization.

Table 4. Separate Cox Regression Analyses Performed to Determine Independent Predictors of MACE and TVR at Two-Year Follow-Up

	HR	95% CI	p Value
MACE*			
Use of SES	0.58	0.43–0.80	0.001
Total stented length (per 10-mm increment)	1.12	1.06–1.18	<0.001
Previous PCI	1.71	1.20–2.43	0.003
Diabetes mellitus	2.00	1.42–2.80	<0.001
Left main stenting	2.23	1.19–4.16	0.01
Cardiogenic shock at entry	4.19	2.04–8.59	<0.001
TVR†			
Use of SES	0.45	0.37–0.68	<0.001
Acute coronary syndrome at entry	0.56	0.37–0.83	0.004
Total stented length (per 10-mm increment)	1.14	1.07–1.22	<0.001
Previous PCI	1.73	1.11–2.69	0.016
Diabetes mellitus	2.05	1.33–3.17	0.001

*Tested variables: age, gender, multivessel disease, hypertension, current smoking, right coronary artery stenting, type C lesion, number of stents, number of segments treated, use of 33-mm stent, total stent length, previous intervention, diabetes, left main stenting, cardiogenic shock, stent type. †Tested variables: current smoking, bifurcation stenting, number of segments treated, number of stents, acute coronary syndrome at entry, total stented length, previous intervention, diabetes, stent type. Variables were included if significant on univariate analysis or if clinically relevant.

CI = confidence interval; HR = hazard ratio; PCI = percutaneous coronary intervention; other abbreviations as in Table 3.

Multivariate predictors of outcomes. Cox regression analysis was performed to identify predictors of MACE at two years (Table 4). Cardiogenic shock at entry, stenting of the left main stem, diabetes, history of previous interventions, and longer stented lengths were all associated with adverse occurrences of MACE (Table 4). A separate Cox regression analysis was performed, and predictors of TVR were diabetes, previous interventions, and longer stented lengths, whereas acute coronary syndromes at entry was protective. When adjusted for independent predictors, the use of SES conferred a significant protective effect against both TVR (HR 0.45, 95% CI 0.29 to 0.68; p < 0.001) and MACE (HR 0.58, 95% CI 0.43 to 0.80; p = 0.001) at two-year follow-up.

DISCUSSION

This present paper reports that the beneficial effects of SES compared to BMS are maintained out to two years in a real-world population. At the end of two years, significantly less MACE occurred in the SES group compared to the pre-SES group. In the second year following stent implantation, a trend toward fewer repeat revascularizations occurred in the SES arm with no late catch-up seen.

The reduction in the composite end point of MACE in the SES group was entirely driven by the component of TVR; the incidences of death and MI were similar in both groups in the follow-up period. This extends the finding of a large meta-analysis of drug-eluting trials that demonstrated no reduction in death or MI out to one year with drug-eluting stents (12).

In this study, although there was a trend toward fewer events in SES-treated patients (p = 0.16) between one and

two years, the beneficial effect seen with SES at two years was driven primarily by the reduction in events in the first year. Thus, once the important beneficial effect of neointimal suppression had occurred during the period after stenting, the next step was to detect whether a later rebound phenomenon (as seen in porcine models) occurred in humans. This first-in-man study with serial angiographic and intravascular ultrasound studies was encouraging, demonstrating in a small population that neointimal suppression was preserved out to two years. In the RAVEL study, however, some nonsignificant late catch-up effect was noted in the SES arm, with six TLR versus none in the bare group seen between one- and three-year follow-ups; however, the overall incidence of TLR in the SES arm of remained significantly less than the bare group at three years (4,13).

In our registry, we did not observe any late catch-up phenomenon such as seen with radioactive stents and brachytherapy. In fact, during the second year, a trend toward a lower TVR rate was seen in the SES group compared with the pre-SES group (4.0% vs. 2.6%, respectively; $p = 0.3$) (Table 3). In addition to the previously described events, approximately 1% of patients in each group required repeat intervention for progressive disease in a previously nontreated vessel (non-TVR revascularization). Because these lesions do not benefit from the beneficial local effects of SES, it is imperative that intensive risk factor reduction, both physical and pharmaceutical, are implemented to reduce the potential for progression of remote lesions (14).

Although it was encouraging that no late angiographic stent thrombosis events were seen in either group out to two years, observation and interpretation of this rare and unexpected late complication requires a much larger sample size and longer term follow-up (15).

Conclusions. The medium-term follow-up of the RESEARCH registry demonstrates that in the real world SES reduce the incidence of major adverse cardiac events at two years of follow-up, primarily by a smaller need for repeat revascularization of the target vessel compared to bare-metal stents, already evident during the first year. The reduction in events was maintained during the second year with no evidence of a late-catch up effect. No late angiographic stent thrombosis was seen out to two years in this cohort of patients studied.

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Chapter 6

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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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 ($p < 0.01$).

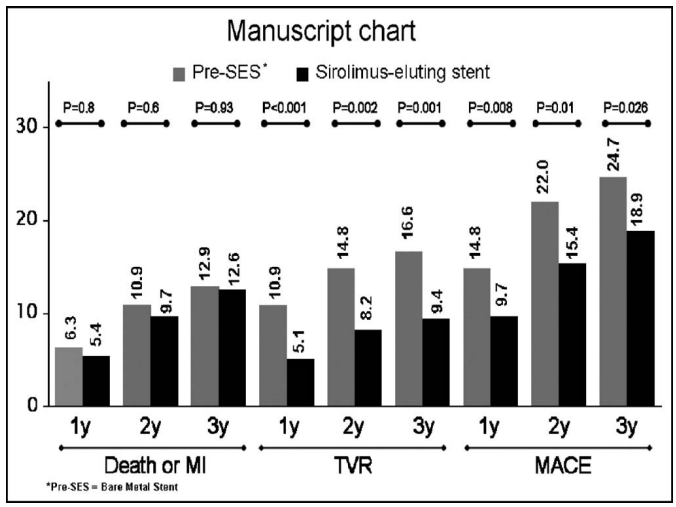

Figure 1. Cumulative incidence of adverse events at 1, 2, and 3 years in patients treated with SESs *(black bars)* and BMSs *(gray bars)*. MI = myocardial infarction; TVR = target vessel revascularization.

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.

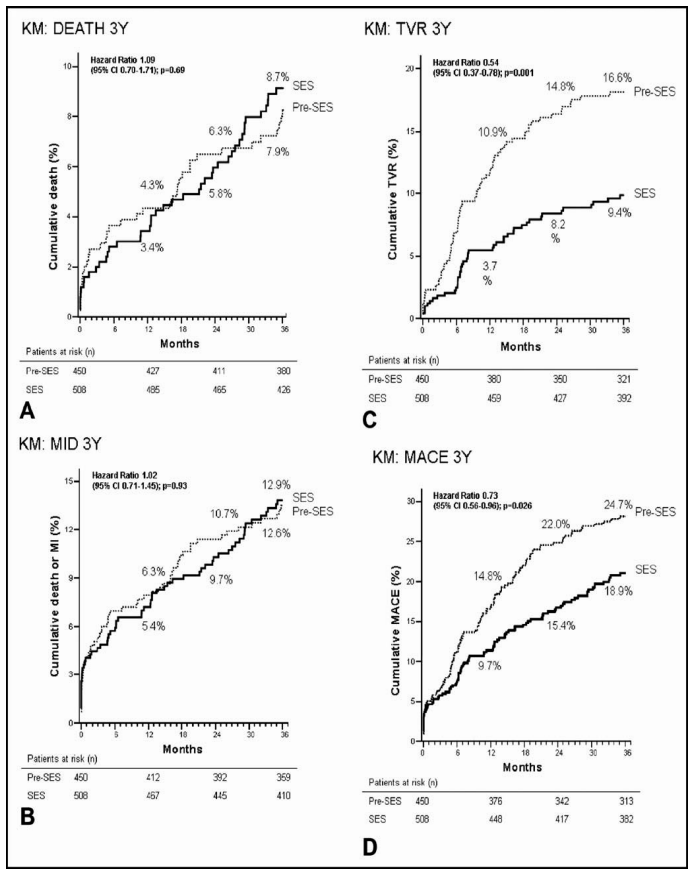

Figure 2. Three-year adverse events in patients treated with BMSs (pre-SES) and SESs: *(A)* cumulative risk of death, *(B)* death or myocardial infarction (MID), *(C)* target vessel revascularization, *(D)* death, myocardial infarction, or target vessel revascularization. CI = confidence interval; other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

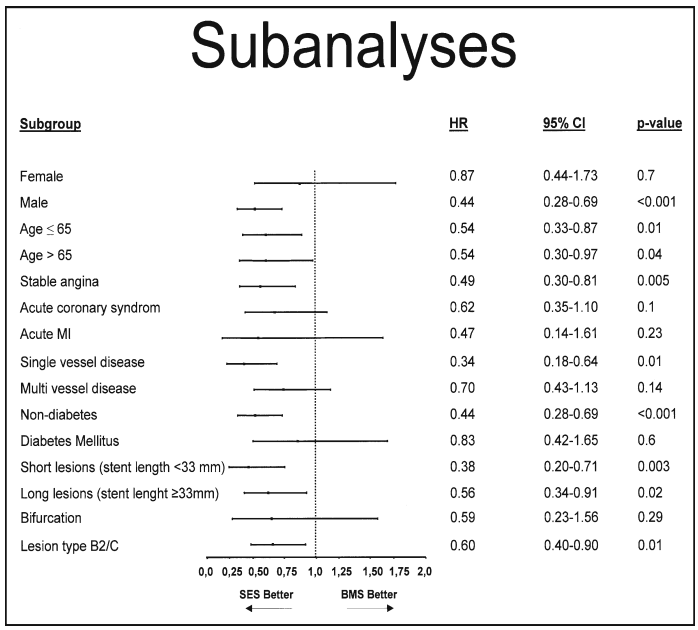

Figure 3. Hazard ratios (HRs) of stent type at 3-year follow-up for target vessel revascularization in subgroups of patients according to baseline and procedural characteristics. Other abbreviations as in Figure 2.

Acknowledgment: We appreciate the critical review of this report provided by Brian G. Firth, MD, and Neville Kukreja, MRCP.

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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PART II.

THE ROTTERDAM T-SEARCH AND RESEARCH REGISTRIES

II.III PUSHING THE BOUNDARIES I - THE UNRESTRICTED USE OF DRUG-ELUTING STENTS IN SPECIFIC PATIENT SUB-GROUPS

Chapter 7

Comparison of Short- (One Month) and Long- (Twelve Months) Term Outcomes of Sirolimus- Versus Paclitaxel-Eluting Stents in 293 Consecutive Patients With Diabetes Mellitus (from the RESEARCH and T-SEARCH Registries).

Andrew T. L. Ong, Jiro Aoki, Carlos A. G. van Mieghem, Gaston A. Rodriguez Granillo, Marco Valgimigli, Keiichi Tsuchida, Karel Sonnenschein, Evelyn Regar, Willem J. van der Giessen, Peter P. T. de Jaegere, Georgios Sianos, Eugene P. McFadden, Pim J. de Feyter, Ron T. van Domburg, and Patrick W. Serruys.
Am J Cardiol. 2005;96:358-62.

Comparison of Short- (One Month) and Long- (Twelve Months) Term Outcomes of *Sirolimus*- Versus *Paclitaxel*-Eluting Stents in 293 Consecutive Patients With Diabetes Mellitus (from the RESEARCH and T-SEARCH Registries)

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This study evaluated and compared the efficacy of sirolimus-eluting stents (n = 145 patients) with that of paclitaxel-eluting stents (n = 148 patients) in 293 consecutive unselected patients who had diabetes mellitus. Baseline clinical characteristics and presentations were similar: mean age of 64 years, 50% presented with unstable angina or myocardial infarction, and 66% had multivessel disease. Angiographic and procedural characteristics differed, with more complex lesions and more vein grafts managed in the paclitaxel-eluting stent group. Overall mean stented length was 46 ± 32 mm. There were no differences in unadjusted outcomes by stent type (1-year major adverse cardiac event rates of 20.4% for sirolimus-eluting stents vs 15.6% for paclitaxel-eluting stents, p = 0.12) or when adjusted for multivariate predictors (adjusted hazard ratio 0.68, 95% confidence interval 0.37 to 1.24, p = 0.21). Independent predictors of outcome in patients who had diabetes mellitus were stenting of the left main artery, stenting of the left anterior descending artery, creatinine clearance, and female gender. Patients who required insulin had a significantly higher, crude major adverse cardiac event rate at 1 year compared with those who used oral agents, but this rate became nonsignificant when adjusted for independent predictors of outcome. **(Am J Cardiol 2005;96:358–362)**

The Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) and Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registries are identical sequential prospective registries that were specifically set up to evaluate the universal utilization of sirolimus- and paclitaxel-eluting stents (SESs and PESs, respectively) in an unrestricted population.[1,2] The present study evaluated short- (1 month) and long-term (12 months) efficacies of SESs and PESs in patients with diabetes mellitus (DM).

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We performed a prospective cohort study to investigate the outcomes of drug-eluting stent implantation in patients who had DM. Since April 2002, our institution has adopted a policy of universal drug-eluting stent implantation for all patients who undergo percutaneous coronary intervention that requires stenting. All patients are prospectively entered into a dedicated database. The initial results of this approach have been published elsewhere.[1,2] Until February 2003, SESs (Cypher, Cordis, a Johnson & Johnson Company, Miami Lakes, Florida) were exclusively used; subsequently, PESs (Taxus, Boston Scientific Corp., Natick, Massachusetts) became the default stent.

Follow-up was complete for 98% of patients. Survival status was obtained from municipal civil registries at 1, 6, and 12 months. All repeat interventions (surgical and percutaneous) and rehospitalizations were prospectively collected during follow-up. Questionnaires concerning anginal status and medication use were sent to all living patients at 6 and 12 months. Referring physicians and institutions were contacted for additional information, if required. Written informed consent was obtained from every patient.

From April 2002 to December 2003, 293 unselected consecutive patients who had DM and de novo coronary artery disease were treated exclusively with drug-eluting stents; 145 patients received SESs and 148 received PESs. The 2 groups were sequential and are part of the RESEARCH and T-SEARCH prospective registries, respectively. Patients who have DM constitute 18% of the patient population treated percutaneously at our institution and were defined by

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therapy; those on oral medications were classified as requiring noninsulin and those on insulin therapy as requiring insulin.

All interventions were performed according to current standard procedures using routine high-pressure balloon inflations, with the final interventional strategy (including direct stenting, postdilatation, use of periprocedural glycoprotein IIb/IIIa inhibitors, and use of intravascular ultrasound) at the operator's discretion.[3] Angiographic success was defined as a residual stenosis ≤30% by visual analysis in the presence of Thrombolysis In Myocardial Infarction grade 3 flow. All patients were advised to maintain lifelong use of aspirin (≥80 mg/day). All patients were pretreated with 300 mg of clopidogrel. Postprocedurally, patients who received PESs were prescribed ≥6 months of clopidogrel (75 mg/day),[4] and those who received SESs were prescribed clopidogrel for ≥3 or 6 months depending on the complexity of the procedure.[1]

The primary outcome was the occurrence of major adverse cardiac events, defined as a composite of all-cause death, nonfatal myocardial infarction, or target vessel revascularization. Myocardial infarction was diagnosed by an increase in creatine kinase-MB fraction of >3 times the upper limit of normal.[5] In patients who underwent coronary artery bypass surgery during follow-up, periprocedural myocardial infarction was diagnosed by an increase in creatine kinase-MB level of 5 times the upper limit of normal.[6] For patients who presented with an acute myocardial infarction, a diagnosis of repeat myocardial infarction in the acute phase required a decrease and then increase in creatine kinase-MB of 50% above the previous level.[7] Target lesion revascularization was defined as a repeat intervention (surgical or percutaneous) to control a luminal stenosis within the stent or in the 5-mm distal or proximal segments adjacent to the stent. Target vessel revascularization was defined as a reintervention that was influenced by any lesion in the same epicardial vessel. Angiographic 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 a previously successfully stented artery in the first 30 days. Suspected stent thrombosis was defined as unexplained sudden death or nonfatal myocardial infarction that was unrelated to a periprocedural complication without repeat angiography. Two independent cardiologists (AO and JA) reviewed all major adverse cardiac events.

Continuous variables are presented as mean ± SD and were compared with Student's unpaired *t* test. Categorical variables are presented as counts and percentages and were compared by Fisher's exact test. All statistical tests were 2-tailed. Cox's proportional hazards analysis was performed to identify independent predictors of major adverse cardiac events using significant univariate variables and clinically important variables listed in Tables 1 and 2 (tested variables were age, gender, insulin requirement, creatinine clearance,

Table 1
Baseline clinical characteristics

Variable	SES Group (n = 145)	PES Group (n = 148)	p Value
Men	66%	67%	0.8
Age (yrs)	62.6 ± 10.2	64.6 ± 10.3	0.08
Non–insulin-requiring DM	73%	77%	0.4
Insulin-requiring DM	27%	23%	0.4
Hypertension	68%	70%	0.7
Hypercholesterolemia*	66%	85%	<0.001
Current smoking	23%	20%	0.7
Previous myocardial infarction	37%	42%	0.5
Previous coronary angioplasty	23%	21%	0.8
Previous coronary bypass grafting	10%	14%	0.5
Single-vessel coronary disease	34%	31%	0.7
Multivessel coronary disease	66%	69%	0.7
Clinical presentation			0.4
Stable angina pectoris	49%	56%	
Unstable angina pectoris	38%	34%	
Acute myocardial infarction	13%	10%	
Hemoglobin-A1c (%)	7.3 ± 1.3	7.6 ± 1.5	0.09
Creatinine clearance (ml/min)	87.6 ± 33.0	80.8 ± 33.4	0.10
Body mass index (kg/m^2)	28.4 ± 4.1	27.9 ± 3.8	0.3

Values are means ± SD or percentages.
* Defined as a fasting cholesterol level >5.5mmol/L or use of lipid-lowering therapy.

Table 2
Angiographic and procedural characteristics

Variable	SES Group (n = 145)	PES Group (n = 148)	p Value
Treated coronary vessel*			
Left anterior descending artery	60%	48%	0.05
Left circumflex artery	40%	34%	0.3
Right artery	32%	42%	0.11
Left main artery	8%	8%	1.0
Bypass graft	3%	10%	0.02
Lesion type†			
A	17%	8%	0.02
B1	37%	24%	0.02
B2	45%	47%	0.7
C	47%	56%	0.13
No. of coronary vessels treated			0.5
1	61%	64%	
2	35%	28%	
3	4%	8%	
Multivessel treatment	39%	36%	0.6
Bifurcation stenting	19%	14%	0.4
No. of stented vessels	1.4 ± 0.6	1.4 ± 0.7	0.9
No. of implanted stents	2.4 ± 1.5	2.3 ± 1.4	0.6
Total stented length per patient (mm)	45.3 ± 32.1	48.5 ± 33.8	0.4
Nominal stent diameter ≤2.5 mm	40%	47%	0.2
Chronic total occlusion (>3 mos)	14%	12%	0.6
Glycoprotein IIb/IIIa inhibitor use	18%	28%	0.04
Angiographic success of all lesions	94%	97%	0.4

Values are means ± SD or percentages.
* Expressed as percentage of patients with vessel type treated. Total exceeds 100%.
† Expressed as percentage of patients with lesion type. Total exceeds 100%.

Table 3
Major adverse cardiac events in the first month after stent implantation

Patients With Events at 0–1 month	SES Group (n = 143)	PES Group (n = 148)	p Value*
Death	5 (3.4%)	5 (3.4%)	1.0
Nonfatal myocardial infarction	5 (4.1%)	3 (2.0%)	0.3
Target lesion revascularization	5 (3.4%)	1 (0.7%)	0.1
Target vessel revascularization†	5 (3.4%)	3 (2.0%)	0.5
Any event	14 (9.7%)	9 (6.1%)	0.3
Angiographically proved stent thrombosis	3 (2.1%)	1 (0.7%)	0.4
Suspected stent thrombosis	1 (0.7%)	2 (1.4%)	1.0
Total stent thrombosis	4 (2.8%)	3 (2.0%)	0.7

* By Fisher's exact test.
† Includes target lesion revascularization.

presenting symptoms, lesion type, multivessel disease, bifurcation stenting, stenting of the left main artery, stenting of the left anterior descending artery, stent type, number of stents, total stent length, and minimum stent diameter). Stent type and requirement for insulin were forced into the model, whereas other variables were entered in a forward stepwise method (entry and removal criteria of 0.05 and 0.10, respectively). The cumulative incidence of adverse events was estimated according to the Kaplan-Meier method.

Baseline clinical characteristics were similar for the 2 groups with the exception of hypercholesterolemia (Table 1). Sixty-six percent were men and 25% required insulin. Multivessel coronary disease was present in 66% of patients, and 50% presented with an acute coronary syndrome (unstable angina or acute myocardial infarction). Mean hemoglobin A1c levels were 7.6 ± 1.5% in the PES group and 7.3 ± 1.3% in the SES group. More patients in the PES group were classified as having hypercholesterolemia (defined as a fasting serum cholesterol level >5.5mmol/L or use of lipid-lowering therapy at the time of the procedure) due to the more widespread use of lipid-lowering agents in the latter period.

Significant differences were noted in terms of angiographic and procedural characteristics (Table 2). In the PES group, more patients received treatment in a bypass graft (10% vs 3% in the SES group, p = 0.02) and fewer patients received treatment in the left anterior descending artery (48% vs 60% respectively, p = 0.05). The use of glycoprotein IIb/IIIa inhibitors was greater in the PES group (28% vs 18%, p = 0.04). More complex lesions were treated in the PES group, with fewer type A or B1 lesions treated (p = 0.02). Multivessel treatment was performed in 40% of patients. Total stented length was similar in the 2 groups (48.5 ± 33.8 mm in the PES group and 45.3 ± 32.1 mm in the SES group, p = 0.4), as was the number of stents implanted (2.3 ± 1.3 vs 2.4 ± 1.5 stents, respectively, p = 0.6).

In the first month after stent implantation, there were 10 deaths that were equally divided between groups (Table 3). Three deaths were clinically suspected to be due to stent thrombosis (Table 3). There were 8 myocardial infarctions, 5 in the SES group and 3 in the PES group. Of the 6 target lesion revascularizations, 4 were for stent thrombosis and 2 were the result of a procedural complication that required urgent coronary surgery. In total, 4 patients (2.8%) in the SES group and 3 (2.0%) in the PES group had suspected or

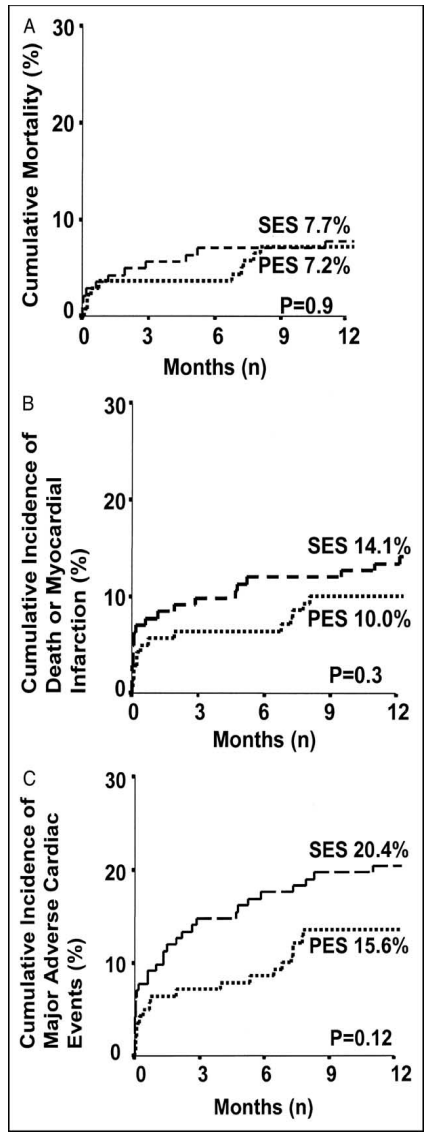

Figure 1. Event curves at 1 year for cumulative risks of *(A)* death, *(B)* death or myocardial infarction, and *(C)* death, myocardial infarction, or target vessel revascularization.

proved stent thrombosis (p = 0.7). A major adverse cardiac event occurred in 9.7% of patients in the SES group and 6.1% of patients in the PES group within the first 30 days.

At 1 year, there were no differences in the incidence of death between groups (SES 7.7%, PES 7.2%, p = 0.9; Figure 1). The incidence of death or myocardial infarction was also similar (SES 14.1%, PES 10.0%, p = 0.3). The composite end point of death, myocardial infarction, or target vessel revascularization was also nonsignificantly different (SES 20.4%, PES 15.6%, p = 0.12), with a trend favoring PES. Incidences of target lesion revascularization were 8.8% in the SES group and 5.7% in the PES group (p = 0.08; Figure 2

When patients were classified by insulin requirement, patients who required insulin (n = 72) developed more events compared with those who did not require insulin (n = 221, crude major adverse cardiac events 27.4% vs 14.6%, respectively, p = 0.008; Figure 3). Hemoglobin A1c levels were higher in the insulin-requiring DM group than in the non–insulin-requiring DM group, although not significantly (7.6% vs 7.2%, p = 0.4).

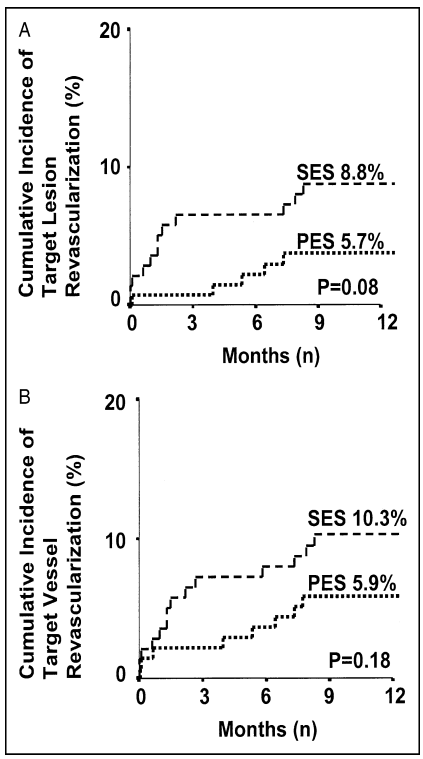

Figure 2. One-year cumulative risks of *(A)* target lesion revascularization and *(B)* target vessel revascularization.

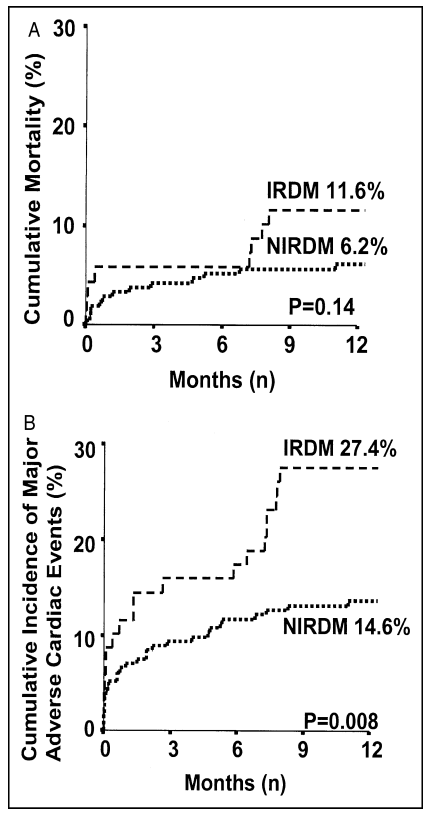

Figure 3. Cumulative risks of *(A)* death and *(B)* major adverse cardiac events stratified by diabetic type. IRDM = insulin-requiring DM; NIRDM = non–insulin-requiring DM.

Table 4
Multivariate predictors of major adverse cardiac events at one year (Cox's proportional hazards model)

Variable	Adjusted HR	95% CI	p Value
Stenting of left anterior descending artery	2.79	1.44–5.39	0.002
Stenting of left main artery	2.78	1.24–6.25	0.013
Creatinine clearance (/ml/min increment)	0.99	0.98–1.00	0.03
Women	1.90	1.02–3.53	0.04
Use of PES	0.68	0.37–1.24	0.21
Use of insulin	1.48	0.80–2.74	0.22

CI = confidence interval; HR = hazard ratio.

Stenting of the left anterior descending artery, stenting of the left main coronary artery, and female gender were independently associated with worse outcomes, whereas better renal function (defined as milliliter-per-minute incre-

ment in creatinine clearance) was associated with improved outcomes (Table 4). Insulin requirement, significant in univariate analysis, became nonsignificant in the multivariate model (adjusted hazard ratio 1.48, 95% confidence interval 0.80 to 2.74, p = 0.22), and no significant differences were noted with stent type (adjusted hazard ratio 0.68, 95% confidence interval 0.37 to 1.24, p = 0.21).

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The major finding of this study is that unrestricted use of PESs in a universal drug-eluting stent environment is associated with a nonsignificantly lower incidence of major adverse cardiac events at 1 year compared with SESs (adjusted hazard ratio 0.68, 95% confidence interval 0.37 to 1.24, p = 0.21). Patients with DM and who required insulin had a significantly higher crude incidence of major adverse cardiac events compared with those who did not require insulin in a combined drug-eluting population; this significance became nonsignificant after adjustment for multivariate predictors.

Mortality rate at 1 year between groups in our study was similar (7.7% in SES group and 7.2% in PES group, p = 0.9). It is difficult to compare between studies; however, as a guide, this result lies between that reported in the stent arm of the randomized Arterial Revascularization Therapy Study (6.3%)[8] and a multivessel report from the database of the Cardiovascular Research Foundation (14% to 15%),[9] with the caveat that baseline demographics were different. For a population that had DM, the use of glycoprotein IIb/IIIa inhibitors in this study was very low; more frequent use may have improved mortality rates.[10]

This study has described the experience of a single-center registry of drug-eluting stents in a moderate number of patients. Routine angiographic follow-up was not performed, thus precluding an assessment of restenotic rates. The low use of glycoprotein IIb/IIIa inhibitors is a limitation but was a reflection of the "real-world" practice of the operators. The results of this study should be viewed as an exploratory analysis that reported outcomes after the unrestricted use of drug-eluting stents in the real world in patients who had DM.

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Chapter 8

One Year Clinical follow-up of Paclitaxel-Eluting Stents for Acute Myocardial Infarction Compared to Sirolimus-Eluting Stents.

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INTERVENTIONAL CARDIOLOGY AND SURGERY

One year clinical follow up of paclitaxel eluting stents for acute myocardial infarction compared with sirolimus eluting stents

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Objective: To compare clinical outcome of paclitaxel eluting stents (PES) versus sirolimus eluting stents (SES) for the treatment of acute ST elevation myocardial infarction.
Design and patients: The first 136 consecutive patients treated exclusively with PES in the setting of primary percutaneous coronary intervention for acute myocardial infarction in this single centre registry were prospectively clinically assessed at 30 days and one year. They were compared with 186 consecutive patients treated exclusively with SES in the preceding period.
Setting: Academic tertiary referral centre.
Results: At 30 days, the rate of all cause mortality and reinfarction was similar between groups (6.5% *v* 6.6% for SES and PES, respectively, p = 1.0). A significant difference in target vessel revascularisation (TVR) was seen in favour of SES (1.1% *v* 5.1% for PES, p = 0.04). This was driven by stent thrombosis (n = 4), especially in the bifurcation stenting (n = 2). At one year, no significant differences were seen between groups, with no late thrombosis and 1.5% in-stent restenosis (needing TVR) in PES versus no reinterventions in SES (p = 0.2). One year survival free of major adverse cardiac events (MACE) was 90.2% for SES and 85% for PES (p = 0.16).
Conclusions: No significant differences were seen in MACE-free survival at one year between SES and PES for the treatment of acute myocardial infarction with very low rates of reintervention for restenosis. Bifurcation stenting in acute myocardial infarction should, if possible, be avoided because of the increased risk of stent thrombosis.

The efficacy of drug eluting stents to treat coronary artery stenosis in stable patients has been proved in recent trials with single digit restenosis rates for non-complex lesions.[1–4]

The potential risk of higher thrombogenicity, however, has led to prolonged antiplatelet treatment and cautious use of these stents for acute coronary syndromes. We have recently shown that the use of sirolimus eluting stents (SES) for acute myocardial infarction is safe and not associated with higher thrombogenicity.[5] The safety and efficacy of paclitaxel eluting stents (PES) in this setting has not been reported yet.

A recent meta-analysis clearly showed the benefit of primary percutaneous coronary intervention (PCI) over administration of thrombolytics for the treatment of acute myocardial infarction.[6] The superiority of (bare metal) stenting over balloon angioplasty has been well documented in the setting of acute myocardial infarction.[7]

We report the one year clinical outcome of a consecutive patient cohort treated solely with PES in the setting of primary PCI for acute ST elevation myocardial infarction. We compared their outcome with that of an earlier published patient population treated with SES.

METHODS

Patients

Since 16 February 2003, PES (Taxus; Boston Scientific, Galway, Ireland) has been implemented in our hospital as the default stent for all patients. Data were collected for the T-SEARCH (Taxus stent evaluated at Rotterdam Cardiology Hospital) registry.[8] This is a prospective single centre registry set up with the main purpose of evaluating the safety and efficacy of PES implantation for patients treated in daily practice. Until September 2003, 136 consecutive patients received exclusively PES in the setting of primary PCI for acute myocardial infarction. All patients were enrolled in the analysis including patients in cardiogenic shock (defined as persistent systolic blood pressure < 90 mm Hg or the need for vasopressors or intra-aortic balloon pumping required to maintain blood pressure > 90 mm Hg with evidence of end organ failure and increased left ventricular filling pressures). Patients who underwent rescue PCI after failed thrombolysis were not included in this study.

One year clinical outcome was compared with the one year data from the first 186 patients treated exclusively with SES in the setting of primary PCI for acute myocardial infarction between April 2002 and January 2003, when SES was the default stent in our centre.[5]

This study protocol was approved by the local ethics committee, and written informed consent was obtained from every patient.

Treatment strategy and definitions

The interventional strategy and use of glycoprotein IIb/IIIa inhibitors was left entirely to the discretion of the operator. Clopidogrel was recommended for six months, in addition to

Abbreviations: ASA, acetylsalicylic acid; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention; PES, paclitaxel eluting stents; SES, sirolimus eluting stents; T-SEARCH, Taxus stent evaluated at Rotterdam Cardiology Hospital; TIMI, thrombolysis in myocardial infarction; TVR, target vessel revascularisation

lifelong acetylsalicylic acid (ASA) 80 mg. The loading dose of 300 mg clopidogrel was given before the intervention. If the patient was not taking ASA, 250 mg of intravenous ASA was given at the start of the procedure.

The occurrence of major adverse cardiac events (MACE) was evaluated at one year. MACE were all cause mortality, non-fatal myocardial infarction, and target lesion revascularisation or target vessel revascularisation (TVR).

Reinfarction was defined as new symptoms or new ECG changes in association with an increase in creatine kinase MB fraction concentrations of 1.5 times the previous value if measured within 48 hours or > 3 times the upper normal limit if measured > 48 hours after the index infarction. Target lesion revascularisation 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 repeat intervention driven by any lesion located in the same epicardial vessel treated at the index procedure. Thrombotic stent occlusion was angiographically documented as a complete occlusion (TIMI (thrombolysis in myocardial infarction) flow grade 0 or 1) or a flow limiting thrombus (with TIMI flow 1 or 2) of a previously successfully treated artery.

Follow up

All patients were clinically followed up. Repeat angiography was clinically driven by symptoms or signs of ischaemia. Information about in-hospital outcomes was obtained from our institutional electronic clinical database and by review of the hospital records for patients discharged to referring hospitals (patients were referred from 14 local hospitals). Postdischarge survival status was obtained from the municipal civil registries at one, six, and 12 months. Data on all repeat interventions (surgical and percutaneous) and repeat

Table 2 Major adverse cardiac events at 30 days and one year

	SES (n = 186)	PES (n = 136)	p Value*
0–1 month			
Death	5.9%	5.9%	1.0
Death or re-MI	6.5%	6.6%	1.0
TLR	1.1%	4.4%	0.07
TVR	1.1%	5.1%	0.04
Death, re-MI, or TVR	7.5%	10.3%	0.4
Stent thrombosis	0%	2.9%	0.03
0–12 months			
Death	8.1%	8.1%	1.0
Death or re-MI	9.2%	10.3%	0.7
TLR	1.1%	5.9%	0.02
TVR	1.1%	6.6%	0.01
Death, re-MI, or TVR	9.7%	14.7%	0.22
Stent thrombosis	0%	2.9%	0.03

*By Fisher's exact test.
re-MI, reinfarction; TLR, target lesion revascularisation; TVR, target vessel revascularisation.

Table 1 Baseline characteristics

	SES (n = 186)	PES (n = 136)	p Value
Men	74.7%	83.8%	0.06
Age (years)	59.7 (11.7)	59.2 (12.1)	0.7
Diabetes	10.8%	3.7%	0.02
Current smoking	45.7%	44.9%	0.9
Hypercholesterolaemia	33.9%	30.1%	0.5
Hypertension	24.2%	20.6%	0.5
Previous myocardial infarction	14.4%	10.6%	0.4
Previous PCI	6.5%	5.9%	1.0
Previous CABG	1.6%	2.2%	0.7
Coronary artery disease			0.9
1 vessel	54.8%	52.2%	
2 vessel	27.4%	28.7%	
3 vessel	17.7%	19.1%	
Cardiogenic shock	13.4%	11.8%	0.7
Time from symptom onset to PCI (hours)	3.2 (1.9)	3.1 (2.4)	0.7
Infarct related vessel			0.6
LAD	52.7%	51.5%	
LCx	8.2%	8.8%	
RCA	37.4%	36.0%	
Left main stem	1.6%	2.2%	
Saphenous vein graft	0%	1.5%	
Bifurcation lesion	8.6%	9.6%	0.8
Number of vessels treated			1.0
1	84.9%	86.0%	
>1	15.1%	14.0%	
TIMI flow baseline grade			0.4
0–1	73.1%	78.7%	
2	16.5%	11.0%	
3	10.4%	10.3%	
TIMI flow final grade			0.7
0–1	2.1%	2.2%	
2	14.8%	11.8%	
3	83.0%	86.0%	
Number of stents	1.9 (1.2)	1.8 (1.1)	0.4
Total stented length (mm)	34.7 (23.5)	35.9 (22.9)	0.6
Mean nominal stent diameter (mm)	2.89 (0.16)	3.11 (0.33)	<0.001
Glycoprotein IIb/IIIa inhibitor	36.6%	55.1%	0.001
Peak CK (IU)	3126 (3126)	3234 (2567)	0.8
Peak CK-MB (IU)	296 (255)	359 (330)	0.2

Data are mean (SD) or percentage.
CABG, coronary artery bypass graft; CK, creating kinase; LAD, left anterior descending coronary artery; LCx, left circumflex artery; PCI, percutaneous coronary intervention; PES, paclitaxel eluting stents; RCA, right coronary artery; SES, sirolimus eluting stents; TIMI, thrombolysis in myocardial infarction.

hospitalisations were prospectively collected during follow up. Questionnaires regarding anginal status and medication use were sent to all living patients at six and 12 months. Referring physicians and institutions were contacted for additional information if required.

Statistical analysis

Continuous variables are presented as mean (SD) and were compared by Student's unpaired *t* test. Categorical variables are presented as counts and percentages and compared by Fisher's exact test. All statistical tests were two tailed. The cumulative incidence of adverse events was estimated according to the Kaplan-Meier method and compared by the log rank test. Cox proportional hazards survival models were used to assess risk reduction. Multivariate analyses were performed to identify independent predictors of long term MACE. Significant baseline and procedural characteristics at univariate analysis (tested variables: age, diabetes, cardiogenic shock, multivessel disease, left main stem as the infarct related artery, postprocedural TIMI flow, bifurcation treatment, multivessel treatment, and duration of pain), sex, and stent type were tested for their multivariate predictive value. The first model was built by backwards stepwise variable selection with the exit criteria set at the $p = 0.1$ level; the final model was built by forcing stent type together with all significant predictors.

RESULTS

In total 136 patients were treated with PES only in the setting of primary PCI for acute myocardial infarction in the study period. These patients were compared with 186 patients treated with SES for the same indication in the period before our centre switched to PES as the default strategy. Follow up of the 186 patients with SES from our earlier report[3] was extended from 300 days to one year for the comparison. At one year after the procedure, follow up was available for 98.4% of patients.

Table 1 lists baseline characteristics. Fewer PES patients had diabetes (3.7% *v* 10.8%, $p = 0.02$). PES patients had a larger nominal stent size (3.11 *v* 2.89 mm, $p < 0.001$) and a higher percentage of periprocedural glycoprotein IIb/IIIa inhibitor use (55.1% *v* 36.6%, $p = 0.001$). Despite inclusion of consecutive patients in both SES and PES groups, the prevalence of diabetes differed significantly. This does not reflect selection bias. The smaller nominal stent size in the SES group reflects the unavailability of SES > 3.0 mm at the time of the study.

MACE were analysed at one month and one year. Table 2 shows the results. No significant difference was seen in death and death or reinfarction between the two groups either in the first month or at late follow up. However, a significant difference in TVR was seen in favour of SES, which was already apparent at 30 days driven by stent thrombosis.

Six of seven patients with TVR within 30 days in the PES group received target lesion reintervention. Of these, four interventions were necessary because of subacute stent thrombosis (table 3). Only one of these patients had been treated with periprocedural glycoprotein IIb/IIIa inhibitor during the index procedure.

Two of four stent thromboses were in patients treated with bifurcation lesions (one patient with crush bifurcation stenting without kissing balloon postdilatation but with periprocedural glycoprotein IIb/IIIa inhibitor and one patient with T stent bifurcation stenting without kissing balloon postdilatation and without glycoprotein IIb/IIIa inhibitor). The two remaining cases were caused by stent underexpansion, diagnosed at reintervention.

Table 4 Bifurcation lesions: treatment strategy

	SES (n = 16)	PES (n = 13)	p Value
Main branch stent only	3 (18.8%)	3 (23.1%)	0.4*
Crush	2 (12.5%)	4 (30.8%)	
Culotte	0	1 (7.7%)	
T stent	9 (56.3%)	3 (23.1%)	
V stent	2 (12.5%)	2 (15.4%)	
Final kissing balloon	6 (42.9%)	8 (61.5%)	0.3

*Across all strategies by χ^2 test.

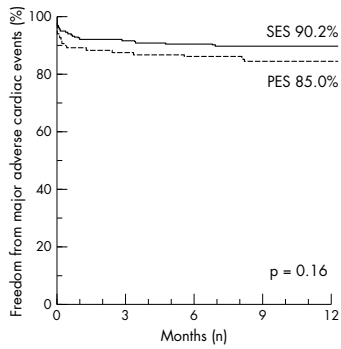

Figure 1 Survival free of death, reinfarction, or target vessel revascularisation of patients who received a sirolimus eluting stent (SES) versus a paclitaxel eluting stent (PES) by Kaplan-Meier estimate.

Table 3 Characteristics of individual cases of PES stent thrombosis

	Patient number			
	1	2	3	4
Patient age (years)	59	50	52	47
Sex	Male	Male	Female	Female
Time to thrombosis	1 hour	4 days	4 days	6 days
Lesion type (AHA classification)	B2	B2	C	C
Number of stents	1	1	2	2
Total stent length (mm)	28	24	44	36
Smallest stent diameter (mm)	3.0	3.5	2.25	2.5
Treated vessel	RCA	LAD	LCx, OMCx	LAD, 1st diagonal
Bifurcation stenting	No	No	T stent	Crush
Kissing balloon postdilatation	NA	NA	No	No
Abciximab during index procedure	No	No	No	Yes

AHA, American Heart Association; NA, not applicable; OMCx, obtuse marginal branch of the left circumflex artery.

Table 5 Final Cox regression model of independent predictors of major adverse cardiac events at one year with stent type forced in

Independent predictor	HR	95% CI	p Value
TIMI flow grade			
3 (reference)	1.00	NA	NA
2	2.90	0.86 to 9.77	0.09
0 or 1	10.24	2.61 to 40.13	0.001
Cardiogenic shock	4.38	1.63 to 11.8	0.003
Diabetes mellitus	4.77	1.61 to 14.1	0.005
Duration of pain (per hour increment)	1.17	0.98 to 1.39	0.08
Multivessel disease	2.13	0.79 to 5.78	0.14
Use of PES	2.07	0.78 to 5.48	0.14

CI, confidence interval; HR, hazard ratio.

The bifurcation stenting percentage was not significantly different between groups (8.6% *v* 9.6% for SES and PES, respectively, p = 0.8). Although across all strategies no significant difference was found in bifurcation lesion treatment between SES and PES patients, a trend was seen towards more crush stenting and less T stenting in PES patients (table 4).

MACE-free survival at 12 months was 90.2% for SES and 85% for PES patients (p = 0.16, by Kaplan-Meier estimate) (fig 1).

On multivariate analysis, stent type was not an independent predictor of MACE at one year and, when forced into the model of significant predictors, remained non-significant (p = 0.14) (table 5). However, independent predictors were TIMI flow 0 or 1 (hazard ratio (HR) 10.2), cardiogenic shock (HR 4.4), and diabetes mellitus (HR 4.8).

DISCUSSION

The main finding of this sequential registry report is that patients treated with drug eluting stents for acute myocardial infarction have a very low rate of repeat revascularisation for restenosis at one year's follow up.

Although no significant difference in MACE at one year was found between the two drug eluting stents, a trend to worse outcome was seen in the patients treated with PES, despite more favourable baseline characteristics such as less diabetes, higher use of glycoprotein IIb/IIIa inhibitors, and larger nominal stent diameter.

Short term follow up

The largest difference between the groups was TVR in the first 30 days. These were mainly driven by stent thrombosis.

With respect to these observations of two of 13 stent thromboses in bifurcation lesions and two of 123 in non-bifurcation lesions, it seems prudent to try to avoid using two stents for bifurcation treatment in acute myocardial infarction. If this is unavoidable, the risk for stent thrombosis may be reduced by kissing balloon postdilatation and periprocedural glycoprotein IIb/IIIa inhibitor. In a separate study of 2500 patients we confirmed that bifurcation stenting in acute myocardial infarction was a significant predictor of stent thrombosis and conferred a 13-fold increase in risk.[9] It may be advisable to keep procedures short and simple for patients undergoing angioplasty for acute myocardial infarction.

The overall rate of stent thrombosis was 1.2% (four of 322) for drug eluting stent use in acute myocardial infarction. This is comparable with the stent thrombosis rate with bare stents[9 10] and drug eluting stents[9] used in the treatment of patients for stable coronary lesions.

Long term follow up

Between 30 days and one year two patients treated with PES were referred for TVR, both for in-stent restenosis (1.5%), compared with no additional interventions for the SES patients.

No late stent thrombosis was diagnosed in either group. In this study, the risk for late stent thrombosis after stopping clopidogrel, which was prescribed for six months for the PES and 3–6 months for the SES group, does not seem to be increased for treatment of patients with acute coronary syndromes with drug eluting stents. It is important that, to address this potential problem conclusively, larger studies specifically looking at this end point be performed. Furthermore, until more is known, complete cessation of antiplatelets should be avoided if possible to avoid the risk of late thrombosis, as McFadden *et al*[11] recently pointed out.

Early and one year mortality was identical in both groups (5.9% at 30 days and 8.1% at one year for SES and PES). This is very comparable with earlier studies[6] despite the presence of cardiogenic shock in 12% of patients and multivessel disease in almost half. As shown before, mortality is not changed by the use of drug eluting stents.[5] Their benefit is reduction of reintervention as in elective PCI.

The recommendations in the most recent National Institute for Health and Clinical Excellence guidelines explicitly exclude acute myocardial infarction and lesions with visible thrombus as indications for use of drug eluting stents.[12] Our results are reassuring and do not indicate that patients with acute myocardial infarction should be denied the benefit of the very low reintervention rates with drug eluting stents.

Conclusions

The use of PES for the treatment of acute myocardial infarction seems safe. No significant differences were seen with the results of SES at one year's follow up with a very low rate of reintervention for restenosis. However, a trend towards more early reinterventions was evident, mainly due to stent thrombosis. Bifurcation stenting should be avoided in the setting of primary PCI, if possible.

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Chapter 9

Drug-Eluting Stent-Supported Percutaneous Coronary Intervention in High Risk Patients Refused Cardiac Surgery.

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Drug-eluting stent-supported percutaneous coronary intervention in high risk patients refused cardiac surgery

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KEYWORDS
Coronary disease, drug-eluting stents, mortality, CABG, EuroSCORE

Abstract

Aims: Randomized trials of drug-eluting stents (DES) have demonstrated their ability to improve clinical outcome in relatively simple lesion/patient subsets. Their potential in patients for whom the risk of coronary bypass grafting is judged prohibitive, remains largely unexplored. To investigate periprocedural and one-year outcome of percutaneous coronary intervention (PCI) using DES in patients refused for coronary artery bypass grafting (CABG).

Methods and results: At our institution, the therapeutic approach for all patients with multi-vessel disease is decided, by consensus at a conjoint session with the clinical cardiologist, interventionalist and cardiothoracic surgeon enabling unequivocal identification of patients, refused surgery, who were referred for PCI. The EuroSCORE was used to predict peri-operative mortality. From April 2002 to December 2003 we identified 84 such patients. The mean age was 70.9±10.1 years and 68% were men. More than one third had prior CABG. Most patients presented with stable or unstable angina pectoris. The reasons for refusal for CABG were: unsuitable coronary anatomy (37%), poor functional status (28%), patent grafts other than the culprit vessel (25%), prior CABG (28%), severe left ventricular dysfunction (13%), co-existing malignancy (18%), prior disabling stroke (12%) and morbid obesity (11%). Using the standard and logistic EuroSCORE methods, the predicted in-hospital mortality rates were 7.8±3.3% and 13.2±11.1% respectively. In this study, the actual mortality rate was 1.2% at 30 days, 3.6% at 6 months and 4.8% at 1 year follow-up.

Conclusions: PCI in high risk patients who were refused for CABG in the DES-era resulted in an early and 1-year mortality rate that was significantly lower than the predicted operative mortality.

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Introduction

Percutaneous coronary intervention (PCI) has evolved to become the preferred alternative to coronary artery bypass grafting (CABG) in many lesion/patient subsets[1] and the advent of drug eluting stents (DES), which dramatically reduce the need for reintervention[2], may soon extend these indications to patients with more complex or extensive lesions in whom CABG has traditionally been the recommended approach[3-7].

Given the less invasive nature of percutaneous intervention, it is often used as a "bailout" procedure in patients, in whom the site or extent of the vascular lesions would normally be considered an indication for surgery, but who are judged to have a prohibitively high risk of adverse outcomes with CABG because of cardiac or extracardiac comorbidities.

The Angina With Extremely Serious Operative Mortality Evaluation (AWESOME) trial compared CABG with PCI in patients at high risk for CABG with medically refractory ischemia; bare stents were implanted in 54% of patients; the authors concluded that PCI was a safe alternative to CABG with comparable survival, but a higher rate of reintervention in the PCI group[8,9]. We evaluated procedural and 1-year outcome in patients in whom CABG was not considered an option for revascularization, based on a consensus decision of the referring cardiologist, interventionalist and cardiothoracic surgeon, who were subsequently treated with PCI with a DES as the default stent. The expected in-hospital mortality rate was calculated with both the standard and logistic EuroSCORE, a validated surgical outcome tool and compared with the observed mortality[10-15].

Methods

Our institutional policy requires that the revascularization strategy, for patients referred to our center, for elective treatment of multivessel coronary artery disease be decided, by consensus at a multidisciplinary case conference, where the referring cardiologist, an interventional cardiologists and a cardiothoracic surgeon are present. For emergent referrals, a similar strategy is applied on an ad-hoc basis in the catheterization laboratory.

Since April 2002, our institution has implemented a policy of universal DES utilization for all patients requiring coronary stent implantation. Until February 2003, sirolimus-eluting stents (Cypher®, Cordis, a Johnson & Johnson Company, Miami Lakes, FL, USA) were used, since then we have used paclitaxel-eluting stents (Taxus™, Boston Scientific Corporation, Natick, MA, USA). Clinical, procedural and follow-up data for all patients receiving DES have been prospectively collected as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH)[3] and Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH)[4] registries respectively.

The study population comprised consecutive patients treated between April 2002 and December 2003, by percutaneous coronary intervention, after a consensus decision, that surgical intervention (or re-intervention) carried an unacceptably high risk.

The EuroSCORE, a validated tool to assess surgical risk, was used to obtain an objective assessment of the expected post-operative mortality in the group[10,13,15]. Both the standard and the logistic score were calculated[11,12,14].

Follow-up and endpoint definition

Clinical follow-up was obtained for all patients. Clinical endpoints were all-cause mortality and major adverse cardiac events (MACE), defined as a composite of death, myocardial infarction and target vessel revascularization (TVR) at one year. Survival status was obtained from the the Municipal Civil Registries at 6 months and 1 year post-procedure. Myocardial infarction was defined as a rise in creatinine kinase-MB fraction more than 3 times the upper limit of normal; TVR was defined as any re-intervention within the stented vessel. Myocardial infarctions and re-interventions were prospectively recorded on our institutional database. Surviving patients received a health questionnaire at 6 months and one year. Further clinical information was obtained from the referring cardiologist or general practitioners, where required.

Results

Baseline and procedural characteristics are presented in Tables 1 and 2. The mean age of the patients was 70.9±10.1 years and 68% were men. More than a third (37%) had prior CABG. Glycoprotein IIb/IIIa-blockers were used in 24% of patients. Drug-eluting stents were used in 88% of patients; in 15% of the patients bare metal stents were used due to the unavailability of large diameter DES for the treated vessels. The mean number of implanted stents was 2.8±1.8 mm, with a total length of 55.5±37.6 mm. Mean stent diameter was 2.97±0.50 mm.

The reasons for refusal for CABG were: unsuitable coronary anatomy (37%), poor general condition (28%, mostly due to advanced age), patent grafts other than the culprit vessel (25%), prior CABG (28%), severe left ventricular (LV) dysfunction (13%), co-existing malignancy (18%), prior disabling stroke (12%) and morbid obesity (BMI > 35 kg/m^2) (11%). Multiple reasons were present in 62%. The reasons for surgical refusal are detailed in Table 3.

The predicted in-hospital mortality rate, calculated using the standard and logistic EuroSCORE, was 7.8±3.3% and 13.2±11.1% respectively. The observed mortality was, however, significantly lower: 1.2% at 30 days, 3.6% at 6 months and 4.8% at 1 year follow-up (Table 4 and Figure 1). The incidence of myocardial infarction was 1.2% at 30 days, 3.6% at 6 months and 3.6% at 1 year. Repeat revascularization of the target vessel occurred in no patient at 30 days, 1.2% at 6 months, and in 3.6% at 1 year. Overall MACE was relatively low: 2.4%, 7.1% and 10.7% at 30 days, 6 months and 1 year follow-up respectively (Table 4 and Figure 2).

Discussion

The randomized controlled trials that compared PCI with CABG or that compared bare metal stents with DES excluded patients with high risk features, such as prior CABG, unsuitable anatomy or poor LV function. The AWESOME investigators randomized a subgroup of such patients to PCI or CABG and concluded that PCI was an alternative to CABG, with comparable survival, although the reintervention rate was, as expected, higher in the PCI group[8,9]. During the study period, stents were used in just over half of the patients. The advent of DES with their dramatic effect on the need for reintervention led us to evaluate outcome in consecutive patients who were refused CABG but were treated in our institution with PCI and default DES use[3,4].

Table 1. Baseline characteristics (N=84)

Age, years±SD	70.9±10.1
Male, %	68
Diabetes, %	34
Hypercholesterolemia, %	61
Current smoker, %	10
Hypertension, %	48
BMI, kg/m^2±SD	27±4
Previous MI, %	38
Previous PCI, %	22
Previous CABG, %	37
Time from first CABG, years±SD	12.5±5.4
Serum creatinine, mmol/L±SD	123±129
1-vessel, %	7
2-vessel, %	32
3-vessel, %	57
Left main, %	4
Left ventricular dysfunction, %	48
Standard EuroSCORE, mean±SD	7.8±3.3
Logistic EuroSCORE, mean±SD	13.2±11.1

Table 2. Procedural characteristics

Indication for the procedure	
Stable Angina, %	50
Unstable angina, %	43
Acute myocardial infarction, %	7
Time to procedure, days±SD	38±54
IIb/IIIa-antagonist use, %	24
Any drug-eluting stent use, %	88
Sirulimus-eluting stents, %	51
Paclitaxel-eluting stents, %	36
Bare metal stents, %	15
Mean stent diameter, mm±SD	2.97±37.6
Total stent length, mm±SD	55.5±37.6
Number of stents, mean±SD	2.8±1.8
Use of small stents (≤ 2,5 mm), %	30
Vein grafts, %	12
Bifurcations, %	13
TIMI-0 flow pre-intervention, %	8

The major finding of the study was that PCI in high-risk patients refused CABG and subsequently treated with DES was associated with low periprocedural and 1-year mortality rates, that were significantly lower than the mortality rates predicted by the EuroSCORE method, a validated tool for surgical risk assessment.

To estimate the peri-operative mortality, we used the standard (or additive) and logistic EuroSCORE, a validated surgical outcome tool. The logistic EuroSCORE is more suitable for patients with very high risk features, i.e. patients with a standard EuroSCORE of 6 or more or patients with CABG and concomitant valve surgery[14]. In a single centre report, the standard EuroSCORE score had significantly bet-

Table 3. Reason for surgical refusal (%)

Unsuitable anatomy	37
Poor functional status	28
Patent grafts	25
Grafts adherent to sternum	4
Re-thoracotomy	22
Re-re-thoracotomy	6
Severe LV dysfunction	13
Concomitant valvular disease	4
No suitable venous material	5
Malignancy	18
Neurologic	12
Morbid obesity (BMI >35 kg/m^2)	11
Renal failure	7
Severe lung disease	6
Other extra-cardiac co-morbidity	9
Multiple risk factors	62

Table 4. Components of MACE at 30 days, 6 months and one year

	30 Days	6 Months	1 Year
Death, n (%)	1 (1.2%)	3 (3.6%)	4 (4.8%)
Myocardial infarction, n (%)	1 (1.2%)	3 (3.6%)	3 (3.6%)
Target vessel revascularization, n (%)	0 (0%)	1 (1.2%)	3 (3.6%)
Major adverse cardiac events, n (%)	2 (2.4%)	6 (7.1%)	9 (10.7%)

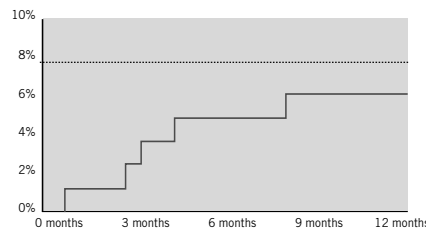

Figure 1. Kaplan-Meier curve for cumulative all cause mortality plot for patients refused for CABG; the dotted line indicates the peri-operative mortality derived from the standard Euroscore.

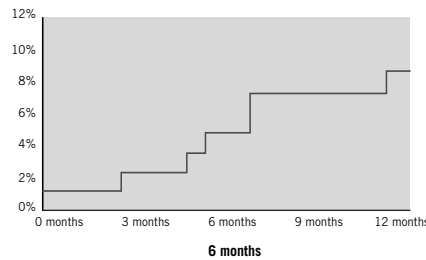

Figure 2. Kaplan-Meier curve for MACE (death/ MI/ TVR) in patients refused for CABG.

ter discriminatory power to predict 30-day mortality rate than the Society of Thoracic Surgeons (STS) risk score system[15].

In this study unsuitable anatomy, prior CABG, patent grafts and LV dysfunction were the most important cardiac factors for the heart team to decline surgical revascularization in a patient. The extracardiac factors were poor functional status, malignancy, neurological disability, morbid obesity, renal failure and chronic obstructive pulmonary disease. Overall, two-thirds of patients had multiple risk factors that precluded CABG.

The major randomised controlled trails comparing PCI with bare stents versus CABG concluded that no statistical differences are observed between CABG and stenting for mortality or acute myocardial infarction, but that CABG is associated with reduced rates of major adverse cardiac events, mostly driven by reduced repeat revascularisation[1,16]. With the extended use of DES, the rate of repeat revascularisation in our study was very low at 1-year (Table 4); in former studies a major drawback compared with surgery, although the long term results are not yet known in our particular group of patients.

A recent trial randomized patients with carotid stenosis to percutaneous intervention with stent implantation or to surgery showed that the outcome did not differ significantly[17]. This study had parallel registries documenting outcome in patients, refused for surgery or for percutaneous intervention, who were subsequently treated with either method. Interestingly, the outcome in patients refused for surgery who were treated percutaneously, did not differ significantly from that of the patients who were judged suitable for randomisation. Our study highly suggests that in the DES era, PCI is a reasonable alternative for patients requiring revascularization in whom the risk of adverse outcomes with CABG is judged to be unacceptably high. Further studies are needed to confirm our results, although randomized controlled trials in this group of patients would be difficult, especially if compared with medical therapy.

Limitations

The present study has several limitations: it is non-randomized, has an observational design and a heterogenous study population. Not all patients were strictly inoperable; i.e. patients with patent grafts to the LAD were not reoperated on at the first instance. Other patients would have been operative candidates, albeit at a much higher risk, if percutaneous treatment was not an option. Although the decision is reached by consensus, it is very operator dependent as the composition of the heart team changes and there are no accepted guidelines. Also, a control group of conservative, medically treated patients were not available.

Conclusions

Percutaneous coronary intervention in high risk patients refused CABG and subsequently treated with drug-eluting stents is associated with low early and 1-year mortality, significantly lower than EuroSCORE predicted rates. The 1-year incidence of major adverse cardiac events, especially the repeat revascularisation, is low as compared to former trials comparing bare stents versus CABG.

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PART II.

THE ROTTERDAM T-SEARCH AND RESEARCH REGISTRIES

II.IV PUSHING THE BOUNDARIES II - THE UNRESTRICTED USE OF DRUG-ELUTING STENTS IN SPECIFIC LESION SUB-GROUPS

Chapter 10

Full Metal Jacket Using Drug-Eluting Stents for De Novo Coronary Lesions.

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Am Heart J 2005; 150:994-9

''Full metal jacket'' (stented length ≥64 mm) using drug-eluting stents for de novo coronary artery lesions

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Background Stented segment length was a predictive factor for restenosis in the bare metal stent era. The objective of the study was to evaluate the medium-term clinical outcome and the potential for adverse effects when very long segments (ie, ≥64 mm of stented length) are treated by drug-eluting stent (DES) implantation, an approach colloquially referred to as a ''full metal jacket.''

Methods Since April 2002, we have used DES as the default stent for all percutaneous coronary interventions. From our prospective institutional database we identified 122 consecutive patients, with de novo coronary lesions, in whom a coronary artery was treated with at least 64 mm of overlapping DES: 81 patients were treated with sirolimus-eluting stents and 41 with paclitaxel-eluting stents.

Results The mean number of stents per lesion was 3.3 ± 1.1, and the median stented length was 79 mm (range 64-168 mm). Periprocedural Q-wave myocardial infarction (MI) occurred in 2 patients (1.6%) and subacute stent thrombosis in 1 patient (0.8%). During 1-year follow-up, 5 patients (4.1%), including 3 patients treated for acute MI with cardiogenic shock, died and 10 patients (8.2%) had nonfatal MI (creatine kinase–MB >3 times). The 1-year target vessel revascularization rate was 7.5% and the overall incidence of major adverse cardiac events was 18%. Outcomes in sirolimus-eluting stents and paclitaxel-eluting stents groups did not differ statistically.

Conclusions The use of DES for the treatment of diffuse lesions was associated with a low rate of repeat revascularization, irrespective of stent type. No safety concerns were raised at medium-term follow-up. (Am Heart J 2005;150:994-9.)

In the bare metal stent era, the length of a stented segment was an independent predictor of in-stent restenosis.[1-3] Recent randomized trials, in low-risk patient/lesion cohorts, showed that drug-eluting stents (DES) reduce the need for repeat intervention compared with bare metal stents.[4-7] Drug-eluting stents are rapidly replacing bare metal stents and there has been a tendency toward longer stented segment lengths, given the full lesion coverage from a proximal to a distal "angiographically normal" segment to avoid stent gaps and the incomplete coverage of lesions which have been associated with restenosis after DES implantation.[5,8] However, the clinical effect of very long and overlapping DES implantation in the so-called full metal jacket approach and the potential effects of increased metal and local drug exposures are unknown. In this report, we investigate the clinical outcome after very long sirolimus-eluting stent (SES) and paclitaxel-eluting stent (PES) implantations in a consecutive group of 122 patients (124 lesions) who were treated with at least 64 mm of DES without any gap in the same vessel.

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Methods

Patient selection and procedure

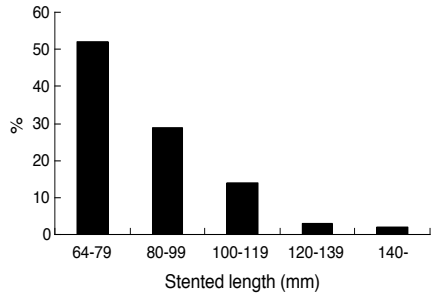
Since April 2002, we have adopted a policy of universal DES implantation for all percutaneous coronary interventions requiring stents at our center, irrespective of clinical presentation or lesion morphology. Sirolimus-eluting stents were exclusively used until March 2003. Since March 2003, PES has been exclusively used. In total, 122 consecutive

Table I. Patient characteristics

	All (n = 122)	SES (n = 81)	PES (n = 41)
Age (y)	63 ± 11	62 ± 12	63 ± 11
Male (%)	75	69	88*
Hypertension (%)	42	43	39
Hyperlipidemia (%)	67	62	76
Current smoking (%)	25	26	24
Diabetes mellitus (%)	19	20	17
Prior MI (%)	44	43	46
Prior CABG (%)	5	5	5
Prior PCI (%)	19	17	22
Multivessel disease (%)	70	70	68
Unstable angina (%)	26	31	17
AMI (%)	11	11	12
AMI with shock (%)	3	2	5

CABG, Coronary artery bypass graft surgery; *PCI*, percutaneous coronary intervention; *AMI*, acute MI.
*$P < .05$ for the comparison between SES and PES groups.

Figure 1



The distribution of stented length.

patients were treated with at least 64 mm of DES without any gap in the same vessel for diffuse coronary lesions, chronic total occlusion, or extensive dissections; this represents 7% of our patients treated exclusively with DES in the same period. The longest available individual stent length was 33 mm in SES and 32 mm in PES. We defined a full metal jacket as 64 mm of continuous stent, calculated as the total of the 2 longest PES lengths.

All interventions were performed using standard techniques. Written informed consent was obtained from all patients as part of the prospective consecutive database. Periprocedural use of glycoprotein IIb/IIIa and intravascular ultrasound (IVUS) was at the discretion of the operator. All patients received a loading dose of 300-mg clopidogrel followed by a daily dosage of 75 mg for 6 months, in addition to life-long aspirin therapy.

End point definition and clinical follow-up

Patients were followed up prospectively and major adverse cardiac events (MACEs) were evaluated. Major adverse cardiac event was defined as death, nonfatal myocardial infarction (MI), or target vessel revascularization (TVR). Myocardial infarction was defined as a creatine kinase–MB (CK-MB) level that was >3 times the upper limit of normal, based on the recommendations in the American College of Cardiology/American Heart Association guidelines.[9] For patients who presented with an acute coronary syndrome and elevated baseline enzyme, a diagnosis of periprocedural MI required a fall and rise of CK-MB of 50% above the previous level.[10] Target vessel revascularization was defined as a reintervention in the treated vessel. Stent thrombosis was angiographically documented as a complete occlusion or a flow-limiting thrombus of a successfully stented segment. Information regarding repeat interventions was prospectively collected by means of an electronic database. Survival status was assessed by written inquiries to the Civil Registry. Questionnaires to assess clinical status were sent to all living patients. The patient, referring physician, and peripheral hospitals were directly approached whenever necessary for additional information. Follow-up angiography was planned only in patients who were enrolled during the first 6 months (n = 38).

Statistical analysis

Continuous variables were expressed as mean ± SD. Discrete variables were presented as percentages. Continuous variables were compared with Student *t* test or Wilcoxon ranked scores when applicable. The Fisher exact test was used for categorical variables. The cumulative incidence of adverse events was calculated according to the Kaplan-Meier method and differences were assessed using the log-rank test. All statistical tests were 2-tailed, and $P < .05$ was considered statistically significant. Patient, lesion, and procedural characteristics associated with 1-year MACE on univariate analysis (P value for selection <.2) were tested for their multivariate predictive value (tested values were cardiogenic shock, female sex, multivessel disease, bifurcation stenting, and use of IIb/IIIa inhibitors). The final model was built by backward stepwise variable selection with entry and exit criteria set at the $P = .05$ and $P = .1$ levels, respectively.

Results

Patient characteristics

Of the 122 consecutive patients, 81 patients (82 lesions) were treated with SES (SES group) and 41 patients (42 lesions) were treated with PES (PES group). Patient characteristics are reported in Table I; 19% had diabetes and 39% underwent the index procedure for an acute coronary syndrome. There were no statistical differences between groups, apart from a higher proportion of men in the PES group. Figure 1 presents the distribution of stented length in this study.

Procedural characteristics

Lesion and procedural characteristics are presented in Table II. The mean number of stents implanted per lesion was 3.3 ± 1.1 (range 2-7 stents), and the median

Table II. Lesion and procedural characteristics

	All (n = 124)	SES (n = 82)	PES (n = 42)
Treated vessel			
LAD (%)	25	29	17
LCX (%)	12	16	5
RCA (%)	63	55	79*
Lesion type			
B1 (%)	1	1	0
B2 (%)	2	2	0
C (%)	98	96	100
CTO (%)	40	38	43
Total occluded length (mm ± SD)	23.2 ± 10.9	22.9 ± 11.2	23.7 ± 10.6
Stent number/vessel	3.3 ± 1.1	3.1 ± 1.0	3.7 ± 1.1*
Mean stent diameter (mm)	2.9 ± 0.3	2.7 ± 0.2	3.0 ± 0.3*
Median stent length/vessel (mm) (range)	79 (64-168)	77 (64-140)	84 (64-168)*
Bifurcation stenting (%)	13	15	10
Use of IIb/IIIa inhibitor (%)	37	38	36
Pre-RD (mm)	2.61 ± 0.55	2.55 ± 0.52	2.74 ± 0.60
MLD (mm)	0.44 ± 0.52	0.46 ± 0.52	0.40 ± 0.51
DS (%)	82.3 ± 20.6	80.8 ± 21.6	85.2 ± 18.4
Post-RD (mm)	2.73 ± 0.49	2.67 ± 0.47	2.86 ± 0.51*
MLD (mm)	2.26 ± 0.46	2.20 ± 0.42	2.37 ± 0.52*
DS (%)	17.4 ± 10.9	17.4 ± 10.8	17.2 ± 11.4

LAD, Left descending coronary artery; *LCX*, left circumflex coronary artery; *RCA*, right coronary artery; *CTO*, chronic total occlusion; *RD*, reference diameter; *MLD*, minimal lumen diameter; *DS*, diameter stenosis.
*$P < .05$ comparison between SES and PES groups.

Table III. Thirty days and 1 year clinical outcomes cumulative events rate estimated by Kaplan-Meier

	All (n = 122)	SES (n = 81)	PES (n = 41)	P*
30 d				
Death (%)	1.6	1.2	2.4	.63
MI (%)	5.8	6.2	4.9	.77
TVR (%)	1.7	2.5	0	–
Death, MI (%)	7.4	7.4	7.3	.97
MACE (%)	8.2	8.6	7.3	.79
1 year				
Death (%)	4.1	2.5	7.3	.20
MI (%)	10.0	11.2	7.4	.53
TVR (%)	7.5	7.5	7.6	.96
Death, MI (%)	12.3	12.3	12.2	.98
MACE (%)	18.0	18.5	17.1	.87

TVR, target vessel revascularization; *MACE*, major adverse cardiac events.
*Comparison between SES and PES groups (log rank).

Table IV. Paired quantitative angiographic analysis (mandatory angiographic follow-up group)

SES (n = 38)	Pre	Post	Follow-up
RD (mm)	2.56 ± 0.53	2.68 ± 0.44	2.76 ± 0.37
MLD (mm)	0.43 ± 0.58	2.24 ± 0.38	2.13 ± 0.58
DS (%)	81.9 ± 24.6	16.2 ± 9.4	23.4 ± 19.5
Late loss (mm)			0.12 ± 0.58
Binary restenosis rate (%)			5.3

RD, reference diameter; *MLD*, minimal lumen diameter; *DS*, diameter stenosis.

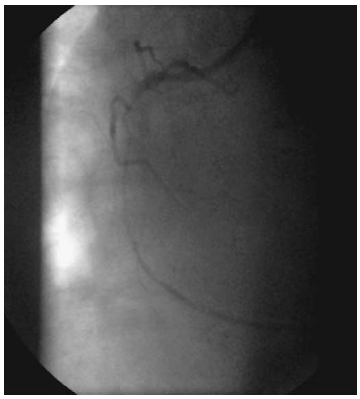
total stented length was 79 mm (range 64-168 mm). Glycoprotein IIb/IIIa inhibitors were used in 37% of patients. In the PES group, the mean stent diameter was larger (3.0 ± 0.3 vs 2.7 ± 0.2 mm, $P < .001$), with longer median stented length (77 vs 84 mm, $P = .03$), compared with the SES group.

Clinical outcome

Complete clinical follow-up information was available for all patients. Table III shows 30-day clinical outcomes as estimated by the Kaplan-Meier method. A periprocedural MI occurred in 5 patients (4.0%). Each CK-MB level was 191, 141, 82, 338, and 159 U/L (normal upper limit of CK-MB is 23 U/L in our institute). Among these patients, 2 patients (1.6%) had Q-wave MI. The causes of periprocedural MI were side-branch occlusion (1 patient), distal embolism (1 patient), distal dissection (1 patient), and dissection of other treated lesion (2 patients). Subacute stent thrombosis occurred in 1 patient (0.8%) in the SES group.

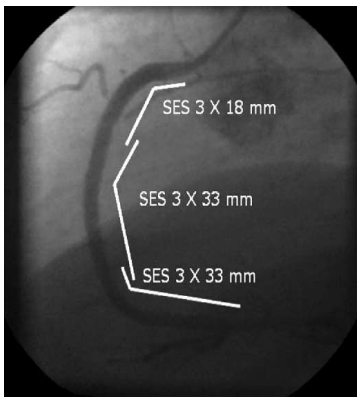
One-year clinical outcomes, estimated by the Kaplan-Meier method, are presented in Table III. Five patients (4.1%) died during the first year, 2 received SES, and 3 received PES. In the SES group, 1 patient who received SES for acute MI with cardiogenic shock died the next day from cardiogenic shock and the other died of a pulmonary embolism 275 days after the procedure. In the PES group, 1 patient who presented with acute MI

Figure 2



Baseline angiography showing diffuse right coronary artery disease.

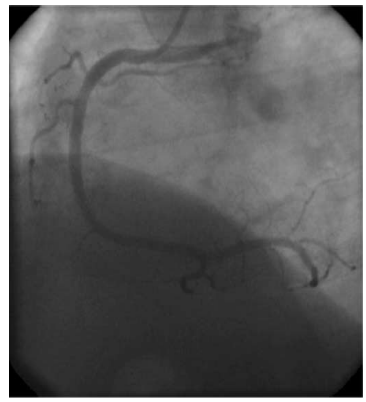
Figure 3



The patient was successfully treated with 3 Cypher stents (total length was 84 mm).

with cardiogenic shock died 6 days later from ongoing heart failure. The second patient underwent an unsuccessful percutaneous coronary intervention 55 days after the initial procedure to treat another lesion, requiring emergent coronary artery bypass surgery and died 1 day after surgery. The remaining patient died of congestive heart failure 244 days after the initial procedure. This patient had already suffered MIs twice before the index procedure and had severe left ventricular dysfunction.

Figure 4



Follow-up angiography (216 days after the index procedure) documenting the absence of in-stent restenosis.

The overall TVR rate was 7.5% and the incidence of MACE was 18.0% at 1 year. There were no statistically significant differences between the SES and the PES groups. Multivariate predictors of 1-year MACE were cardiogenic shock (hazard ratio 8.96, 95% CI 2.11-28.66, P = .0006) and female sex (hazard ratio 2.71, 95% CI 1.06-6.02, P = .02). Mean late loss was 0.12 $\pm$ 0.58 mm in 38 patients who were consecutively enrolled in the first 6 months of our experience and who, for this reason, underwent mandatory follow-up angiography (Table IV).

Figures 2-4 are a representative example of a patient successfully treated with 3 stents (SES) with a total stent length of 84 mm.

Discussion

In this study, median stented length was 79 mm (range 64-168 mm). The incidence of subacute stent thrombosis was 0.8% (1 patient) and the TVR rate was 7.5% at 1 year. Of the 6 patients who had in-stent restenosis within 1 year, 5 (83.3%) patients had focal restenosis easily treated with repeat coronary stenting (mean stent length 20.0 $\pm$ 8.9 mm).

In the bare metal stent era, the stented length is an important predictor of in-stent restenosis. However, there are no precious reports regarding full metal jacket. The results of this present study are promising when compared with published data on bare metal stents with long stented lengths or multiple stenting despite significantly longer lengths in this study (Table V).[11-14] A group of 21 consec-

Table V. One year TLR or TVR and MACE rate in this study, compared data from patients with long length or multiple bare metal stenting

Trial	n	Stented length (mm)	No. of stents/lesion	TLR/TVR (1 y) (%)	MACE (1 y) (%)
Kornowski et al[11]	117	28 ± 5	–	14.5/–	18.7
Kornowski et al[12]	117	–	3.3	13.3/–	24.5
ADVANCE trial stent group[13]	145	26.1 ± 7.7	1-3	–/17.9	23.4
TULIP trial angiographic-guided group[14]	71	35 ± 11	1.1 ± 0.4	23/–	27
TULIP trial IVUS-guided group[14]	73	42 ± 11	1.4 ± 0.6	10/–	12
Historical BMS (≥64 mm)	21	79 (64-115)*	3.5 ± 1.0	–/21.6	38.1
This study	122	79 (64-168)*	3.3 ± 1.1	–/7.5	18.0

TLR, target lesion revascularization; *TVR*, target vessel revascularization; *MACE*, major adverse cardiac events.
*Median (range).

utive patients from our institution, treated with at least 64 mm of continuous bare metal stents (BMS) in the same vessel from the immediate period preceding the introduction of DES, is included as a comparison (unpublished data). The 1-year TVR rate in the BMS group was approximately 3 times higher than the DES population from this study.

Concerns have been raised regarding the clinical impact of high local drug concentration in the tissue wall caused by long stented lengths and overlapped stents (eg, the development of coronary aneurysms).[15,16] We did not observe aneurysm formation in patients who underwent follow-up angiography beyond 6 months. Nor was there any evidence of systemic complications, related to the use of multiple DES, in our patient cohort up to 1 year.

A limitation of treating diffuse coronary disease with long stented lengths in the bare metal stent era was a high incidence of periprocedural MI; this was documented in several stent trials that enrolled patients with long lesions.[11,13,17] In the ADVANCE study, 21.4% had elevated CK-MB, with 7.1% >5 times elevated in the bail out stenting group.[13] The definition of MI after percutaneous coronary interventions differed among studies.[18-20] Even in case of not long length stenting, reports in the literatures indicated that 8.5% had elevated CK-MB (>5 times[17] or >3 times[21]) after stent implantation. If an MI is defined as a CK-MB of >5 times the upper limit of normal, the incidence of periprocedural MI was 3.3% in our study. Based on our results, DES use does not increase the incidence of periprocedural MI compared with published bare metal stent data.

SES and PES were used in this study in consecutive periods. This study is limited by its single-arm design and moderate sample size, and follow-up angiography was performed in one third of patients, precluding reporting of quantitative angiographic variables and our main purpose was not to compare the clinical effect of 2 different types of DES. Procedural characteristics were not similar between both groups (in the PES group, the mean stent diameter was larger and the median stented length was longer compared with the SES group). However, we found that despite extremely long stent lengths, the incidence of TVR was quite low for both SES and PES. Percutaneous coronary intervention using DES therefore seems to be a feasible, effective, and safe option for the treatment of patients with diffuse coronary disease.

Conclusion

Stented length of ≥64 mm with DES for de novo coronary artery lesions was safe. Drug-eluting stents had similar clinical results with low TVR rates. The use of DES for the treatment of diffuse coronary lesions is a feasible percutaneous alternative.

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Chapter 11

Immediate and One-Year Outcome of Percutaneous Intervention of Saphenous Vein Graft Disease With Paclitaxel-Eluting Stents.

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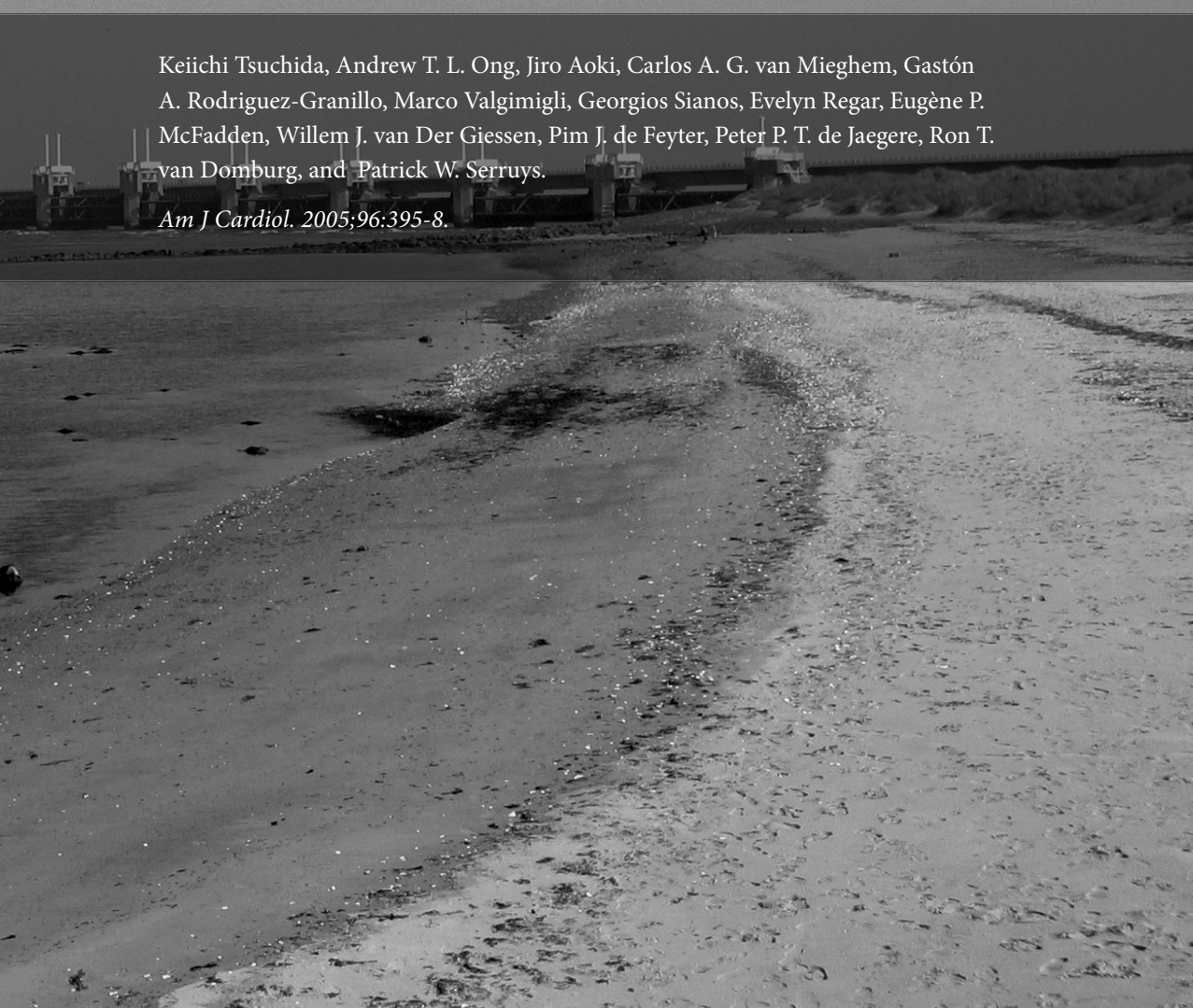

Immediate and One-Year Outcome of Percutaneous Intervention of Saphenous Vein Graft Disease With *Paclitaxel*-Eluting Stents

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The aim of this study was to evaluate the outcome after paclitaxel-eluting stent implantation in 40 patients with 52 saphenous vein graft lesions. By Kaplan-Meier estimates, the probability of major adverse cardiac event-free survival for 1 year was 92.5%. A paclitaxel-eluting stent for saphenous vein graft disease appears to be feasible and safe, with a low rate of reintervention at 1 year, but late follow-up is needed to confirm these observations. **(Am J Cardiol 2005;96:395–398)**

Trials in native coronary arteries have demonstrated that sirolimus-eluting stents dramatically reduce restenosis.[1,2] More recently, our group reported that sirolimus-eluting stents result in a low rate of target vessel revascularization in saphenous vein graft disease.[3] Paclitaxel-eluting stents (PESs), the second commercially available stent coated with an antiproliferative agent, have also shown excellent results in reducing restenosis in native vessels.[4,5] The aim of this study was to investigate the immediate and 1-year outcome of PES implantation in patients with saphenous vein graft disease.

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Since February 2003, PESs have been used as the device of choice for every patient treated with percutaneous coronary intervention at our institution. Between February and December 2003, coronary intervention was performed in 50 consecutive patients with 62 vein graft lesions. Eight patients received bare metal stents, because PESs were not available in diameters >3.5 mm. Two patients presented with cardiogenic shock subsequent to acute myocardial infarction, and, despite the successful deployment of a PES, they died of refractory left ventricular failure immediately after the procedure. Thus, a total of 40 consecutive patients with 52 vein graft lesions underwent elective coronary intervention using PESs, exclusively and constituted the study population. The stent used in this study was the TAXUS Express2 PES (Boston Scientific, Natick, Massachusetts), with paclitaxel incorporated in a slow-release co-polymer carrier system.

All of the present cohort were treated with life-long aspirin therapy and received a loading dose of 300 mg clopidogrel followed by 75 mg/day for 6 months. During the procedure, intravenous heparin was administered to maintain an activated clotting time of >250 seconds. The use of glycoprotein IIb/IIIa inhibitors, thrombectomy devices, or distal protection devices was at the discretion of the operator. The local ethics committee approved the study protocol, and all patients provided written informed consent.

Angiographic variables were assessed before and after each procedure. Degenerated grafts were defined as grafts with luminal irregularities or ectasia involving >50% of its total length.[6] A plaque was considered ulcerated if a small crater consisting of a discrete luminal widening in the area of the stenotic lesion, not extending beyond the normal vascular lumen, was seen on angiography.[6] A lesion was classified as containing thrombus if angiography demonstrated an intraluminal filling defect or an abrupt vessel cutoff.[7] Postprocedural remaining stenosis (41% to 50% diameter stenosis on quantitative coronary angiography) was also identified.[8] In this study, the term "de novo lesion" referred to a treatment site without previously implanted stents. The quantitative analysis was performed using the computer-based quantitative coronary angiography system CAAS II (Pie Medical, Maastricht, The Netherlands), as previously described.[9]

Patients were followed up prospectively and evaluated for survival free of major adverse cardiac events (MACEs), defined as (1) death, (2) myocardial infarction (MI), (3) target lesion revascularization (TLR), or (4) target vessel revascularization. MI was defined as the occurrence of an

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Table 1
Baseline patient characteristics (n = 40)

Variable	All Patients (n = 40)	De Novo* (n = 33)	Restenosis† (n = 7)
Age (yrs) (mean ± SD)	70 ± 8	70 ± 8	73 ± 6
Men	36 (90%)	30 (91%)	6 (86%)
Previous MI	24 (60%)	19 (58%)	5 (71%)
Diabetes	16 (40%)	15 (46%)	1 (14%)
Hypertension	17 (43%)	13 (39%)	4 (57%)
Hypercholesterolemia‡	36 (90%)	29 (88%)	7 (100%)
Current smoker	2 (5%)	2 (6%)	0 (0%)
Indication for revascularization			
Stable angina pectoris	16 (40%)	14 (42%)	2 (29%)
Unstable angina pectoris	24 (60%)	19 (58%)	5 (71%)
No. of coronary arteries narrowed ≥50%			
1	6 (15%)	3 (9%)	3 (43%)
3	34 (85%)	30 (91%)	4 (57%)
Left ventricular ejection fraction§			
Normal (≥0.55)	19 (48%)	15 (46%)	4 (57%)
Moderate dysfunction (0.31–0.54)	10 (25%)	9 (27%)	1 (14%)
Poor (≤0.30)	6 (15%)	5 (15%)	1 (14%)

* Patients with lesions without previous stents.
† Patients treated in previously stented lesions.
‡ Defined as total cholesterol ≥220 mg/dl or known statin therapy.
§ Left ventriculography was not performed in 5 patients.

elevated creatine kinase-MB fraction >3 times the upper limit of normal measured during the first 24 hours after the procedure. TLR was defined as surgical or percutaneous reintervention driven by significant (≥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. Target vessel revascularization was defined as reintervention in the treated vessel outside the target lesion.

The numeric data are expressed as the mean ± SD and the frequency as percentages for descriptive purposes. Kaplan-Meier event-free survival curves were constructed.

Table 1 describes the baseline patient demographics of the total study population and the 2 subgroups designated according to their previous history. The de novo group comprised patients without previous stents and the restenosis group comprised patients with previously stented lesions. The proportion of men and prevalence of hypercholesterolemia were great. More patients were treated for unstable angina. The demographics were similar between the 2 groups.

The procedural characteristics are reported in Table 2. The mean graft age was 13 ± 5 years. Sequential grafting, or construction of a venous conduit anastomosed at multiple vessel sites, was predominant in this population (62%). Either the PercuSurge GuardWire system (Medtronic, Minneapolis, Minnesota) or FilterWire EX (Embolic Protection, Boston Scientific) was used as distal protection device.

Lesions located in the body of the vein graft were the most common. Direct stenting was the strategy preferred (58%) over predilation followed by stenting. After the procedure, untreated remote sites with a diameter stenosis of 41% to 50% in the target vein graft were observed in 7 vessels (Table 2). The reference graft vessel diameter was

Table 2
Procedural characteristics

Baseline graft characteristics (n = 42 vessels)	
Graft age (yrs) (mean ± SD)	13 ± 5
Saphenous vein - coronary anastomosis	
LAD	2 (5%)
Left circumflex	8 (19%)
Right	6 (14%)
Jump graft (multiple distal anastomoses)	26 (62%)
Jump graft anastomosed at LAD	8/26 (31%)
Degenerated graft	12 (29%)
Multiple treatment site	12 (29%)
Initial TIMI flow 0 or 1	9 (21%)
Use of glycoprotein IIb/IIIa inhibitor	11 (26%)
Use of distal protection device	22 (52%)
Use of transluminal extraction catheter	3 (7%)
Postprocedural graft characteristics (n = 42 vessels)	
Postprocedural stenoses 41%–50% at unstented sites	7 (17%)
Final TIMI flow	
0	1 (2%)
1	0 (0%)
2	4 (10%)
3	37 (88%)
Baseline lesion characteristics (n = 52 lesions)	
Treatment site	
Ostial	7 (14%)
Body	35 (67%)
Distal	10 (19%)
Diffuse (lesion length ≥20 mm)	15 (29%)
De novo lesion	41 (79%)
Eccentricity	24 (46%)
Ulcer	11 (21%)
Thrombus containing lesion	12 (23%)
Target lesion angulation ≥45°	3 (6%)
No. of stents per lesion (mean ± SD)	1.6 ± 1.1
Total stent length per lesion (mm) (mean ± SD)	30 ± 29
Direct stenting	30 (58%)

LAD = left anterior descending; TIMI = Thrombolysis In Myocardial Infarction.

Table 3
Quantitative coronary angiography

Paclitaxel-eluting Stent (n = 52 lesions)	Value
Baseline	
Lesion length (mm)	19.1 ± 23.6
Reference diameter (mm)	2.9 ± 0.5
Minimum lumen diameter (mm)	0.8 ± 0.5
Diameter stenosis (%)	73 ± 16
Postprocedural (in-stent)	
Stented segment length (mm)	25.7 ± 22.7
Reference diameter (mm)	3.1 ± 0.6
Minimum lumen diameter (mm)	2.5 ± 0.4
Diameter stenosis (%)	18 ± 9

Data presented as mean ± SD.

Table 4
Results of saphenous vein graft stenting—published reports with mid-term follow-up (one year or less)

First Author/ Reference	Years of Enrollment	Follow-up	Patients (n)	Age (yrs)	Graft Age (yrs)	Reference Diameter (mm)	Lesion Length (mm)	MACE* Free (%)
Strumpf[15]	1990–1991	5 mo	26	68	8.8	3.6†	8.2	85
Fenton[16]	1990–1991	1 yr	198	66	8	3.4	8.6	70
Wong[17]	1990–1992	1 yr	582	66	9	3.0–5.0‡	<15‡	76.3
Brener[12]	1990–1992	1 yr	377	66	9	3.6	<15‡	77
Savage[11]	1993–1995	8 mo	108	66	10.1	3.18	9.6	73
Ahmed[18]	1994–1998	1 yr	951 (men)	67	9	3.5	10.1	70–80§
Hanekamp[13]	1996–1998	1 yr	77	66.9	11.8	3.33	10.6	76.3
Hoye[3]	2002	1 yr	19	67	NA	2.8	15.6	84
Present study	2003	1 yr	40	70.6	12.7	2.9	19.1	92.5

* MACE included death, myocardial infarction, TLR, or target vessel revascularization.
† Only mean minimum luminal diameter after stenting is available.
‡ Only inclusion criteria available.
§ Estimated from event-free survival curve.

<3 mm, and the mean lesion length at baseline was 19.1 ± 23.6 mm (Table 3).

One patient (2.5%) developed a non–Q-wave MI related to the procedure as an in-hospital MACE. During the 1-year follow-up (average 472 ± 150 days), no patient died. One patient (2.5%) underwent TLR, and a second (2.5%) underwent treatment of a new lesion within the same vessel (repeat PCI in these 2 cases). The cumulative MACE rate was 7.5%. The Kaplan-Meier estimate of the 1-year event-free survival among patients without MACEs was 92.5%. No MACEs occurred in patients treated for in-stent restenosis (restenosis group).

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The results of this study indicate that the use of PESs for the treatment of saphenous vein graft narrowing is associated with low clinical event rates, including death, MI, and the need for repeat revascularization. This is the first study to evaluate the performance of PESs in vein graft disease.

Coronary intervention in patients with vein graft disease is still challenging because of the high risk of restenosis.[10] Stent implantation has been associated with more favorable outcomes than balloon angioplasty.[11–13] However, the use of bare metal stents in vein graft disease has not been proved to decrease morbidity and mortality and is associated with a high 6-month restenosis rate.[11] Pathologic findings have identified a constant inflammatory reaction over the years around bare metal stents implanted in vein grafts.[14] Consequently, stents coated with anti-inflammatory agents such as sirolimus and paclitaxel may exert a preventive effect on persistent inflammation.

Our study population had the following characteristics compared with other studies of bare metal stents[11–13,15–18]: (1) complex saphenous vein graft lesions, including acute coronary syndrome, long lesions, and multiple stenting; (2) an older graft age; and (3) a smaller reference vessel size.

In the present study, we evaluated consecutive patients without acute MI, who had more severe complex lesions in contrast to other studies that had excluded patients with long lesions, thrombotic lesions, or stenoses at the ostial or anastomotic site[11–13,15–18] (Table 4). In addition, nonstaged stenting in multiple lesions was performed in 29% of our population. This population also included 7 patients treated for in-stent restenosis. The treatment result of the subgroup was excellent. As is true in native coronary arteries, treatment of in-stent restenosis lesions in vein grafts is safer than treatment of de novo vein graft lesions.[6,19] This subgroup may have favorably influenced the global results.

Our patients had older vein grafts (13 years) than those in other studies[11–13,15–18]. Plaques in older vein grafts may be softer and more friable, as well as being larger and more frequently associated with thrombus formation.[20]

With regard to the impact of the smaller reference size in these patients, the larger diseased graft would generally contain more bulky lesions, which may distally embolize, with subsequent myocardial damage. In that respect, the present study population might be somewhat more favorable. However, smaller graft vessels have also been reported to be 1 of the independent predictors for restenosis.[17] Despite a mean vessel size of <3.0 mm, only 1 patient underwent TLR.

Our findings strongly suggest that PESs exert a preventive effect against restenosis, not only in native coronary artery disease, but also in vein graft lesions.

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Chapter 12

Drug-Eluting Stent Implantation for Chronic Total Occlusions: Comparison Between the Sirolimus- and Paclitaxel-Eluting Stent.

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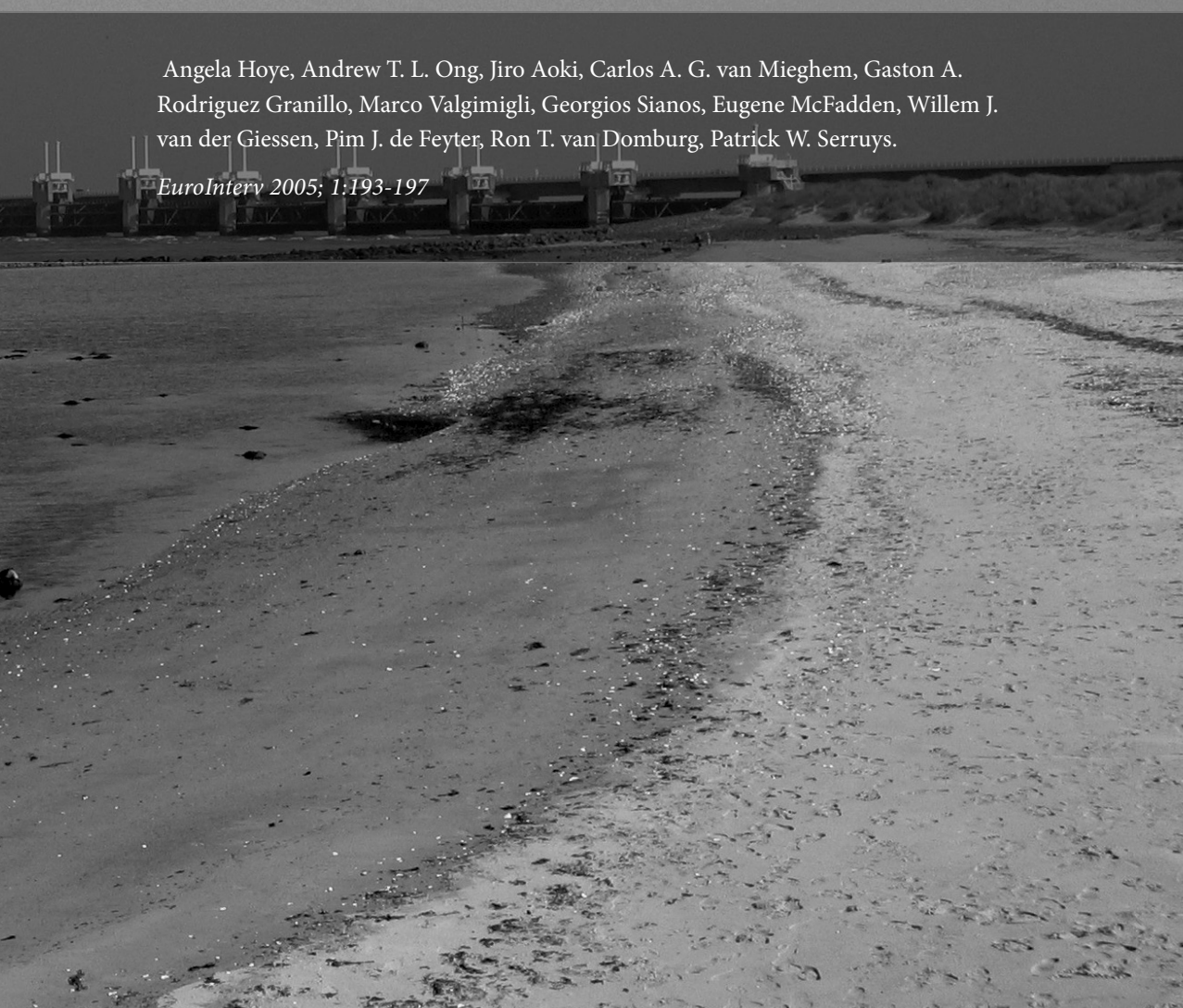

Drug-eluting stent implantation for chronic total occlusions: comparison between the Sirolimus- and Paclitaxel-eluting stent

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KEYWORDS
Occlusion, stents, restenosis

Abstract

Aims: Long-term results following percutaneous coronary intervention (PCI) with bare metal stents in the treatment of chronic total occlusions (CTOs) is hindered by a significant rate of restenosis and re-occlusion. Drug-eluting stents have shown dramatically reduced restenosis rates for the treatment of relatively simple non-occlusive lesions, though there is only limited data as to the efficacy in CTO's. We evaluated the long-term results of the sirolimus-eluting stent (SES) and paclitaxel-eluting stent (PES) for the treatment of CTOs.

Methods and results: From April 2002, all patients at our institution were treated with SES as the device of choice during PCI. During the first quarter of 2003 the default strategy changed to the use of PES. Drug-eluting stent implantation was carried out in CTOs (defined as >3 months' duration) in 9% of *de novo* PCI procedures. A total of 76 consecutive patients were treated with SES implantation, followed by a consecutive series of 57 patients treated with PES implantation. These patients were compared with a similar group of patients (n=26) treated with BMS in the 6-month period preceding April 2002.

At 400 days, the cumulative survival-free of target vessel revascularization was 80.8% in the BMS group versus 97.4% and 96.4% in the SES and PES groups respectively (p=0.01).

Conclusions: The use of both the SES and PES in the treatment of chronic total coronary occlusions reduces the need for target vessel revascularization compared to bare metal stents.

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Introduction

Successful percutaneous therapy of chronic total occlusions (CTOs) has been shown to improve symptoms of angina and left ventricular function, and reduce the subsequent need for coronary artery bypass surgery[1-5]. In addition, in the long-term, recanalization of a CTO can reduce mortality compared with those with an unsuccessful attempt at recanalization[6]. However, the long-term outcome of percutaneous coronary intervention (PCI) for chronic total coronary occlusions is subject to an increased risk of restenosis and re-occlusion compared with non-occlusive lesions[1,7]. The advent of drug-eluting stents is revolutionising the practice of interventional cardiology. Several randomized trials have demonstrated a dramatic reduction in restenosis rates compared with bare metal stents when used for the treatment of relatively simple lesions[8-11]. In addition, preliminary data has confirmed the efficacy utilizing the sirolimus-eluting stent (SES) for the treatment of chronic total occlusions[12]. In the present report, we evaluate the use of drug-eluting stent implantation for chronic total occlusions in a consecutive series of patients, with comparison between the sirolimus- and paclitaxel-eluting stents.

Methods

The sirolimus-eluting stent (Cypher™, Johnson & Johnson - Cordis unit) received CE mark approval in April 2002. Since that time, all patients undergoing percutaneous therapy in our institution have been treated with drug-eluting stent implantation as the default strategy. During the first quarter of 2003, our strategy switched from the sirolimus- to the paclitaxel-eluting stent (Boston Scientific) enabling a comparison of the two stent types. All consecutive patients with successful chronic occlusion recanalization were enrolled. Those patients treated with drug-eluting stent implantation were compared to all those treated for a CTO in the preceding 6-months with bare metal stents (BMS), identified from the departments' dedicated database. All groups were treated by the same operators utilizing standard techniques; the only difference being the type of stent.

During the procedure, heparin was given to maintain an activated clotting time ≥ 250 seconds. All patients received lifelong aspirin, and before the procedure were pre-treated with a loading dose of 300mg clopidogrel, additional anti-platelet therapy was given with clopidogrel for 1 month in the BMS group, and for 6-months in the drug-eluting stent groups. The use of Glycoprotein IIb/IIIa inhibitor therapy was at the discretion of the operator and was only given once wire passage was confirmed as successful. The protocol was approved by the local 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. All patients signed a written informed consent

Chronic total occlusion definition

Complete occlusion of a coronary artery on angiography, with no antegrade filling of the distal vessel other than via collaterals. All patients included had a native vessel occlusion estimated to be of at least 3-months' duration, based on either a history of sudden chest pain, a previous acute myocardial infarction in the same target vessel territory, or the time between the diagnosis made on coronary angiography and PCI.

Length of occlusion

This was measured by quantitative coronary angiography (CAAS II; Pie Medical Imaging, The Netherlands) either utilizing antegrade filling via collaterals, or assessment of the retrograde collateral filling achieved through making a simultaneous injection into both the left and right coronary arteries to delineate the distance between the site of occlusion and the most proximal part of the vessel filled retrogradely. This length evaluated only the occluded vessel, and did not therefore include stenosis of the vessel pre- and post- the occlusion.

Follow-up

Patients were prospectively followed-up for clinical events, and evaluated for survival-free of major adverse cardiac events (MACE) using questionnaires and telephone enquiries. MACE was predefined as: 1) death, 2) non-fatal myocardial infarction (AMI), or 3) repeat target vessel revascularization (TVR). The diagnosis of AMI required an elevation of creatine kinase to twice the upper limit of normal, together with a rise in creatine kinase-MB fraction. TVR was defined as either surgical or percutaneous reintervention driven by significant (>50%) luminal narrowing within the treated vessel, and was undertaken in the presence of either anginal symptoms or objective evidence of ischemia. Follow-up angiography was undertaken in all patients in the presence of anginal symptoms at clinical evaluation; in addition those patients treated during the first 6-months of DES implantation were invited.

Statistical analysis

Discrete variables are presented as percentages and compared with Pearson's chi-square test. Continuous variables are expressed as mean ± standard deviation and compared with one-way ANOVA. Cumulative survival and MACE-free survival were calculated according to the Kaplan-Meier method. The log-rank test was used to compare MACE-free survival between the groups. A p value of <0.05 was considered as significant.

Results

There were no significant differences between the groups with respect to baseline patient characteristics (table 1). Procedural characteristics are presented in table 2. One patient in both the BMS and PES groups had stent implantation in 2 chronic occlusions. Occlusion length was able to be measured in 74.1%, 84.2%, and 72.4%of the BMS, SES, and PES groups respectively (p=0.3). Both drug-eluting stent cohorts were treated with a higher number of stents resulting in a longer length of stented segment.

At one year, there was a single death occurring in hospital, 22 days after successful RCA recanalization and PES implantation. The patient had been admitted 1 week previously, with no evidence of a cardiac problem, and the cause of death was related to an inoperable glioblastoma. There were 4 patients who had an acute myocardial infarction, all having been treated with drug-eluting

Table 1. Baseline patient demographics

	BMS n=26	SES n=76	PES n=57	p value
Mean age (years)	60.3±11.0	61.1±10.6	58.4±10.4	0.3
Male sex (%)	92.3	65.8	80.7	0.3
Current smoker (%)	30.8	18.4	22.8	0.5
Diabetes mellitus (%)	7.7	14.5	19.3	0.4
Hypertension (%)	42.3	42.1	50.9	0.7
Hypercholesterolemia (%)	57.7	67.1	75.4	0.6
Previous myocardial infarction (%)	46.2	51.3	43.9	0.8
Previous CABG (%)	0	3.9	5.3	0.5
Glycoprotein IIb/IIIa inhibitor usage (%)	23.1	18.4	19.3	0.9
PCI in at least one additional (non-occluded) major epicardial vessel during the index procedure (%)	26.9	38.2	47.4	0.4

SES: sirolimus-eluting stents, PES: paclitaxel-eluting stents, CABG: coronary artery bypass grafting, PCI: percutaneous coronary intervention

Table 2. Baseline procedural characteristics

Number of CTO lesions treated	BMS n=27	SES n=76	PES n=58	p value
Target vessel				0.5
LAD (%)	29.6	46.1	22.4	
LCX (%)	25.9	19.7	27.6	
RCA (%)	44.4	34.2	50.0	
Bifurcation stenting (%)	7.4	13.2	13.8	0.7
Mean length of occlusion (mm)	13.0±7.2	10.3±5.9	11.2±6.6	0.2
Mean number of stents in the target vessel	1.8±0.8	2.2±1.2	2.6±1.3	0.03
Mean nominal diameter of stent in the main vessel (mm)	3.0±0.6	2.8±0.3	2.8±0.4	< 0.001
Mean total lengths of stent in the main vessel (mm)	41.5±23.3	48.8±27.4	58.0±32.8	0.04
Post-procedure QCA data				
Reference vessel diameter (mm)	2.34±0.43	2.35±0.51	2.60±0.49	0.008
Minimal lumen diameter (mm)	2.12±0.51	2.04±0.43	2.26±0.42	0.02
Diameter stenosis (%)	11.6	12.9	14.1	0.6

SES: sirolimus-eluting stents, PES: paclitaxel-eluting stents, LAD: left anterior descending artery, LCX: circumflex artery, RCA: right coronary artery

stent implantation. The first had SES implantation for a RCA CTO together with PCI of the LAD. There was a peri-procedural elevation of creatine kinase (maximum elevation of 854 IU/l) related to loss of a sizeable septal branch related to the LAD stent (non-occluded vessel). The second related to subacute thrombosis occurring 11 days after SES implantation (a 2.5x33mm and a 3.0x33mm) in a LAD occlusion. IVUS suggested that 2.5mm stent was under-expanded and the patient was treated with a glycoprotein IIb/IIIa inhibitor and balloon dilatation. The third had PES implantation for a RCA CTO together with treatment of the left main stem. On day 14, he complained of chest pains and had a maximum CK elevation of 819. Angiography demonstrated an excellent result in the RCA, but haziness of the ostium of the left circumflex artery which was subsequently treated with further PCI (culprit lesion in other vessel). The fourth patient had SES implantation (a 2.5x33mm and a 3.0x33mm) for a LAD CTO. At 6-months, control angiography demonstrated no evidence of restenosis, but he was admitted 4 months later to another hospital with a myocardial infarction that was managed medically.

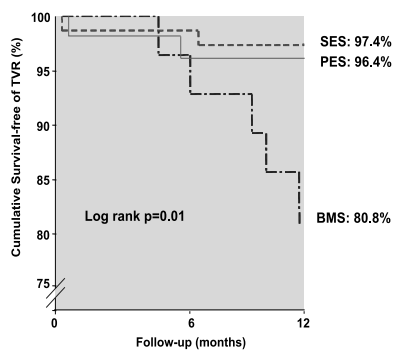

Figure 1. Kaplan-Meier estimates of the cumulative survival-free of target vessel revascularization following stent implantation in a chronic total occlusion for patients treated with sirolimus-eluting (SES), paclitaxel-eluting (PES), or bare metal stent (BMS) implantation.

All events in the bare stent group related to the need for target vessel revascularization. At one year, the survival-free of target vessel revascularization was significantly higher in the SES and PES groups compared with the BMS group (97.4% and 96.4% versus 80.8% respectively, p=0.01) Figure 1.

Discussion

In the present report we have demonstrated the efficacy of drug-eluting stent implantation for the percutaneous treatment of chronic total occlusions when compared to bare metal stents. In addition, we have shown that both the sirolimus- and paclitaxel-eluting stent are associated with a low rate of target vessel revascularization at 6 months.

There have been several randomized trials that have demonstrated the efficacy of stent implantation over balloon-only angioplasty for the percutaneous treatment of CTOs, reducing the 6-month restenosis rate from 68-74% to 32-55%[13-17]. Initial randomized studies of drug-eluting stent implantation, demonstrated efficacy in reducing restenosis compared to conventional stent implantation, but excluded patients with CTOs[8-11]. However, recent preliminary data from our own group have shown that the efficacy of the SES is applicable in the treatment of CTOs (defined as >1 months' duration), with a one year cumulative survival-free of major adverse cardiac events of 96.4%[12]. In the present study, we evaluate a larger series of consecutive patients treated for a truly chronic total occlusion (>3 months in duration) with drug-eluting stent implantation. We have shown that both the SES and PES significantly reduce the need for TVR, with a cumulative survival-free of TVR of 80.8% in the BMS group versus 97.4% and 96.4% in the SES and PES groups respectively (p=0.01) Figure 1.

Importantly, there were no significant differences in baseline demographics between the groups, and all procedures were carried out in the same centre by the same operators. Restenosis following BMS implantation is known to be inversely related to the post-procedural MLD and the number of stents utilized[18]. In the current study, the mean nominal diameter of stent used was significantly greater in the BMS cohort, related to a maximum available SES and PES diameter of 3.0mm and 3.5mm respectively. In addition, despite utilizing a greater number of stents, both the SES and PES demonstrated efficacy over the BMS. Furthermore, the beneficial effect of the SES occurred despite a smaller post-procedural MLD.

All major adverse cardiac events in the BMS group related to the need for TVR, including 1 patient who required coronary artery bypass surgery. Within the drug-eluting stent groups there were 5 additional non-TVR events. One patient had a subacute thrombosis, but this might have been avoidable with evidence from IVUS demonstrating a possible underlying mechanism of inadequate stent expansion. In addition, there is good evidence in a further 3 of these cases that the event was unrelated to treatment of the occluded vessel. One patient died of non-cardiac causes, and 2 of the myocardial infarctions were thought to be related to intervention carried out in another (non-occluded) vessel. The fifth patient presented with an AMI in the territory of the target vessel, 4 months after control angiography demonstrated patent stents. Clopidogrel medication had been stopped at the time of the follow-up angiogram, such that the patient was on aspirin therapy alone. The duration of dual anti-platelet therapy needed to reduce / abolish the risk of late stent thrombosis in patients treated with DES, particularly for complex disease, is still unclear. Recently, Ong *et al.* reported on late (>30 days) stent thrombosis following DES implantation in a consecutive cohort of >2000 patients, they found a low incidence of 0.35% (95% confidence limits 0.17% to 0.72%)[19]. Importantly, there were no episodes in patients continuing on dual anti-platelet therapy. However, whether there is a true benefit in continuing clopidogrel in addition to aspirin, over and above the possible disadvantages, requires further large scale evaluation.

In patients with significant coronary artery disease, although a CTO is found in at least one third, the majority are treated with either medical therapy or are referred for coronary artery bypass surgery, with percutaneous treatment of CTOs accounting for only 10-15% PCI procedures[20]. The major limitation of PCI for CTOs is the inability to cross the lesion with a wire, however great advancements have been made in the manufacture of specialized wires, and there are additionally, promising novel technologies such as the Intraluminal™ wire and Frontrunner catheter[21-23]. The current report has demonstrated the efficacy of drug-eluting stent implantation in CTOs and, together with improvements in recanalization rates, a strategy of percutaneous therapy of CTOs will become more widely applicable.

Study limitations

The study was not randomized, and angiographic follow-up data was not routinely obtained in all patients, so additional events such as silent re-occlusion cannot be excluded. However, clinical follow-up was obtained in >99% patients (all but one patient), and assessment of symptomatic status in those that did not require re-intervention, showed that all were symptomatically well at follow-up. The study was not randomized, and used a retrospective comparative population; however the same operators and interventional techniques were utilised.

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Chapter 13

Short- and Long-term Clinical Outcome after Drug-Eluting Stent Implantation for the Percutaneous Treatment of Left Main Coronary Artery Disease. Insights from the Rapamycin Eluting- and Taxus-Stent Evaluated At Rotterdam Cardiology Hospital Registries (RESEARCH and T-SEARCH).

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Short- and Long-Term Clinical Outcome After Drug-Eluting Stent Implantation for the Percutaneous Treatment of Left Main Coronary Artery Disease

Insights From the Rapamycin-Eluting and Taxus Stent Evaluated At Rotterdam Cardiology Hospital Registries (RESEARCH and T-SEARCH)

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Background—The impact of drug-eluting stent (DES) implantation on the incidence of major adverse cardiovascular events in patients undergoing percutaneous intervention for left main (LM) coronary disease is largely unknown.

Methods and Results—From April 2001 to December 2003, 181 patients underwent percutaneous coronary intervention for LM stenosis at our institution. The first cohort consisted of 86 patients (19 protected LM) treated with bare metal stents (pre-DES group); the second cohort comprised 95 patients (15 protected LM) treated exclusively with DES. The 2 cohorts were well balanced for all baseline characteristics. At a median follow-up of 503 days (range, 331 to 873 days), the cumulative incidence of major adverse cardiovascular events was lower in the DES cohort than in patients in the pre-DES group (24% versus 45%, respectively; hazard ratio [HR], 0.52 [95% CI, 0.31 to 0.88]; $P=0.01$). Total mortality did not differ between cohorts; however, there were significantly lower rates of both myocardial infarction (4% versus 12%, respectively; HR, 0.22 [95% CI, 0.07 to 0.65]; $P=0.006$) and target vessel revascularization (6% versus 23%, respectively; HR, 0.26 [95% CI, 0.10 to 0.65]; $P=0.004$) in the DES group. On multivariate analysis, use of DES, Parsonnet classification, troponin elevation at entry, distal LM location, and reference vessel diameter were independent predictors of major adverse cardiovascular events.

Conclusions—When percutaneous coronary intervention is undertaken at LM lesions, routine DES implantation, which reduces the cumulative incidence of myocardial infarction and the need for target vessel revascularization compared with bare metal stents, should currently be the preferred strategy. **(*Circulation*. 2005;111:1383-1389.)**

Key Words: stents ■ angioplasty ■ arteries

Despite the recognition that coronary revascularization, in selected patients with multivessel disease, can presently be accomplished by either a surgical or a percutaneous approach with no significant difference in long-term mortality,[1,2] coronary artery bypass grafting (CABG) is still considered the treatment of choice in patients with left main (LM) disease.[3] Several trials have reported on the safety and feasibility of stent implantation to treat LM stenosis.[4,5] However, particularly in this subset of patients, restenosis remains a major, and potentially fatal, complication, precluding more widespread use of percutaneous coronary intervention (PCI).[4,6] In the first observational report of patients treated with a sirolimus-eluting stent (SES) for LM disease, a low rate of binary restenosis and a favorable clinical outcome were reported.[7] However, the benefit of drug-eluting stents (DES) on the short- and long-term incidence of major adverse cardiovascular events in this setting, compared with bare metal stents (BMS), remains largely unknown.

The purpose of the present study was to investigate, in this subset of patients undergoing revascularization in a tertiary referral center, the differential impact of DES as opposed to conventional BMS on the occurrence of short- and long-term major cardiovascular events.

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Methods

Study Design and Patient Population

Since April 16, 2002, SES (Cypher, Johnson & Johnson, Cordis unit) have been used as a default strategy for every PCI at our institution as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. From the first quarter of 2003, paclitaxel-eluting stents (PES) (Taxus, Boston Scientific Corporation) became commercially available, replacing SES as the strategy of choice in every PCI because of cost-effectiveness considerations, as part of the Taxus Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registry. As a policy, all elective patients presenting with significant (>50% by visual estimation) LM disease, referred to our institution for coronary revascularization, are evaluated by both interventional cardiologists and cardiac surgeons, and the decision to opt for PCI or surgery is reached by consensus on the basis of a comprehensive evaluation of the following items: suitable anatomy and lesion characteristics for stenting and size and quality of vessels distal to the disease and of arterial and/or venous conduits for grafting. Finally, patient and/or referring physician preferences for a percutaneous approach, with both aware of the procedural risks and contraindications to surgery on the basis of the presence of comorbidity as evaluated by a cardiac surgeon, are also considered.

From April 16, 2002, to December 31, 2003, a total of 95 consecutive patients were treated exclusively with ≥1 DES in the LM as part of an elective or nonelective revascularization procedure and constitute the DES group of the present report. Fifty-two patients in the first cohort (of whom procedural details and medium-term follow-up were previously reported for 31[7]), received SES exclusively (available, at that time, in diameters from 2.25 to 3.00 mm), whereas in the following group of 43 patients, PES (available in diameters from 2.25 to 3.5 mm) were implanted. A control group for comparison was composed of 86 consecutive patients who received conventional BMS (available in diameters from 2.5 to 5.00 mm) for LM treatment in the period immediately before the introduction of SES. The following BMS were used: BX Sonic or BX Velocity in 35% (Cordis, Johnson & Johnson Company), R-Stent in 29% (Orbus Medical Technologies), Multi-Link Penta in 28% (Guidant Corp), Multi-Link Tetra in 8% (Guidant Corp), and other stents in 4%. Therefore, the total study population comprised all 181 consecutive patients who underwent percutaneous LM treatment from April 2001 to December 2003 with either BMS or DES in the 2 study phases, respectively. To stratify the study population into high– and low–surgical risk groups, the Parsonnet surgical risk score was calculated for each patient.[8] A score >15 was used to identify patients at high risk, as previously suggested.[6,9] Protected LM segment was defined as the presence of at least 1 patent arterial or venous conduit to at least 1 left coronary segment. Nonelective treatment was defined as a procedure performed on referral before the beginning of the next working day.[10]

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.

Procedures and Postintervention Medications

All interventions were performed according to current standard 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 the stent utilization. Angiographic success was defined as residual stenosis <30% by visual analysis in the presence of Thrombolysis in Myocardial Infarction (TIMI) 3 flow grade. All patients were advised to maintain the use of aspirin lifelong. One-month clopidogrel treatment (75 mg/d) was recommended for patients treated in the pre-DES phase. For patients treated with either SES or PES, clopidogrel was prescribed for 6 months.

End Point Definitions and Clinical Follow-Up

The primary outcome was the occurrence of major adverse cardiac events, defined as (1) death, (2) nonfatal myocardial infarction (MI), or (3) target vessel revascularization. Patients with >1 event have been assigned the highest ranked event, according to the previous list. All deaths were considered to be of cardiac origin unless a noncardiac origin was established clinically or at autopsy. MI was diagnosed by a rise in the creatine kinase level to more than twice the upper normal limit with an increased creatine kinase-MB fraction. Target vessel revascularization was defined as a repeated 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, including the ostium of the left anterior descending artery (LAD) and/or circumflex artery. Information about in-hospital outcomes was obtained from an electronic clinical database for patients maintained at our institution and by review of hospital records for those discharged to referring hospitals (patients were referred from a total of 14 local hospitals). Postdischarge survival status was obtained from the Municipal Civil Registries. Information on occurrence of MI or repeated interventions at follow-up was collected by consulting our institutional electronic database and by contacting referring physicians and institutions and all living patients.

Statistical Analysis

Continuous variables are shown as mean±SD and were compared by Student unpaired *t* test. Categorical variables are presented as counts and percentages and were compared with the Fisher exact test. Survival curves were generated by the Kaplan-Meier method, and survival among groups was compared with the log-rank test. Cox proportional hazards models were used to assess risk reduction of adverse events. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. Univariate analysis was performed with the consideration of all variables reported in Tables 1 and 2. Multivariate analyses, with consideration of all variables with a value of $P<0.10$, were performed to identify independent predictors of adverse events. Probability was significant at a level of <0.05. All statistical tests were 2-tailed. Statistical analysis was performed with the use of Statistica 6.1 (Statsoft Inc).

Results

Baseline and Procedural Characteristics

Baseline and procedural characteristics are shown in Table 1 and Table 2. The 2 groups were well matched for all baseline characteristics, including comorbidities. Overall, the average left ventricular ejection fraction was slightly >40%, and approximately half of the patients in both groups were admitted with acute coronary syndromes. Acute MI was the indication to the procedure in 19%; 10% of the patients presented with severe hemodynamic compromise at entry. The distal LM was involved in two thirds of cases in both groups, whereas patients treated with DES had significantly more 3-vessel disease, more bifurcation stenting, a higher number of stents, and greater total stent length per patients. The nominal stent diameter, as a result of limited size availability, was on average smaller in the DES group, which explains the more common practice of postdilatation in this group of patients. Procedural success was 99% in patients receiving DES: in 1 patient who presented with acute MI and shock, a final TIMI 1 flow grade was obtained, and the patient died 3 hours after the procedure. The procedural success was 98% in patients treated in the pre-DES phase: in 2 patients with acute MI and TIMI 0 flow grade in the left coronary artery, the LM and proximal LAD were stented, and subsequently CABG was performed because of residual critical stenosis in the left circumflex artery.

TABLE 1. Baseline Characteristics of the Study Population

Variables	Pre-DES Group (n=86)	DES Group (n=95)	*P*
Age, y *	66±10	64±12	0.18
Men, %*	62	66	0.53
Body mass index, kg/m^2*	26±4	27±4	0.31
Diabetes, %*	22	30	0.23
Non–insulin-dependent, %	17	20	0.71
Insulin-dependent, %	5	10	0.17
Hypertension, %*	57	53	0.65
Hypercholesterolemia, %	55	56	0.88
Current smoking, %	19	18	0.8
Creatinine, μmol/L*	102±80	95±31	0.36
LVEF, %*	42±13	41±14	0.85
Medical history, %			
Protected LM	22	16	0.17
PCI	35	28	0.42
MI	41	38	0.58
Transient ischemic attack/stroke	8	11	0.81
Heart failure*	16	20	0.36
Severe COPD*†	5	8	0.38
Peripheral arterial disease*	24	22	0.86
Carotid artery disease*	6	6	0.98
Clinical presentation, %			
Stable angina	50	48	0.8
Unstable angina	33	33	1
Acute MI*	17	20	0.70
Cardiogenic shock at entry*	9	12	0.66
Parsonnet score	16±11	19±12	0.17

LVEF indicates left ventricular ejection fraction; COPD, chronic obstructive pulmonary disease.

*Parameters included in the Parsonnet classification.

†Resulting in functional disability or hospitalization, requiring chronic bronchodilator therapy, or forced expiratory volume in 1 second <75% of predicted.[8]

Thirty-Day Outcomes

There were no significant differences between the DES and the pre-DES groups in the incidence of major adverse cardiovascular events during the first 30 days (Table 3). In the DES group, all deaths except 3 occurred in patients presenting with ST-segment elevation acute MI and cardiogenic shock at entry. In all these patients except 4 with severe peripheral artery disease, an intra-aortic balloon was placed during PCI. In the elective population, a total of 2 deaths occurred; both patients presented with unstable angina with mild troponin elevation and were refused by surgeons because of old age (84 years), low left ventricular ejection fraction (≤30%), and diabetic chronic renal insufficiency in 1 patient and diffuse 3-vessel disease associated with small-caliber vessels in the second. In this second patient the right coronary artery was occluded. The reason for death was pulmonary infection, which developed 19 days after the procedure in the first patient, and cardiogenic shock, which developed during the intervention, resistant to hemodynamic support (left ventricular assist device) in the other patient. In the pre-DES group, all 6 deaths occurred in patients with ST-segment elevation acute MI, of whom 4 were in cardiogenic shock at entry. No documented thrombotic stent occlusion occurred in the first 30 days or thereafter.

TABLE 2. Angiographic and Procedural Characteristics of the Study Population

Variables	Pre-DES Group (n=86)	DES Group (n=95)	*P*
Lesion location, %			
Ostium	18	27	0.20
Body	40	37	0.31
Distal	66	65	0.9
Pure LM disease, %	2	3	1
LM plus 1-vessel disease, %	29	17	0.4
LM plus 2-vessel disease, %	42	21	<0.001
LM plus 3-vessel disease, %	27	59	0.003
Right coronary artery >70% stenosis, %	27	53	0.02
Right coronary artery occlusion, %	13	19	0.43
No. of implanted stents	1.2±0.5	1.4±0.6	0.01
Nominal stent diameter, mm	3.6±0.5	3.1±0.32	<0.001
Total stent length per patient, mm	20±9	24±13	0.02
Predilatation, %	67	71	0.62
Cutting balloon, %	5	6	0.94
Rotational atherectomy, %	1	3	0.8
Directional atherectomy, %	6	0	0.007
Postdilatation, %	58	80	0.01
Larger balloon inflated, mm	4±0.6	3.9±0.4	0.07
Maximal pressure, atm	17±2	17±3	0.85
Bifurcation stenting, %	10	26	0.02
Culotte*	11	36	0.4
T technique*	88	44	0.35
Crush*	0	12	0.56
Kissing technique*	0	8	0.91
Intravascular ultrasonography, %	23	27	0.36
Glycoprotein IIb/IIIa inhibitors, %	26	28	0.83
Intra-aortic balloon pump, %	16	15	0.88
Left ventricular assist device, %	0	2	0.52
Minimal lumen diameter, mm, preintervention	1.05±0.59	1.09±0.44	0.58
Minimal lumen diameter, mm, postintervention	2.97±0.6	2.83±0.49	0.09
Reference vessel diameter, mm, postintervention	3.37±0.6	3.25±0.5	0.2

*Relative to patients with bifurcation stenting.

Long-Term Outcome

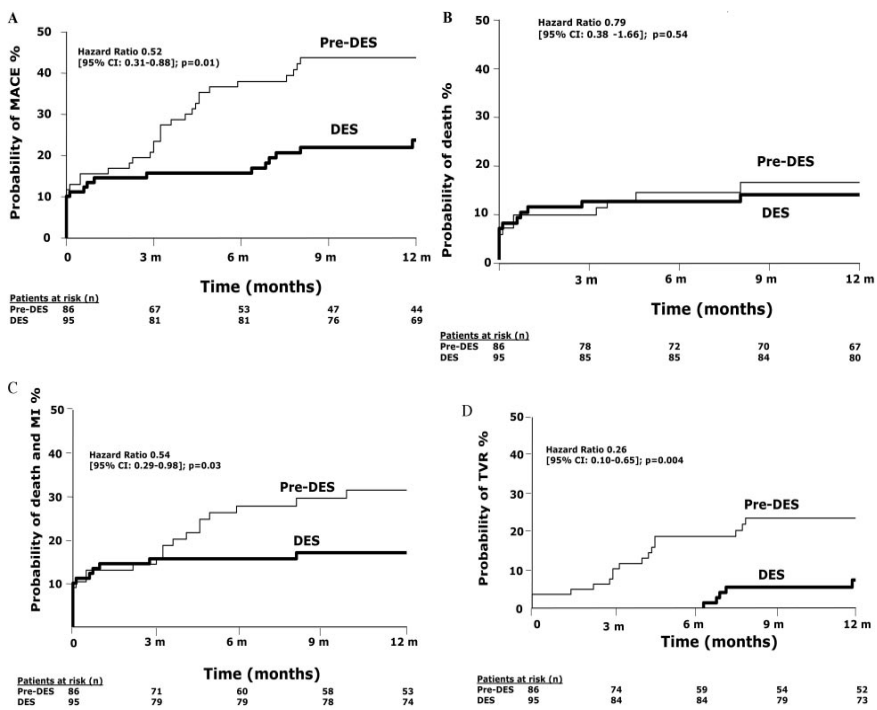
After a median follow-up of 503 days (range, 331 to 873 days), the cumulative incidence of major adverse cardiovascular events (death, MI, or target vessel revascularization) was significantly lower in the DES patients than in the pre-DES patients (24% versus 45%, respectively; hazard ratio

TABLE 3. Thirty-Day Outcomes

Variables	Pre-DES Group (n=86)	DES Group (n=95)	*P**
Death, n (%)	6 (7)	10 (11)	0.60
Nonfatal MI, n (%)	8 (9)	4 (4)	0.24
Death or nonfatal MI, n (%)	14 (16)	14 (15)	0.84
Target vessel revascularization, n (%)	2 (2)	0 (0)	0.22
Repeated PCI	1 (1)	0 (0)	
CABG	1 (1)	0 (0)	
Any event, n (%)	16 (19)	14 (15)	0.56
Stent thrombosis, n (%)†	0 (0)	0 (0)	1

*By Fisher exact test.
†Angiographically documented.

[HR], 0.52 [95% CI, 0.31 to 0.88]; *P*=0.01) (Figure, A). Mortality was similar in the DES (14%) and pre-DES cohort (16%; HR, 0.79 [95% CI, 0.38 to 1.66]; *P*=0.54) (Figure, B), whereas there was a significant reduction in both the rate of MI (4% versus 12%, respectively; HR, 0.22 [95% CI, 0.07 to 0.65]; *P*=0.006) and composite death/MI (Figure, C) as well as in the need for target vessel revascularization (6% versus 23%, respectively; HR, 0.26 [95% CI, 0.10 to 0.65]; *P*=0.004) (Figure, D) in the DES group. Seventy-four percent of the deaths were cardiac, whereas 3 of 13 in the DES group and 4 of 14 in the pre-DES phase were attributed to extracardiac reasons. In Table 4, the baseline and procedural characteristics of those patients in the DES group who underwent target vessel revascularization during follow-up are reported. In all cases, the lesion was located in the distal LM, in 50% of cases diabetes was present, and all except 1 were women. In 3 cases, in-stent restenosis occurred; in 2 patients intimal hyperplasia developed at the distal edge of the stent, whereas in 1 patient severe ostial side branch restenosis (circumflex artery) necessitated reintervention. In all cases, restenosis was focal (<10 mm in length) and was successfully treated with repeated PCI. In the pre-DES group, 13 cases of pure in-stent restenosis, of which 3 were focal, were treated with PCI (9 patients) or CABG (4 patients). In 2 patients, diffuse intimal hyperplasia associated with progression of atherosclerotic disease in other vessels was treated with CABG, and in 5 patients (3 with ST-segment elevation acute MI as the indication for LM intervention), staged reintervention with CABG (in 4 patients) and PCI (in 1 patient) was performed because revascularization remained incomplete at the time of the index procedure.



One-year adverse events in patients treated with BMS before the introduction of DES (pre-DES group) and in patients treated exclusively with DES implantation (DES group). Cumulative risk of major adverse cardiovascular events (MACE) (A), death (B), death or MI (C), and target vessel revascularization (TVR) (D) is shown.

TABLE 4. Characteristics of Patients in the DES Group Who Underwent Target Vessel Revascularization During Follow-Up

	Patient No.					
	1	2	3	4	5	6
Age, y	66	77	36	70	52	56
Gender	F	F	F	M	F	F
Diabetes	Yes	No	No	Yes	No	Yes
Lesion location	Distal	Distal	Distal	Distal	Distal	Distal
Severe calcification	Yes	No	No	No	No	No
Stent type	SES	SES	PES	PES	PES	PES
Stent No.	2	2	1	2	1	2
Total stent length, mm	16	36	20	48	16	36
Bifurcation stenting	No	Yes	No	Yes	No	Yes
Technique	...	Crush	...	Culotte	...	Culotte
Postdilatation	Yes	Yes	Yes	Yes	Yes	Yes
Final kissing	No	No	No	Yes	No	No
Gap between stents	No	No	No	No	No	No
Stent underexpansion	Yes	No	No	No	No	No
Restenosis location	In-stent	In-stent*	RS	In-stent	DER	DER*
Revascularization type	PCI	PCI	PCI	PCI	PCI	PCI
QCA after PCI						
Reference vessel diameter, mm	3.74	3.27	3.53	2.65	2.44	2.76
Minimal lumen diameter, mm	2.12	1.06	3.34	2.49	1.94	2.32
Lesion length, mm	13.4	19.7	13.5	21.3	8.9	18.9
QCA at follow-up						
Reference vessel diameter, mm	3.87	3.43	3.21	2.32	1.82	2.36
Minimal lumen diameter, mm	1.23	0.57	0.98	0.99	0.6	0.71
Restenosis length, mm	5.8	9.06	3.6	5.48	7.72	9.5

QCA indicates quantitative coronary angiography; In-stent, restenosis located within the stent margins; RS, restenosis located in the side branch (the ostium of the circumflex artery); and DER, distal edge restenosis located within the 5-mm segment distal to the stent.

*More than 1 focal site.

Predictors of Adverse Events

The Parsonnet score, ranging from 2.5 to 55.5 (mean value, 18±2; interquartile range, 16.5) was 16±11 and 19±12 in the pre-DES and DES groups, respectively (P=0.17) (Table 1), with a trend toward a higher rate of patients considered at high surgical risk (58% versus 46%, respectively; P=0.13) in the DES compared with the pre-DES cohort.

On univariate analysis, Parsonnet classification, use of intra-aortic balloon pump, presence of shock at entry, lesion located in the distal LM, nonelective PCI, troponin elevation at entry, TIMI flow grade before and after PCI, reference vessel diameter, left ventricular ejection fraction, and the use of DES were identified as significant predictors of adverse events. On multivariate analysis, Parsonnet classification, troponin elevation at entry, lesions located at distal site, reference vessel diameter, and the use of DES were independent predictors of major adverse cardiovascular events (Table 5).

Discussion

Despite the feasibility and the high procedural success rate of percutaneous LM intervention, the long-term incidence of adverse events in the pre-DES "era" was often reported to be unacceptably high in this subset of patients.[4,6] This reflected the inclusion of high-risk patients, such as those not considered "good surgical candidates," as well as the dramatic impact of treated vessel failure in this specific anatomic context. In consecutive patients receiving elective BMS for unprotected LM treatment, the 3-year cumulative incidence of death was recently reported to be ≈16%.[6] In that series, 28% of the population was at high surgical risk. More than 50% of our study population was at high surgical risk according to the Parsonnet classification, thus explaining the relatively high rate of adverse events we observed. In this setting, when patients treated with DES were compared with those treated with BMS, a marked benefit with respect to the rate of major adverse cardiac events, as evidenced by a 47% relative risk reduction, emerged in the former. This was mainly due to the difference in the incidence of MI (67% relative risk reduction) and target vessel revascularization (65% relative risk reduction), with no effect on mortality. The higher prevalence of 3-vessel disease and bifurcation stenting in the DES group makes the observed benefit even more convincing. The difference in the incidence of events between

TABLE 5. Univariate and Multivariate Cox Proportional Hazards Analysis

Variables	*P*	Hazard Ratio (95% CI)	χ^2
Univariate analysis			
Distal LM disease	0.003	2.7 (4.8–1.53)	13.3
DES use	0.019	0.54 (0.9–0.32)	5.48
Nonelective PCI	0.0047	2.1 (3.5–1.3)	8
Intra-aortic balloon pump use	0.0002	2.9 (4.9–1.7)	14
LVEF, %	0.00001	0.95 (0.97–0.93)	20
Parsonnet score	>0.00001	1.07 (1.09–1.05)	44
Reference vessel diameter	0.00001	0.36 (0.58–0.32)	19
Shock at entry	>0.00001	4.48 (7.9–2.5)	21
TIMI flow before PCI	0.03	0.75 (0.96–0.58)	4.3
TIMI flow after PCI	0.03	0.58 (0.85–0.39)	4.7
Troponin T >0.02 μg/L at entry	0.0002	3.15 (5.26–1.9)	18
Multivariate analysis 1			
Distal LM disease	0.0007	2.94 (5.5–1.57)	76
DES use	0.00009	0.33 (0.57–0.19)	
LVEF, %	0.09	0.98 (1.001–0.95)	
Parsonnet score	0.0009	1.04 (1.07–1.01)	
Reference vessel diameter	0.005	0.51 (0.79–0.33)	
Troponin T >0.02 μg/L at entry	0.02	2.3 (4.4–1.2)	
Multivariate analysis 2			
Distal LM disease	0.00017	3.3 (6.1–1.7)	68
DES use	0.00018	0.35 (0.6–0.20)	
LVEF, %	0.00013	0.95 (0.98–0.94)	
Reference vessel diameter	0.0011	0.48 (0.74–0.30)	
Shock at entry	0.006	3.49 (8.6–1.4)	
Troponin T >0.02 μg/L at entry	0.016	2.27 (4.2–1.17)	

Multivariate analysis model 1 was performed with all major adverse cardiovascular event predictors on univariate analysis; in multivariate analysis model 2, the Parsonnet score was removed because of colinearity between the variables included in the model and those used in the calculation of the score, such as left ventricular ejection fraction (LVEF), use of intra-aortic balloon pump, and presence of shock.

the 2 groups emerged slowly after the procedure, with no clear advantage at 30 days, possibly reflecting the specific mechanism of action of DES on intimal hyperplasia.

The overall advantage of DES remained significant after adjustment for the Parsonnet score, the anatomic site of obstruction, and troponin status at entry. Therefore, our data suggest that when percutaneous treatment of LM coronary artery disease is undertaken, DES should be used as the default strategy.

The LM bifurcation was frequently involved (>60%) in our series, and even when the obstruction was more proximally located and did not directly involve the LAD or left circumflex artery ostia, its treatment often required the management of LM bifurcation. To date, the results of SES implantation to treat bifurcated lesions have been relatively disappointing, with high rates of restenosis in the side branch.[11] Our present findings are in keeping with these previous observations, confirming that in the DES era distal LM location is an independent predictor of adverse events at follow-up. Furthermore, because the strategy and technical aspects of bifurcation management were left entirely to the preference of treating physicians, no clear conclusions can be drawn in this regard.

Inconsistent findings have been reported thus far with regard to the effect of DES on long-term cumulative incidence of MI. In the first randomized clinical trials comparing SES or PES with BMS, no difference in the incidence of MI was observed.[12,13] Second-generation randomized trials assessing the benefit of DES in patients selected to be at intermediate risk for in-stent restenosis or all-inclusive registries reported trends toward MI reduction in the DES group, but none of them reached statistical significance.[14,15] Recently, a clear reduction in the cumulative incidence of MI in the DES group was reported in the SES-SMART trial, in which a selected group of high-risk patients has been evaluated.[16] Similarly, in our patient population, a reduced incidence of MI was observed in the DES group. Of note, 2 and 1 cases of MI in the pre-DES phase were related to target vessel revascularization and not related to target vessel revascularization, respectively. Whether this difference between studies is the reflection of a type II error in studies enrolling patients at low or intermediate risk remains unclear, but when the retrospective nature of our investigation is considered, data from prospective studies are needed to confirm our findings.

Limitations of the Study

The present study is a single-center experience from a tertiary referral center and lacks the clear advantages of a multicenter randomized study. In keeping with the aim of our investigation, an "all-comers" population has been enrolled, clearly resulting in a heterogeneous group of patients. Further studies, with larger sample sizes, are required to investigate the differential impact of DES versus BMS in prespecified subgroups, stratified according to clinical presentation (stable versus unstable) or protected versus unprotected type of treatment.

Despite the fact that the study was conducted over a relatively short period, we cannot exclude the possibility that improvements in technique or differences in drug prescription could have partially accounted for the difference observed in terms of major adverse cardiovascular events between groups. However, conducting randomized trials that seek to assess the efficacy of DES versus BMS in this specific subset of patients seems unlikely, and our understanding of the benefit of drug-coated stents to treat this group of patients will probably also rely in the near future on well-conducted registries that are able to record and monitor our daily clinical practice.

Conclusions

The use of DES as a default strategy to treat LM disease was associated with a significant reduction in adverse events. The effectiveness of DES persisted even after adjustment for clinical and procedural variables, including the Parsonnet

surgical risk score. Our findings apply to a selected group of patients referred for percutaneous LM treatment and suggest that in this setting routine DES implantation, by reducing the cumulative incidence of major adverse cardiovascular events, should be currently regarded as the strategy of choice. Until new evidence is provided by randomized clinical trials directly comparing the surgical and percutaneous approaches, CABG should remain the preferred revascularization treatment in good surgical candidates presenting with LM coronary artery disease.

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Chapter 14

Treatment of De Novo Bifurcation Lesions: Comparison of Sirolimus- and Paclitaxel-Eluting Stents.

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Treatment of de novo bifurcation lesions: comparison of Sirolimus- and Paclitaxel-eluting stents

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KEYWORDS
Drug eluting stent, bifurcation lesions, Sirolimus, Paclitaxel.

Abstract

Objective: Both the sirolimus-(SES) and paclitaxel-eluting (PES) stents have been shown to reduce restenosis rates when used in relatively simple lesions. This study aimed to evaluate the results of a consecutive series of patients treated with drug-eluting stent implantation for *de novo* bifurcation lesions, and compared outcomes with respect to stenting strategy and stent type.

Patients: From April 2002 to September 2003, all patients at our institution were treated with drug-eluting stent implantation. A consecutive series of 144 patients were treated for 167 *de novo* bifurcation lesions with SES, followed by 104 patients treated with PES for 113 lesions.

Results: Clinical follow-up at 6 months was obtained in 99% patients with survival-free of major adverse cardiac events (MACE) of 93.7% for SES versus 85.8% for PES, p=0.05. By multivariate analysis, factors predictive for MACE were age, diabetes mellitus, previous CABG, multivessel disease, treatment for acute myocardial infarction, and treatment with PES. Survival-free of target lesion revascularization (TLR) was 95.7% for SES versus 86.8% for PES, p=0.01, with stent type being the only independent predictor. Technique of stenting was not a predictor of either MACE or TLR.

Conclusions: MACE rates for both the SES and PES are low compared with historical data of bare metal stents. The most effective techniques for bifurcation stenting remain undefined. Our data suggests a higher need for TLR for the PES compared with the SES, however further randomized studies are needed to fully evaluate both stenting strategy, and any difference between the stents.

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Introduction

The outcome of percutaneous therapy (PCI) of bifurcation lesions with bare metal stents is hindered by an increased rate of procedural complications[1], and a high rate of restenosis particularly when both the main vessel and side branch are stented[2,3,4,5,6]. The advent of drug-eluting stents is revolutionising the practice of interventional cardiology by demonstrating a reduction in the subsequent rate of restenosis. There is evidence of efficacy in randomized trials for both the sirolimus- (SES) and paclitaxel-eluting (PES) stents for the treatment of relatively simple lesions[7,8]. In addition, the sirolimus-eluting stent for the treatment of bifurcation lesions has demonstrated a low rate of adverse cardiac events compared with historical data utilizing bare metal stents[9,10]. However, the most effective technique of stenting for bifurcation lesions with drug-eluting stents is currently unknown. In the present report we evaluate the rate of major adverse cardiac events following PCI for bifurcation lesions treated with either SESs or PESs in a consecutive series of patients. In addition, outcomes were assessed with respect to the baseline bifurcation anatomy and type of stenting strategy employed.

Methods

Bifurcation classification: All lesions were classified on baseline angiography according to the Duke classification (figure 1).

Procedure: The sirolimus-eluting stent (Cypher™, Johnson & Johnson - Cordis unit) received CE mark approval in April 2002. Since that time, all patients undergoing percutaneous therapy in our institution have been treated with drug-eluting stent implantation as the default strategy. During the first quarter of 2003, our strategy switched from the sirolimus- to the paclitaxel-eluting stent (Boston Scientific) enabling a comparison of the two stent types. All consecutive patients were enrolled irrespective of clinical presentation and lesion characteristics, and the incidence of major adverse cardiac events (MACE) was prospectively evaluated during the follow-up.

All procedures were performed with standard interventional techniques. The strategy of bifurcation stenting employed, and the use of kissing balloon dilatation post-procedure were at the operators' discretion. One of 6 methods of stenting was used: stenting of the main vessel with balloon-only angioplasty of the side branch; type A T-stenting (stenting first of the side branch, followed by stenting of the main vessel); type B T-stenting (stenting of the main vessel followed by stenting of the side branch because of a sub-optimal result)[2]; the 'crush' technique[11]; culotte stenting[12]; or kissing stents (simultaneous implantation in the main vessel and side branch with the proximal edges of the stents side by side). SESs were available in diameters from 2.25 mm to 3.00 mm and lengths from 8 mm to 33 mm. PESs were available in diameters from 2.25 mm to 3.5 mm and lengths from 8mm to 32mm. During the procedure, intravenous heparin was given to maintain an activated clotting time ≥250 seconds. Patients were preloaded with 300 mg clopidogrel, and received life-long aspirin together with 75 mg clopidogrel per day for 6-months. The use of glycoprotein IIb/IIIa inhibitors was at the discretion of the operator. The protocol was approved by the Institutional ethics committee and is in accordance with the principles of Good Clinical Practice for Trials of Medicinal Products in the

FIGURE 1.

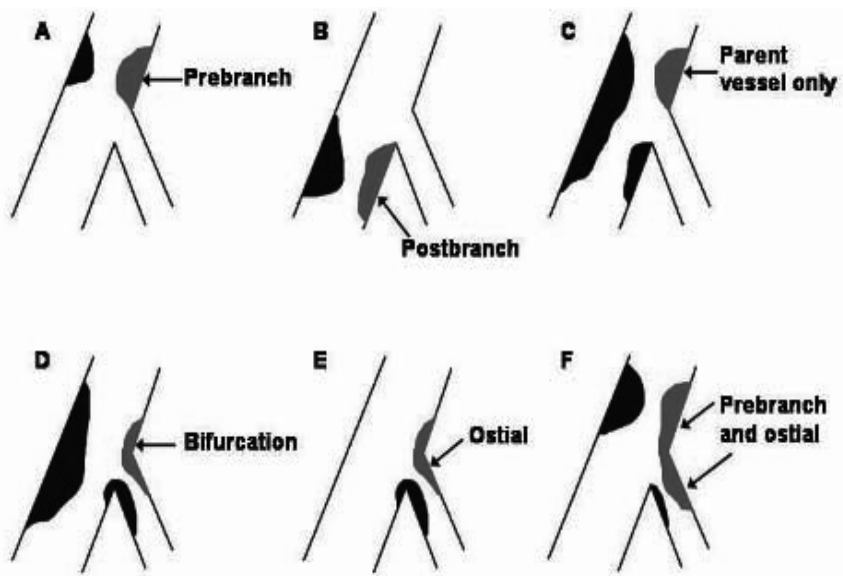

Fig. 1: The Duke classification of bifurcation lesions.

European Community and the Declaration of Helsinki. All patients signed a written informed consent

Follow-up: Clinical follow-up was obtained using telephone calls and questionnaires, and evaluated the rate of major adverse cardiac events (MACE) which were pre-defined as death, acute myocardial infarction (AMI), or target vessel revascularization (TVR). The diagnosis of AMI required an elevation of creatine kinase levels to twice the upper limit of normal, together with a rise in creatine kinase-MB fraction. Target lesion revascularization was defined as either surgical or percutaneous reintervention driven by significant (>50%) luminal diameter narrowing either within the stent or the 5mm borders proximal and distal to the stent, and was undertaken in the presence of either anginal symptoms or objective evidence of ischemia. Target vessel revascularization was defined as revascularization within the target vessel including encompassing the target lesion. The definition of stent thrombosis was the presence of intra-stent thrombosis, with or without stent occlusion, documented on angiography, and was categorized as acute if occurring within 24 hours or subacute if within 30 days after stent implantation.

Statistical analysis: Discrete variables are presented as percentages and compared with Fisher exact test. Continuous variables are expressed as mean ± standard deviation and compared with Student's t test. Cumulative survival and MACE-free survival were calculated according to the Kaplan-Meier method. The log-rank test was used to compare MACE-free survival between the two groups. All tests were two-tailed, and a p value of <0.05 was considered as significant. Logistic regression models were established to investigate independent predictors of MACE (death, AMI, or TVR), and target lesion revascularization. Variables entered were age, gender, diabetes mellitus, hypertension, hypercholesterolemia, smoking, multivessel disease, prior AMI, prior CABG, clinical presentation, use of a glycoprotein IIb/IIIa inhibitor, target vessel, bifurcation anatomy, stent type, stenting technique, diameter of stent, total length of stents, and use of kissing balloon post-dilatation. Odds ratio with corresponding 95% confidence intervals are reported.

Results

The baseline patient and procedural characteristics for the SES and PES cohorts are presented in tables 1 and 2 respectively. There were no significant differences between the 2 groups with respect to baseline patient characteristics, though there was a trend towards an increased usage of glycoprotein IIb/IIIa inhibitors in the PES group (38.5% versus 27.8% in the SES group, p=0.07). There was no significant difference in the number of stents used, however, the mean nominal diameter of stent used in the main vessel was greater with the PES (2.93 ± 0.34mm versus 2.85 ± 0.23 for the SES, p=0.007). For those patients treated with stent implantation in the side branch, though there was no significant difference in the number of stents used, the total length of stented segment in the side branch was longer for the PES-treated patients (18.8 ± 10.5mm versus 14.1 ± 7.6mm, p=0.0001). The choice of stenting strategy during the 2 treatment periods is presented in figure 2. The total number of lesions treated with each stenting technique was single stent utilization in 55 (19.6%), type A T-stenting in 47 (16.8%), type B T-stenting in 46 (16.4%), crush stenting in 88 (31.4%), culotte stenting in 24 (8.6%), and kissing stents in 20 (7.1%). There was no difference with respect to the use of kissing balloon post-dilatation between the SES and PES cohorts.

Clinical follow-up was obtained in 99.2% patients. Angiographically documented stent thrombosis occurred in 2 patients treated with SES (1.4%) and 3 patients treated with PES (2.9%), p=0.4 (Table 3). All episodes of stent thrombosis were subacute (within 30 days following stent implantation), and were treated percutaneously, all patients survived. The cumulative incidence of major adverse cardiac events at 6-months for the SES and PES groups are presented in Table 4, and the survival-free of MACE at 6-months is illustrated in figure 3. The independent predictors for MACE and TLR by multivariate analysis are shown in Table 5. The only factor found to be predictive for TLR was stent type. Neither the baseline bifurcation anatomy, nor the type of stenting strategy utilized, were predictive of events.

At 6-months, survival-free of TLR was 95.7% for SES versus 86.8% for PES, p=0.01 (figure 4). TLR was for subacute thrombosis in 5 patients (see above), was for restenosis of the main vessel in 4 lesions treated with SES (2.4%) and 6 lesions treated with PES (5.3%), for restenosis of the side branch in 3 lesions treated with SES (1.8%) and 3 treated with PES (2.7%), and for restenosis of both branches in 2 lesions treated with SES (1.2%) and 2 treated with PES (1.8%).

Discussion

In the present report we have demonstrated low rates of major adverse cardiac events at 6-months for both the sirolimus- and paclitaxel-eluting stents when used for the treatment of *de novo* bifurcation lesions. Independent predictors for MACE were age, diabetes mellitus, multivessel disease, previous CABG, treatment in the setting of acute myocardial infarction, and therapy with PES. Target lesion revascularization (TLR) at 6-months was higher in the PES group than the SES group, with a survival-free of TLR of 86.8% versus 95.7% respectively, p=0.01. By multivariate analysis, the use of PES was the only factor predictive for TLR.

The most effective strategy for the treatment of bifurcation lesions with drug-eluting stents is currently unknown. In the present study, the choice of stenting strategy was at the operators' discretion. Previous data from our group following bifurcation stenting with the SES, demonstrated an overall restenosis rate of 23%[9]. The majority of restenoses of the side branch occurred at the ostium following T-stenting. Indeed, the restenosis rate in the side branch following T-stenting was 16.7% whilst that following other stenting techniques was 7.1%. We hypothesised that these restenoses might relate to inadequate / incomplete coverage of the ostium of the side branch thereby reducing the efficacy of the drug-eluting stent. This led to a shift away from a strategy of T-stenting, towards methods which ensure complete coverage - the crush and culotte techniques of stenting (figure 2). One potential disadvantage of these strategies however, is that they lead to an area of double or triple layer of stent struts raising theoretical concerns that the increased dosage of drug at this site might induce endothelial dysfunction and potentiate the risk of thrombosis. Despite the change in stenting technique in the present study, the choice of strategy was not an independent pre-

Table 1. Baseline patient demographics

	SES n=144	PES n=104	p value
Mean age (years)	62.4 ± 10.5	60.3 ± 11.8	0.1
Male sex (%)	74.3	73.1	1
Current smoker (%)	27.1	27.9	1
Diabetes mellitus (%)	18.8	17.3	1
Hypertension (%)	43.1	46.2	0.7
Hypercholesterolemia (%)	56.9	62.5	0.3
Previous myocardial infarction (%)	35.4	38.5	0.2
Previous CABG (%)	4.9	3.8	0.9
Clinical presentation			0.4
Stable angina (%)	65.3	67.3	
Unstable angina (%)	21.5	17.3	
Acute ST-elevation myocardial infarction (%)	13.2	16.3	
Glycoprotein IIb/IIIa inhibitor usage (%)	27.8	38.5	0.07
PCI in at least one additional major epicardial vessel during the index procedure (%)	40.3	39.4	1

SES: Sirolimus-eluting stents, PES: Paclitaxel-eluting stents, CABG: coronary artery bypass grafting, PCI: percutaneous coronary intervention.

Table 2. Baseline procedural characteristics

Total number of bifurcation lesions treated	SES 167	PES 113	p value
Target vessel			0.3
LAD / diagonal (%)	61.1	56.6	
LCX / obtuse marginal (%)	19.2	17.7	
RCA bifurcation (%)	9.6	8.0	
LMS (%)	10.2	17.7	
Bifurcation classification			0.4
A (%)	4.8	3.5	
B (%)	7.2	5.3	
C (%)	8.4	6.2	
D (%)	17.5	20.4	
E (%)	8.4	3.5	
F (%)	44.0	50.4	
Total occlusion (TIMI 0 flow) (%)	9.6	10.6	
Pre-dilatation of main vessel (%)	59.3	54.0	0.4
Pre-dilatation of the side branch (%)	42.5	31.9	0.07
Pre-dilatation with kissing balloons (%)	15.0	13.3	0.9
Mean number of stents in the main vessel	1.56 ± 0.84	1.48 ± 0.67	0.4
Mean nominal diameter of stent in the main vessel (mm)	2.85 ± 0.23	2.93 ± 0.34	0.007
Mean total lengths of stent in the main vessel (mm)	30.4 ± 17.7	30.3 ± 17.8	1.0
Mean number of stents in side branch	1.11 ± 0.36	1.13 ± 0.39	0.8
Mean nominal diameter of stent in the side branch (mm)	2.53 ± 0.29	2.60 ± 0.35	0.06
Mean total lengths of stent in the side branch (mm)	14.1 ± 7.6	18.8 ± 10.5	0.0001
Nominal diameter of balloon in side branch for POBA	2.28 ± 0.44	2.19 ± 0.49	0.5
Post-dilatation with kissing balloons (%)	47.3	45.1	0.9

SES: Sirolimus-eluting stents, PES: Paclitaxel-eluting stents, LAD: left anterior descending artery, LCX: circumflex artery, RCA: right coronary artery, LMS: left main stem, POBA: plain old balloon angioplasty.

FIGURE 2.

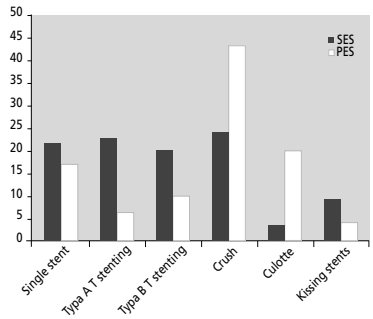

Fig. 2: The type of stenting strategy employed for the Sirolimus-eluting (SES) and Paclitaxel-eluting stent (PES).

FIGURE 3.

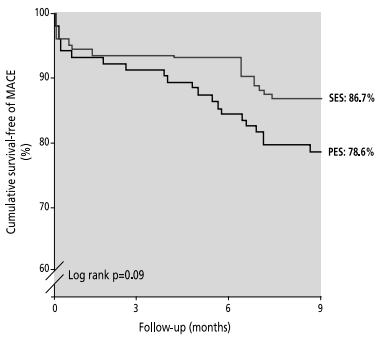

Fig. 3: Kaplan-Meier curves for survival-free of major adverse cardiac events (MACE) for the Sirolimus-eluting (SES) and Paclitaxel-eluting stent (PES).

FIGURE 4.

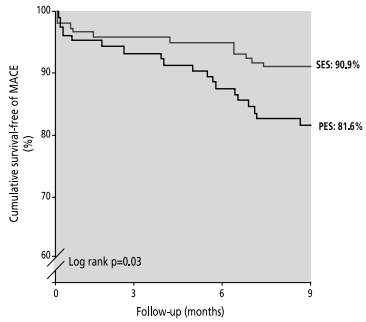

Fig. 4: Kaplan-Meier curves for survival-free of target lesion revascularization (TLR) for the Sirolimus-eluting (SES) and Paclitaxel-eluting stent (PES).

Table 4. Cumulative incidence of major adverse cardiac events at 6-months for the Sirolimus- and Paclitaxel-eluting stents

	SES n=144	PES n=104	p value (log rank)
Death (%)	1.4	3.2	0.4
Death or AMI (%)	4.9	7.1	0.5
Death, AMI, or TLR (%)	6.3	13.2	0.08
Death, AMI, or TVR (%)	6.3	14.2	0.05

SES: Sirolimus-eluting stents, PES: Paclitaxel-eluting stents, AMI: acute myocardial infarction, TLR: target lesion revascularization, TVR: target vessel revascularization.

Table 5. Independent predictors of major adverse cardiac events and target lesion revascularization at 6 months

	Odds ratio	95% confidence intervals
MACE		
Age	1.02	1.01 to 1.05
Prior CABG	2.75	1.1 to 7.2
Diabetes mellitus	2.15	1.2 to 4.0
Multivessel disease	1.36	1.0 to 1.9
Presentation with acute myocardial infarction	2.35	1.1 to 5.0
Therapy with Sirolimus-eluting stent	0.71	0.4 to 1.0
TLR		
Therapy with Sirolimus-eluting stent	0.45	0.19 to 0.95

MACE: major adverse cardiac event; CABG: coronory artery bypass graft surgery; TLR: target lesion revascularization

Table 3. Demographic of the 5 patients angiographically documented stent thrombosis

Age, sex	Stent type	Target vessel	Time to thrombosis, days	Diabetes mellitus	Use of GP IIb/IIIa inhibitor	Clinical presentation at index	Stenting strategy	Kissing balloon post-dilatation
74yr F	SES	LAD	1	N	N	SA	Crush	Y
57yr M	SES	LAD	18	Y	Y	AMI	Type B "T"	N
66yr M	PES	LCx	7	N	N	UA	Crush	N
46yr F	PES	LAD	6	N	N	AMI	Crush	N
51yr F	PES	LCx	4	N	Y	AMI	Type B "T"	Y

SES: Sirolimus-eluting stent; PES: Paclitaxel-eluting stent; LAD: left anterior descending; LCx: left circumflex; SA: stable angina; AMI: acute myocardial infarction; UA: unstable angina.

dictor for either MACE or the need for TLR. The current study is limited by the lack of angiographic follow up, so cannot fully evaluate restenosis which, particularly when occurring in the side branch, may be clinically silent.

Currently, there is only one published randomized evaluation of drug-eluting stents for bifurcation lesions[10]. This randomized 85 patients to a single SES with balloon-angioplasty of the side branch, versus implantation of 2 SESs. The overall rate of restenosis at 6 months was 26% (19% in the single stent group versus 28% in the double stent group, p=NS). However, the study was limited by the high crossover rate with 51% of the patients in the single stent group crossing to the double stent group because of a suboptimal result in the side branch. In addition, the approach to stenting technique was not uniform. However, both this randomized study, and the registry data from our group demonstrate an improvement in the restenosis rates compared with historical data of bare metal stenting.

Restenosis following bare stent implantation is related to the length of stent, and inversely related to the diameter[13]. The majority of TLRs were for restenosis within the main vessel stent, yet the nominal stent diameter was actually bigger for the PES. This probably related to a larger available diameter of PES (3.5mm versus 3.0mm for the SES), and throughout the study, post-dilatation was carried out whenever necessary. The mean total length of stent used in the side branch of the PES group was significantly longer than the SES group. However, neither stent diameter nor length was an independent predictor for subsequent MACE or need for TLR.

Previous data of bare metal stent implantation in bifurcation lesions, demonstrate rates of target lesion revascularization of between 16% and 38%[2,3,4,5,6]. Compared with this historical data, in the current study, TLR was certainly lower for the SES (survival-free of TLR of 95.7% at 6 months). However, multivariate analysis demonstrated a significantly higher need for TLR following stenting with the PES compared with the SES, with the majority of TLRs in the main vessel. This might reflect a difference in the efficacy of the 2 drugs, at least at the current dosages, or relate to differences in stent design[14]. The SES is a closed-design stent whereby each cell is bound on all sides with the junction of each strut pair joined to another strut pair junction. The PES however, is an open-cell design meaning that some of the junction nodes are unattached within the stent structure. A previous of 54 patients undergoing elective stenting showed that platelet activation was lower in those receiving a closed versus open-cell designed stent[15]. In the present study, though not significantly different between the 2 groups, subacute thrombosis did occur in a higher percentage of the PES patients (2.9% versus 1.4%, p=0.4). The same authors[15] examined stent implantation in the pig model and found that more tissue prolapse occurred following implantation of a stent with an open cell design. Both the SES and PES have been evaluated in large randomized studies and compared with their respective bare stents (Bx Velocity™ and Express™)[16,17]. Though the inclusion criteria in these studies were not absolutely identical, both studies were very similar and included patients with stable or unstable angina and single *de novo* lesions; bifurcation lesions were excluded. Both the mean lesion length, and reference vessel diameter were similar. Evaluation of the angiographic follow-up of those treated with bare stents, showed a mean in-stent lumen loss of 1.00 ± 0.70mm in SIRIUS (Bx Velocity™), and 0.92 ± 0.58mm in TAXUS-IV (Express™). The higher late lumen loss in the Bx Velocity™ stent conflicts with the suggestion that the lower TLR rate with SES in the present study might relate to the difference in stent design. Both the SES and PES are covered by polymer coatings to facilitate drug-elution. Previous evaluation of other polymers has suggested that these can in themselves promote varying degrees of an inflammatory response and restenosis[18]. In the same randomized studies, evaluation of the drug-eluting stent cohorts showed a mean in-stent late loss of 0.17 ± 0.45mm in SIRIUS, and 0.39 ± 0.50mm in TAXUS-IV, perhaps suggesting the SES is more efficacious at inhibiting the development of neointimal hyperplasia than the PES.

Interpretation of the results of the present study with respect to stent type is limited by the lack of randomization. The REALITY study is a multicenter evaluation of more than 1300 patients with multivessel disease, randomized to either SES or PES implantation. Initial results were recently presented at the American College of Cardiology meeting in 2005[19]. There was no significant difference with respect to the overall rates of MACE between the stent types (9.2% for SES versus 10.6% for PES, p=0.41). However, in keeping with the difference in the degree of platelet activation related to stent design[15], the rate of stent thrombosis was higher for the PES group (1.8% versus 0.4%, p=0.0196). Furthermore, all angiographic parameters with respect to efficacy of suppression of neointimal growth were better following SES implantation. The in-stent late loss was 0.09 ± 0.43mm for the SES, versus 0.31 ± 0.44mm for the PES, p<0.001. Such a difference may potentially be clinically relevant when treating complex lesions such as bifurcations, particularly when vessels with a small diameter are stented. Patients with bifurcation lesions were not excluded from this study, and a more detailed analysis of subgroups such as those treated for a bifurcation lesion is awaited.

The most effective strategy for percutaneous therapy of bifurcation lesions with drug-eluting stents needs to be carefully evaluated in future studies. Interpretation of future randomized studies should take into account baseline anatomical differences of bifurcation lesions as the best strategy for a true bifurcation lesion (involving both the main vessel and side branch) may not necessarily be the same as that for lesions affecting only one of the branches. In addition, restenosis particularly at the side branch may not always lead to a recurrence in symptoms and follow-up angiography should be carried out to fully evaluate the results.

Study limitations

The major limitations of this study are that it is a single centre registry and is non-randomized, with the choice of stenting strategy left entirely at the operators' discretion. In addition, routine angiographic follow-up data was not obtained, and additional restenoses giving rise to minimal / no symptoms, particularly at the ostium of the side branch, cannot be excluded. However, clinical follow-up data was available for >99% providing an accurate reflection of the rate of clinically important adverse events following therapy of bifurcation lesions in a consecutive series of patients without exclusion.

Conclusions

The use of both the sirolimus- and paclitaxel-eluting stents for the treatment of *de novo* bifurcation lesions appears feasible and safe, both demonstrating low rates of major adverse cardiac events at 6-months. The increased rate of target lesion revascularization following PES implantation needs to be further evaluated in a randomized fashion, and at present, the most appropriate technique for bifurcation stenting with drug-eluting stents remains unclear.

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PART III.

EARLY AND LATE STENT THROMBOSIS – THE CAVEAT OF DRUG-ELUTING STENTS

Chapter 15

Thirty-Day Incidence and Six-Month Clinical Outcome of Thrombotic Stent Occlusion After Bare-Metal, Sirolimus, or Paclitaxel Stent Implantation.

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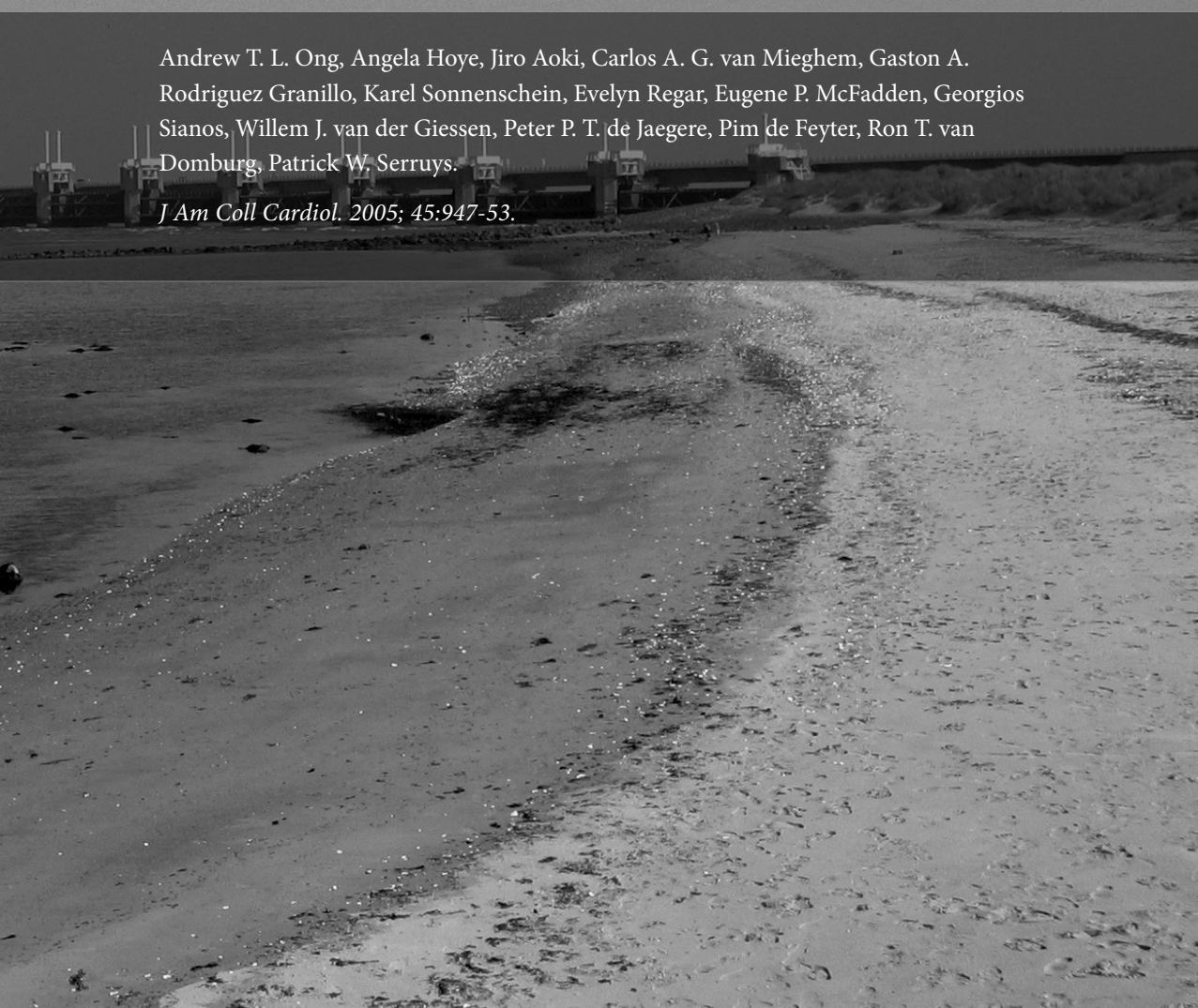

Thirty-Day Incidence and Six-Month Clinical Outcome of Thrombotic Stent Occlusion After Bare-Metal, Sirolimus, or Paclitaxel Stent Implantation

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OBJECTIVES We sought to determine the real-world incidence of angiographically confirmed and possible stent thrombosis (ST) in an unrestricted population during the first 30 days after bare-metal stent (BMS), sirolimus-eluting stent (SES), and paclitaxel-eluting stent (PES) implantation.

BACKGROUND Current data on ST in drug-eluting stents (DES) have come from randomized trials with strict entry criteria, which limits their generalizability to daily practice.

METHODS The study population comprised three sequential cohorts of 506 consecutive patients with BMS, 1,017 consecutive patients with SES, and 989 consecutive patients treated with PES.

RESULTS In the first 30 days after stent implantation, 6 BMS (1.2%, 95% confidence interval [CI] 0.5% to 2.6%; $p = 0.9$), 10 SES (1.0%, 95% CI 0.5% to 1.8%), and 10 PES (1.0%, 95% CI 0.6% to 1.9%) patients developed angiographically proven ST. Multiple potential risk factors were identified in most patients with ST. Bifurcation stenting in the setting of acute myocardial infarction was an independent risk factor for angiographic ST in the entire population (odds ratio [OR] 12.9, 95% CI 4.7 to 35.8, $p < 0.001$). In patients with DES who had angiographic ST, 30-day mortality was 15%, whereas another 60% suffered a nonfatal myocardial infarction; no further deaths occurred during six months of follow-up. Including possible cases, 7 BMS (1.4%, 95% CI 0.7% to 2.8%), 15 SES (1.5%, 95% CI 0.9% to 2.4%), and 16 PES (1.6%, 95% CI 1.0% to 2.6%) patients had ST.

CONCLUSIONS The unrestricted use of SES or PES is associated with ST rates in the range expected for BMS. Stent thrombosis was associated with a high morbidity and mortality. Bifurcation stenting, when performed in patients with acute myocardial infarction, was associated with an increased risk of ST. (J Am Coll Cardiol 2005;45:947–53) © 2005 by the American College of Cardiology Foundation

Drug-eluting stents (DES) reduce clinical events related to restenosis. Concerns have been raised regarding the incidence of stent thrombosis (ST) with the unrestricted use of these stents. Data from the bare-metal stent (BMS) era report a high morbidity and mortality with ST (1,2). Evidence for ST in DES has come from randomized controlled trials with strict entry criteria for the treatment of single lesions, limiting conclusions that are applicable to the real-world setting (3–6). Other information has come from electronic registries with inherent biases that preclude generalization of the findings. A single-center registry recently reported its results with sirolimus-eluting stents (SES) (7). The aim of this present study is to describe the incidence of ST (both angiographically proven and including possible cases) in three consecutive populations while analyzing the unrestricted use of a control BMS group, SES, and paclitaxel-eluting stents (PES).

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METHODS

Study design and patient population. Since April 2002, SES (Cypher; Cordis Corp., Miami Lakes, Florida, a Johnson & Johnson Company) have been the stents of choice for all percutaneous coronary interventions irrespective of their clinical presentation or clinical outcome (8). In the first quarter of 2003, PES (Taxus; Boston Scientific Corp., Natick, Massachusetts) replaced SES as the default stent.

This present study comprises three sequential cohorts: a control group of the last 506 consecutive patients treated with BMS before April 2002; 1,017 consecutive patients with SES treated between April 2002 and February 2003; and 989 consecutive patients with PES treated between February 2003 and December 2003.

Procedure and antiplatelet management. All interventions were performed according to current standard guidelines, and the final interventional strategy including periprocedural glycoprotein IIb/IIIa and intravascular ultrasound use, was left to the discretion of the operator. Patients were pretreated with aspirin and a loading dose of 300 mg of clopidogrel. After their procedure, all patients were prescribed a lifelong aspirin regimen. Clopidogrel was pre-

Abbreviations and Acronyms

AMI = acute myocardial infarction
BMS = bare-metal stents
CI = confidence interval
DES = drug-eluting stents
MI = myocardial infarction
OR = odds ratio
PES = paclitaxel-eluting stents
SES = sirolimus-eluting stents
ST = stent thrombosis
TIMI = Thrombolysis In Myocardial Infarction

scribed for at least one month in the BMS group, for at least three months in the SES group (8), and for at least six months in the PES group.

Follow-up. As part of the national health system, our institution as a tertiary referral center is the only interventional facility within our catchment area. The survival status of our patients at one and six months after discharge was obtained from the Municipal Civil Registries. Details of all repeat interventions (surgical and percutaneous) were collected prospectively during follow-up. Referring physicians and institutions were contacted whenever necessary for additional information. This protocol was approved by the Hospital Ethics Committee, and written, informed consent was obtained from every patient.

Definitions. Stent thrombosis was considered to have occurred when confirmed angiographically: either Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 or 1 or the presence of flow-limiting thrombus (TIMI flow grade 1 or 2) occurring in an acute (within 24 h of stent implantation) or subacute (between 1 and 30 days) time period after stent implantation (9). In addition, a clinical definition of "possible stent thrombosis" was used for patients who within the first 30 days experienced sudden death, who suffered a fatal out-of-hospital cardiac arrest, or who suffered a myocardial infarction (MI) that was not clearly attributable to another coronary lesion and who did not undergo repeat angiography. All deaths and MIs were reviewed independently by two interventional cardiologists (A.O., E.Mc.F) for "possible stent thrombosis."

Statistical analysis. Categorical variables were compared using the Fisher exact test and continuous variables with the Student *t* test or one-way analysis of variance where appropriate. Univariate and forward stepwise (entry criteria of 0.05 and exit criteria of 0.10) multivariate logistic regression analysis were performed to identify characteristics or variables independently associated with stent thrombosis. From the univariate analysis, the following baseline, clinical, angiographic and procedural variables were entered into the multivariate model: bifurcation stenting, diabetes, smallest stent diameter, multilesion stenting, and acute myocardial infarction (AMI) as the indication. All probability values are

Table 1. Baseline and Procedural Characteristics

	BMS (n = 506)	SES (n = 1,017)	PES (n = 989)	p Value
Baseline characteristics				
Age, yrs, mean ± SD	61.0 ± 11.4	61.9 ± 11.3	61.7 ± 11.4	0.3
Male, %	73	70	74	0.1
Diabetes, %	16	18	17	0.6
Hypercholesterolemia, %	52	55	60	<0.01
Current smoker, %	35	28	28	<0.01
Hypertension, %	40	41	41	0.9
Previous MI, %	43	32	35	<0.01
Previous PCI, %	22	25	26	0.2
Previous CABG, %	11	9	8	0.2
Multivessel disease, %	54	57	56	0.4
Indication for index procedure				<0.01
Stable angina, %	42	43	41	
Unstable angina, %	35	36	30	
Acute MI, %	20	19	26	
Silent ischemia, %	3	2	3	
Number of vessels treated, mean ± SD	1.4 ± 0.6	1.4 ± 0.6	1.4 ± 0.6	0.8
LAD, n	281	594	540	
LCx, n	164	332	333	
RCA, n	194	398	384	
Others, n	29	75	90	
Total stent length, mm (mean ± SD)	31.9 ± 22.1	42.5 ± 29.6	44.2 ± 29.4	<0.01
Stents implanted, mm (mean ± SD)	1.9 ± 1.1	2.3 ± 1.5	2.2 ± 1.4	<0.01
At least one ≤2.5 mm stent implanted (%)	23	38	38	<0.01
Bifurcations stented, %	5	18	17	<0.01
Glycoprotein IIb/IIIa use (%)	37	21	28	<0.01

BMS = bare metal stent; CABG = coronary artery bypass grafting; LAD = left anterior descending; LCx = left circumflex; MI = myocardial infarction; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent; RCA = right coronary artery; SES = sirolimus-eluting stent.

Table 2. Outcome Following Angiographic Stent Thrombosis

	BMS	SES	PES	p Value
Angiographic stent thrombosis, n (%)	6 (1.2%)	10 (1.0%)	10 (1.0%)	0.9
Clinical presentation				
Acute MI, n	5	7	8	
Angina, n	1	3	2	
Maximum total CK, mean ± SD	4,983 ± 2,570	1,268 ± 476	3,361 ± 1,404	<0.01
Maximum CK-MB, mean ± SD	397 ± 186	171 ± 80	322 ± 166	<0.01
Outcome				
30-day mortality, n	0	0	3	
6-month mortality, n	0	0	3	

CK = creatine kinase; other abbreviations as in Table 1.

two-sided, and statistical significance was set at the 0.05 level. A cumulative event graph consisting of patients with angiographic stent thrombosis was generated plotting the proportion of patients with stent thrombosis (Y-axis) against time (X-axis) stratified by stent type. Incidences of stent thrombosis are reported as a percentage with associated 95% confidence intervals (CIs).

RESULTS

Baseline and procedural characteristics. The patients in our cohort were at high risk, with unstable angina or AMI being the indication in more than one-half of the cases (Table 1). Multivessel disease was present in more than one-half of the population. One-third of the population had a previous AMI, whereas one-quarter had previous coronary interventions. Glycoprotein IIb/IIIa use was lower in the SES and PES groups compared with the BMS group.

Clinical outcome. Angiographic ST was documented in 26 of 2,512 patients (Table 2). Six cases occurred in the BMS group (1.2%, 95% CI 0.5% to 2.6%), 10 cases occurred in the SES group (1.0%, 95% CI 0.5% to 1.8%), and 10 cases occurred in the PES group (1.0%, 95% CI 0.6% to 1.9%). The first two SES patients with ST have been reported previously (10). Most stent thromboses occurred in the first 11 days, regardless of stent type, with a mean time to event of 5.8 ± 5.4 days (Fig. 1).

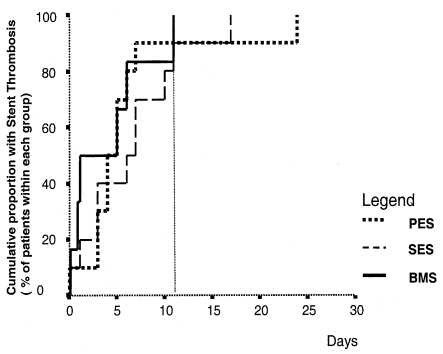

Figure 1. Cumulative incidence of angiographic stent thrombosis stratified by groups against time. **Vertical line** = day 11 on horizontal axis. BMS = bare-metal stents; PES = paclitaxel-eluting stents; SES = sirolimus-eluting stents.

In the BMS population, there were two acute stent thromboses and four subacute stent thromboses. Among the six patients, ST presented as AMI in five patients. None died during the six months of follow-up (Table 2). In the combined group of SES and PES (2,006 patients), there were 2 cases of acute ST and 18 cases of subacute ST (Fig. 1). A detailed description of these patients is given in Table 3. Analysis via intravascular ultrasonography was performed in four patients. In most patients, at least one recognized risk factor for ST (i.e., long stented length, use of small stents, use of multiple stents, and residual dissection after stent implantation) was present. Importantly, 2 of the 20 patients had not taken clopidogrel.

Mortality and morbidity. Overall, 20 of 26 patients (77%) re-presented with an AMI, whereas the other 6 re-presented with angina pectoris (Table 2). Of these 26 patients, 3 (Patients #12, #18, and #20 from Table 3—all in the DES population) died at days 11, 5, and 3, respectively. Two patients died during reintervention from intractable ventricular fibrillation, whereas the third underwent emergency surgery after a suboptimal reintervention and could not be weaned from bypass. The incidence of death at 30 days was 12%, whereas another 65% suffered a nonfatal MI. Among the survivors of ST, there were no further deaths in the six months after reintervention.

Possible ST. Thirty-day survival data was complete for 98% of patients (Table 4). There were 12 patients who were judged with "possible stent thrombosis," of which 9 died and 3 had nonfatal MIs. Of the nine deaths, four were out-of-hospital sudden deaths, three occurred in hospital with ventricular tachycardia as the initiating preterminal rhythm, and two had ST-segment elevation and died before they could undergo reangiography. Among those with MIs, one patient developed a postprocedural enzyme leak, and another developed ventricular fibrillation requiring multiple cardioversions the day after the procedure. Repeat coronary angiography six months later demonstrated occluded stents in both of these patients; whereas a third underwent coronary angiography 14 days after stent implantation because of an increase in cardiac enzyme levels, which demonstrated an in-stent filling defect which was treated

Table 3. Detailed Description of Drug-Eluting Stent Patients With Angiographic Stent Thrombosis

Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Type of DES	**SES**	**SES**	**SES**	**SES**	**SES**	**SES**	**SES**	**SES**	**SES**	**SES**
Time to Thrombosis (days)	**0.125**	**11**	**7**	**10**	**1.08**	**6**	**3**	**7**	**17**	**3**
Baseline characteristics										
Age (yrs)	72	61	86	57	75	55	53	58	58	74
Gender	F	F	F	M	F	F	M	M	M	M
Diabetes	+	+	–	+	–	–	+	–	+	–
Current smoker	–	–	–	+	–	–	–	–	–	–
Previous MI	–	+	–	+	–	–	+	–	+	+
Previous intervention	–	–	–	+	–	+	+	–	–	–
Index procedure										
Indication for procedure	UAP	AP	UAP	AMI, ST	AP	AP, ISR	UAP post-AMI	AP	AMI	UAP post-AMI
Glycoprotein IIb/IIIa use	–	–	–	Y	–	–	–	Y	Y	–
Angiographic features of index procedure										
Culprit vessel	LAD	LAD	LAD	LAD	LAD/DIAG	LAD/DIAG	RCA	LAD	DIAG	LAD
Lesion type (AHA)	B1	C	C	C	B2	C	B2	B2	B2	B2
Bifurcation technique (where performed)	–	–	–	–	crush	t-stent	–	–	t-stent	–
Final kissing balloons in bifurcation stenting	–	–	–	–	Y	N			N	
Minimum stent diameter (mm)	2.25	2.5	3	3	3	2.5	3	2.75	3	2.75
Total stent length (mm)	26	66	41	26	36	41	41	18	31	36
Total stents implanted	2	2	3	2	2	2	2	1	2	2
Reintervention										
Clinical presentation	AMI	AP	AMI	AP	AMI	AMI	AMI	AP	AMI	AMI
Additional stent implanted	Y	–	Y	Y	–	–	Y		–	–
IVUS findings (where performed)	RD	UD	–	RD	–	–	–		–	UD
Site of thrombosis in bifurcation lesions	–	–	–	–	MB+SB	SB	–	–	SB	–
Incomplete oral anti-platelet therapy	–	–	–	–	–	–	–	–	Y	–
Successful procedural outcome	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

AMI = acute myocardial infarction; AP = angina pectoris; DIAG = diagonal branch; IM = intermediate branch; LAD = left anterior descending artery; LCx = left circumflex artery; MB = mainbranch; N = no; OMCx = obtuse marginal branch; RCA = right coronary artery; RD = residual dissection; SB = sidebranch; ST = stent thrombosis; UAP = unstable angina pectoris; UD = underdeployment; Y = yes; other abbreviations as in Table 1.

with abciximab, and subsequently underwent repeat percutaneous coronary intervention two weeks later. Including the suspected cases, the combined incidence of angiographic and possible ST was 1.4% (95% CI 0.7% to 2.8%) in the BMS control group, 1.5% (95% CI 0.9% to 2.4%) in the SES group, and 1.6% (95% CI 1.0% to 2.6%) in the PES group. In the combined total of 38 documented and possible ST, there were 12 deaths (32%) and 20 nonfatal MIs (53%) in the first 30 days.

Multivariate analysis. By univariate analysis, bifurcation stenting was the only significant factor ($p = 0.01$). Multivariate analysis was performed with the following covariates based on their significance on univariate analysis as well as their potential clinical impact: diabetes ($p = 0.07$), smallest stent diameter ($p = 0.13$), multilesion stenting ($p = 0.17$), AMI as the indication ($p = 0.3$), and bifurcation stenting. By multivariate analysis, bifurcation stenting was the only independent predictor of ST (odds ratio [OR] 3.0, 95% CI 1.3 to 6.8, $p < 0.01$). When the interaction of bifurcation stenting by AMI was entered as a covariate, it was highly significant (OR 12.9, 95% CI 4.7 to 35.8, $p < 0.001$), and bifurcation stenting as a covariate was no longer significant.

DISCUSSION

The main findings in this study can be summarized as follows: 1) the incidence of angiographic ST in an unselected, complex DES population was low (~1.0%), within the same range as the corresponding BMS population and concordant with previously published results from the BMS

Table 4. Incidence of Stent Thrombosis Classified by Definition

Stent Type	**Number of Patients**	**Angiographically Proven Stent Thrombosis n (% [95% CI])**	**Possible Stent Thrombosis n (% [95% CI])**	**All Stent Thrombosis n (% [95% CI])**
BMS	506	6 (1.2% [0.5%–2.6%])	1 (0.2% [0.0%–1.1%])	7 (1.4% [0.7%–2.8%])
SES	1,017	10 (1.0% [0.5%–1.8%])	5 (0.5% [0.2%–1.1%])	15 (1.5% [0.9%–2.4%])
PES	989	10 (1.0% [0.6%–1.9%])	6 (0.6% [0.3%–1.3%])	16 (1.6% [1.0%–2.6%])

CI = confidence interval; other abbreviations as in Table 1.

Table 3 Continued

11 PES 0.04	12 PES 4	13 PES 7	14 PES 6	15 PES 3	16 PES 4	17 PES 24	18 PES 5	19 PES 5	20 PES 3	Mean ± SD, % 6.3 ± 5.7
59	50	67	47	61	52	60	54	65	31	59.7 ± 11.9
M	M	M	F	M	F	M	M	M	M	13 M:7 F
–	–	–	–	+	–	–	–	–	–	30%
–	–	–	+	+	+	–	+	–	+	30%
–	–	+	–	+	–	+	–	+	–	45%
–	–	+	–	–	–	–	–	–	+	25%
AMI	AMI	AP	AMI	AP	AMI	AP	AMI	AP	AP	
–	–	–	Y	–	–	–	Y	Y	–	30%
RCA	LAD	OMCX	LAD/DIAG	LCx	LCx/OMCx	LCx	LAD/Diag	LAD/IM/LCx	LAD	
B2	B2	C	C	B2	C	C	C	C	B2	
–	–	crush	crush	–	t-stent	–	crush	culotte crush	–	40%
–	–	N	N	–	N	–	N	Y	–	
3	3.5	2.5	2.5	2.5	2.25	2.25	2.75	2.25	3	2.7 ± 0.3
28	24	32	36	20	44	32	36	140	84	41.2 ± 27.8
1	1	2	2	1	2	2	2	8	4	2.2 ± 1.5
AMI	AMI	AMI	AMI	AMI	UAP	UAP	AMI	AMI	AMI	AMI = 75%
–	–	Y	–	Y	–	Y	–	–	–	Yes = 35%
–	–	–	–	–	–	–	–	–	–	
–	–	SB	SB	–	SB	MB+SB	SB	MB+SB	–	
–	–	–	–	Y	–	–	–	–	–	10%
Y	Died	Y	Y	Y	Y	Y	Y	Died	Died	Death = 15%

era; 2) the inclusion of possible ST increases the overall incidence of ST to ~1.5%; 3) angiographically proven ST was associated with a high mortality and morbidity; 4) patients who developed ST often had multiple high-risk features, regardless of stent type; and 5) the association of bifurcation stenting for AMI was a highly significant independent risk factor for ST.

The availability of DES as the default stent at our institution has allowed us to analyze this new technology in an unrestricted population (8), a population that would have comprised any BMS population in the pre-DES era. Therefore, this availability allows us to analyze incidences in an "all-comers" population because patients were enrolled irrespective of clinical presentation or outcome. In this population sample, angiographic ST rates in the first 30 days for both DES, i.e., SES and PES, occurred within the range as that reported in the BMS era (1,2,11,12).

The angiographic definition used is the most accurate for diagnosis but may underestimate the true incidence of ST because some patients who have a presumed ST may die before receiving medical attention. Conversely, the use of major adverse cardiac events (i.e., death and MI in addition to the angiographic findings) to define ST overestimates the true incidence because not all patients who die suddenly or suffer a MI do so because of ST (13). This consideration is important in our heterogeneous unrestricted population with multivessel disease, previous MI, and previous revascularization. Furthermore, not all patients who die will

Table 5. Clinical Trials on Drug-Eluting Stents

Trial Name	Number of Patients in Drug-Eluting Arm	Total Stent Length mm (Mean ± SD)	Incidence of Stent Thrombosis in the First 30 Days (%)
SIRIUS (3)	533	23.0 ± 8.6	0.2*
E-SIRIUS (6)	157	21.5 ± 6.7	1.1*
C-SIRIUS (5)	50	23.8 ± 8.4	2.0*
TAXUS-IV (4)	662	21.9 ± 8.1	0.3†
SES group	1,017	42.5 ± 29.6	‡1.0–1.5§
PES group	989	44.2 ± 29.4	‡1.0–1.6§

*Definition of stent thrombosis was not stated. †Stent thrombosis defined as angiographically proven, or cardiac death or myocardial infarction in the first 30 days. ‡Stent thrombosis defined as angiographically proven. §Stent thrombosis defined as angiographically proven, or adjudicated death or myocardial infarction in the first 30 days.
Abbreviations as in Table 1.

undergo autopsy studies to determine the cause of death. To attenuate this overestimation and to provide an accurate figure, we have adjudicated all deaths and noncatheterized, nonfatal MIs within the first 30 days in the three groups and included them with the angiographically proven patients to provide an overall incidence for each group.

The incidences of ST for both groups of DES are within the range reported in the larger randomized clinical trials of DES (3–6) despite longer total stent length, multivessel treatment, and a heterogeneous population (Table 5). This incidence complements information already available from the randomized trials regarding the safety of these new devices.

Angiographic ST was associated with a high mortality and morbidity in our study. Within the DES population, 15 patients (75%) experienced a MI as their diagnosis at the second presentation, and 3 (15%) died during the reintervention procedure. The inclusion of possible ST patients increased the mortality to 32%. Given the small number of events, the fact that no deaths occurred in the BMS group was most likely due to chance. These results are in concordance with the results of a large BMS registry (2).

Previous studies have demonstrated that residual dissection (1,11), long stents (1), small final lumen diameter (1), and use of multiple stents (2) are risk factors for the development of ST. In our series, multiple risk factors were identified in most patients who developed ST. Patients with ST had more multiple lesions treated, smaller minimum stent diameters, and longer stent lengths compared with those without ST; however, these factors were not significant on univariate analysis. What did emerge and which has not been previously reported is that patients undergoing bifurcation stenting had a higher incidence of ST compared with those without bifurcation stenting. A recent study on bifurcations reported a 3.5% incidence of ST, which is higher than the overall incidence in this population (14).

Although stent implantation for AMI was not significant on univariate analysis, the interaction of AMI and bifurcation stenting when entered as a covariate for ST on multivariate analysis emerged as a highly significant independent predictor, and bifurcation stenting as a covariate was no longer significant. This result confirms a clinical suspicion in our department regarding the increased risk of ST in patients treated with bifurcation stenting in the setting of AMI.

Mechanical reasons that predispose to ST can be modified by interventional technique. Optimizing stent placement including, if necessary, intravascular ultrasound-guided postdilation, kissing balloon postdilation with bifurcation stenting, and careful inspection for residual dissection after stent implantation, may further reduce the incidence of ST.

Pharmacologic reasons for ST, i.e., inadequate antiplatelet therapy, are patient-specific factors. Recent research literature has focused on "resistance" to either aspirin (15) or to clopidogrel (16). Currently, most laboratories do not routinely test for antiplatelet resistance. In our series, two patients who had not taken their prescribed clopidogrel after the procedure developed ST.

This report covers ST occurring in the first 30 days after stent implantation only, during which all patients received dual antiplatelet therapy. The duration of clopidogrel therapy differed among the three groups; in part, it reflects uncertainty with regards to re-endothelialization after DES implantation. Late ST has been reported to occur with BMS (17) and with DES (18), including a reported fatality (19) after clopidogrel discontinuation. At this stage, the incidence of late ST in the DES era is unknown, and further studies are required to clarify this potential late complication.

Comment on sample size and statistical comparisons. Because ST occurs at a low incidence (~1.0 to 1.5%), a small sample size may underestimate or overestimate the true incidence. In a previously published report from our institution, we reported an angiographic incidence of 0.4% in 508 patients (8). In the present study we extended the population to incorporate the entire period of DES used to date at our institution (n = 2,006) to allow a more accurate analysis of the true incidence of ST in the DES population. Despite having 2,512 patients, the low and small/negligible absolute difference in incidence precludes formal statistical comparisons of ST rates among the three groups because it lacks sufficient statistical power. To achieve adequate power would require sample sizes in the order of >100,000 patients. To date, this study is the largest series of patients reported on in the DES era.

Study limitations. These single-center registry data complement available randomized data, as they reflect the results of unrestricted DES use.

Conclusions. Despite having a more complex cohort with high-risk inclusion criteria, longer stent lengths, and more complex procedural features, the incidence of ST with DES are in the same range as the BMS population observed in our present study. They also are in agreement with previously reported data by others from the BMS era and with those results reported on in the earlier randomized DES trials. Furthermore, the two groups of DES, i.e., SES and PES, share an incidence of ~1.0% to 1.5%. Stent thrombosis is associated with a high morbidity and mortality.

As extensively documented in previous reports with BMS, mechanical reasons were observed to be frequent associations for ST with DES. In this study, bifurcation stenting in the setting of AMI was a highly significant independent predictor for angiographic ST.

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Chapter 16

Late Thrombosis in Drug-Eluting Coronary Stents After Discontinuation of Antiplatelet Therapy.

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Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy

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Although the safety profiles of coronary stents eluting sirolimus or paclitaxel do not seem to differ from those of bare metal stents in the short-to-medium term, concern has arisen about the potential for late stent thromboses related to delayed endothelialisation of the stent struts. We report four cases of angiographically-confirmed stent thrombosis that occurred late after elective implantation of polymer-based paxlitaxel-eluting (343 and 442 days) or sirolimus-eluting (335 and 375 days) stents, and resulted in myocardial infarction. All cases arose soon after antiplatelet therapy was interrupted. If confirmed in systematic long-term follow-up studies, our findings have potentially serious clinical implications.

Metallic coronary stents are implanted in more than 1·5 million patients per year. Polymer-based coronary stents eluting sirolimus or paclitaxel substantially reduce the need for repeat percutaneous intervention compared with bare-metal stents, and drug-eluting stents are rapidly replacing bare-metal stents. A meta-analysis[1] of 11 randomised trials (5013 patients) showed no evidence that the short-to-medium-term safety profiles of sirolimus-eluting or paclitaxel-eluting stents differed from those of bare-metal stents. However, these trials were not powered to detect or exclude an effect of drug-eluting stents on rare events such as stent thrombosis.

Stent thrombosis usually results in ST-segment elevation myocardial infarction or death. Angiographically documented late (>6 months) stent thrombosis is extremely rare with bare-metal stents except after intracoronary irradiation, which delays vascular healing. There is concern that drug-eluting stents might also be susceptible to late thrombosis related to delayed endothelialisation of the stent struts.[2] We report four cases of late stent thrombosis when antiplatelet therapy was interrupted after elective implantation of drug-eluting stents.

In March, 2003, a 63-year-old man presented with unstable angina and angiographically significant lesions (>50% diameter stenosis) in the left anterior descending artery and a non-dominant right coronary artery. He underwent percutaneous intervention of the left anterior descending artery in June, 2003, with one paclitaxel-eluting stent (3 mm diameter, 16 mm long; Taxus Express 2, Boston Scientific, Natick, MA, USA) and had no further angina. Aspirin was stopped in May, 2004, before elective resection of bladder polyps. 5 days later, 343 days after stenting, the patient presented with an anterior myocardial infarction. Angiography showed stent occlusion. Percutaneous intervention restored vessel patency; peak concentration of creatine kinase was 6500 IU/L.

A 73-year-old man sustained an aborted out-of-hospital cardiac arrest with documented ventricular fibrillation. In the preceding weeks, he had atypical chest pain. The admission electrocardiogram was normal. Coronary angiography showed an isolated proximal lesion of the left anterior descending artery (figure 1A). Electrophysiological investigations were negative. The patient underwent percutaneous intervention with one paclitaxel-eluting stent (3·5 mm diameter, 16 mm long; Taxus Express 2), in April, 2003 (figure 1B and 1C) and was subsequently asymptomatic. In June, 2004, aspirin was discontinued before resection of a newly diagnosed colon carcinoma. 1 week later, on the evening of surgery, 442 days after stenting, the patient developed anterior myocardial infarction. Angiography showed stent occlusion (figure 1D) and extensive thrombus after guidewire passage (figure 1E). Percutaneous intervention restored vessel patency; peak concentration of creatine kinase was 3500 IU/L.

A 42-year-old man admitted to hospital with chest pain in May, 2003, developed ventricular fibrillation. After successful cardioversion, angiography showed significant lesions in the left anterior descending artery (the culprit lesion) and left circumflex artery. Two bare-metal stents (3·0 mm diameter, 18 mm long; Vision, Guidant Santa Clara, CA, USA) were placed in the left anterior descending artery. 2 days later, the patient underwent elective stenting of the left circumflex artery with one sirolimus-eluting stent (3 mm diameter, 33 mm long; Cordis, Miami Lakes, FL, USA) in a second obtuse marginal branch, and was subsequently asymptomatic. In November, 2003, after negative nuclear stress testing, clopidogrel was discontinued. In May, 2004, the patient stopped taking aspirin. 2 weeks later, 375 days after stenting, he presented with chest pain. Angiography showed patent bare-metal stents (figure 2A) but the sirolimus-eluting stent was occluded (not shown). Intravascular ultrasonography after thrombectomy ruled out both malapposition (figure 2B) and edge restenosis. Percutaneous intervention was successful.

A 62-year-old man with stable angina and two-vessel coronary disease underwent successful percutaneous intervention with one sirolimus-eluting stent (3 mm diameter, 18 mm long; Cordis) in the left anterior descending artery, and one bare-metal stent (3 mm diameter, 18 mm long; Vision) in an obtuse marginal

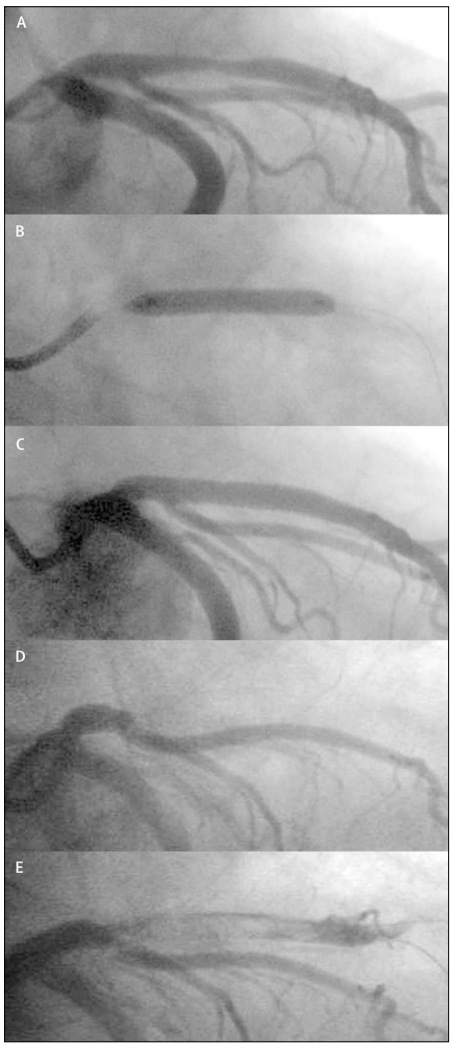

Figure 1: **Coronary angiography showing implantation of a paclitaxel-eluting stent and subsequent thrombosis**
Concentric lesion in the mid left anterior descending artery at baseline (A), during (B) and after (C) implantation of a paclitaxel-eluting stent. (D) Occlusion at the proximal margin of the stent. (E) Angiogram after passage of guidewire showing large thrombus in the stent.

branch in July, 2003. In June, 2004, the patient stopped clopidogrel and aspirin before colonoscopy and polypectomy. 4 days later, 335 days after stenting, he presented with an anterior myocardial infarction. Angiography showed occlusion of the sirolimus-eluting stent, whereas the bare-metal stent was patent. Percutaneous intervention was successful.

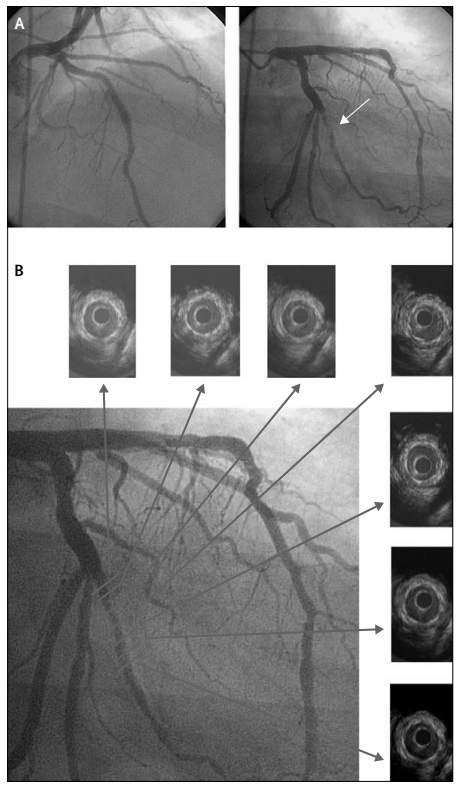

Figure 2: **Angiographic and intravascular ultrasound images on presentation with stent thrombosis in a patient previously treated with sirolimus-eluting and bare-metal stents**
(A) Left coronary angiogram, after mechanical thrombectomy, showing the widely patent bare-metal stent in the left anterior descending coronary artery (left) with residual thrombotic material (white arrow) in the sirolimus-eluting stent (right). There was no "edge" restenosis. (B) Intravascular ultrasound images within the stent (white lines), after mechanical thrombectomy, showing optimal stent apposition.

Late thrombosis after bare-metal stenting is a well documented, albeit rare, complication when intracoronary irradiation is used as an adjunct to stent placement to reduce restenosis after percutaneous intervention. This problem has been attributed to delayed vascular healing that renders the surface of the stent prothrombotic, and, in the presence of an appropriate physiological stimulus, can result in thrombotic occlusion.

Studies in animals have generated concern that drug-eluting stents could also be prone to late stent thrombosis, although extrapolation of such findings to human beings might be unreliable.[2] Evidence from animal models suggests that the Cypher sirolimus-eluting stent does not impede endothelialisation.[3] By contrast, animal studies with paclitaxel-eluting stents

clearly show delayed re-endothelialisation.[4] However, these studies were done with stents in which the polymer coating, design, and drug-release kinetics differed substantially from those of the Taxus paclitaxel-eluting stents; to our knowledge, no reports have been published about the effects of Taxus stents on re-endothelialisation. There are also differences between the drug-release kinetics of Cypher and Taxus stents. With the Taxus stent, about 10% of the paclitaxel is released by 10 days; the rest remains in the polymer indefinitely. With the Cypher stent, almost all the sirolimus has eluted by 6 weeks, leaving a polymer-coated bare-metal stent. It is unclear whether this difference is of any clinical importance, in terms of the potential for long-term adverse events.

Based on the design of the pivotal clinical trials that led to approval of such stents, dual antiplatelet therapy is prescribed on an empirical basis, for 2–3 months after implantation of sirolimus-eluting stents, and for 6 months after implantation of paclitaxel-eluting stents, with life-long aspirin. Our report shows that thrombosis can arise very late after uncomplicated placement of a single drug-eluting stent, in a large vessel, when antiplatelet therapy is discontinued. In two of four patients, a bare-metal stent implanted in a different vessel, at or around the same time, remained patent when the drug-eluting stent occluded.

Three of these late occlusions happened when antiplatelet therapy was discontinued for non-cardiac surgery. In the bare-metal stent era, an initial report showed that non-cardiac surgery more than 2 weeks after stent placement was associated with a prohibitive rate of adverse events (32% mortality).[5] Findings from a subsequent larger series suggested that discontinuation of antiplatelet therapy, later than 6 weeks after placement of a bare-metal stent, for non-cardiac surgery was relatively safe.[6] The time window of the occlusions we encountered far exceeds that reported for bare-metal stents.

Our report has limitations. Intravascular ultrasound definitively excluded restenosis as a contributing factor to late thrombosis in only one patient. The others were haemodynamically unstable, precluding intravascular ultrasound. However the absence of symptoms after stenting, coupled with the acute presentation and the angiographic findings, suggest that the mechanism was purely thrombotic. Second, we only report angiographically-confirmed cases; highly suspect presumed cases have been reported; thus, the true rate might be higher.[7]

We report these cases to draw attention to a problem, with serious clinical implications, that might be under-reported. We suggest that the potential risk of stent occlusion should be considered when discontinuation of antiplatelet therapy is contemplated in patients with drug-eluting stents. Finally, as the use of drug-eluting stents becomes widespread, careful long-term follow-up of patients with such stents is needed to assess the true rate of late thrombosis.

Contributors

E P McFadden and E Stabile wrote and revised the report; both authors contributed equally. The other authors reviewed the report. For the authors in Europe: E P McFadden did initial procedures for two patients and follow-up procedure for one patient; E Regar did the other follow-up procedure; A T L Ong collected data; P W Serruys, as head of the department, was also responsible for patient care. For the authors in the USA: E Stabile was involved in data collection and patient care; E Cheneau and T Kinnaird helped in adjudicating the events and drafting the manuscript; W O Suddath participated in patient care; N J Weissman assessed the intravascular ultrasound; R Torguson was the research coordinator and helped in data collection; K M Kent, A D Pichard, and L F Satler participated in care of patients; R Waksman helped in drafting the letter and participated in patient care.

Conflict of interest statement

E P McFadden has received travel grants and/or speaker's fees from Boston Scientific, Cordis, Centocor (a Johnson and Johnson company), Guidant, Medtronic, and Sorin Biomedica, and has no other conflicts of interest. The authors declare that they have no conflict of interest.

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Chapter 17

Late Angiographic Stent Thrombosis (LAST) Events With Drug-Eluting Stents.

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Late Angiographic Stent Thrombosis (LAST) Events With Drug-Eluting Stents

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OBJECTIVES We sought to describe the incidence of late angiographic stent thrombosis (LAST) events in an unselected drug-eluting stent (DES) population.

BACKGROUND Concerns have been raised that LAST may be a potential limitation of DES.

METHODS We have previously reported the angiographic incidence of early stent thrombosis (1.0%) in this prospective cohort of 2,006 patients treated with either sirolimus-eluting stents (SES) (n = 1,017) or paclitaxel-eluting stents (PES) (n = 989). We continued long-term follow-up to determine the incidence of LAST events, defined as angiographically proven stent thrombosis associated with acute symptoms more than 30 days after DES implantation. All patients had at least 1 year of follow-up, mean duration 1.5 years.

RESULTS There were eight angiographically confirmed LAST events in seven patients: three with SES (at 2, 25, and 26 months) and five with PES (at 6, 7, 8, 11, and 14.5 months). Three cases were related to complete cessation of antiplatelet therapy, two cases occurred while patients were on aspirin therapy within one month of cessation of clopidogrel, and three cases occurred at a time when patients were apparently clinically stable on aspirin monotherapy. We observed no cases of LAST in patients who were on dual antiplatelet therapy. Two deaths occurred directly as a result of LAST.

CONCLUSIONS Angiographically proven late stent thrombosis occurs with an incidence of at least 0.35% (95% confidence limits 0.17% to 0.72%) in patients treated with DES. Importantly, it may also occur when patients are stable on antiplatelet monotherapy. (J Am Coll Cardiol 2005; 45:2088–92) © 2005 by the American College of Cardiology Foundation

Drug-eluting stents (DES) have revolutionized the practice of interventional cardiology with their proven efficacy in reducing restenosis rates. In the U.S., up to 80% of stent implantations currently are with DES. A meta-analysis of 11 randomized trials confirmed the efficacy and safety profile of these stents, but these trials were not powered to detect or exclude an effect of DES on rare events such as stent thrombosis (1). Since April 2002, we have adopted a policy of universal DES implantation for all patients irrespective of clinical presentation or angiographic features, the "all-comers" approach. Based on this approach, we were able to define the incidence of early stent thrombosis (<30 days) in a DES population of 2,006 patients (2).

Our institution has been confronted with patients presenting with late angiographic stent thrombosis (LAST) events, an unexpected occurrence given the long period of dual antiplatelet therapy prescribed in comparison to bare stents (3). Late angiographic stent thrombosis events were uncommon with bare stents except after brachytherapy (4), and subsequent to that report, dual antiplatelet therapy was prolonged for that population. Furthermore, in animal models, DES may delay or cause incomplete healing to a greater degree than with bare-metal stents (5). Therefore, we sought to investigate the incidence of LAST events in the DES population.

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METHODS

Study design and patient population. Briefly, since April 2002, we have adopted a policy of universal DES implantation for all patients irrespective of clinical presentation or angiographic characteristics, known as an "all-comers population." We have previously reported on the incidence of early stent thrombosis (defined as stent thrombosis occurring within the first 30 days following stent implantation) in 2,006 consecutive patients after DES implantation (2). This study population thus comprises 1,017 patients treated with sirolimus-eluting stents (SES) from April 2002 to February 2003, and 989 patients treated with paclitaxel-eluting stents (PES) from February 2003 to December 2003. We continued a long-term (minimum one year) follow-up on this cohort of patients to determine the incidence of LAST.

Follow-up. Post-discharge survival status was obtained from the Municipal Civil Registries. A health questionnaire was sent to all living patients with specific questions on re-hospitalization and adverse events. As the principal referral center within the region, repeat procedures are normally performed at our institution and recorded prospec-

Abbreviations and Acronyms

DES = drug-eluting stents
IVUS = intravascular ultrasound
LAST = late angiographic stent thrombosis
MI = myocardial infarction
PES = paclitaxel-eluting stents
SES = sirolimus-eluting stents
TIMI = Thrombolysis In Myocardial Infarction

tively in our database. For patients who suffered an adverse event at another center, medical records or discharge summaries from the other institutions were systematically reviewed. General practitioners, referring cardiologists, and patients were contacted as necessary for additional information.

Procedure and antiplatelet management. All interventions were performed according to current standard guidelines, with the interventional strategy including periprocedural glycoprotein IIb/IIIa inhibitor and intravascular ultrasound (IVUS) use left to the discretion of the operator. Patients were pretreated with aspirin and a loading dose of 300 mg clopidogrel.

Duration of clopidogrel therapy. Upon completion of the index procedure, patients are advised to maintain lifelong aspirin therapy. Patients who received SES were prescribed clopidogrel for three or six months depending on the complexity of the procedure, whereas patients treated with PES were given a six-month prescription. In the Netherlands, clopidogrel after stenting is not reimbursed by medical insurance companies and our department has covered the cost for patients treated here. As a tertiary referral center, most of our patients are referred from other institutions and after discharge from our institution, are managed by referring physicians at peripheral centers. Late decisions regarding antiplatelet therapy are at their discretion.

Definition of LAST. Late angiographic stent thrombosis is defined as late—occurring at least one month after DES implantation with acute symptoms; angiographic—stent thrombosis confirmed angiographically; stent thrombosis—defined as Thrombolysis In Myocardial Infarction (TIMI) flow 0 or 1 or the presence of flow-limiting thrombus (TIMI flow 1 or 2).

RESULTS

Baseline and procedural characteristics. The average age of our patients was 62 years, with 72% being male (Table 1). Over half had multivessel disease on angiography, one-third presented with unstable angina, and 22% with an acute myocardial infarction (MI) as the indication for treatment. Stent type was approximately equally distributed as was the enrolment period. On average, 1.9 lesions in 1.4 vessels were treated with 2.3 stents implanted, totaling 43 mm/patient.

Findings. Follow-up was complete for 98% of the population. Mean follow-up was 1.5 ± 0.5 years. There were eight LAST events in seven patients, three with SES and five with PES (Tables 2 and 3), with an overall incidence of 0.35% (95% confidence limits 0.17% to 0.72%). All patients were male, and all presented at the time of LAST with an acute ST-segment elevation MI. Figure 1 is a representative example of LAST. No differences in patient characteristics (Table 1) were noted between patients with and without LAST. None of the 20 patients described in the previous report with early stent thrombosis (2) developed LAST.

There were two deaths in the seven patients with LAST. One death (Patient #6) occurred in a patient who received a SES to the left anterior descending coronary artery (LAD). Late angiographic stent thrombosis 25 months later resulted in a large anterior MI with cardiogenic shock and the patient died from refractory left ventricular failure two days later. The second death occurred in a patient (Patient #7) who had a pre-existing occlusion of the right coronary artery that received collaterals from the LAD. A single SES was implanted at a proximal LAD lesion. Late angiographic stent thrombosis 26 months later resulted in a large acute anterior MI with cardiogenic shock and the patient died on the catheterization table. Of note, in both these patients, initial attempts to pass a wire through the previous stent were unsuccessful because the wires, on each occasion, appeared to pass between the outside of the stent and the

Table 1. Baseline and Procedural Characteristics of Drug-Eluting Population

	Drug-Eluting Stents (n = 2,006)
Baseline characteristics	
Age, yrs, mean ± SD	61.9 ± 11.3
Male, %	72
Diabetes, %	17
Hypercholesterolemia, %	58
Current smoker, %	28
Hypertension, %	41
Previous myocardial infarction, %	33
Previous PCI, %	25
Previous CABG, %	9
Multivessel disease, %	57
Indication for index procedure	
Stable angina, %	42
Unstable angina, %	33
Acute myocardial infarction, %	22
Silent ischemia, %	3
Procedural characteristics	
Number of lesions treated, mean ± SD	1.9 ± 1.0
Number of vessels treated, mean ± SD	1.4 ± 0.6
LAD, n	1,135
LCx, n	665
RCA, n	784
Others, n	163
Patients treated with SES, n	1,017
Patients treated with PES, n	989
Total stented length, mm (mean ± SD)	43 ± 31
Number of stents implanted, n (mean ± SD)	2.3 ± 1.5
At least one ≤2.50 mm stent implanted (%)	38
Bifurcations stented, %	18
Glycoprotein IIb/IIIa use (%)	25

CABG = coronary artery bypass grafting; LAD = left anterior descending; LCx = left circumflex; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent; RCA = right coronary artery; SES = sirolimus-eluting stent.

Table 2. Characteristics of Patients With LAST

Pt. No.	Age, Gender	Months to Event	DES Type	Treated Vessel	Nominal Stent Diameter, mm	Total Stented Length, mm	Antiplatelet Therapy at Time of LAST	Notes	Clinical Presentation	Clinical Outcome at Hospital Discharge
1	74, Male	2	SES	Mid LAD	2.5	23	Nil	Aspirin and clopidogrel stopped 5 days prior	STEMI	Alive
2	57, Male	7	PES	RCA	3.0	68	Aspirin	Clopidogrel stopped 28 days prior	STEMI	Alive
3a	64, Male*	6	PES	Prox LAD†	3	32	Aspirin	Clopidogrel stopped 21 days prior	STEMI	Alive
3b‡	64, Male*	11	PES	Prox LAD	3	16	Nil	Aspirin stopped 5 days prior for surgery	STEMI	Alive
4‡	74, Male	14.5	PES	Prox LAD	3.5	20	Nil	Aspirin stopped 7 days prior for surgery	STEMI	Alive
5	39, Male	8	PES	Mid RCA†	3	20	Aspirin	Clopidogrel stopped 2 months prior	STEMI	Alive
6	63, Male	25	SES	Prox LAD	3	46	Aspirin	Clopidogrel stopped 19 months prior	STEMI with shock	Dead
7	71, Male	26	SES	Prox LAD	3	36	Aspirin	Clopidogrel stopped 23 months prior	STEMI with shock	Dead

*This patient had two separate episodes of late stent thrombosis. †Late stent thrombosis occurred within a stent-in-stent segment. ‡These two patients were included in a previous report (3).
LAST = late angiographic stent thrombosis; STEMI = ST-segment elevation myocardial infarction; other abbreviations as in Table 1.

vessel wall. This is highly suggestive of acquired aneurysm formation at the stented site because on review, the initial procedural result was optimal. Due to hemodynamic instability, IVUS was not attempted. Autopsy was refused in both cases.

One patient (Patient #3) treated with a PES to the LAD developed two LAST events. The first occurred 11 months after the index procedure and re-presented with an anterior ST-segment elevation MI. He was treated with a new PES inside the original PES stent and lifelong clopidogrel was recommended; before discharge he was given his first prescription of six months worth of clopidogrel. He completed the prescribed six-month course of dual antiplatelet therapy and did not renew the prescription of clopidogrel. Twenty-one days later, he re-presented with lateral ST-segment elevation. Three new PES were used to re-canalize a diagonal branch occluded with thrombus. Intravascular ultrasound study did not reveal a specific contributory factor, in particular, there was no evidence of incomplete stent apposition.

With regard to antiplatelet therapy, three events occurred when patients had stopped all antiplatelet therapy (two were for non-cardiac surgery, and one due to non-compliance). Five events occurred in patients on aspirin monotherapy who had completed their prescribed course of clopidogrel. Two of these events occurred soon after (21 and 28 days) clopidogrel was stopped.

Treatment. Balloon angioplasty was performed in all patients, followed by new DES implantation in seven of eight (Table 3). Glycoprotein IIb/IIIa inhibitors were used in five cases. Intravascular ultrasound was performed in two patients with no evidence of incomplete stent apposition noted. A thrombectomy device was used in two cases. After an episode of late stent thrombosis, prolonged clopidogrel therapy was empirically recommended.

DISCUSSION

The purpose of this report is to highlight that LAST occurs with an incidence of at least 0.35% and possibly up to 0.72% after DES implantation. Furthermore, we have now observed that LAST may also occur not only in temporal relation to complete cessation of antiplatelet therapy (3), but may also occur shortly after clopidogrel is stopped but aspirin continued, and unexpectedly remote from clopidogrel cessation when patients were clinically stable on long-term aspirin therapy. We observed no episodes of LAST while patients were on dual antiplatelet therapy.

In the randomized trials of DES, late stent thrombosis has been reported. Two presumed late stent thromboses related to clopidogrel discontinuation were reported in the TAXUS-II trial (6). With SES, there has been one published report of LAST from the European multicenter, randomized, double-blind study of the SIRolImUS-coated Bx velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions (E-SIRIUS)

Table 3. Treatment of Patients With LAST

Pt. No.	Age, Gender	IVUS	Glycoprotein IIb/IIIa Use	Treatment	Post-LAST Clopidogrel Recommendation
1	74, Male	No	Abciximab	Balloon angioplasty, SES 2.75*18 mm	Lifelong
2	57, Male	Yes	Abciximab	Thrombectomy, balloon angioplasty, PES 3.5*20 mm	1 year
3a	64, Male*	Yes	Abicixmab	Balloon angioplasty, PES 2.25*8mm, 3.5*8 mm, 3.5*8 mm	Lifelong
3b	64, Male*	No	Abciximab	Balloon angioplasty, PES 3*32 mm	Lifelong
4	74, Male	No	No	Thrombectomy, balloon angioplasty, PES 3.5*12 mm	Not stated
5	39, Male	No	No	Balloon angioplasty, inotropes, atropine	Not stated
6	63, Male	No	Integrellin	Balloon angioplasty, PES 2.5*24 mm, intra-aortic balloon pump, inotropes	—
7	71, Male	No	No	Balloon angioplasty, PES 3*20 mm, 3*8 mm, 3*12 mm, intra-aortic balloon pump, inotropes	—

*This patient had two separate episodes of late stent thrombosis.
IVUS = intravascular ultrasound; other abbreviations as in Tables 1 and 2.

trial, with accompanying histological findings showing acquired aneurysm formation with eosinophilic infiltrates; the investigators concluded that LAST was due to a hypersensitive reaction to the polymer coating of the stent (7). Two of the LAST events we report occurred more than two years after SES implantation and both patients died. The timing of the events and the intraprocedural difficulty in wiring the lesion in both patients are potentially compatible with a similar etiology of LAST.

Late stent thrombosis was a major problem with the now discontinued QP2 stent program (8). The ongoing occurrence of stent thrombosis (3.2%, 7.1%, and 10.3% at 1, 6, and 12 months) in the Study to COmpare REstenosis Rate between QueST and QuaDDS-QP2 (SCORE) trial was attributed to the long duration of high-dose drug release and proinflammatory nature of the polymer sleeves.

Several mechanisms of LAST have been postulated: a local drug effect delaying endothelialization or results in the formation of a dysfunctional endothelium, a hypersensitivity, or inflammatory reaction to the polymer, or the development of neointimal hyperplasia with occlusive thrombus formation as the acute event. Furthermore, it is known that previous treatment with brachytherapy is associated with an increased risk of late stent thrombosis when on mono-antiplatelet therapy (4); however, no patient in this report had previous brachytherapy in the stented segment. The use of IVUS, if clinically feasible at the time of stent thrombosis, may help facilitate the elucidation of its etiology. However, their clinical condition often precludes a pre-intervention IVUS.

In patients with documented LAST, we empirically prescribe long-term dual antiplatelet therapy in an attempt to reduce recurrence. The use of long-term dual antiplatelet therapy for the primary prevention of LAST is more problematic. Although it would seem intuitive to do so, there is debate in published literature. There are data from the pre-DES era to suggest that in selected patients, prolonged dual antiplatelet therapy is associated with a reduction in major adverse cardiac events (9,10); however, such potent inhibition of platelet function is associated with an increased risk of major bleeding complications (11,12).

It is difficult to compare the incidence we have reported with that from the bare stent era due to the paucity of reports; a single center registry reported a late stent thrombosis incidence (defined as >30 days) of 0.76%, a figure not dissimilar to this report (13).

The results of this preliminary report expand our previous observations that LAST occurs with DES, demonstrate that it may occur when patients are receiving antiplatelet monotherapy, and provide an estimate of the expected rate in an unselected DES population. Its incidence is low, but potentially problematic given the rapid uptake of such stents. It is imperative that cardiologists and other doctors who treat these patients are aware of this potential late complication, and any decision to stop antiplatelet therapy for whatever reason must take this into account.

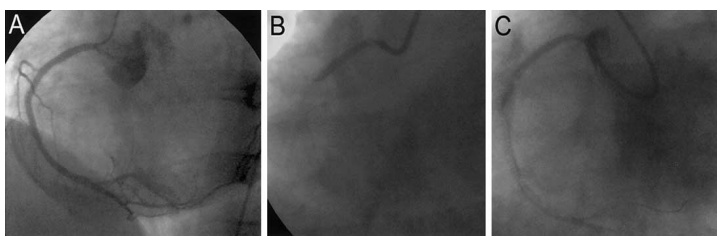

Figure 1. Representative film of late angiographic stent thrombosis (LAST). **(A)** Index procedure, post-stent implantation, right coronary artery. **(B)** Late angiographic stent thrombosis with ST-segment elevation. **(C)** After wire passage, LAST demonstrating large thrombus burden.

Study limitations. This report is confined to patients who presented with acute symptoms and angiographically proven late stent thrombosis. The low frequency of postmortem studies performed in the Netherlands, which would have accurately determined the cause of death, precluded an accurate assessment of the overall rate of late stent thrombosis.

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PART IV.

THE TRUE COST-EFFECTIVENESS OF DRUG-ELUTING STENTS IN THE REAL WORLD

Chapter 18

Cost-Effectiveness of the Unrestricted Use of Sirolimus-Eluting Stents Versus 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;
Sirolimus;
Real-world;
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.

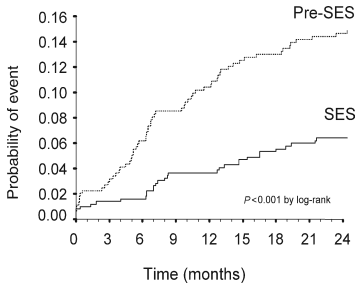

Figure 1 Clinically driven re-intervention (TVR) in the RESEARCH Registry at 2-year follow-up.

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.

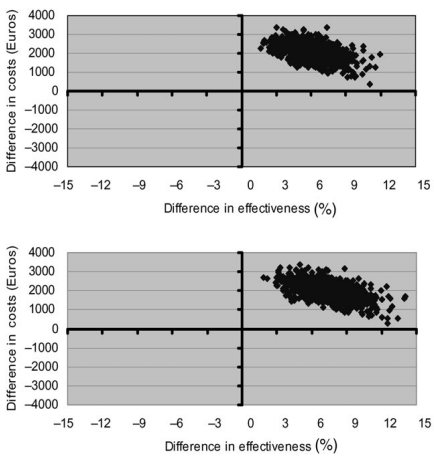

Figure 2 Estimates of differences in cost and effects after bootstrapping analysis based on the normal distributions surrounding the estimates of the relative risks at one (top panel) and 2 years (bottom panel), respectively. All points reside in the top-right quadrant, signifying that SESs are more 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

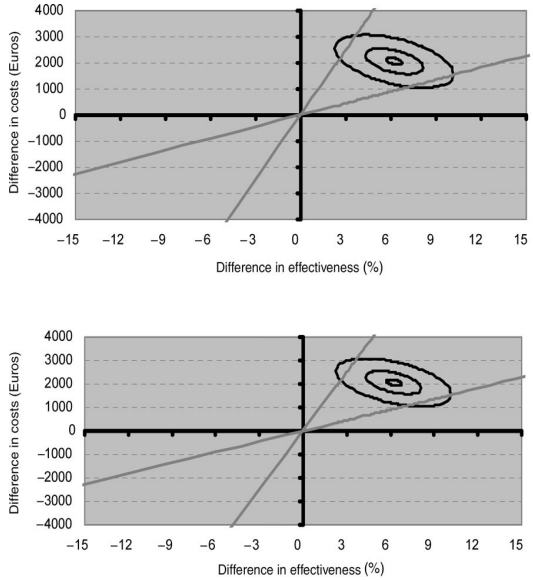

Figure 3 Estimates of differences in costs and effects following bootstrapping, with associated probability ellipses of 5, 50, and 95% (from innermost to outermost ellipse) at one (top panel) and 2 years (bottom panel), respectively. Note that the probability ellipses reside in the top-right quadrant, 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.

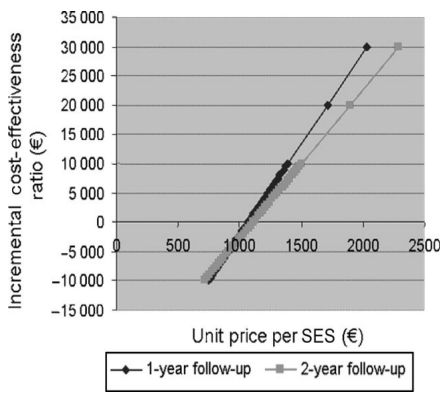

Figure 4 Graph depicting the relationship between the ICER and the unit price per SES in the RESEARCH registry at both 1 and 2-year follow-up.

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.

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Conflict of interest: no conflict of interest.

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PART V.

THE FUTURE OF DRUG-ELUTING STENTS: MULTIVESSEL DISEASE: - FROM THE BARE PAST TO THE ELUTING FUTURE

V.I LANDMARK PAPERS

Chapter 19

Five Year Outcomes After Coronary Stenting Versus Bypass Surgery for the Treatment of Multivessel Disease: The Final Analysis of the ARTS Randomised Trial.

Patrick W. Serruys, Andrew T. L. Ong, Lex A. van Herwerden, J. Eduardo Sousa, Adib Jatene, Johannes J. R. M. Bonnier, Jacques P. M. A. Schönberger, Nigel Buller, Robert Bonser, Clemens Disco, Bianca Backx, Paul G. Hugenholtz, Brian G. Firth, Felix Unger.

J Am Coll Cardiol 2005; 46:575-81

Five-Year Outcomes After Coronary Stenting Versus Bypass Surgery for the Treatment of Multivessel Disease

The Final Analysis of the Arterial Revascularization Therapies Study (ARTS) Randomized Trial

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OBJECTIVES The long-term (five-year) comparative results of treatment of multivessel coronary artery disease with stenting or coronary artery bypass grafting (CABG) is at present unknown.

BACKGROUND The Arterial Revascularization Therapies Study (ARTS) was designed to compare CABG and stenting in patients with multivessel disease.

METHODS A total of 1,205 patients with the potential for equivalent revascularization were randomly assigned to CABG (n = 605) or stent implantation (n = 600). The primary clinical end point was freedom from major adverse cardiac and cerebrovascular events (MACCE) at one year; MACCE at five-year follow-up constituted the final secondary end point.

RESULTS At five years, there were 48 and 46 deaths in the stent and CABG groups, respectively (8.0% vs. 7.6%; p = 0.83; relative risk [RR], 1.05; 95% confidence interval [CI], 0.71 to 1.55). Among 208 diabetic patients, mortality was 13.4% in the stent group and 8.3% in the CABG group (p = 0.27; RR, 1.61; 95% CI, 0.71 to 3.63). Overall freedom from death, stroke, or myocardial infarction was not significantly different between groups (18.2% in the stent group vs. 14.9% in the surgical group; p = 0.14; RR, 1.22; 95% CI, 0.95 to 1.58). The incidence of repeat revascularization was significantly higher in the stent group (30.3%) than in the CABG group (8.8%; p < 0.001; RR, 3.46;95% CI, 2.61 to 4.60). The composite event-free survival rate was 58.3% in the stent group and 78.2% in the CABG group (p < 0.0001; RR, 1.91;95% CI, 1.60 to 2.28).

CONCLUSIONS At five years there was no difference in mortality between stenting and surgery for multivessel disease. Furthermore, the incidence of stroke or myocardial infarction was not significantly different between the two groups. However, overall MACCE was higher in the stent group, driven by the increased need for repeat revascularization. (J Am Coll Cardiol 2005;46: 575–81) © 2005 by the American College of Cardiology Foundation

A meta-analysis including nine trials of multivessel coronary artery disease treated by percutaneous balloon angioplasty alone or coronary artery bypass grafting (CABG) showed a statistically significant benefit in terms of survival in favor of surgery at five and eight years (1). However, these survival data were from early studies that did not use stents in the initial revascularization procedure. The Stent or Surgery Trial (SoS), which involved the use of stents, reported similar findings after a median follow-up of two years (2). However, the Argentine Randomized Trial: Coronary Angioplasty with Stenting versus Coronary Bypass Surgery With Multivessel Disease (ERACI-II) suggested that the trend in favor of CABG for survival at 2.5 years was no longer present in the stent era (3).

There are currently no data available on the comparative survival after multivessel stenting or CABG beyond three years. The present study reports on the five-year survival and event-free survival of the patients enrolled in the Arterial Revascularization Therapies Study (ARTS) trial (4).

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Abbreviations and Acronyms

ARTS = Arterial Revascularization Therapies Study
CABG = coronary artery bypass grafting
CI = confidence interval
MACCE = major adverse cardiac and cerebral event
PCI = percutaneous coronary intervention
RR = relative risk

METHODS

The study protocol, summarized here, has been previously published (4,5).

Population. Between April 1997 and June 1998, 1,205 patients from 67 participating centers were randomized to either stent implantation (n = 600) or CABG (n = 605). The study population included 208 diabetic patients. The indications for revascularization included silent ischemia, 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 surgeon and interventional cardiologist that an equivalent degree of revascularization could potentially be obtained using either approach.

Specific exclusion criteria from the randomized trial may be summarized as follows: left ventricular ejection fraction <30%, left main stenosis, history of a cerebrovascular accident, transmural myocardial infarction within the preceding week, and severe hepatic or renal disease and need for concomitant major surgery. All patients gave written informed consent.

Five-year clinical follow-up. The study protocol required all patients to have follow-up clinic visits with an electrocardiogram at one, two, and three years. In addition, at the five-year clinical follow-up, 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 electrocardiograms.

Subgroup analysis. Pre-specified analyses were performed on diabetics versus non-diabetics and two- versus three-vessel disease. In addition, post-hoc analyses were performed on the following subgroups: proximal left anterior descending versus non-proximal left anterior descending lesions, renal status, gender, and age.

Clinical end points and effectiveness. The primary end point was defined as the absence of any of the following major adverse cardiac and cerebral events (MACCE) within 12 months after randomization: death (all-cause mortality), cerebrovascular accident, documented non-fatal myocardial infarction adjudicated by either new abnormal Q-wave or predefined enzymatic changes, or repeat revascularization by coronary stenting or CABG (4,5).

Secondary objectives of the study were to compare both strategies at three and five years. The MACCE were counted from the time of randomization, whereas the clinical status and medications were assessed at predetermined times of one, two, three, and five years post-procedure. Of 1,205 patients enrolled in the trial, complete follow-up was available at five years in 590 of 600 (98.3%) stent patients and 584 of 605 (96.6%) CABG patients (Fig. 1).

Statistical analysis. Statistical analysis was performed with SAS 6.12 software (SAS Institute Inc., Chicago, Illinois). Binary outcome variables are reported as frequencies and percentages and were compared in terms of relative risk with 95% confidence intervals calculated by the formula of Greenland and Robins (6). The Fisher exact test was used for categorical variables. All analyses were based on the intention-to-treat principle, and statistical tests were two-tailed. Event-free survival was estimated using the Kaplan-Meier method, and differences were assessed using the log-rank test. The sample size calculation to achieve adequate power for an inferiority study was based on the difference in event-free survival at one year (4). For this five-year report on late outcomes, no new calculations were performed.

RESULTS

Table 1 shows the baseline and procedural characteristics of the ARTS trial's randomized patients. The randomized groups were similar with respect to their demographic and anatomic characteristics. Five patients, one assigned to stenting and four assigned to surgery, did not undergo coronary revascularization and instead continued to receive only medical therapy (4). The average interval between randomization and treatment was 27 ± 39 days (range, 0 to 362 days) for patients in the surgery group and 11 ± 16 days (range, 0 to 173 days) for patients in the stenting group. Three patients died while waiting for surgery, 6 patients randomly assigned to stent implantation were instead treated surgically, and 19 patients randomly assigned to bypass surgery were instead treated with stent implantation. A total of 99% of patients in the stenting group (593 patients) and 93% in the surgery group (579 patients) received the assigned treatment. An equivalent anatomical degree of revascularization was achieved in each group.

During the initial hospital stay, after complicated or unsatisfactory angioplasty procedures, 14 patients assigned to stent implantation underwent bypass surgery, 3 urgently and 11 electively. Conversely, two patients underwent an angioplasty procedure after surgical revascularization during their initial hospital stay (Fig. 1).

Five-year clinical outcome. At five years, there were 48 deaths in the stent group and 46 deaths in the surgical group, which represents 8.0% and 7.6% of the respective cohorts (p = 0.83; relative risk [RR], 1.05; 95% confidence interval [CI], 0.71 to 1.55) (Table 2, Fig. 2). The incidence of cardiac death was not significantly different between the groups (Table 3). Of the 94 deaths, 6 occurred within 30 days after a repeat revascularization procedure.

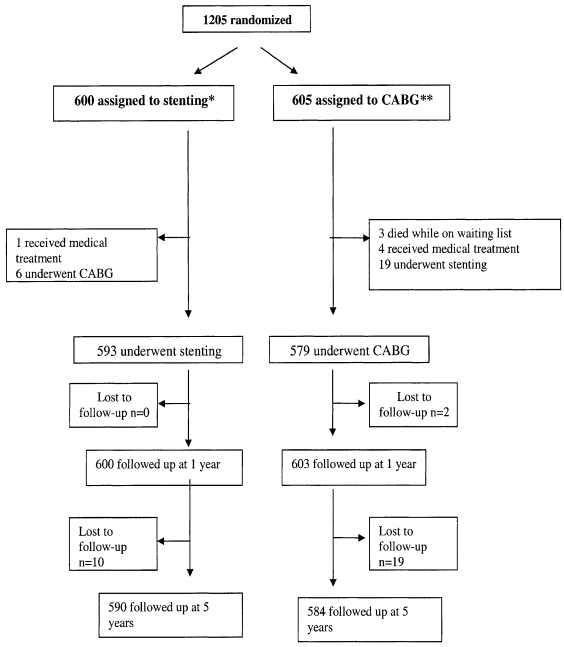

Figure 1. Flow chart. CABG = coronary artery bypass grafting.

The incidence of death, stroke, or myocardial infarction was not significantly different among the groups (18.2% in the stent group vs. 14.9% in the surgical group; p = 0.14; RR, 1.22; 95% CI, 0.95 to 1.58).

The incidence of repeat revascularization was significantly higher in the stent group (30.3%) than in the CABG group (8.8%; p < 0.001; RR, 3.46; 95% CI, 2.61 to 4.60). At the end of five years, 10.5% of patients originally assigned to stenting required CABG and 23.2% underwent a second percutaneous coronary intervention (PCI). Conversely, 1.2% of patients assigned to CABG required re-operation and 8.3% required revascularization with PCI. In the stent group, the majority of re-interventions (69%) took place within the first year, whereas in the CABG group, the majority of the re-interventions (57%) occurred after the first year. The overall MACCE-free survival at five years was 58.3% in the stent group and 78.2% in the CABG group (p < 0.0001).

At five years, there was a significant difference in the presence of anginal symptoms between the two treatment groups (21.2% of the stent patients vs. 15.5% of the CABG patients, p < 0.05). More of the stent patients were on short-acting nitrates (6.1% vs. 2.4%, p = 0.003), long-acting nitrates (19.6% vs. 11.6%, p < 0.001), beta-blocker therapy (53.9% vs. 46.5%, p = 0.016), and calcium-channel antagonists (29.1% vs. 18.9%, p < 0.001).

Table 1. Baseline and Procedural Characteristics of ARTS Population

	Stent (n = 600)	CABG (n = 605)
No. of patients not revascularized	1	7*
No. of cross-overs	6	19
Age (yrs), ± SD	61 ± 10	61 ± 9
Male gender (%)	77	76
Body mass index (kg/m^2), ± SD†	27.2 ± 3.7	27.4 ± 3.7
Diabetes (%)‡	19	16
Hypertension (%)§	45	45
Hypercholesterolemia (%)‖	58	58
Current smoker (%)	28	26
Previous myocardial infarction	44	42
Unstable angina (%)	37	35
Ejection fraction (%)	61 ± 12	60 ± 13
No. of diseased vessels (% of patients)		
1	2	0
2	68	67
3	30	33
No. of lesions with stenosis >50%	2.83 ± 1.02	2.80 ± 1.04
No. of lesions treated	2.60 ± 1.10	2.60 ± 1.00
Lesions treated with stent (%)	89	–
Patients with arterial conduit (%)	–	93

*Includes three patients who died while waiting for surgery. †The body mass index is determined as the weight in kilograms divided by the square of the height in meters. ‡Diabetes was defined as a patient whose condition was controlled by diet, oral hypoglycemics, or insulin. §Hypertension was defined as a blood pressure of ≥ 160/95 mm Hg in repeated measurements or patients on anti-hypertensive medication and/or requiring medical treatment. ‖Hypercholesterolemia was defined as a total cholesterol >6.5 mmol/l or patients on anti-hypercholesterolemic therapy.

CABG = coronary artery bypass graft; SD = standard deviation.

Table 2. Total Number of Patients With Major Clinical Events Within Interval of Time (Randomization to 1, 3, and 5 Years)

Event	Stent		CABG		Relative Risk (95% CI)	p Value†
	n*	%*	n*	%*		
Death						
0–1 yr	15	2.5	17	2.8	0.89 (0.45–1.77)	0.86
0–3 yrs	22	3.7	28	4.6	0.79 (0.46–1.37)	0.47
0–5 yrs	48	8.0	46	7.6	1.05 (0.71–1.55)	0.83
CVA						
0–1 yr	12	2.0	13	2.1	0.93 (0.43–2.02)	1.00
0–3 yrs	20	3.3	20	3.3	1.01 (0.55–1.86)	1.00
0–5 yrs	23	3.8	21	3.5	1.10 (0.62–1.97)	0.76
Q-wave MI						
0–1 yr	32	5.3	26	4.3	1.24 (0.75–2.06)	0.42
0–3 yrs	36	6.0	30	5.0	1.21 (0.76–1.94)	0.45
0–5 yrs	40	6.7	34	5.6	1.19 (0.76–1.85)	0.47
Non–Q-wave MI						
0–1 yr	4	0.7	2	0.3	2.02 (0.37–10.97)	0.45
0–3 yrs	8	1.3	4	0.7	2.02 (0.61–6.67)	0.26
0–5 yrs	11	1.8	5	0.8	2.22 (0.78–6.35)	0.14
Composite death/CVA/MI						
0–1 yr	57	9.5	52	8.6	1.11 (0.77–1.58)	0.62
0–3 yrs	79	13.2	70	11.6	1.14 (0.84–1.54)	0.43
0–5 yrs	109	18.2	90	14.9	1.22 (0.95–1.58)	0.14
CABG						
0–1 yr	40	6.7	4	0.7	10.0 (3.63–28.0)	< 0.001
0–3 yrs	55	9.2	7	1.2	7.92 (3.64–17.3)	< 0.001
0–5 yrs	63	10.5	7	1.2	9.08 (4.19–19.7)	< 0.001
Repeat PCI						
0–1 yr	94	15.7	20	3.3	4.74 (2.96–7.58)	< 0.001
0–3 yrs	120	20.0	37	6.1	3.27 (2.30–4.65)	< 0.001
0–5 yrs	139	23.2	50	8.3	2.80 (2.07–3.80)	< 0.001
Any revascularization						
0–1 yr	126	21.0	23	3.8	5.52 (3.59–8.49)	< 0.001
0–3 yrs	160	26.7	40	6.6	4.03 (2.91–5.60)	< 0.001
0–5 yrs	182	30.3	53	8.8	3.46 (2.61–4.60)	< 0.001
Any event						
0–1 yr	159	26.5	73	12.1	2.20 (1.71–2.83)	< 0.001
0–3 yrs	205	34.2	103	17.0	2.01 (1.63–2.47)	< 0.001
0–5 yrs	250	41.7	132	21.8	1.91 (1.60–2.28)	< 0.001

*Number of patients and percentage of patients with at least one occurrence of the specified clinical event during the time interval indicated in the table. †p value calculated by the Fisher Exact test.

CABG = coronary artery bypass grafting; CI = confidence interval; CVA = cerebrovascular accident; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Patients with diabetes. In patients with diabetes, those who underwent stenting had a mortality rate of 13.4%, versus 8.3% in those who underwent CABG (p = 0.27; RR, 1.61; 95% CI, 0.71 to 3.63) (Tables 4 and 5). Within the stent group, diabetic patients had a significantly higher mortality rate than non-diabetic patients (13.4% vs. 6.8%; p = 0.03; RR, 1.98; 95% CI, 1.11 to 3.52). In stent diabetic patients, death was attributed to a cardiac cause in 50% of cases versus 38% (p = 0.43; RR, 1.32; 95% CI, 0.68 to 2.58) in non-diabetic stent patients. There was no significant mortality difference between the diabetic and non-diabetic patients within the CABG group (8.3% vs. 7.5%; p = 0.8; RR, 1.12; 95% CI, 0.54 to 2.32).

Diabetic patients treated with stenting also had a lower event-free survival at five years than non-diabetic patients. The MACCE rate at five years in diabetic patients treated with stents was 54.5%, versus 38.7% in non-diabetics (p = 0.003). Conversely, there was no significant difference in the five-year MACCE rate between diabetic and non-diabetic patients treated with CABG (25.0% vs. 21.2%, p = 0.42). The difference in MACCE rate between diabetic and non-diabetic patients treated with stenting is largely attributable to the higher rate of repeat revascularization in diabetic patients (42.9% vs. 27.5%, p = 0.002).

Two- versus three-vessel treatment. There was no significant difference in event-free survival rate between patients with two or three vessels treated with stenting (56.7% vs. 60.1%) or CABG (79.4% vs. 75.7%), respectively. However, the event-free survival rate was significantly higher for patients treated with CABG than with stenting for both two and three vessels (p < 0.001 and p = 0.001, respectively).

Other subgroup analyses. There were also no significant differences in event-free survival within the respective treat-

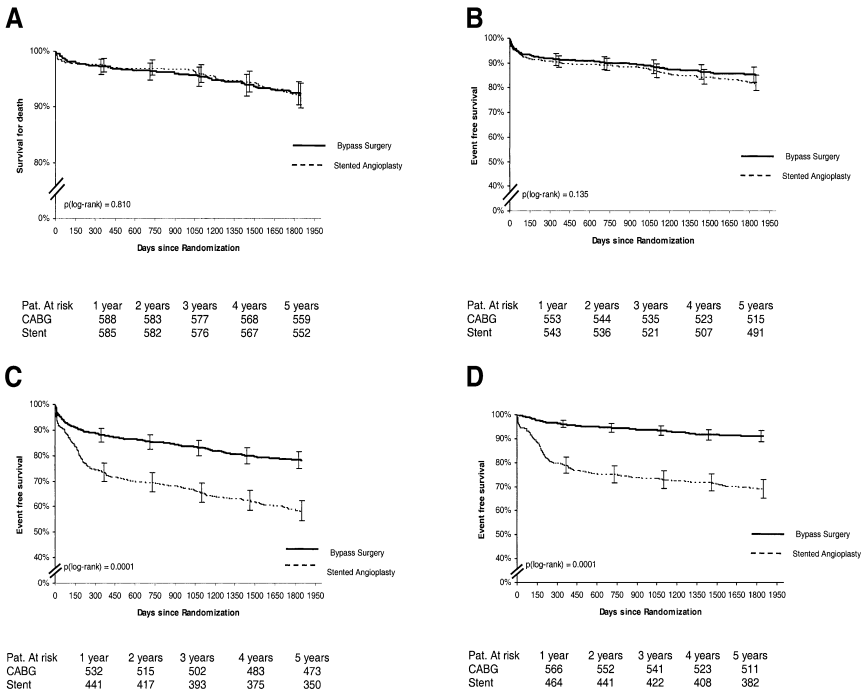

Figure 2. **(A)** Kaplan-Meier curves showing freedom from death. **(B)** Kaplan-Meier curves showing freedom from death/cerebrovascular accident/myocardial infarction or revascularization. **(C)** Kaplan-Meier curves showing freedom from death/cerebrovascular accident/myocardial infarction or revascularization. **(D)** Kaplan-Meier curves showing freedom from revascularization. CABG = coronary artery bypass grafting.

ment groups based on renal function, gender, age, or hypercholesterolemia at the time of randomization. At five years, 65.9% in the stent group and 61.5% in the CABG group were on lipid-lowering agents. Outcomes in patients who were treated for proximal left anterior descending lesions or otherwise were not significantly different stratified by treatment group.

DISCUSSION

This is the first randomized trial to report on five-year outcomes of patients with multivessel coronary artery disease treated with bare metal stenting versus CABG. Although this study was not specifically powered to detect a difference in five-year mortality, there was no clinically relevant difference (p = 0.83) with these two forms of treatment. This contemporary finding differs from the meta-analysis of previous randomized trials of balloon angioplasty alone versus CABG conducted in patients with multivessel disease, which showed a significantly higher mortality rate with percutaneous treatment at five years (risk difference, 2.3%; 95% CI, 0.29 to 4.3%; p = 0.025) (1).

In this study, mortality in the CABG arm was 7.6% at five years, lower than the composite death rate of 8.9% seen in the CABG patients from the meta-analysis (1), evidence that improved peri-operative management and intra-operative techniques over time have resulted in a reduction in mortality. Similarly, mortality in the stent arm was 8.0%, a risk difference of 0.4% (95% CI, 1.1% to 1.9%; p = 0.83). From one to five years, the risk difference changes from 0.3% in favor of stenting at one year, to 0.9% in favor of

Table 3. Listing of Deaths and Causes of Death

	Randomized to	
	PCI n = 600	**CABG n = 605**
Total deaths	48	46
Unknown	2	1
Non-cardiac	25	28
Cardiac	21	17
Related to repeat revascularization*	5	1
Repeat revascularization within 30 days of index procedure	4†	0
Repeat revascularization >30 days of index procedure	1	1

*Cardiac death related to repeat revascularization was defined as death within 30 days of repeat procedure. †Three died within 30 days of the index procedure as a result of subacute stent thrombosis, one died of a myocardial tear after CABG for a failed PCI on day 12.

Abbreviations as in Table 2.

Table 4. Major Adverse Cardiac Events at 5 Years in Patients With Diabetes Stratified According to Treatment

	Stent Diabetes n = 112 n* (%*)	Bypass Diabetes n = 96 n* (%*)	Relative Risk (95% CI)	Stent Versus CABG p Value†
Death	15 (13.4)	8 (8.3)	1.61 (0.71–3.63)	0.27
CVA	7 (6.3)	7 (7.3)	0.86 (0.31–2.36)	0.79
MI	12 (10.7)	7 (7.3)	1.47 (0.60–3.59)	0.47
Q-wave MI	9 (8.0)	4 (4.2)	1.93 (0.61–6.07)	0.39
Non–Q-wave MI	3 (2.7)	3 (3.1)	0.86 (0.18–4.15)	1.00
Composite death/CVA/MI	28 (25.0)	19 (19.8)	1.26 (0.76–2.11)	0.41
(re) CABG	17 (15.2)	2 (2.1)	7.29 (1.73–30.7)	0.001
(re) PTCA	34 (30.4)	9 (9.4)	3.24 (1.64–6.41)	<0.001
Any revascularization	48 (42.9)	10 (10.4)	4.11 (2.20–7.68)	<0.001
Any MACCE	61 (54.5)	24 (25.0)	2.18 (1.48–3.20)	<0.001

*Number of patients and percentage of patients with at least one occurrence of the specified clinical event during the time interval indicated in the table. †p value calculated using the Fisher exact test.
Abbreviations as in Table 2.

stenting at three years, to 0.4% in favor of CABG at five years (all not significant), indicating a strong effect of chance. Furthermore, this difference is not clinically relevant and is much lower than the 2.3% of the meta-analysis.

There was a 3.3% absolute difference in the composite end point of death, stroke, and myocardial infarction in favor of CABG, primarily driven by a higher incidence of myocardial infarctions in the stent arm. Although suggestive, this study was underpowered to detect a significant difference in the end point. Based on this difference, a population of 4,000 patients would be required for statistical significance.

The risk difference for revascularization at five years, as reported in this same meta-analysis, was 38% (95% CI, 30% to 47%). Specifically, the risk difference for subsequent CABG was 24% and for subsequent percutaneous transluminal coronary angioplasty was 23%. The current observed differences in the ARTS trial for any revascularization at five years is 21.5%, for subsequent CABG is 9.3%, and for subsequent PCI is 14.9%. It is worth noting that almost 90% of patients initially treated with stenting did not require CABG over the succeeding five years. The difference in the rate of repeat revascularization between the two groups increases over time from 17.2% at 1 year to 21.5% at five years without a concomitant difference in mortality over this time period. Despite the additional risk of repeat revascularization in the stent group compared with the CABG group, this did not translate into an increase in mortality (Table 3).

In this study, four-fifths of all patients in both groups were free of anginal complaints at five years. Although significantly different, this high proportion of patients free of symptoms is encouraging in this population of patients with chronic multivessel coronary artery disease. Correspondingly, more stent patients than CABG patients were on anti-anginal medications ($p < 0.001$) at five-year follow-up.

In diabetic patients from three trials comparing balloon angioplasty with surgery, the risk difference for all death was 8.6% in favor of CABG ($p = 0.01$; 95% CI, 2.2% to 15%) ($n = 537$ patients) at four years (1). In the present study involving 208 diabetic patients, mortality at five years was 5.1% higher in stent patients compared with CABG patients ($p = 0.27$). Conversely, in non-diabetic patients the mortality rate was 0.7% lower in the stent cohort. However,

Table 5. Major Adverse Cardiac Events at 5 Years in Patients Without Diabetes Stratified According to Treatment

	Stent Non-Diabetic n = 488 n* (%*)	Bypass Non-Diabetic n = 509 n* (%*)	Relative Risk (95% CI)	Stent Versus CABG p Value†
Death	33 (6.8)	38 (7.5)	0.91 (0.58–1.42)	0.71
CVA	16 (3.3)	14 (2.8)	1.19 (0.59–2.42)	0.71
MI	38 (7.8)	31 (6.1)	1.28 (0.81–2.02)	0.32
Q-wave MI	31 (6.4)	30 (5.9)	1.08 (0.66–1.75)	0.79
Non–Q-wave MI	8 (1.6)	2 (0.4)	4.17 (0.89–19.55)	0.059
Composite death/CVA/MI	81 (16.6)	71 (13.9)	1.19 (0.89–1.60)	0.25
(re) CABG	46 (9.4)	5 (1.0)	9.60 (3.85–23.95)	<0.001
(re) PTCA	105 (21.5)	41 (8.1)	2.67 (1.90–3.75)	<0.001
Any revascularization	134 (27.5)	43 (8.4)	3.25 (2.36–4.48)	<0.001
Any MACCE	189 (38.7)	108 (21.2)	1.83 (1.49–2.23)	<0.001

*Number of patients and percentage of patients with at least one occurrence of the specified clinical event during the time interval indicated in the table. †p value calculated using the Fisher exact test.
Abbreviations as in Table 2.

the study was not powered to show mortality differences between diabetic and non-diabetic patients.

Repeat revascularization was higher in diabetic patients randomized to the stent arm versus CABG (an absolute difference of 32.5% [42.9% vs. 10.9%, respectively]), compared with non-diabetic patients (a 19.1% absolute difference [27.5% vs. 8.4%, respectively, both $p < 0.001$]). Based on the available evidence, surgery should continue to be viewed as the preferred therapy for diabetic patients with multivessel disease when using bare metal stents.

The advent of drug-eluting stents has drastically reduced the need for repeat revascularization in both diabetic and non-diabetic patients. The relative reduction in need for re-intervention with drug-eluting stents is very similar in diabetic and non-diabetic patients (7,8). The difference in outcomes seen between bare metal stents versus CABG for the treatment of multivessel disease is likely to narrow substantially with the advent of drug-eluting stents. The U.S. National Institutes of Health is sponsoring a large multicenter trial specifically to evaluate the difference in outcomes in diabetic patients with multivessel coronary disease treated with drug-eluting stents versus CABG. A European multicenter trial comparing drug-eluting stents versus CABG for the treatment of multivessel and left main stem coronary disease in an all-comers population is currently in progress.

Despite the increasing age and concomitant increased co-morbidity of patients presenting for CABG, clinical outcomes have continued to improve (9). This was evident from the lower mortality seen in the CABG arm of this study compared with the older studies. The off-pump coronary bypass technique, developed to minimize the invasiveness of CABG, has in several large retrospective studies suggested a reduction in morbidity and/or mortality when compared with CABG (10). Larger randomized trials are required to address this issue definitively because the three reported randomized prospective studies comparing off-pump coronary bypass with CABG were not large enough to detect a difference in operative mortality or stroke (10). Finally, the routine use of post-procedural medications—aspirin, statins, and control of risk factors—will further improve outcomes in both the CABG and the stent groups in future trials.

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Chapter 20

Arterial Revascularization Therapies Study Part II - Sirolimus-Eluting Stents for the Treatment of Patients With Multivessel De Novo Coronary Artery Lesions.

Patrick W. Serruys, Andrew T. L. Ong, Marie-Claude Morice, Bernard De Bruyne, Antonio Colombo, Carlos Macaya, Gert Richardt, Jean Fajadet, Christian Hamm, Keith Dawkins, A. James O'Malley, Marco Bressers, Dennis Donohoe, on behalf of the ARTS II Investigators.

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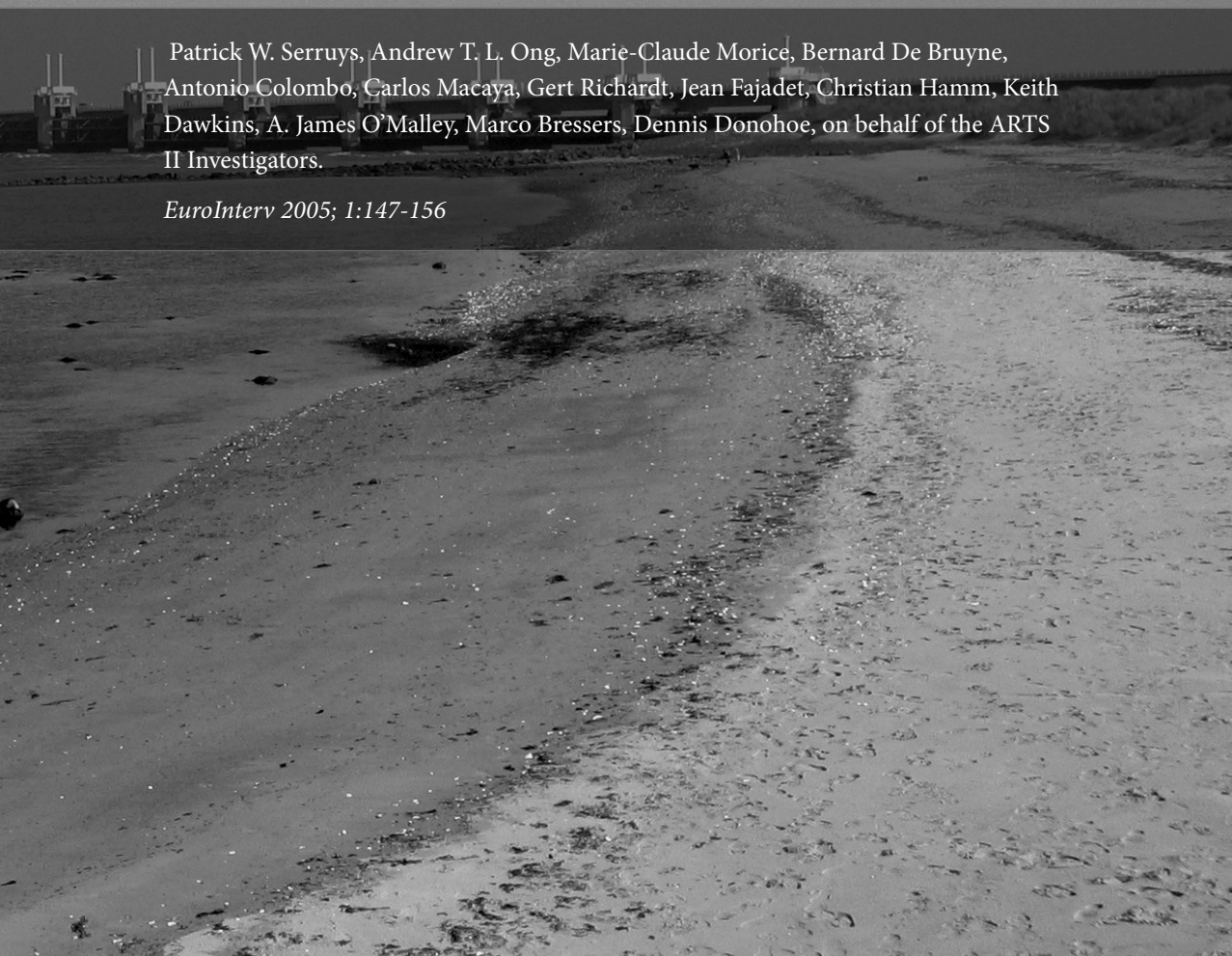

Arterial Revascularisation Therapies Study Part II - Sirolimus-eluting stents for the treatment of patients with multivessel *de novo* coronary artery lesions

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KEYWORDS
Multicenter, historical controlled trial, sirolimus, drug-eluting stents, multivessel disease, percutaneous coronary intervention, coronary artery bypass surgery

Abstract

Aim: To determine the safety and effectiveness of CYPHER® sirolimus-eluting stent implantation in patients with multivessel disease; and to compare outcomes against the historical results of the two arms of the Arterial Revascularisation Therapies Study (ARTS I).

Methods and results: ARTS II is a 45 center, 607 patient single arm trial; the1-year outcomes were compared to the historical controls of the ARTS I trial, using conventional and Bayesian statistical methods. Patients were stratified by clinical site to ensure that at least one-third had 3-vessel disease to achieve the number of treatable lesions per patient comparable to ARTS I. Multivessel stenting was performed with sirolimus-eluting stents according to local institutional practice with the goal of achieving complete revascularisation.

The majority of patients (53.5%) had 3-vessel disease and diabetes was present in 26.2%. Mean stented length was 72.5mm, with 3.7 stents implanted per patient. The 1-year survival rate was 99.0%, the composite of death / stroke and MI-free survival was 96.9%, freedom from revascularisation was 91.5% and the composite endpoint of MACCE-free survival was 89.5% (the primary endpoint). Diabetic patients treated with sirolimus-eluting stents were more likely to undergo repeat revascularisation (RR 1.97, 95% CI 1.16 - 3.34) and experience a MACCE (RR 1.85, 95% CI 1.16 - 2.97) than non-diabetics at 1-year. In the unadjusted comparison with the historical control arms of ARTS-I-CABG and ARTS-I-PCI, the respective relative risks (RR) and associated 95% confidence intervals (CI) for the endpoints were: (1) freedom from repeat revascularisation RR 2.03 (1.23-3.34) and RR 0.44 (0.31-0.61) respectively; and (2) MACCE free survival RR 0.89 (0.65-1.23) and RR 0.39 (0.30-0.51) respectively.

Conclusion: The low incidence of MACCE and repeat revascularisation in ARTS II suggests that contemporary PCI with sirolimus-eluting stents is safe and efficacious for the treatment of multivessel coronary artery disease. Compared to the historical population of ARTS I, surgery still afforded a lower need for repeat revascularisation although overall MACCE rates in ARTS II approached the surgical results and were significantly better than bare stenting in ARTS I.

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Introduction

Restenosis and the need for repeat revascularisation remain the major limitations of coronary angioplasty for patients with multivessel disease[1-4]. Drug-eluting stents have made a major impact on the effectiveness of percutaneous coronary interventions. The Cypher® sirolimus-eluting stent has been shown to significantly reduce restenosis and in-stent neointimal hyperplasia in patients with single vessel disease[5,6].

Results from the randomized, multicenter Arterial Revascularisation Therapies Study (ARTS I) showed no significant difference in terms of death, stroke and myocardial infarction between the two groups, an overall 17% difference in repeat revascularisation in favour of surgery, and lower costs (US$ 2,973) at 12 months in favour of stenting[1]. This was confirmed by other similar randomized trials[2,3]. The RAVEL and SIRIUS trials with the sirolimus-eluting stent demonstrated a marked reduction in repeat revascularisation versus bare metal stents in patients with single vessel stenting[5,6], as well as sustained efficacy and no evidence of late safety problems out to 3 years[7]. The RESEARCH single-centre registry demonstrated the feasibility, safety and effectiveness of sirolimus-eluting implantation in multivessel and complex patients[8,9]. Against this background, we performed the ARTS II trial with a similar inclusion criteria as ARTS I. The objective was to obtain information on the sirolimus-eluting stent in multivessel disease in a population whose baseline characteristics were to be at least of similar complexity and comparable to ARTS I[10].

Methods

Study design

ARTS II is a multicenter, non-randomized, open labelled, stratified trial designed to evaluate sirolimus-eluting stent implantation in patients with multivessel disease; with the surgical group of ARTS I as an historical control[8]. After obtaining written informed consent, the patients were enrolled via a central telephone service. 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. In addition, checks on the success of matching with the historical control were performed regularly during the conduct of the trial.

Patient selection

Patients were eligible for coronary revascularisation 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 ischemia and at least two new lesions located in different major epicardial vessels and / or their sidebranches (not including the left main coronary artery) that were potentially amenable to stent implantation. Patients were required to have multivessel disease with need for treatment of the left anterior descending (LAD) artery and at least 1 other significant lesion (>50% diameter stenosis) in another major epicardial coronary artery. The goal was to achieve complete revascularisation. One totally occluded major epicardial vessel or side branch could be included. The stenosis had to be amenable to stenting using a stent 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 included: 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 and endpoints

The primary objective of ARTS II is to compare the safety and effectiveness of coronary stent implantation using the sirolimus-eluting stents with that of surgery as observed in ARTS I. Endpoints are measured in terms of major adverse cardiac and cerebrovascular events (MACCE) at 1 year comprising all-cause death, any cerebrovascular event, non-fatal myocardial infarction, or any repeat revascularisation (either percutaneous or surgical).

The secondary objectives of this study are to compare the ARTS II patients to both arms of ARTS I with respect to: MACCE at 30 days, 6 months, 3 and 5 years; the combined end point death, myocardial infarction and stroke, and the itemized outcomes death, myocardial infarction, revascularisation procedure, stroke; resource use at 30 days and 1 year; cost effectiveness at 1 year, and quality of life at 6 months, and 1, 3, and 5 years.

End point definitions

Death from all causes were reported, and categorized as cardiac unless there was documentation to the contrary. Cerebrovascular events were divided into three main categories: stroke, transient ischemic attacks, and reversible ischemic neurologic deficits. 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 (according to the Minnesota code) 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[1,11,12] 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 were sufficient for a diagnosis of myocardial infarction. This two-part method of defining myocardial infarction was developed for ARTS I to address the difficulty of diagnosing a myocardial infarction after surgery. A myocardial infarction was confirmed only after the relevant electrocardiograms had been analyzed by the electrocardiographic core laboratory and adjudicated by a clinical-events committee. All repeat revascularisation procedures were recorded.

End point measurement

In ARTS II, the procedure was performed within 48 hours after inclusion, while in ARTS I patients were randomized after informed consent had been obtained and then entered a waiting list, with 3 deaths in the ARTS I-CABG arm while on the waiting list. 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[1].

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 end point. 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%.

Count variables are given as group rates and their matching 95% confidence interval. Continuous variables are given as group means, and the difference between groups presented with 95% confidence intervals. Time-to-event variables are presented as Kaplan-Meier curves. Safety data at 30 days and 1 year are presented as Kaplan-Meier estimates, with relative risks and 95% confidence intervals. Further analyses will be performed at 3 years with the final analysis at 5 years.

A separate multivariate regression analysis was performed to determine independent predictors of MACCE within the ARTS II population only. Clinically important baseline and procedural characteristics were tested on a per patient basis by univariate analysis to determine suitability for inclusion in the multivariate model. These variables were then entered into a stepwise logistic regression model with entry and stay criteria of 0.20 and 0.05 respectively.

A historical controlled trial design was used for this study. Unlike the gold standard of randomized controlled trials, historical controlled trials may differ in baseline and procedural characteristics, which potentially may affect outcome[13]. In order to overcome such differences, comparative statistical methodology, using both Bayesian and frequentist methodology, were used for the analysis of the trial[10]. Bayesian methods were used to test the additional hypothesis that the MACCE- free rate, adjusted for observed patient characteristics, is lower in ARTS II than in the two arms of ARTS I. A logistic regression model that incorporated the complexities of the design of each trial and the heterogeneity between patients within a trial was fit using Bayesian analysis (an approach well equipped for incorporating historical data in an analysis). An important feature of this approach is that it controls for unmeasured variables that predict MACCE in addition to observed predictors thereby facilitating comparisons between patients with different characteristics in different trials. However, in order to estimate the model, data from a second historical trial (RAVEL) needed to be included in the analysis[5].

Results

Patients

Between February and November 2003, 607 patients from 45 participating centers were treated (Figure 1). Table 1 presents their baseline demographic and angiographic characteristics. Patients treated in ARTS II were a high risk population with a mean age of 63 years, and three quarters were male. Diabetes mellitus was present in 26% of patients and three vessel disease was present in the majority (54%). Seven patients in ARTS II did not receive any stents at the index procedure (4 underwent elective CABG, 1 required emergent CABG, 1 underwent percutaneous treatment 35 days later and 1 remained on medical therapy). The mean number of significant lesions per patient was 3.6±1.3 in ARTS II and 3.7±1.5 stents were implanted with average total stented length of 73±32 mm per patient. The mean duration of the procedure was 85 minutes and patients were hospitalized for 3.4 days post-procedurally.

In comparison to the ARTS I population, patients in ARTS II were significantly older, had a significantly higher percentage of patients with diabetes mellitus, hypertension, hypercholesterolemia and silent ischemia and a lower percentage of current smokers or had a history of prior myocardial infarction. ARTS II patients were also significantly more complex procedurally, with more three vessel disease (54% versus 30% in ARTS I-CABG and 27% in ARTS I-PCI) more significant lesions present (3.6±1.3 versus 2.8±1.0 in ARTS I-CABG and 2.8±1.0 in ARTS I-PCI). More stents and longer total stent lengths were implanted in ARTS II (3.7±1.5, 73 ± 32 mm) compared to ARTS I-PCI (2.8±1.3, 48 ± 22 mm respectively) At discharge, significantly more patients were prescribed medications for the secondary prevention of coronary artery disease in ARTS II compared to ARTS I.

Clinical outcomes

First 30 days (Table 2): In the ARTS II population, the 30-day composite MACCE rate was 3.1%. There were no deaths, 1 patient suffered a CVA and a Q-wave myocardial infarction occurred in 5 patients (0.8%); giving a combined endpoint of death, stroke or myocardial infarction of 1.0%. A repeat revascularisation via a percutaneous approach occurred in 6 patients (1.0%) and bypass surgery was required in 7 (1.2%). Thrombotic stent occlusions occurred in 0.8% of patients.

This 30-day MACCE rate was significantly lower than in ARTS I-CABG (6.3%, RR 0.50, 95% CI 0.29-0.85) and ARTS I-PCI (9.2%, RR 0.34, 95% CI 0.21-0.57). The lower incidence of death, stroke and myocardial infarction in ARTS II was less than in the ARTS I population (ARTS I-CABG 5.5%, RR 0.18, 95% CI 0.08-0.43) and ARTS I-PCI 5.2%, RR 0.19, 95% CI 0.08-0.46). The incidence of thrombotic stent occlusions was lower in ARTS II (0.8%) versus ARTS I-PCI (2.8%), p=0.009.

One year (Table 3 & Figures 2 and 3): At 1-year follow-up, the Kaplan-Meier estimate of the survival free of MACCE in the ARTS II trial was 89.5%. Six deaths occurred (1.0%), a further 5 (0.8%) suffered a stroke while 8 patients (1.3%) had a myocardial infarction, to give a composite death, stroke or myocardial infarction rate of 3.0%. Of the 6 deaths, four were adjudicated by the events committee to be of cardiac origin, although only one occurred suddenly and unexpectedly. The incidence of repeat revascularisation was 8.5% at one year with 39 patients (6.4%) who required a repeat percutaneous procedure, while 13 patients (2.1%) underwent bypass surgery in the follow-up period. The incidence of angiographically documented late stent occlusion (between 30 days and 1 year) was 0.3% (2 patients) in 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 sex (%)	77	76	77	0.6% (-4.2%, 5.4%)	-0.4% (-5.2%, 4.4%)
Age (years±SD)	63±10	61±9	61±10	1.6 (0.5, 2.7)	2.2 (1.1, 3.3)
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%)
Hypercholesterolemia (%)	74	58	58	16.3% (11.0%, 21.5%)	15.9% (10.6%, 21.2%)
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	60	57	-6.5% (-12.0%, -0.9%)	-3.6% (-9.2%, 2.0%)
Unstable angina (%)	36	35	37	1.0% (-4.4%, 6.4%)	-0.9% (-6.4%, 4.5%)
Silent ischemia (%)	10	5	6	5.4% (2.4%, 8.4%)	4.5% (1.5%, 7.6%)
Angiographic characteristics					
Ejection fraction (%)	60±12	60±13	61±12	-0.2 (-1.6, 1.3)	-0.8 (-2.20.7)
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, 09)
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)					
Discreet (<10mm)	61	68	66	-7.3% (-10.4%, -4.2%)	-4.7% (-7.9%, -1.5%)
Tubular (10-20mm)	27	25	27	2.0% (-0.9%, 4.9%)	-0.1% (-3.0%, 2.8%)
Diffuse (>20mm)	12	7	7	5.3% (3.4%, 7.2%)	4.8% (2.9%, 6.7%)
Lesion classification (% of lesions)					
A	7	7	6	0.0% (-1.6%, 1.6%)	0.9% (-0.7%, 2.5%)
B1	23	31	26	-7.9% (-10.8%, -5.1%)	-3.0% (-5.8%, -0.2%)
B2	56	54	60	1.9% (-1.3%, 5.1%)	-3.7% (-6.9%, -0.5%)
C	14	8	8	6.0% (4.0%, 8.0%)	5.9% (3.9%, 7.8%)
Procedural characteristics					
Bifurcation requiring double wiring (% of patients)	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±3.0	-	1.7 (1.4, 2.1)
Direct stenting (%)	34.6	-	3.3	-	31.3% (29.1%, 33.6%)
Duration of procedure (mins)	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)
Medications					
Glycoprotein IIb/IIIa inhibitors during procedure (%)	33	-	-	-	-
Lipid lowering agents at discharge (%)	90	32	39	58.0% (53.5%, 62.4%)	51.1% (46.5%, 55.7%)
Beta blockers at discharge (%)	78	55	60	22.8% (17.6%, 28.0%)	17.7% (12.5%, 22.8%)
Angiotensin converting enzyme inhibitors at discharge (%)	50	15	26	34.7% (29.8%, 39.6%)	24.3% (19.0%, 29.6%)

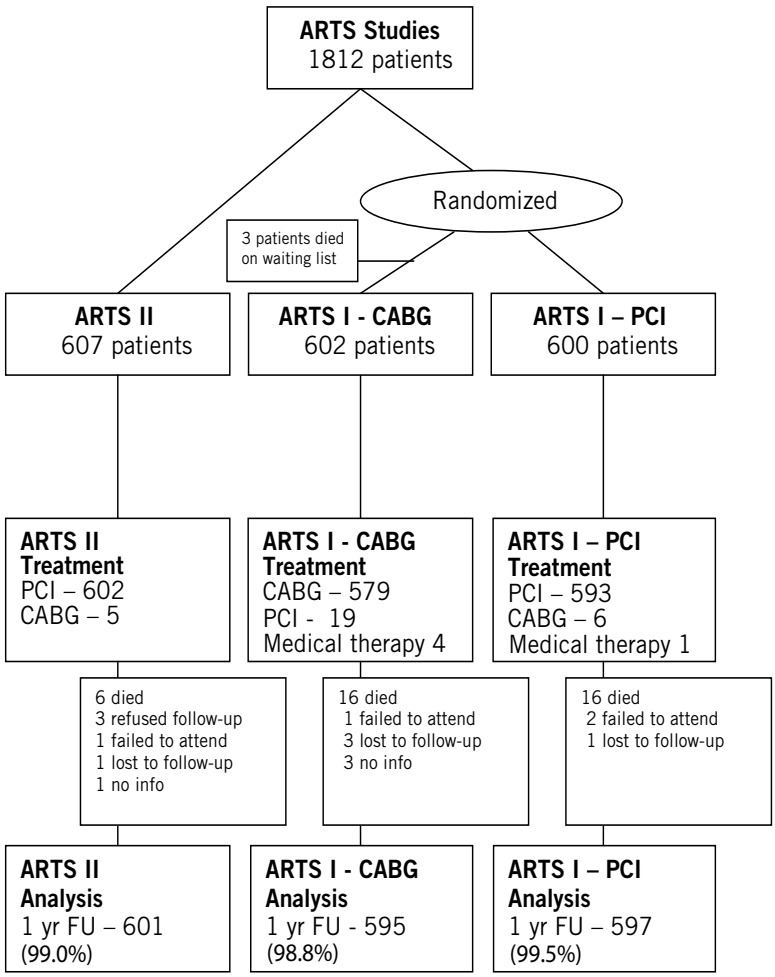

Figure 1. Flow chart of ARTS II and ARTS I.

The composite 1-year MACCE rate in ARTS II was in the same range as the ARTS I- CABG results (10.5% versus 11.7%, RR 0.89, 95% CI 0.65-1.23), with less events in the combined death, stroke or myocardial infarction endpoint (3.0% versus 8.0%, RR 0.37, 95% CI 0.22-0.63) balanced by a significantly higher need for repeat revascularisation in ARTS II (8.5% versus 4.2%, RR 2.03, 95% CI 1.23-3.34). Predictably, the 1-year MACCE rate in ARTS II was much lower than the ARTS I-PCI group (26.5%, RR 0.39, 95% CI 0.30-0.51), driven by the higher incidence of events in all measured endpoints. In particular, the repeat revascularisation rate in ARTS I-PCI was 21.3% (RR 0.44, 95% CI 0.31-0.61). Angiographically documented late stent thrombosis was not measured in ARTS I.

Diabetic versus non-diabetic patients (Table 4 and Figure 4)

In the ARTS 2 population, diabetic patients had significantly higher one year MACCE rates by Kaplan Meier estimates compared to the non-diabetic population (15.8% versus 8.6%, RR 1.85, 95% CI 1.16-3.34, p (logrank) <0.01). This difference was driven by the increased need for repeat revascularisation in the diabetic population (13.4% versus 6.8%, RR 1.97, 95% CI 1.16-3.34, p (logrank) <0.01).

Multivariate analysis (Table 5)

Multivariate analysis was performed on the ARTS II population to determine independent predictors of outcome in the sirolimus-elut-

Table 2. Clinical endpoints at one month (hierarchical and non-hierarchical MACCE up to 30 days, per patient) counted since date of procedure

MACCE Up to 30 days	ARTS II N=607 N (%)	ARTS I CABG N=602 N (%)	ARTS I PCI N=600 N (%)	ARTS II:I-CABG Relative risk (95% CI)	ARTS II:I-PCI Relative risk (95% CI)
Hierarchical					
Death	0 (0.0)	8 (1.3)	10 (1.7)	-	-
CVA	1 (0.2)	6 (1.0)	5 (0.8)	0.17 (0.02 - 1.37)	0.20 (0.02 - 1.69)
MI	5 (0.8)	19 (3.2)	16 (2.7)	0.26 (0.10 - 0.69)	0.31 (0.11 - 0.84)
MI Q-wave	5 (0.8)	19 (3.2)	15 (2.5)	0.26 (0.10 - 0.69)	0.33 (0.12 - 0.90)
MI non-Q-wave	0 (0)	0 (0.0)	1 (0.2)	-	-
Death / CVA / MI	6 (1.0)	33 (5.5)	31 (5.2)	0.18 (0.08 - 0.43)	0.19 (0.08 - 0.46)
(re) CABG	7 (1.2)	2 (0.3)	12 (2.0)	3.47 (0.72 - 16.64)	0.58 (0.23 - 1.45)
(re) PTCA	6 (1.0)	3 (0.5)	12 (2.0)	1.98 (0.50 - 7.89)	0.49 (0.19 - 1.31)
Any MACCE	19 (3.1)	38 (6.3)	55 (9.2)	0.50 (0.29 - 0.85)	0.34 (0.21 - 0.57)
Non-hierarchical					
Death	0 (0.0)	8 (1.3)	10 (1.7)	-	-
CVA	1 (0.2)	6 (1.0)	6 (1.0)	0.17 (0.02 - 1.37)	0.20 (0.02 - 1.69)
MI	5 (0.8)	23 (3.8)	20 (3.3)	0.22 (0.08 - 0.56)	0.31 (0.11 - 0.84)
MI Q-wave	5 (0.8)	22 (3.7)	18 (3.0)	0.23 (0.09 - 0.59)	0.33 (0.12 - 0.90)
MI non-Q-wave	0 (0.0)	1 (0.2)	2 (0.3)	-	-
(re) CABG	8 (1.3)	2 (0.3)	17 (2.8)	3.97 (0.85 - 18.60)	0.58 (0.23 - 1.45)
(re) PTCA	7 (1.2)	3 (0.5)	19 (3.2)	2.31 (0.60 - 8.91)	0.49 (0.19 - 1.31)

Table 3. Clinical endpoints at one year (hierarchical and non-hierarchical MACCE up to 365 days, per patient) counted since date of procedure

MACCE Up to 365 days	ARTS II N=607 N (%)	ARTS I CABG N=602 N (%)	ARTS I PCI N=600 N (%)	ARTS II:I-CABG Relative risk (95% CI)	ARTS II:I-PCI Relative risk (95% CI)
Hierarchical					
Death	6 (1.0)	16 (2.7)	16 (2.7)	0.37 (0.15 - 0.94)	0.37 (0.15 - 0.94)
CVA	5 (0.8)	11 (1.8)	11 (1.8)	0.45 (0.16 - 1.29)	0.45 (0.16 - 1.29)
MI	7 (1.2)	21 (3.5)	30 (5.0)	0.33 (0.14 - 0.77)	0.23 (0.10 - 0.52)
MI Q-wave	5 (0.8)	21 (3.5)	27 (4.5)	0.24 (0.09 - 0.62)	0.18 (0.07 - 0.47)
MI non-Q-wave	2 (0.3)	0 (0)	3 (0.5)	-	0.66 (0.11 - 3.93)
Death / CVA / MI	18 (3.0)	48 (8.0)	57 (9.5)	0.37 (0.22 - 0.63)	0.31 (0.19 - 0.52)
(re) CABG	12 (2.0)	4 (0.7)	28 (4.7)	2.98 (0.97 - 9.17)	0.42 (0.22 - 0.83)
(re) PCI	33 (5.4)	18 (3.0)	74 (12.3)	1.82 (1.04 - 3.19)	0.44 (0.30 - 0.65)
Any MACCE	63 (10.4)	70 (11.6)	159 (26.5)	0.89 (0.65 - 1.23)	0.39 (0.30 - 0.51)
Non-hierarchical					
Death	6 (1.0)	16 (2.7)	16 (2.7)	0.37 (0.15 - 0.94)	0.37 (0.15 - 0.94)
CVA	5 (0.8)	12 (2.0)	12 (2.0)	0.41 (0.15 - 1.17)	0.41 (0.15 - 1.16)
MI	8 (1.3)	25 (4.2)	35 (5.8)	0.32 (0.14 - 0.70)	0.23 (0.11 - 0.48)
MI Q-wave	5 (0.8)	24 (4.0)	31 (5.2)	0.21 (0.0 - 0.54)	0.16 (0.06 - 0.41)
MI non-Q-wave	3 (0.5)	1 (0.2)	4 (0.7)	2.98 (0.31 - 28.5)	0.74 (0.17 - 3.30)
(re) CABG	13 (2.1)	5 (0.8)	40 (6.7)	2.58 (0.92 - 7.19)	0.32 (0.17 - 0.59)
(re) PTCA	39 (6.4)	21 (3.5)	94 (15.7)	1.84 (1.10 - 3.09)	0.41 (0.29 - 0.59)

ing stent population. Variables significant in the univariate analysis were: treated lesions in the left circumflex, tubular lesions, diabetes mellitus, current smoker, number of lesions with a stenosis greater than 50%, Type B2/C lesions, age, and lesions with moderate to heavy calcification. Diabetes and the presence of tubular lesions were independently associated with adverse outcome, while patients who were smokers at the time of intervention were associated with a better outcome.

Bayesian statistical adjustment

Based on the logistic regression model fit using Bayesian methods, the adjusted MACCE rate was calculated to be 8.1±1.6% in ARTS II versus 13.1± 2.4% in ARTS I-CABG. To summarize the difference in treatment rates between the trial, the probability given the data from both trials that the MACCE rate in ARTS II is lower than the MACCE rate in ARTS I CABG was evaluated. The probability was 0.953, a value that would enable a significant difference at the 0.05-level to be claimed.

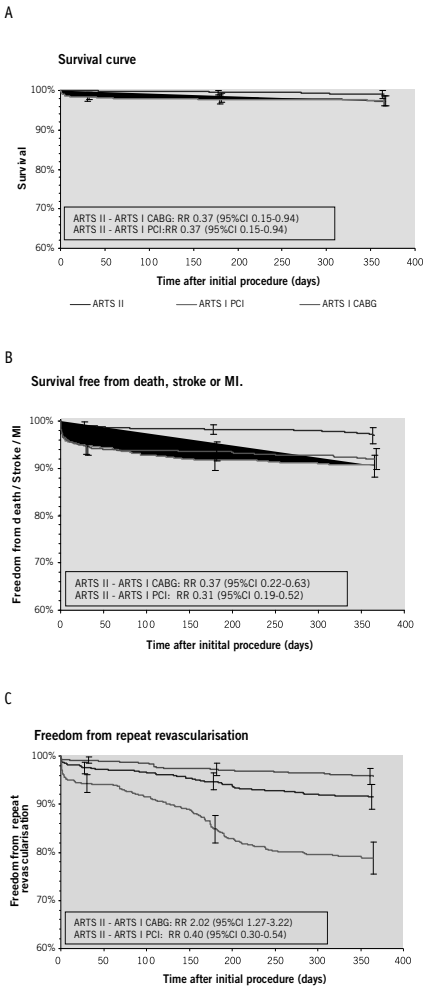

Figure 2. Kaplan-Meier curves out to 1 year in ARTS II and ARTS I: (A) Survival free; (B) Freedom from Death/CVA/MI; (C) Freedom from repeat revascularisation.

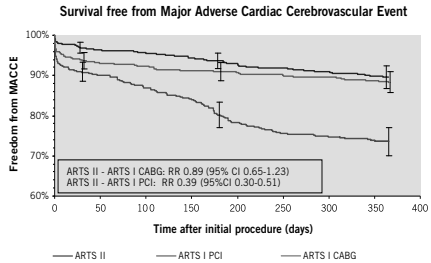

Figure 3. Kaplan-Meier curves out to 1 year in ARTS II and ARTS I: Freedom from Major Adverse Cardiac and Cerebral Events (MACCE).

Table 4. Frequency of MACCE up to 365 days (since date of procedure) in diabetic vs non-diabetic patients in ARTS II

MACCE Up to 365 days	ARTS II No diabetes (n=448) N (%)	ARTS II Diabetes (n=159) N (%)	Diabetes: no diabetes Relative risk (95% CI)
Hierarchical			
Death	2 (0.4)	4 (2.5)	5.64 (1.04 - 30.5)
CVA	5 (1.1)	0 (0.0)	-
MI	6 (1.3)	1 (0.6)	0.47 (0.06 - 3.87)
MI Q-wave	4 (0.9)	1 (0.6)	0.70 (0.08 - 6.26)
MI non-Q-wave	2 (0.4)	0 (0.0)	-
Death/ Stroke/ MI	13 (2.9)	5 (3.1)	1.08 (0.39 - 2.99)
(re-) CABG	7 (1.6)	5 (3.1)	2.01 (0.65 - 6.25)
(re) PTCA	18 (4.0)	15 (9.4)	2.35 (1.21 - 4.55)
Any MACCE	38 (8.5)	25 (15.7)	0.92 (0.86 - 0.99)
Non-hierarchical			
Death	2(0.4)	4 (2.5)	5.64 (1.04 - 30.5)
CVA	5 (1.1)	0 (0.0)	-
MI	7 (1.6)	1 (0.6)	0.40 (0.05 - 3.25)
MI Q-wave	4 (0.9)	1 (0.6)	0.70 (0.08 - 6.26)
MI non-Q-wave	3 (0.7)	0 (0.0)	-
(re-) CABG	8 (1.8)	5 (3.1)	1.76 (0.58 - 5.30)
(re) PTCA	23 (5.1)	16 (10.1)	1.96 (1.06 - 3.61)

Discussion

The main findings of this study are: (1) contemporary percutaneous coronary intervention for complex multivessel disease using sirolimus-eluting stents was associated with low 1-year event rates for repeat revascularisation and overall MACCE, (2) the MACCE rate at 1-year was in the same range as that obtained in the historical bypass surgery arm of the ARTS I trial; (3) re-intervention rates in this contemporary group were still higher than the historical surgical cohort (4) the overall MACCE and especially re-intervention rates in this contemporary group were markedly reduced compared to the ARTS I-PCI arm.

The primary endpoint of this study, which was the composite endpoint of MACCE in ARTS II, was low, occurring in 10.5% of patients, and was within the same range as that seen with the historical surgical arm of ARTS I. A lower repeat revascularisation rate was noted in the surgically treated patients at one-year; this was balanced by a higher incidence of death / stroke and myocardial infarction.

In the secondary comparison between the two percutaneous arms, the significantly better MACCE rate with this contemporary PCI population treated with SES (ARTS II) compared to the bare stent PCI population treated in 1997-8 was primarily due to the lower reintervention rate; in spite of the higher baseline and procedural charac-

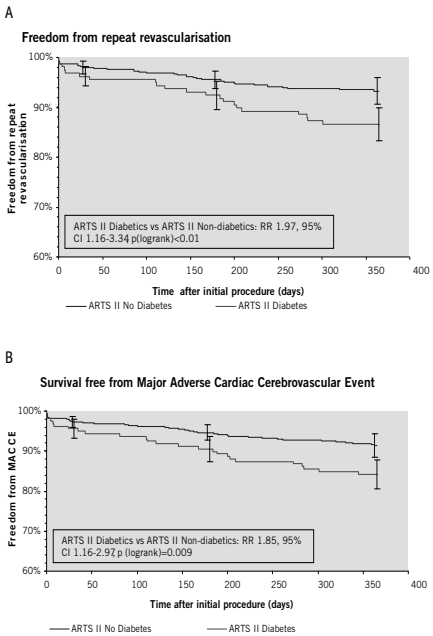

Figure 4. Kaplan-Meier curves out to 1 year in non-diabetic versus diabetic patients in the ARTS II arm: (A) Repeat revascularisation, (B) MACCE (Black represents No Diabetes, grey represents Diabetes).

Table 5. Independent predictors of MACCE in the ARTS II group

Multivariate predictors of MACCE at 365 days	Odds Ratio	95% Confidence Interval	P-Value
Current smoker	0.36	0.14-0.93	0.035
# Tubular lesions (10 - 20 mm)	1.39	1.06-1.83	0.019
Diabetes Mellitus	1.76	1.02-3.06	0.044

teristic risk profile. Indeed, statistical analyses that adjusted for the independent predictors of outcome tended to find wider differences between the studies than unadjusted analyses. The incidence of stent thrombosis in the first month, as a surrogate for the acute safety profile of sirolimus-eluting stents in multivessel disease occurred in 0.8% despite increases in complexity and total stented length, compared with 2.8% in the bare stent arm of ARTS I-PCI confirming its safety in contemporary settings.

Within the ARTS II population, diabetic patients experienced a higher MACCE rate than non-diabetic patients, driven by an almost 2-fold increased need for repeat revascularisation in the first year, a finding confirmed by the multivariate analysis. Although event rates are markedly reduced compared to what has been seen with bare metal stents, diabetic patients continue to remain more resistant to the beneficial effects of sirolimus-eluting stents than non-diabetic patients. This phenomenon requires further investigation.

This present study was designed to determine whether the findings of the randomized trials with the sirolimus-eluting stent in single vessels could be extended to multivessel stenting. While a randomized trial design was always the preferred option, financial circumstances at the time of trial design dictated that only a single arm could be funded for such a study. This trial was thus seen as an intermediate step towards a full-fledged randomized trial with the original intention of a non-inferiority comparison using a historical control as stated in the protocol[8]. The use of historical controls, as opposed to a randomized control is the subject of debate[13,14]. Randomized controlled trials, by virtue of their experimental design, provide a reliably unbiased estimate of treatment effects[13]. Historical controlled trials, on the other hand, suffer from a selection bias and of systemic differences in outcomes that may not be due to the treatment itself. Sacks found that this type of trial design over-estimated the treatment effect[15]. However, in two recent studies that compared both trial designs, no difference in treatment effect was seen[16,17]. Importantly, trials, both randomized and observational for a particular topic must be collectively and not individually examined to determine the accuracy in their results[14]. Hence, well designed historical controlled trials with appropriate matching, stratification and adjustment can be successfully used to guide the development of new trials.

Although arithmetically possible, the non-inferiority comparison between groups was replaced with descriptive comparisons due to the lack of randomisation coupled with concerns that the performance of the CABG group would have been better if assessed in the current environment as opposed to 5 years ago. The historical rates of ARTS I are thus viewed as standards against which the ARTS II study is compared. The low event rates, including that of stent thrombosis noted in this study as compared to ARTS I may in part be explained by the more contemporary percutaneous coronary intervention methods used. Specifically, the use of lower profile and more easily deliverable devices may have resulted in less vessel trauma, a shorter procedure time; more comprehensive diseased vessel coverage with stents; and adjunctive glycoprotein IIb/IIIa inhibitor and/or intravascular ultrasound use may have contributed to the results. In addition, better secondary prevention practices, such as the more frequent use of lipid lowering agents, beta-blockers, and angiotensin-converting enzyme inhibitors may have contributed an added beneficial effect. Although the anti-restenotic effects of sirolimus-eluting stents are incontrovertible, one is unable to completely attribute the treatment effect to the device alone due to the non-randomized study design.

The role of complex multivessel stenting with drug-eluting stents will be addressed in two major randomized trials: FREEDOM and SYNTAX. The former will randomize 2400 patients with diabetes and multivessel disease to bypass surgery or drug-eluting stenting using approved devices, currently sirolimus-eluting and paclitaxel-eluting stents; while SYNTAX will randomize 1500 patients with 3-vessel or left-main disease to bypass surgery or paclitaxel-eluting stents. Nested preference registries are an added feature of both trials.

Study limitations

The results observed in this study require the following caveats in addition to those already mentioned. First, a five year time lag exists between the groups that are being compared. Both technology and

medical practice have improved with time, as have surgical mortality rates[18,19]. Second, this study is non-randomized 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, of which two methods of statistical analysis, namely frequentist and Bayesian, were performed in order to present robust results. 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 based on patients actually enrolled in the study since those enrolled in ARTS II were more complex than those enrolled in ARTS I. Finally, the results of the primary endpoint are reported for the one year timepoint only. While encouraging, the efficacy of sirolimus-eluting stents in the treatment of multivessel disease can only be definitively evaluated when long- term results become available in the future.

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Appendix

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Chapter 21

The SYNergy Between Percutaneous Coronary Intervention With TAXus™ and Cardiac Surgery (SYNTAX) Study: Design, Rationale and Run-In Phase.

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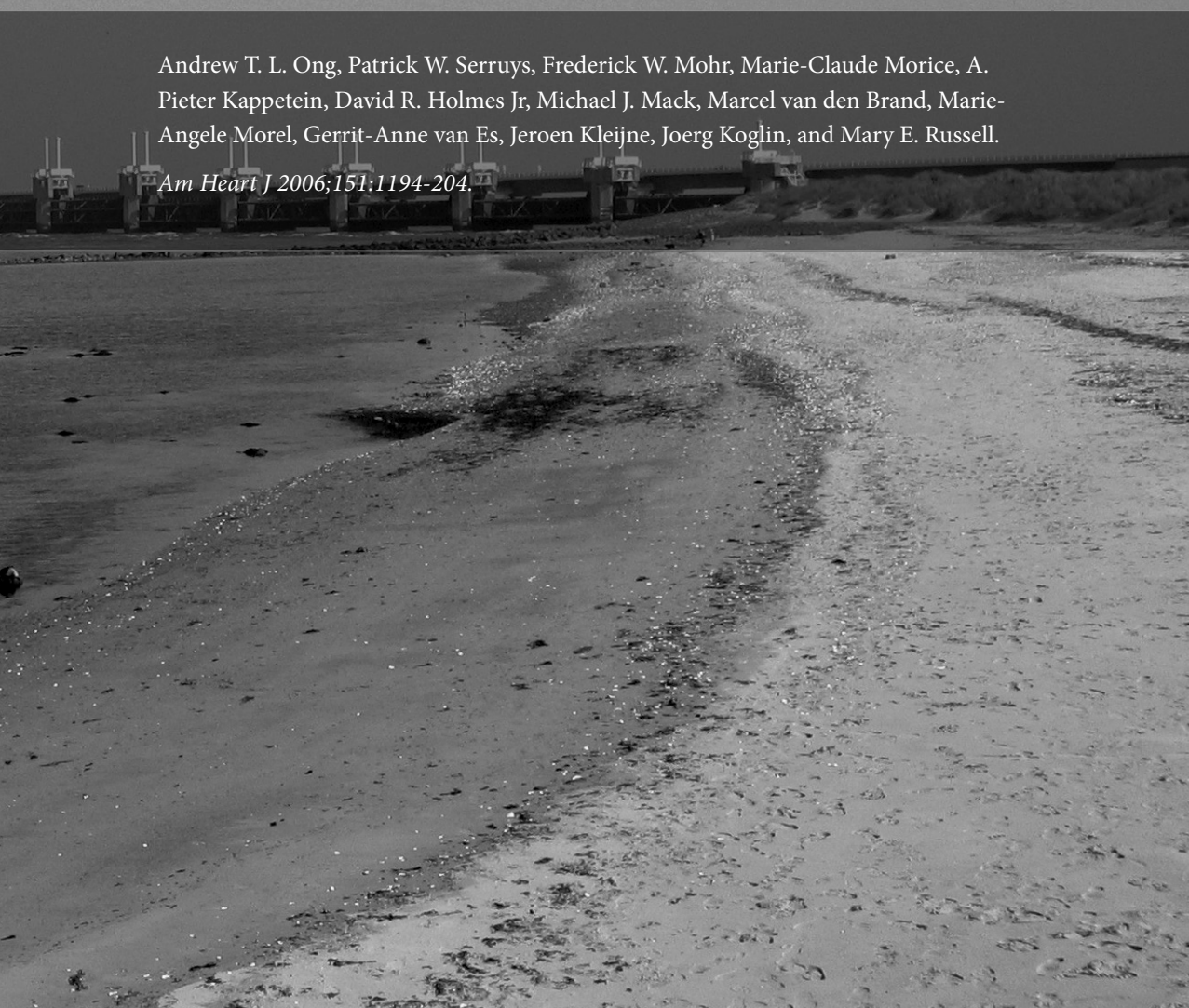

The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: Design, rationale, and run-in phase

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Background Changes in the treatment of coronary artery disease both surgically and percutaneously have rendered the major randomized trials historical. Furthermore, the restrictive criteria of previous trials excluded most patients treated in daily practice. Although coronary surgery is still considered the current, evidence-based, gold-standard treatment of left main (LM) and 3-vessel coronary disease, the added benefit of drug-eluting stents has further expanded the use of percutaneous coronary intervention (PCI) beyond less complex populations in daily practice.

Study Design The 1500-patient, prospective, multicenter, multinational (European and North American), randomized SYNTAX study with nested registries will enroll "all-comers." Consecutive patients with de novo 3-vessel disease (3VD) and/or LM disease will be screened for eligibility by the Heart Team (composed of an interventionalist, a cardiac surgeon, and the study coordinator) at each site and then allocated to either (1) the randomized cohort, if comparable revascularization can be achieved by either PCI or coronary artery bypass surgery (CABG), or (2) to one of the nested registries for CABG-ineligible patients (PCI registry) or for PCI-ineligible patients (CABG registry). Randomized patients will be stratified based on LM disease and diabetes by site. The primary end point for the randomized comparison is noninferiority of major adverse cardiac and cerebral events between the 2 groups at 1 year.

To adequately project the expected enrollment rate per site, a run-in phase was mandated for each site interested in participating in the trial. Both cardiothoracic and interventional cardiology departments within the same institution were asked to complete a questionnaire regarding their frequency of treatment of LM and 3VD over a retrospective 3-month period.

Implications By replacing most traditional inclusion and exclusion criteria with the real-world decision between the cardiothoracic surgeon and the interventionalist, this study will define the roles of CABG and PCI using drug-eluting stents in the contemporary management of LM and 3VD. Results of the run-in phase were used by the steering committee to determine eligibility and to project enrollment for each site. (Am Heart J 2006;151:1194-204.)

The management of coronary artery disease has evolved over the last 30 years. Coronary artery bypass surgery (CABG) was introduced in 1968 and was rapidly established as the gold standard for treatment.[1] Percutaneous coronary intervention (PCI) began in 1977 with the first percutaneous transluminal coronary angioplasty performed by Andreas Gruntzig as a nonsurgical alternative.[2] Because of 2 landmark studies[3,4] and improvements in antiplatelet therapy, coronary artery stenting has replaced balloon angioplasty as the preferred method of PCI. Four large, multicenter, randomized studies conducted in the mid- to late 1990s compared bypass surgery to coronary stenting for the treatment of multivessel disease,[5-8] and although seminal, these trials are now historical in applicability in contemporary practice because of improvements in treatment options.

The development of coronary stents that provide local delivery of drugs with demonstrated superiority over bare metal stents in reducing restenosis has had a major impact on

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the management of coronary artery disease.[9,10] Coupled with improvements in peri- and postprocedural medical care for both CABG and PCI, a new comparison is required to determine the standard of care for left main (LM) and 3-vessel disease (3VD) and to allow the development of new guidelines for their management.

Revascularization versus medical therapy

The randomized Veterans Affairs cooperative study was the first landmark study to report a survival benefit with CABG over medical therapy for the treatment of significant LM disease and established the role of CABG as the treatment of choice.[11] This study was followed by the randomized ECSS, which demonstrated a significant survival benefit of surgery over medical therapy at 5 years for both patients with 3VD and patients in whom stenosis in the proximal third of the left anterior descending artery constituted a component of either 2- or 3-vessel disease.[12] The RITA-2 compared PCI (9% stent use) to medical therapy in 1018 patients with 1- to 3-vessel disease with no difference in mortality seen at 2.7 years of follow-up.[13]

Stenting versus balloon angioplasty

The development of coronary stents opened a second avenue for PCI. The pivotal BENESTENT trial demonstrated that, in single lesion disease, clinical and angiographic outcomes were better in patients who received a stent than in those who received standard coronary angioplasty.[3] At 1 year, no significant differences in mortality, stroke, myocardial infarction (MI), or coronary bypass graft surgery were found between the stent and balloon angioplasty groups. However, the requirement for a repeat angioplasty procedure was significantly lower in the stent group than in the balloon angioplasty group (10% vs 21%, $P = .001$).[14]

In the United States, the STRESS trial mirrored the findings of BENESTENT.[4] Stent placement resulted in an improved rate of procedural success, a lower rate of angiographically detected restenosis, a similar rate of clinical events after 6 months, and a less frequent need for revascularization of the original coronary lesion.

Stenting versus coronary artery bypass surgery

Multivessel stenting

The 4 most contemporary, multicenter, randomized studies comparing PCI to surgery involve the use of coronary stenting and were conducted in the mid- to late 1990s.[5-8] They were the ARTS,[5] SoS,[6] ERACI-2,[7] and AWESOME trial.[8] The ARTS trial was the largest trial with 1205 patients from 69 centers and clearly established that for patients with multivessel disease, mortality at 1 and 5 years was similar irrespective of whether the patient underwent stent implantation or surgery.[5,15] However, the primary end point, freedom from major adverse cardiac and cerebral events (MACCE), a composite of freedom from death, MI, cerebrovascular accident (CVA), and any repeat revascularization at 1 year were lower in the stent group (73.8% vs 87.8%, $P < .001$), which was attributable to an increased need for repeat revascularization in the stent group (21.0% vs 3.8%, $P < .001$). Importantly, the late (5-year) outcome from this trial was the first in the stent era to demonstrate a similar mortality rate for stenting versus CABG, which differs from the balloon era where surgery was associated with an improved survival rate over balloon angioplasty at 5 years.[16] Furthermore, a meta-analysis of the results of ARTS, SoS, ERACI-2, and MASS-2 confirmed that in 3051 patients, there was no 1-year mortality difference.[17]

Given similar survival between stenting and CABG, the major remaining limitation to multivessel stenting is the excess in repeat intervention, predominantly due to restenosis, in the stent group. Multiple randomized trials have consistently demonstrated that drug-eluting stents (DES) reduce restenosis compared with bare metal stents in single lesions with no excess mortality or MI.[18] Various single-center registries have also reported the efficacy of DES for multivessel disease.[19,20] The RESEARCH and T-SEARCH Registries have shown in an "all-comers" population low reintervention rates in an unrestricted setting.[21,22]

The ARTS Part 2 multicenter, nonrandomized, open-labeled study used sirolimus-eluting stents to treat multivessel disease. The surgical arm of ARTS was used as a comparative historical control for the primary end point of MACCE at 1 year.[23] This study was seen as an intermediate step preceding a full-fledged, randomized trial between DES and CABG using contemporary techniques. One year results have demonstrated favorable outcomes in the DES group.[24]

Left main stem

Since the publication of the Veteran's Affairs study, surgery has been the gold standard for LM disease. The major limitation of percutaneous treatment in the bare stent was restenosis, occurring in 22% of patients.[25] Consequently, percutaneous treatment of LM disease has remained confined predominantly to emergency cases as a salvage procedure and for high surgical risk patients. In the 3 years since the commercialization of DES, with reductions in restenosis rates of up to 80% in clinical trials, there has been renewed interest regarding percutaneous treatment of LM disease. The first publication on this topic was promising and reported a

restenosis rate of 8% in a small population of 16 patients.[26] More recently, larger studies have confirmed the beneficial effects of DES in this population.[27-29]

Surgical improvements

Recent advances in coronary surgery include improvements in preoperative risk assessment and management, anesthesia, the use of arterial grafts, and improvements in postoperative care.[30-32] These changes have resulted in reduced hospital morbidity and mortality despite the increasing age and comorbidities of patients.[33] Furthermore, with the use of arterial grafts, the occlusion rate of bypass grafts has been reduced.

Philosophy of the SYNTAX trial

The major concern about prior trials of CABG versus PCI has been that only a small percentage of patients treated in the real-life clinical setting fulfilled the multiple inclusion and exclusion criteria, precluding a real-world assessment. That finding, plus the advancements in both PCI and CABG, as well as the increasingly frequent use of PCI for the treatment of LM and 3VD, formed the rationale for the SYNTAX trial. To overcome the major criticism of the exclusion of patients often seen in daily practice, a nested registry to capture and follow patients not suitable for randomization is inherent in the SYNTAX trial.

Study objectives

Purpose of the SYNTAX study

The overall study goal of SYNTAX is to assess the optimum revascularization treatment for patients with de novo 3VD or LM disease (either isolated or in combination with 1, 2, or 3VD) by randomizing patients to either PCI with polymer-based, paclitaxel-eluting TAXUS stents or CABG. Patients not deemed adequate by their treating physicians (cardiothoracic surgeon and interventional cardiologist) for both treatment modalities will be captured through nested CABG and PCI registries. The CABG registry data will be used to define the population in which stenting continues to be considered unsuitable for the treatment of complex, high-risk subsets. Conversely, the PCI registry data, using any interventional techniques or devices with or without the use of DES, will define the patients for whom CABG is considered inappropriate.

Study design

This is a prospective, multicenter, multinational, randomized clinical trial with an all-comers design. All consecutive patients with de novo 3VD or LM disease (isolated or in association with 1, 2, or 3VD) are screened by the local Heart Team (composed of both an interventional cardiologist and a cardiothoracic surgeon supported by the study coordinator). The Heart Team will first confirm the eligibility of the patient for the SYNTAX study based on a limited number of criteria (Table I) and then will agree upon the patient's eligibility for PCI and/or CABG. Patients deemed amenable for both revascularization modalities by the local Heart Team will be randomized and stratified at each site based on the presence or absence of LM disease and medically treated diabetes mellitus (requiring oral medications or insulin). Those patients deemed amenable for only one of the treatment options will be allocated to one of the nested registries for either CABG-ineligible patients (PCI registry) or PCI-ineligible patients (CABG registry). Patients not amenable for either treatment option will not be included in the trial.

Table I. Specific inclusion and exclusion criteria

Specific inclusion criteria
1. Stable or unstable angina pectoris with ischemia; *or* patients with atypical chest pain or asymptomatic with demonstrated myocardial ischemia *(eg, exercise stress test, radionuclide scintigraphy, stress echocardiography)*
2. De novo lesions
3. Eligible for coronary revascularization (both PCI and CABG)
4. At least 1 significant stenosis in all 3 major epicardial territories supplying viable myocardium; OR significant stenosis* in the LM or LM equivalent† with or without stenosis in one of the other vessels
5. Patients with hypoplastic right coronary artery with absence of a posterior descending artery and presence of a lesion in the left anterior descending and left circumflex territories may be included in the trial as a 3-vessel equivalent
6. Vessel size should be at least 1.5 mm in diameter as assessed by diagnostic angiogram
7. Written informed consent
8. Signed Heart Team Decision Form between the interventional cardiologist and surgeon that the selected case meets all of the inclusion and exclusion criteria

Specific exclusion criteria
1. Younger than 21 years
2. Previous PCI or CABG
3. Pregnancy or intention to become pregnant (randomized cohort only)
4. Ongoing acute MI and cardiac enzymes >2 times the upper limit of normal
5. Inability to follow the patient over the period of 1 year after enrollment, as assessed by the investigator
6. Planned need for concomitant other cardiac surgery (eg, valve surgery or resection of aortic or left ventricular aneurysm, etc)
7. Psychiatric illness or organic brain disease rendering the subject unable to understand the nature, scope, and possible consequences of the study or mental retardation or language barrier such that the patient is unable to give informed consent
8. Potential for noncompliance toward the requirements in the study protocol
9. Single or 2-vessel disease without LM disease
10. Participation or planned participation in another cardiovascular clinical study before completion of 1-year follow-up (all cohorts except CABG without follow-up)

*Significant stenosis is defined as: (1) a diameter stenosis of at least 50% reduction in luminal diameter by visual assessment or (2) any total occlusion (no age limitation and no exclusion of unfavorable anatomic features).
†Left main equivalent disease is defined as significant stenosis of the ostium of the left anterior descending and the ostium of the left circumflex.

Primary end point

The primary clinical end point is freedom from MACCE through 1 year after allocation and includes all-cause death, cerebrovascular event (stroke), documented nonfatal MI, and revascularization by percutaneous intervention or bypass surgery; as adjudicated by an independent Clinical Events Committee (CEC).

Secondary end points

The secondary end points include the following: (1) overall MACCE rate at 1 month post procedure and at 6 months, and 3 and 5 years post allocation; (2) rates of the individual components of MACCE at 1 month post procedure and at 6 months, and 1, 3, and 5 years post allocation; (3) freedom from MACCE and its components at 1, 3, and 5 years post allocation; (4) quality of life at 1 month post procedure and at 6 months, 1, 3, and 5 years post allocation; (5) cost and cost-effectiveness at 1, 3, and 5 years post allocation; and (6) analysis of the characteristics (including comorbidity and coronary vascular lesion complexity scoring referred to as the SYNTAX score) of the PCI versus CABG randomized cohort, the PCI registry cohort, and the CABG registry cohort.

Study methods

Patient population

Fifteen hundred patients will be randomized into the PCI versus CABG cohort. Recruitment will be noncompetitive, with each center expected to enroll a preassigned number of patients into the randomized arm according to their real world volume, as assessed in a run-in phase (minimum of 16 patients and a maximum of 32 patients). There will be approximately 90 participating centers, with 60 to 70 sites in Europe and 15 to 20 sites in North America.

To randomize 1500 patients, an estimated 4300 consecutive patients will have to be screened, which will result in the inclusion of an additional 2800 patients in the CABG-only or PCI-only registries. Previous surveys have shown that the number of patients with 3VD or LM disease not amenable to bypass surgery and only treatable by PCI is small (<4%). Hence, of these 2800 patients, approximately 50 patients are expected to be included in the PCI-only registry (CABG-ineligible), with the use of any interventional techniques or devices with or without DES allowed. These patients will be followed up through 5 years post allocation. Of the remaining CABG-only (PCI-ineligible) registry patients (approximately 2750 patients), a randomly selected subgroup of 750 patients will also be followed up through 5 years post allocation so their risk profile can be compared with the randomized patients. At the time of the informed consent procedure, patients may refuse to be randomized because of their personal preference for 1 treatment modality or the other (PCI or CABG). These patients will not be included in the trial, and data from them will not be collected.

For prospectively collected data in the randomized trial as well as in the registry follow-up subsets, an independent CEC will adjudicate all primary clinical end points (12-month MACCE). An independent Data Monitoring Committee will assess the results with respect to patient safety at frequent, prespecified intervals. In addition, patients with complex lesions (LM, bifurcations, chronic total occlusions, a long-stenting cohort treated with >100 mm or 5 stents, and patients with diabetes mellitus) will be tracked as subgroups and followed up for dynamic safety monitoring.

Eligibility criteria

Because of the all-comers design of the study, inclusion is based on the decision between the cardiologist and surgeon of the local Heart Team, which will obviate the need for additional inclusion and exclusion criteria such as age, stenotic, or occlusion status of the vessel, low ejection fraction supported by an intra-aortic balloon pump, and/or mechanical ventilation, stroke, allergy to clopidogrel or acetylsalicylic acid, administration of glycoprotein IIb/IIIa receptor antagonist and/or clopidogrel, and general and vascular comorbidities.

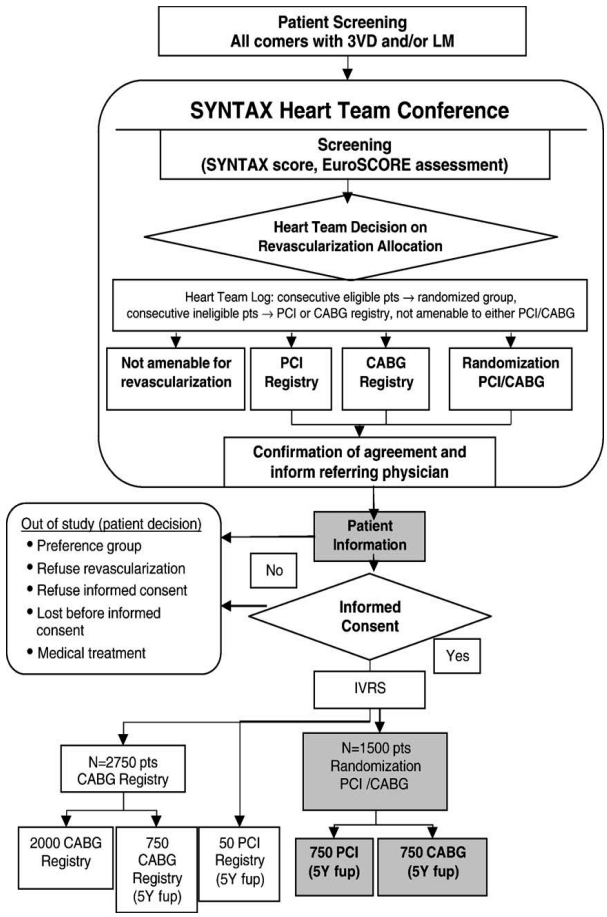
A select number of additional criteria beyond the agreement of the local Heart team are detailed in Table I.

Patient screening and Heart Team Conference

In the SYNTAX study, the investigators commit that *all* patients with 3VD or LM (with or without other lesions in the coronary arteries) will be discussed by the local Heart Team. Consecutive patients with 3VD or LM disease will be screened through the local Heart Team conference as demonstrated in Figure 1. The study coordinator facilitates the local Heart Team conference. During the Heart Team conference, members will review the collected baseline information, such as angiograms, demographic characteristics, coronary vasculature lesion complexity (SYNTAX score), and surgical risk profile (EuroSCORE), to assess whether the patient is eligible for inclusion. They will jointly decide whether the patient is eligible for the PCI and CABG randomized cohort, or for either the CABG- or PCI-only registry. If both members of the Heart Team decide that they can achieve equivalent comparable revascularization by either PCI or CABG, the patient can be randomized. A treatment strategy detailing such information as location of segments or distal anastomoses, number of stents or grafts, and other relevant information will be documented and compared with the procedural results.

If the patient is expected to have a better outcome with 1 of the 2 treatment modalities, then the patient should be assigned to one of the registries. If revascularization is not felt to be possible, the patient will be treated medically and will not be included in the study.

Figure 1



SYNTAX study flowchart.

The final decision of the local Heart Team will be documented on a Heart Team Decision Form. If applicable, the referring physician will be contacted for confirmation of the final decision by the local Heart Team. After this conference, the patient should be asked to provide informed consent for either randomization or inclusion in one of the registries. A Patient Informed Consent form has been specifically designed for each revascularization allocation group.

If the patient or the referring physician has a formal preference for either treatment, the patient will not be enrolled in the study. Any patient who refuses to be followed up will be excluded from the study. In addition, the patient or physician may decide that medical treatment is the preferred option even after informed consent is obtained.

The number of patients screened by the local Heart Team will be recorded in a study log.

Allocation

After informed consent has been obtained, the central allocation service (Interactive Voice Response System

[IVRS]) will prompt the study coordinator to provide the patient's SYNTAX score and EuroSCORE. If the patient is assigned to the randomized cohort, the IVRS will randomize the patient to either PCI with TAXUS or CABG treatment in random block sizes per site based on the presence or absence of LM disease and medically treated diabetes mellitus. If the patient is assigned to one of the registries, the study coordinator must specify the assigned treatment allocation in the IVRS.

Randomization

Randomization will be stratified by clinical site and by absence or presence of LM disease and medically treated diabetes to ensure approximately equal allocation to the 2 revascularization methods at each site and within each stratum. Medically treated diabetes is defined as diabetic patients requiring oral medications or insulin for glycemic control. The sample size is sufficiently large to prevent serious imbalances with respect to other important risk factors. Any MACCEs that occur after IVRS randomization will count toward the primary end point, even if the patient has not yet been treated. The IVRS will randomly select a subset of 750 CABG patients who are to be followed up over a period of 5 years.

Postallocation and pretreatment phase (wait list)

The interval between treatment allocation and actual procedure date may be different between the randomized PCI and CABG cohort and will vary by country. Any events and incurred costs will be allocated to the corresponding treatment group (intent-to-treat) as soon as the IVRS is initiated.

Crossovers: CABG→PCI or PCI→CABG

Crossover is expressly discouraged and will be allowed only under very special circumstances and will be tracked by the Executive Committee. In the event of a crossover to CABG, the interventional cardiologist must be notified in advance and both cardiologist and surgeon must agree that no solution other than CABG is available under the circumstances. Conversely, in the event of a crossover to PCI, the cardiothoracic surgeon must be notified in advance of the possibility of emergent surgery, and both must agree that no solution other than PCI is available under the circumstances.

Study end point definitions

Death. In the primary comparison of the 2 treatment strategies, all deaths will be examined. Death due to specific causes will be investigated and adjudicated by the CEC. All deaths are considered cardiac unless an unequivocal noncardiac cause can be established. All patient deaths will be documented in the electronic case report forms.

Cerebrovascular event (CE, stroke). Cerebrovascular event is any acute event related to the impairment of the cerebral circulation that lasts more than 24 hours and results in irreversible brain damage or permanent body impairment. Strokes may be further classified as ischemic or hemorrhagic based on imaging studies. The definitive evaluation for absence or presence of CVA will be conducted and confirmed in both revascularization arms by a local neurologist. In addition, a neurologist will be included in the CEC to ensure consistency in the adjudication of CVA.

An MI will be considered an event whether it occurred spontaneously or in association with PCI or CABG procedures. A definite diagnosis of MI is made based on the following: within the first 7 days post intervention (PCI or CABG) — either new, abnormal Q waves and 1 ratio of peak creatine kinase-MB (CK-MB)/peak total CK >10% or new, abnormal Q-waves and 1 plasma level of CK-MB 5× upper limit for normal; 7 days after any intervention procedure (PCI or CABG) — either new, abnormal Q waves or enzyme changes defined as more than 10% of the ratio of peak CK-MB/peak total CK on one or more than one sample (if no ratio is available — one or more than 1 plasma level of CK-MB 5× upper limit for normal). The Minnesota Code for pathological Q waves will be used. New abnormal Q waves will be identified by the investigator on the electrocardiogram and recorded. Cardiac enzymes (CK/CK-MB) must be determined in all surgical patients, unless the local institution uses another method for enzymatic determination of perioperative myocardial damage. In this case, all relevant enzymatic data must be reported. An independent central core laboratory will assess all collected samples.

Revascularization procedure. Every subsequent revascularization procedure and its indication will be reported and documented.

Run-in phase

A run-in phase was mandated for each site interested in participating in the trial both to assess the experience of the operators at each site in performing 3VD and LM procedures and to adequately project the expected enrollment rate at each site. Both the interventional cardiology and cardiothoracic surgery units at each site were asked to complete a web-based survey, which collected the anonymous details of each patient treated for 3VD or LM disease at the site over a retrospective, 3-month period from January to March 2004.

As of May 13, 2005, a total of 12158 patients from 104 PCI sites and 104 CABG sites have been entered (Table II). European sites comprise three fourths of all sites, with the remainder from North America. Overall, 2.8 times as many patients per site were treated by CABG, compared with PCI for the combined cohort of LM or 3VD.

On average, European sites performed twice as many 3VD PCIs per site, compared with North American sites.

Table II. Results of the survey of sites by continent

Variable	Europe	North America	P*
PCI			
Total number of sites	77	27	
No. of patients†	34.3 ± 28.6	20.0 ± 27.6	.03
3-vessel treatment†	25.8 ± 24.9	12.1 ± 19.6	.01
Left main treatment†	8.4 ± 8.1	7.9 ± 10.4	.8
Unprotected LM†	5.6 ± 6.3	1.8 ± 2.6	<.001
CABG			
Total number of sites	75	27	
No. of patients†	84.3 ± 50.9	92.3 ± 52.6	.5
3-vessel treatment†	60.0 ± 41.4	61.2 ± 46.0	.9
Left main treatment†	24.2 ± 18.6	31.3 ± 25.8	.21

*P value calculated using independent samples *t* test.
†Results expressed as mean number of patients per site.

Although a similar number of LM vessels were treated by PCI on both continents, 3.1 times more unprotected LMs were treated per site in Europe than in North America during the 3-month period. Similar numbers of 3VD and LM disease patients per site were treated by CABG across both continents.

SYNTAX score and risk profiles

SYNTAX score (coronary vascular lesion complexity)

One of the key objectives of the SYNTAX trial is to provide guidance to physicians on optimal revascularization strategies for patients with higher risk lesions. These recommendations will stem from the complexities of the lesions, the associated approach to revascularization, and the outcomes based on lesion type. The SYNTAX score is being developed to prospectively characterize disease complexity of the coronary vasculature with respect to lesion frequency, location, and angiographic complexities. Higher SYNTAX scores are indicative of a more complex overall vascular tree; it is hypothesized that patients with higher scores would have worse short-term outcomes.

The suggested SYNTAX score incorporates and combines multiple concepts developed over the last decades including the importance of a diseased coronary artery segment ("Leaman score"),[34] adverse characteristics of a lesion for revascularization (American College of Cardiology [ACC]/American Heart Association [AHA] lesion classification),[35] and the plaque anatomy for bifurcation lesions as captured in the modified Duke[36]/Institut Cardiovasculaire Paris Sud System classification.[37] Adverse characteristics are scored for each lesion separately. The SYNTAX coronary vascular lesion complexity will be graded for all significant lesions. The sum of all these individual classifications and the complexity factor (additive score) will be referred to as the patient's general SYNTAX score.

In addition, the SYNTAX score assigned pre procedure based on diagnostic angiography will be assessed by an independent core laboratory. Its utility for predicting outcomes will be examined at 3 junctures during the trial: Phase I will evaluate the SYNTAX score based on patient allocation into the 3 study arms (randomized cohort, PCI-only registry and CABG-only registry), Phase II will evaluate and optimize its utility at predicting early (30 day) procedural outcomes, and Phase III will evaluate and optimize the SYNTAX score for predicting 1-, 3-, and 5-year outcomes. The SYNTAX score may need to be modified as the usefulness of its individual features is determined or as new contributors are identified.

EuroSCORE and Parsonnet score

To estimate operative mortality and balance baseline patient characteristics, variables that are used to calculate the EuroSCORE and the Parsonnet score will be collected.

The EuroSCORE is a prognostic scoring system calculating predicted operative mortality for patients undergoing cardiac surgery.[38] The score was originally developed in Europe and is the most rigorously evaluated scoring system in cardiac surgery. Most EuroSCORE risk factors are derived from the preoperative clinical status of the patient, with 4 risk factors being related to the operation. The additive EuroSCORE is easy to use and gives a reliable estimate of risk in individual patients, unless certain combinations of risk factors coexist.[39] The SYNTAX trial provides an opportunity to explore this higher-risk group.

The Parsonnet risk stratification system was developed in the United States in the 1980s and was the first scoring system in popular use for cardiac surgery.[40] The Parsonnet score will be calculated for all patients enrolled in both the randomized cohort and the nested registries.

Procedural techniques

Stenting technique

Stent implantation will be performed according to routine, local, clinical practice using the femoral or radial approach with the intention of complete revascularization. The TAXUS Express[2] paclitaxel-eluting stent should be attempted for each lesion in a vessel with a diameter >1.5 mm (by visual assessment) that supplies viable myocardium, as assessed on the diagnostic angiogram. Lesions should be completely covered by the stent with an overlap at both edges of at least 3 mm. Unsuccessful stent implantations must be recorded. A stent-to-stent overlap of approximately 4 mm is recommended for multiple stents per lesion. Whenever clinically indicated (eg, ostial lesions, edge dissection, LM stem), intravascular ultrasound guidance is recommended to ensure optimal stent expansion and lesion coverage. Specific guidelines are provided in the protocol with regard to the treatment of bifurcations, chronic total occlusions, aorto-ostial lesions, and LM

stem lesions. An intra-aortic balloon pump or a left ventricular assist device for the elective treatment of LM stem lesions may be used at the operator's discretion.

Concomitant medications are detailed in Table III. Optimizing medical therapy according to ACC/AHA guidelines is strongly recommended for patients enrolled in this trial.[35]

Staged procedures. A staged procedure is allowed provided it is performed within 72 hours after the initial procedure and during the same hospital stay. However, when renal insufficiency is present or contrast-induced nephropathy occurs, the PCI procedure may be staged but must be completed within 14 days. A staged procedure should be documented as planned (before the initial procedure) or provisional (at the time the patient is leaving the catheterization laboratory) and will be adjudicated by the CEC. This practice distinguishes staged procedures from repeat interventions on initially targeted lesions mandated by a clinical problem occurring during the initial hospitalization.

Surgical technique

CABG will be performed at the surgeon's discretion and according to local, clinical practice. It is recommended that patients undergoing coronary bypass surgery should be operated on with the intention of complete revascularization. All vessels with a significant stenosis of at least 50% in a vessel with a diameter of ≥1.5 mm (as previously estimated on the diagnostic angiogram during the local Heart Team conference) should be considered for bypass surgery. In patients <70 years old, arterial revascularization is strongly recommended. The left anterior descending artery and/or the diagonal branches should be revascularized using the pedicled left and/or right internal thoracic artery whenever feasible. The remaining vessels should be bypassed either by use of another mammary artery or any other artery or the greater saphenous vein in the configuration as deemed appropriate by the surgeon. Patients can be operated on either with or without extracorporeal circulation; however, minimally invasive direct CABG may only be included in the CABG registry. Finally, anesthetic techniques will not be standardized. For on-pump surgery with the use of cardioplegia, the type of cardioplegia will be left to the individual operator.

Concomitant medications are detailed in Table III. Optimizing medical therapy according to ACC/AHA guidelines[33] is strongly recommended for patients enrolled in this trial.

Table III. Periprocedural medication guidelines for the SYNTAX trial

STENT	
Pre procedure	Aspirin: >70 mg per day starting at least 12 h before the procedure Clopidogrel: loading dose of at least 300 mg starting at least 24 h before procedure is required (given that these are high-risk patients with complex lesions), followed by 75 mg once daily. OR ticlopidine*: 48 hours pre procedure: 2 × 250 mg
Procedural	Heparin: initial bolus IV with additional boluses to maintain an ACT >250 seconds Administration of glycoprotein IIB/IIIA inhibitors and bivalirudin are at the discretion of the operator
Post procedure	Postprocedural heparin is discouraged Aspirin: >70 mg/d indefinitely Clopidogrel: 75 mg once daily for 6 m OR Ticlopidine*: 2 × 250 mg/d for 6 m
CABG	
Pre procedure	Aspirin: >70 mg/d starting at least 12 h before the procedure
Procedural	Aprotinin: permitted
Post procedure	Aspirin: >70 mg/d indefinitely

*Ticlopidine is to be used in cases of clopidogrel intolerance.

Study procedure and follow-up

The 1500 randomized patients will undergo predefined clinical follow-up at 30 days post procedure and at 1, 6, 12, 36, and 60 months post allocation. Twelve-lead electrocardiograms (ECGs) are to be performed preprocedurally, at discharge, and at 1, 3, and 5 years post allocation, with the core laboratory reviewing the first 3 ECGs. Cardiac medications and anginal status (according to the Canadian Cardiovascular Society classification) will be recorded during the initial hospital stay and at all out-patient follow-up clinics. Blood samples are to be obtained for the measurement of creatine phosphokinase and its MB isoenzyme before procedure and at 6 hours and 12 hours post index procedure or at discharge (whichever is earlier). In the case of chest pain with or without ECG changes, additional serial cardiac enzymes must be sampled immediately, 6 and 12 hours after the onset of symptoms. In addition, serum creatinine will be assessed locally. Samples collected from the randomized cohort will be assessed by a central Core Laboratory for the following parameters: high-sensitivity C-reactive protein, hemoglobin A_{1c}, and CK and CK-MB.

Patients allocated to the PCI registry and the 750 randomly selected CABG registry patients will undergo clinical follow-up at 1 month post procedure and at 6, 12, 36, and 60 months post allocation. In addition, these patients will undergo a preprocedural and predischarge ECG.

Costs and cost effectiveness

The analyses of costs, quality of life, and cost effectiveness will be outlined in detail in a separate protocol.

Statistical considerations

Sample size estimate and justification

The primary end point is the MACCE rate through 12 months post allocation. The sample size was calculated for a 2-group test of equivalence in proportions using the commercial software program nQuery Advisor Version 4 (Statistical Solutions, Cork, Ireland). The expected 12-month MACCE rate for both groups is estimated to be 12%, based on data from the ARTS I trial.[5] Given a clinically relevant difference (delta) of 5% and a 1-sided 5% significance level, 725 patients per group will provide 90% power to reject the null hypothesis if it is false. Allowance is made for 3.5% attrition; therefore, the necessary sample size for the study is 1500 patients (750 per group).

The randomized trial will not have sufficient power for analyzing LM disease only. The study of 1500 patients is 80% powered to show a superiority of binary treatment difference of 5.0% or more, assuming there is a 10% MACCE rate in the PCI group.

Statistical testing will be used to determine whether the 12-month MACCE rate for the PCI with TAXUS group is noninferior to the 12-month MACCE rate in the CABG control patients, assuming that a difference of 5 percentage points is clinically significant. The null hypothesis that the true difference in rates is at least 5 percentage points will be tested against the 1-sided alternative that the true difference in rates is less than 5 percentage points, that is,

$$H_0 : P_e - P_c \geq 0.05$$
$$H_1 : P_e - P_c < 0.05$$

where P_e and P_c are the expected 12-month MACCE rates for the PCI with TAXUS and CABG groups, respectively.

For the registry cohorts, the numbers of patients indicated are estimates. As they are used for descriptive purposes only, no statistical justification is required for group size.

Analysis populations

All primary and secondary end points will be analyzed both on an intent-to-treat basis and on a per-protocol basis. For intent-to-treat analyses, all patients who sign the written Informed Consent Form and enroll in the study, that is, who are randomized via IVRS allocation, will be included in the analysis, regardless of the treatment that ensues. For per-protocol analyses, only randomized patients who received the appropriate treatment according to their IVRS allocation will be included. Patients who cross over to the other treatment are excluded from per-protocol analyses. Any difference in results between the populations will be investigated so that they can be explained. Data will also be summarized descriptively for the registry patients.

Predefined subgroups

Three-vessel disease. It is estimated that 1300 patients with 3VD (without LM) will be enrolled, which will result in a power of 86% to show noninferiority of PCI with TAXUS to CABG in this subgroup. A minimum of 1090 patients with 3VD (without LM) are required to guarantee a power of 80%.

Left main isolated or with 1, 2, or 3VD. Although the randomized cohort will not have adequate power to show noninferiority of PCI with TAXUS to CABG for LM disease, this high-risk subset will be analyzed and monitored extensively for safety.

Other predefined subgroups. Other subgroups that will be monitored include patients with bifurcation or trifurcation lesions, chronic total occlusions, long stenting, age (>70, ≤70), sex, diabetes mellitus (including status by type, treatment, and hemoglobin A_{1c} level), and metabolic syndrome.

Interim analysis

No formal interim analysis of the primary end point of this study will be performed.

Statistical analysis

All statistical analyses will be done using The SAS System software, version 8 or above (SAS Institute Inc, Cary, NC). Analyses will be performed using data pooled across all randomization strata (ie, institution, LM disease, and medically treated diabetes mellitus). Continuous variables will be presented using mean, SD, median, 25th and 75th percentile, minimum and maximum values. Discrete variables will be presented in frequencies and percentages.

Other analysis methods

Data collected during the follow-up period will be analyzed using appropriate univariate and multivariate techniques. Kaplan-Meier plots of time-to-event variables will be constructed. The Cox proportional hazards regression model may be used to assess the effects of risk factors on the time-to-event variables. Loglinear models or logistic regression models may be used similarly for discrete outcomes.

If baseline differences are observed between the PCI with TAXUS patients and the CABG patients, a secondary analysis will be performed in which comparisons between treatment groups for principal safety and efficacy end points will be adjusted for those baseline covariates found to be different. The baseline data from the overall study population will be used to describe the subpopulations with respect to the SYNTAX score, EuroSCORE, and their individual components.

Stages of result reporting

Results will be reported for the primary and secondary analysis populations in 4 stages:

1. short-term follow-up (30 days post index procedure);
2. primary end point (1 year post-treatment allocation);
3. medium-term follow-up (3 years post-treatment allocation); and
4. long-term follow-up (5 years post-treatment allocation).

Predictive scoring systems under investigation

The EuroSCORE has only been validated to predict inhospital or 1-month outcomes. In this trial, it will also be used to predict morbidity outcomes at 1, 3, and 5 years post allocation. A score based on coronary lesion complexity assessment (SYNTAX score) will be developed to predict clinical outcomes at 1 month post index procedure and at 1, 3, and 5 years post allocation using logistic regression analysis.

Conclusions

This study will define the roles of CABG and PCI using DES in the contemporary management of LM and 3VD. The development of the SYNTAX score and the validation of the EuroSCORE should provide guidance to physicians as a predictive tool on the optimal revascularization strategy for patients with high-risk lesions. In addition to the 1-year primary end point, both short- (1 month) and long-term (5 year) results will be obtained, enabling determination of the sustainability of DES. Predefined subgroup analyses in this complex population will also provide guidance as to the optimal treatment method for each subgroup.

We thank Blessie Concepcion, Nic Van Dyck, Peter Lam and Luc Verhees (all employees of Boston Scientific Corporation) for their extensive efforts in the development and creation of the study protocol.

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Appendix A

Study organization

Co-Principal Investigators: PCI: Professor Patrick Serruys, **CABG**: Professor Frederick Mohr

Sponsor: Boston Scientific Corporation (BSC)

Executive Operations Committee: PCI Chair, PW Serruys; Cochair, MC Morice; CABG Chair, F Mohr, Cochair, AP Kappetein; Independent Physician, M van den Brand; Chief Medical Officer, ME Russell (BSC); Execution, J Koglin/L Verhees (BSC), GA van Es (Cardialysis); Project Managers, N van Dyck/B Concepcion (BSC), J Kleijne (Cardialysis).

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Chapter 22

Complete Revascularization: Coronary Artery Bypass Graft Surgery Versus Percutaneous Coronary Intervention.

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Complete Revascularization

Coronary Artery Bypass Graft Surgery Versus Percutaneous Coronary Intervention

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The concept of complete revascularization arose from the early studies on coronary artery bypass grafting (CABG) surgery whereby some publications demonstrated that patients who were completely revascularized enjoyed a mortality benefit over those who were incompletely revascularized, thus setting the standard for the field of CABG.[1–3] Over the past 3 decades, CABG has evolved from saphenous vein grafting to more frequent use of arterial grafting, better perioperative management, development of a less invasive approach, and off-pump surgery as a genuine option. The development of percutaneous coronary interventions (PCIs) for the treatment of coronary stenosis has developed out of the treatment of single-vessel disease to become an alternative to CABG in the treatment of multivessel disease.[4,5] PCI has progressed from balloon angioplasty to coronary stents,[6,7] and now drug-eluting stents,[8] with the simultaneous development of new devices to treat chronic total occlusions (CTOs). For both groups of patients treated by either CAGB or PCI, there is recognition that aggressive pharmacological secondary-prevention therapies such as statins and antiplatelet agents are beneficial and are now commonly used.

Despite the mantra of complete revascularization, none of the current guidelines set out by the American or European cardiology societies formally discuss the issue in detail. Although this topic has been addressed separately within each revascularization strategy, to date there has been only 1 report from a randomized trial that compared the end point of complete revascularization between CABG and PCI.[9] This review will therefore address the issue separately for CABG and for PCI and finally provide a comparison of the 2 strategies.

Definition of Complete Revascularization

There is no universal definition for what is meant by "complete" revascularization (Table 1). Different studies employ different definitions, and for that reason, comparisons between studies must be interpreted with caution. For example, revascularization may be declared complete if all stenotic vessels are revascularized, irrespective of size (anatomic revascularization) and territory supplied; others impose minimum diameter criteria; yet others differentiate between main vessels and branch vessels. Second, a functional classification may be used, whereby revascularization is declared complete if all ischemic myocardial territories are reperfused; areas of old infarction with no viable myocardium are not required to be reperfused. Another method that may be used is to count the number of vessels with stenoses and then to count the number of distal anastomoses (an equal number would be declared a complete revascularization). Finally, a scoring system can be used whereby stenoses in different vessels assume different weightings; the overall extent of disease, and its treatment, is then a continuous variable.

Studies that have examined the extent of revascularization in CABG patients usually rely on the surgical report, because routine angiographic restudy in patients immediately after CABG is not commonly performed. PCI studies, on the other hand, have the option of utilizing either operator reports or, more objectively, independent ascertainment of the procedural angiographic results themselves to visually and accurately determine the adequacy of revascularization. Completeness of revascularization is therefore based on the immediate procedural outcome. Failure after an initial successful attempt at revascularization (eg, graft failure with CABG, restenosis with PCI) is not measured directly but is included as part of the end point of repeat revascularization.

CABG Surgery

Since the beginning of the revascularization era, no specific CABG study has been performed with the primary end point of complete revascularization as an outcome. The need to completely revascularize the coronary tree has been stated to be a tenet,[10] even a truism.[11] The following studies on the extent of surgical revascularization are post hoc analyses of major studies and are described in order to obtain an understanding of the literature.

First, in a seminal publication from the Coronary Artery Surgery Study (CASS) Registry, 3372 patients with 3-vessel disease (including left main disease) who underwent isolated first-time CABG between July 1974 and June 1979 were analyzed with a mean follow-up of 4.9 years.[3] The extent of revascularization for this study was defined by the number of the 3 major vessels (or their branches) that received a bypass

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TABLE 1. Different Definitions of Complete Revascularization as Found in the Literature

Revascularization	Definition
Complete anatomic revascularization	
Unconditional	All stenotic vessels are revascularized, irrespective of size and territory supplied.
Conditional	All stenotic vessels greater than a defined diameter are revascularized, OR All stenotic main-branch vessels are revascularized.
Complete functional revascularization	All ischemic myocardial territories are reperfused; areas of old infarction with no viable myocardium are not required to be reperfused.
Complete numeric revascularization	The number of stenotic vessels must equal the number of distal anastomoses applied.
Complete revascularization by a predetermined scoring cutoff value	Scoring of stenoses in different vessels at different locations (weightings may be used). The overall extent of disease is a continuous variable, the treatment is another variable, and the posttreatment score determines completeness of revascularization.
Anatomic	Irrespective of viable myocardium
Functional	Jeopardy score: The postrevascularization score is calculated on the basis of the amount of remaining myocardium at risk.

graft. An average of 3.2 distal anastomoses were performed. Grafts were placed to the left anterior descending artery in 98%. In this study, only 16% of patients received an internal mammary artery conduit, as was the usual practice then. Patients with severe angina (Canadian Cardiovascular Society class III or IV) in whom more complete revascularization was performed (defined as bypassing 3 or more vessels versus 1 or 2) enjoyed improved survival (relative risk [RR] 0.75, 95% confidence interval [CI] 0.59 to 0.94, $P=0.01$) and event-free survival (RR 0.87, 95% CI 0.78 to 0.96, $P=0.01$) independently of any baseline differences. These patients were also more likely to be asymptomatic or to have less severe angina that those with incomplete revascularization. Subset analysis revealed a significant survival benefit in patients with significant left ventricular dysfunction (ie, ejection fraction <0.35) with 3 or more vessels bypassed compared with those with 2 ($P=0.04$).

A criticism of the method described above was that it did not take into account the relative role of each coronary artery in supplying the left ventricle and therefore the effect of coronary stenosis in the particular vessel(s). To address this criticism, a novel functional scoring system that incorporated the amount of myocardium supplied by a particular vessel was developed by Leaman et al and published in *Circulation* in 1981.[12] Two hundred patients were studied by coronary angiography before CABG and at 1 year after surgery and scored on the basis of their coronary anatomy. Angina class and left ventricular function were also recorded. In the group studied, the severity of coronary artery disease (as measured by this score) did not statistically correlate with the frequency of angina. Postoperatively, no relationship between the frequency of angina and the completeness of revascularization could be determined. The principles of this scoring system have been used in the development of the SYNTAX score, an anatomic scoring system created for the SYNergy between Percutaneous Coronary Intervention with TAXus and Cardiac Surgery (SYNTAX) Study that eventually may be used as a tool to predict outcomes.[13,14]

The Bypass Angioplasty Revascularization Investigation (BARI) study compared the outcomes of patients with multivessel coronary artery disease treated with percutaneous transluminal coronary angioplasty (PTCA) versus CABG and enrolled patients from August 1988 to 1991 in either a randomized arm or in a registry arm (due to the patient or physician preference for the type of treatment). Patients had to be suitable for both PTCA and CABG, and left main stenosis was an exclusion criteria. Approximately two thirds of patients had 3-vessel disease. In total, 1526 patients (901 in the randomized arm and 625 in the registry arm) underwent CABG, and 1507 were analyzed in a post hoc report with a mean follow-up of 7.1 years.[11] In this study, the authors attempted to establish different definitions and then apply them to the available results to derive the most appropriate definition of extent of revascularization. They came up with 4 different definitions: (1) Traditional—all coronary arteries with at least 1 significant lesion received a graft. (2) Functional—all diseased "primary" coronary segments were bypassed, with a unique algorithm developed for this definition (primary segments were defined on the basis of the BARI system of dividing the coronary arteries into 29 segments; for example, the main body of the right coronary has 2 segments, and there are additional primary segments based on the anatomy of the branches, including the acute marginal, posterior descending, and up to 3 posterolateral branches). (3) Patients were grouped according to whether or not the number of distal anastomoses was less, equal to, or more than the number of diseased coronary segments. (4) Patients were grouped by whether they had 2 or more grafts to both the left anterior descending coronary artery and to a non-left anterior descending coronary artery system, or whether no system had multiple grafts. The authors found that by either the traditional or functional definition, complete revascularization conferred no independent advantage, but the risk estimates on late mortality were in the direction that favored complete revascularization.

Between 1997 and 1998, the multicenter Arterial Revascularization Therapies Study (ARTS) trial enrolled patients with multivessel disease who could be potentially completely and equivalently revascularized.[4] In total, 1205 patients were randomized to either PCI with stenting or CABG. Left main coronary stenosis was excluded, and 30% of the population had 3-vessel disease. In this contemporary study, 93% of

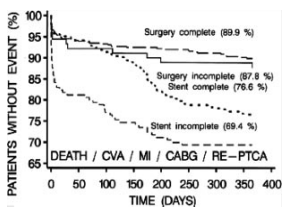
TABLE 2. Ranked MACCE at 1 Year, in Worst Order, in the ARTS Trial, Stratified According to Extent of Revascularization and Treatment Strategy[9]

	CABG			PCI		
Event	Complete (n=477)	Incomplete (n=90)	*P* Within CABG	Complete (n=406)	Incomplete (n=170)	*P* Within PCI
Death	2.5	4.4	NS	1.7	3.5	NS
Cerebrovascular accident	1.9	0	NS	1.7	1.2	NS
Myocardial infarction	3.4	4.4	NS	4.9	5.9	NS
(Repeat) CABG	0.2	1.1	NS	2.0	10.0	<0.05
(Repeat) PCI	2.1	2.2	NS	13.1	10.0	NS
Any MACCE	11.1	12.8	NS	23.4	30.6	<0.05

NS indicates not significant. Values are percentages.

patients received at least an arterial graft. All angiograms were reviewed centrally, and all lesions with a >50% diameter in a segment with a reference diameter of ≥1.50 mm were scored as potentially amenable to treatment. An anatomic definition was used: if all such segments were treated according to the case report form, they were classified as a complete revascularization. In a post hoc analysis from the trial, complete revascularization was not associated with a difference in mortality or in major adverse cerebral or cardiac events (MACCE) compared with patients with incomplete revascularization at 1 year (Table 2; Figure).[9] The respective freedom from MACCE was 89.9% versus 87.8%.

More recently, a single-center retrospective analysis of 1034 patients who underwent first-time CABG with a mean follow-up of 3.3 years was performed.[10] The authors chose a functional classification, with complete revascularization defined as the placement of at least 1 bypass graft distal to a >50% narrowing in each diseased territory. This "real-world" cohort had a mean age of 68 years and included both on- and off-pump CABG, with the choice of technique left to the individual operator's preference. The most common reasons recorded for incomplete surgical revascularization were that the arteries were too small, that they were severely diseased, or both. In this study, compared with completely revascularized patients, incomplete revascularization was associated with a 5-year unadjusted increased overall mortality rate (47.4% versus 17.6%, respectively, $P<0.001$) and cardiac mortality rate (25.5% versus 6.9%, $P<0.001$). After adjustment for predictors of death, incomplete revascularization remained an independent risk factor for death (hazard ratio [HR] 1.85, 95% CI 1.03 to 3.34, $P=0.04$ for all-cause death, and HR 1.73, 95% CI 1.18 to 2.55, $P=0.006$ for cardiac death only).



Kaplan-Meier curve showing survival free of MACCE at 1 year from the ARTS trial, stratified by treatment and completeness of revascularization. Reprinted from van den Brand et al[9] with permission from the American College of Cardiology Foundation. CVA indicates cerebrovascular accident; MI, myocardial infarction.

Controversies

There have been other reports in the literature[15–17] on completeness of revascularization in the CABG population, but in general incompletely revascularized patients tended to be sicker, and outcomes were usually not adjusted to reflect this bias. Second, the development of hybrid or integrated coronary revascularization in the 1990s to treat multivessel disease by combining percutaneous techniques with minimal-access coronary surgery through a minithoracotomy[18,19] has been unsuccessful owing to the increased need for repeat revascularization in these patients, driven by incomplete revascularization and in-stent restenosis.[20] Finally, off-pump CABG has been shown to be a successful alternative to conventional or on-pump CABG, with randomized trials demonstrating that, in the hands of experienced operators, off-pump CABG surgery results in a degree of revascularization that is comparable to on-pump surgery.[21]

Percutaneous Coronary Intervention

Early in the balloon angioplasty era, according to a report of the 1985 to 1986 National Heart, Lung, and Blood Institute PTCA registry, complete revascularization was attempted and achieved in 57% and 46% of patients with 2- and 3-vessel coronary artery disease, respectively.[22] The majority of lesions not amenable to PTCA were total occlusions, and the success rate for attempted occlusions was 54%. In the long-term (9-year) follow-up study from the same registry, the authors report that compared with patients who were completely revascularized, patients who were incompletely revascularized (whether intended, attempted, or not achieved) had no different risks of dying, myocardial infarction, or repeat revascularization by PTCA or CABG after adjustment for baseline characteristics.[23] Incomplete revascularization, however, remained a significant risk factor for subsequent CABG by 9-year follow-up, and incompletely revascularized patients showed a strong trend toward more recurrent angina at long-term follow-up, but this risk became weaker after adjustment.

After this, investigators from the multivessel BARI trial, which enrolled patients from 1988 to 1991, reported 5-year outcomes of patients treated with PTCA in both the randomized and preference registry arms.[24] Similar to the National Heart, Lung, and Blood Institute registry, the adjusted RRs for death, cardiac death, and death or Q-wave myocardial infarction were not different in incompletely revascularized versus completely revascularized patients. As with the previous study, an excess risk of subsequent CABG was seen in the former group.

In the more recent ARTS randomized trial, which mandated equivalence of completeness of revascularization, true anatomic completeness of revascularization, as ascertained by experienced independent observers on review of films after completion of the PCI, occurred in 70.5% of patients, a rate higher than that in previous studies.[9] As with previous studies, patients who could not be completely revascularized had a significantly greater number of diseased segments and vessels. Incompletely revascularized patients also had a 3.6-fold higher incidence of total occlusions than completely revascularized patients (19.4% versus 5.4%, $P<0.001$). In this study, as with previous studies, stented patients who were incompletely revascularized had a higher requirement for subsequent CABG in the first year of follow-up (10% versus 2% in those who were completely revascularized, $P<0.05$), which resulted in a lower overall MACCE-free rate (69.4% versus 76.6%, $P<0.05$; Table 2; Figure).

In the most recent publication on this topic, the investigators of the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) reported on 1308 patients completely revascularized after PCI compared with 648 patients with incomplete revascularization after PCI.[25] Completeness of revascularization was determined using the Duke jeopardy score, a score developed and validated to describe the extent of coronary disease based on the amount of myocardium at risk. Independent predictors of incomplete revascularization were the presence of a total occlusion, a higher pre-PCI Duke jeopardy score, age >65 years, and renal failure. The authors then used a propensity score to correct for the differing baseline characteristics between the 2 populations and concluded that, with a median follow-up of 3.0±1.8 years, complete multivessel PCI was associated with a reduced need for future PCI, a trend toward better survival, and no difference in repeat PCI.

Treatment of Culprit Lesion Versus Total Revascularization

In the only study that has randomized patients with multivessel disease to either PCI limited to the culprit vessel or PCI of all vessels with ≥50% stenosis, 219 patients were randomized and followed up for 5 years.[26] Identification of the culprit vessel was determined by 2 independent interventional cardiologists on the basis of the clinical evidence available with PCI for an acute myocardial infarction, an exclusion criterion. This study demonstrated that at long-term follow-up of 4.6 years, although target-lesion revascularization rates were similar in the completely revascularized group and the culprit vessel–treated group (17.3% versus 12.0%, $P=0.3$), the overall need for repeat PCI was significantly lower (21.2% versus 31.2%, $P=0.06$) in the completely revascularized group. Overall long-term MACCE rates were similar between groups (34.6% versus 40.4% respectively, $P=0.4$), as were estimated costs ($P=0.8$). Despite a relatively low usage of stents (only 55% of the cohort was initially treated with stents), this study suggests that the treatment of other nonculprit lesions at the index procedure (ie, complete revascularization) is linked to a lower need for repeat PCI at long-term follow-up.

The significant difference between this and the other previously described trials was that patients in this trial were actively randomized to treatment groups, and patients here were intentionally left untreated, if randomized to the culprit-vessel treatment arm alone. This is in contrast to the previous trials, in which patients were incompletely revascularized owing to a "failure" of initial revascularization (intended or otherwise) and thus were highly selected and underwent CABG as the second option for revascularization, which was classified as a subsequent CABG. Thus, from a societal perspective, although estimated costs were similar for the two procedures, complete revascularization resulted in less need for a repeat intervention later.

New Developments With PCI: Overcoming CTOs

With the percutaneous approach, the presence of CTOs remains the biggest and most important obstacle and technical challenge to achieving complete revascularization. CTOs occur relatively frequently, appearing in up to 20% of patients undergoing diagnostic coronary angiography. Furthermore, CTOs make up 10% of PCIs in the contemporary practice of a tertiary referral catheterization laboratory.[27] Historically, the success rate of crossing CTOs percutaneously approximates 60% with conventional techniques. This success rate is dependent on operator experience, the number of attempts performed, anatomic considerations, and the choice of devices available.

To overcome this major limitation, new devices and adjunctive methods have been developed to improve the success rate. Multislice computed tomography coronary angiography has provided additional information such as occlusion length and degree of calcification, features that predict procedural success and that are often underestimated by conventional coronary angiography.[28] In the only randomized trial of a device, the TOTAL trial (Total Occlusion Trial with Angioplasty by using Laser guidewire), laser-tipped guidewires were no better than conventional wires.[29] Local delivery of thrombolytic therapy to the site of occlusion via a specialized catheter to facilitate wire crossing was recently reported, with promising results.[30] Japanese device makers have led the development of specialized guidewires to allow the development of a systematic approach. New devices in development include a blunt dissection catheter,[31] a helical screwlike-tipped microcatheter,[32] and a specific system that uses optical coherence reflectometry together with radiofrequency ablation. Optical coherence reflectometry is used to direct the tip of a guidewire in a coaxial plane within the lumen, and radiofrequency ablation delivered at the tip is used to enhance forward wire passage. Two separate registries of this latter device have reported successful recanaliza-

TABLE 3. Summary of Studies Comparing Drug-Eluting Stents With Bare-Metal Stents for Treatment of CTOs

	Hoye et al[27]		Werner et al[36]		Ge et al[37]	
Composition of Groups	Consecutive Cohort	Historical Control	Consecutive Cohort	Matched Control	Consecutive Cohort	Historical Control
Stent type	SES	BMS	PES	BMS	SES	BMS
Patients, n	56	28	48	48	122	259
Diabetes, %	14	7	33	29	28	19
Prior MI	55	46	42	47	55	63
Minimum duration of CTO	1 mo	1 mo	2 wk	2 wk	3 mo	3 mo
Occlusion >3 mo, %	NA	NA	73	65	100	100
CTO length, mm	11.3	12.7	18±13	16±12	10.4±10.2	9.6±6.9
Reference diameter, mm	2.35±0.46	2.37±0.50	2.65±0.65	2.57±0.47	3.05±0.44	3.05±0.55
Postprocedure MLD, mm	2.06±0.48	2.18±0.49	2.26±0.36	2.16±0.60	2.67±0.49	2.69±0.53
Late loss, mm	0.13±0.46	...	0.19±0.62	1.21±0.70	0.28±0.56	1.04±0.87
Binary restenosis rate, %	9.1	...	8.3	51.1	9.2	33.3
Reocclusion, %	1.8	...	2.1	23.4	2.5	6.6
Stent thrombosis within 1 mo, %	1.8	0	0	0	0	0
TLR, %	NA	NA	NA	NA	7.4	26.3
MACCE, %	3.6*	17.9*	12.4*	47.9*	16.4†	35.1†

SES indicates sirolimus-eluting stent; BMS, bare-metal stent; PES, paclitaxel-eluting stent; MI, myocardial infarction; TLR, target-lesion revascularization; and NA, not applicable. Consecutive cohort columns denote the DES groups.

*Clinical follow-up at 12 months.

†Clinical follow-up at 6 months.

tion rates of 51.7% and 54.3% in patients for whom conventional wire techniques had failed previously.[33,34]

Finally, a technique used in peripheral angioplasty has been newly introduced in which a subintimal dissection plane or false lumen is deliberately created parallel to the true lumen that contains the CTO.[35] Under the direct vision of an intravascular ultrasound catheter placed in the false lumen, a guidewire is advanced from the false lumen into the true lumen distal to the occlusion site, bypassing the occlusion, and the newly created track is then stented with drug-eluting stents.

Drug-Eluting Stents

After successful recanalization, the placement of drug-eluting stents has been shown to improve the midterm outcomes of patients with CTOs by reducing restenosis compared with bare-metal stenting. Although no randomized study on CTOs in drug-eluting stents has been published to date, 3 registries, all with angiographic follow-up, convincingly demonstrate a sustained reduction in restenosis rates, need for reintervention, and occurrence of MACCE with drug-eluting stents compared with bare-metal stents (Table 3).[27,36–38]

CABG Surgery Versus PCI

In the stent era, the 3 largest randomized trials comparing CABG surgery to PCI for multivessel disease were performed in the late 1990s.[4,39,40] The largest trial, the ARTS trial, mandated that equivalent revascularization was mandatory.[4] On the other hand, the Stent or Surgery trial encouraged but did not mandate equivalent revascularization,[39] whereas ERACI-2 (Argentine Randomized Study: Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Patients With Multiple-Vessel Disease) mandated complete functional revascularization.[40]

Of the 3 trials, only the ARTS trial has published the 1-year outcomes of patients who were completely or incompletely revascularized.[9] In that study, despite the potential for equivalent revascularization, complete revascularization was more frequently achieved in CABG-treated patients (84.1%) than in stented patients (70.5%, $P<0.001$; Table 2). Although no differences in mortality or the combined end point of death/stroke/myocardial infarction were seen in the comparison of the 4 groups, overall MACCE rates were significantly higher in the incompletely revascularized stented group, driven by an increased need for CABG within the first year of follow-up (Figure).

Advantages and Disadvantages of Each Approach

The advantages of PCI are obvious. It is performed under local anesthetic, postprocedural morbidity is minimal, and patients endure a short hospital stay. With the use of drug-eluting stents, long, diffuse stenoses can be treated effectively. Despite all the technology that has been described, however, it remains restricted by the inability to overcome total occlusions, and success rates vary, as described above. Symptomatic failures will eventually require CABG. CABG surgery has the clear advantage of overcoming chronic occlusions, and necessitating fewer repeated revascularizations, but it is associated with a not-insubstantial postoperative morbidity, longer period of hospitalization, and a slower return to normal activities. Multiple long and diseased coronary segments may be a challenge, with multiple grafts required in small vessels, and longer surgical procedures are associated with higher morbidity.

Future Developments

With the increased use of arterial grafts and perioperative aspirin in CABG, increased experience with drug-eluting stents and other new devices in interventional cardiology, and widespread adoption of better secondary-prevention measures such as use of statins, the results that have been described previously are important but may not be as pertinent today. The ongoing SYNTAX trial will provide new insights into contemporary practice. As with the ARTS trial, patients must have the potential for complete and equivalent revascularization before they may be considered for enrollment. This study will involve 1500 patients with 3-vessel or left main disease randomized to either CABG or PCI with paclitaxel-eluting stents, with the aim of determining the best method of revascularization.[13] Surrounding the randomized arm will be 2 preference registry arms: one for CABG and the other for PCI. As an all-comers trial, consecutive patients will be enrolled, and these registries will monitor patients who cannot be treated by either CABG or PCI owing to technical reasons, physician or patient preferences, or comorbidities. In this trial, CTOs are not an exclusion criterion, and the outcomes of their treatment will be specifically monitored throughout the conduct of the trial. Hence, it is expected that with the new devices not previously available at the time of the previous trials (some of which are described in the present report), a substantial proportion of patients enrolled will have CTOs and will be treated by CABG and PCI. Post hoc analyses of this study, examining the completeness of revascularization and success of CTO recanalization, within and between groups, will provide some useful answers to the current practice of revascularization for multivessel disease.

Conclusions

Completeness of revascularization is not a competition between 2 treatment strategies. Rather, it is an important factor in the decision-making process that requires careful thought before a patient is recommended for either treatment option. The goal should always be complete revascularization, because the overall trend supports it, whether the treatment choice is surgery or percutaneous intervention. From a practical treatment point of view, if a patient undergoing PCI for multivessel disease has a CTO, it would be reasonable to first attempt to cross the occlusion before attempting any other lesion. In that way, if the lesion cannot be crossed percutaneously, the patient would then automatically become a surgical candidate, so as to offer optimal revascularization. Additionally, the ARTS trial demonstrated that, in a study in which equivalent revascularization was believed to be achievable in a joint meeting between cardiologists and surgeons before randomization, it was actually achieved more often in the CABG group than in the PCI group. Despite the discrepancy, irrespective of treatment strategy or completeness of revascularization, there was no mortality difference 1 year after the procedure. Finally, with the multitude of new devices and techniques to overcome CTOs, the SYNTAX trial will provide new contemporary data on completeness of revascularization and outcomes in patients randomized to CABG or PCI in complex coronary disease.

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Disclosures

None.

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KEY WORDS: angioplasty ■ bypass ■ occlusion ■ revascularization ■ surgery ■ stents

PART V.

THE FUTURE OF DRUG-ELUTING STENTS: MULTIVESSEL DISEASE: - FROM THE BARE PAST TO THE ELUTING FUTURE

V.II SUB-STUDIES

Chapter 23

Comparison of Three-Year Outcomes After Coronary Stenting Versus Coronary Atery Bypass Grafting in Patients With Multivessel Coronary Disease, Including Involvement of the Left Anterior Descending Coronary Artery Proximally (A Subanalysis of the Arterial Revascularization Therapies Study Trial).

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The long-term effect of stents in patients with multivessel disease involving the proximal left anterior descending artery was investigated. At 3 years, there was no difference in the combined incidence of death, stroke, and myocardial infarction in either group, but the need for repeat revascularization was more frequent in the group with stenting than in the group with coronary artery bypass grafting. ©2004 by Excerpta Medica, Inc.

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The Arterial Revascularization Therapies Study (ARTS), the Stent or Surgery trial, and the Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty Versus Coronary Artery Bypass Surgery in Multivessel Disease II assessed the effect of stent-assisted percutaneous coronary intervention compared with coronary artery bypass grafting (CABG) in the management of patients with multivessel coronary disease.[1–4] The long-term effect of stents in patients with multivessel coronary disease involving the proximal left anterior descending coronary artery (LAD) is still controversial. We analyzed the 3-year outcomes of patients with multivessel coronary disease involving the proximal LAD who were treated with coronary stenting or CABG in the ARTS to confirm the long-term efficacy of stenting in this group of patients.

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The ARTS trial was a randomized trial comparing CABG and coronary stenting for the treatment of patients with multivessel coronary disease. For each patient, entry into the study required agreement on the part of a surgeon and an interventional cardiologist that an equivalent degree of revascularization could be attained by either approach. A detailed description of the protocol has been previously published.[5] Briefly, patients who had not previously undergone CABG or coronary angioplasty with ≥2 de novo lesions located in different major epicardial coronary arteries potentially amenable to bypass surgery or stent implantation (>50% diameter stenosis in a vessel with a reference diameter of ≥2.75 mm) were eligible for coronary revascularization. Bypass surgery followed current standard techniques, preferably using the left internal mammary artery for revascularization of the LAD. Patients with left main stem stenosis, impaired left ventricular function (left ventricular ejection fraction <30%), previous cerebrovascular accidents (CVAs), myocardial infarctions (MIs) within the week preceding randomization, severe hepatic or renal disease, neutropenia or thrombocytopenia, intolerance of or contraindications to acetylsalicylic acid or ticlopidine, and the need for concomitant major surgery were not included in the study.

TABLE 1 Baseline Characteristics of the Patients Included in the Intent-to-treat Analysis

Characteristic	Stenting (n = 246)	Surgery (n = 253)
Men	77.2%	80.2%
Age (yrs)	60 ± 10	62 ± 10
Previous condition		
Previous MI	43.1%	39.5%
Diabetes mellitus	12.6%	15.4%
Systemic hypertension	42.7%	42.3%
Hypercholesterolemia	61.5%	56.3%
Family history of MI	38.1%	42.9%
Peripheral vascular disease	4.5%	6.3%
Current smoker	70.7%	74.7%
Unstable angina	40.7%	35.2%
Ejection fraction (%)	62 ± 12	61 ± 13
3-vessel coronary disease	29.3%*	41.5%*

*p = 0.005.

Angiographic data, including the characteristics of each lesion and target coronary segment, were adjudicated by an independent core laboratory (Cardialysis BV, Rotterdam, The Netherlands). The proximal LAD was defined as the segment between the branching point of the left main stem and the first major septal branch (segment 6 in the American Heart Association classification[6]). The study protocol required all pa-

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TABLE 2 Clinical End Points at Discharge, One Year, and Three Years in Descending Order of Severity

Variable	Worst Event*		Patients With Events†		
	Stenting (n = 246)	Surgery (n = 253)	Stenting (n = 246)	Surgery (n = 253)	RR (95% CI)
Death					
Up to discharge	1.2%	2.0%	1.2%	2.0%	0.62 (0.15–2.61)
0–1 yr	3.7%	2.8%	3.7%	2.8%	1.32 (0.48–3.61)
0–3 yrs	4.5%	4.3%	4.5%	4.3%	1.03 (0.45–2.33)
CVA					
Up to discharge	0.4%	1.2%	0.8%	1.2%	0.69 (0.11–4.13)
0–1 yr	0.8%	1.6%	1.2%	1.6%	0.77 (0.17–3.48)
0–3 yrs	1.6%	2.0%	2.0%	2.8%	0.73 (0.23–2.34)
MI					
Up to discharge	2.4%	4.0%	3.3%	5.1%	0.63 (0.26–1.55)
0–1 yr	5.3%	4.3%	6.1%	5.5%	1.10 (0.52–2.33)
0–3 yrs	5.7%	4.3%	6.9%	6.3%	1.10 (0.54–2.21)
Q-MI					
Up to discharge	2.4%	3.6%	3.3%	4.7%	0.69 (0.28–1.71)
0–1 yr	4.9%	4.0%	5.7%	5.1%	1.11 (0.51–2.41)
0–3 yrs	4.5%	4.0%	5.7%	5.9%	0.96 (0.45–2.03)
Non-Q-MI					
Up to discharge	0.0%	0.4%	0.0%	0.4%	—
0–1 yr	0.4%	0.4%	0.4%	0.4%	1.03 (0.06–16.5)
0–3 yrs	1.2%	0.4%	1.2%	0.8%	1.55 (0.26–9.31)
Repeat revascularization					
Up to discharge	2.4%	0.0%	3.7%	0.4%	9.26 (1.16–73.6)
0–1 yr	11.7%	2.4%	16.3%	2.8%	5.88 (2.58–13.4)
0–3 yrs	16.3%	4.0%	22.0%	4.8%	4.63 (2.41–8.90)
CABG					
Up to discharge	0.4%	0.0%	0.4%	0.4%	1.03 (0.06–16.5)
0–1 yr	2.4%	0.4%	3.7%	0.8%	4.63 (0.99–21.6)
0–3 yrs	3.7%	0.4%	4.9%	0.8%	6.17 (1.37–27.9)
Repeat PTCA					
Up to discharge	2.0%	0.0%	3.3%	0.0%	—
0–1 yr	9.3%	2.0%	12.6%	2.0%	6.38 (2.44–16.7)
0–3 yrs	12.6%	3.6%	17.1%	4.0%	4.32 (2.11–8.82)
Event-free survival					
Up to discharge			93.5%	92.9%	
0–1 yr			78.5%	88.9%	
0–3 yrs			72.0%	85.4%	
Any event					
Up to discharge			6.5%	7.1%	0.91 (0.46–1.84)
0–1 yr			21.5%	11.1%	1.95 (1.18–3.20)
0–3 yrs			28.0%	14.6%	1.92 (1.34–2.75)

*If a patient required repeat angioplasty and later required CABG, only the worst event (CABG) was counted as an event.

†If a patient required repeat angioplasty and later required CABG, the total count for CABG and percutaneous transluminal coronary angioplasty (PTCA) at 3 years would reflect both events, not just the worst that occurred, but the count for the general variable repeat revascularization would reflect only 1 event.

tients to have follow-up clinic visits with electrocardiograms at 1, 2, and 3 years. Additional information was obtained by telephone interview or from referring physicians when needed.

The primary end point was defined as the absence of any of the following major adverse cardiac or cerebrovascular events (MACCEs) ≤3 years after randomization: death, stroke, transient ischemic attacks, reversible ischemic neurologic deficits, documented nonfatal MIs, and repeated revascularization by percutaneous intervention or surgery. Deaths from all causes were reported. In the first 7 days after intervention, a definite diagnosis of MI was made if there was documentation of new abnormal Q waves (according to the Minnesota code[7]) and either cardiac enzymes >5 times the upper limit of normal or a ratio of peak serum creatine kinase-MB to creatine kinase >0.1. From the eighth day onward, either abnormal Q waves or enzymatic changes were sufficient for a diagnosis of MI. Clinical status was assessed 1, 2, and 3 years after a planned intervention.

All analyses were based on the intention-to-treat principle from the time of randomization. Statistical analysis was performed with SAS version 6.12 software (SAS Institute Inc., Cary, North Carolina). Continuous variables were expressed as means ± SDs and compared with the unpaired Student's *t* test or Wilcoxon ranked scores when applicable. Fisher's exact test was used for categorical variables. Discrete variables were expressed as counts and percentages and compared in terms of relative risks (RRs) with 95% confidence intervals (CIs) calculated by the formula of Greenland and Robins.[8] All statistical tests were 2 tailed. Event-free survival was calculated according to

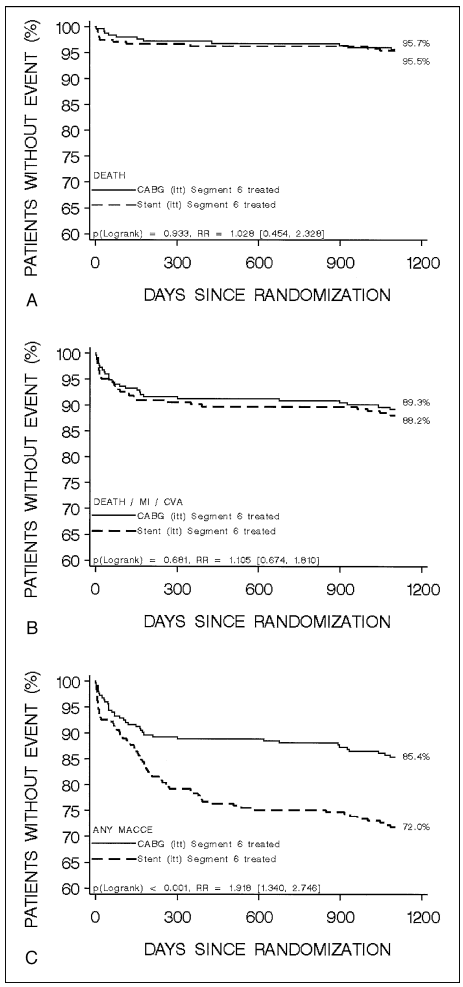

FIGURE 1. Acturial survival *(A)*, Kaplan-Meier estimates of survival without MI or cerebrovascular events *(B)*, and Kaplan-Meier estimates of survival without cerebrovascular events, MI, or repeat revascularization *(C)* in patients assigned to undergo stenting compared with those assigned to undergo CABG. There was a significant difference between the groups in survival without cerebrovascular events, MI, or repeat revascularization (p <0.001 by the log-rank test).

the Kaplan-Meier method, and differences were assessed using the log-rank test. A p value <0.05 was considered statistically significant.

From April 1997 to June 1998, 1,205 patients were randomly assigned to undergo CABG (605 patients) or angioplasty with stent implantation (600 patients) at 67 participating centers in the ARTS. Four hundred ninety-nine patients from the total population had segment-proximal LAD disease, of whom 246 were randomly assigned to undergo stenting and 253 to undergo CABG. In this subcohort of patients, 3 patients allocated to stent implantation were instead treated surgically, and 8 patients allocated to bypass surgery were instead treated with stent implantation. A total of 98.8% of patients in the stenting group (243 patients) and 96.8% of those in the surgery group (245 patients) received the assigned treatment. There were no deaths or CVAs in the 2 groups while on the waiting list. One patient in the stenting group had an MI while on the waiting list for the procedure, whereas in the surgery group, 3 patients had MIs while on the waiting list. Table 1 presents the baseline characteristics of the patients included in the intention-to-treat analysis.

Until hospital discharge, there were no significant differences between the stenting group and the surgery group in the incidence of death, CVAs, and MIs, although the numbers of deaths, CVAs, and MIs in the stenting group were lower than in the surgery group. In the stenting group, 5 patients (2%) had stent thrombosis. Of these 5 patients, 1 died before discharge. Overall, 9 patients (3.7%) in the stenting group underwent additional revascularization (including 1 patient who underwent CABG because of an unsatisfactory angioplasty procedure), compared with 1 patient (0.4%) in the surgery group (RR 9.26, 95% CI 1.16 to 73.62).

The frequency of MACCEs and the numbers of patients in whom each type of event occurred at 1 year are listed in Table 2. At least 1 event occurred in 53 of the 246 patients assigned to stent implantation (21.5%), compared with 28 of the 253 patients assigned to bypass surgery (11.1%; RR 1.95, 95% CI 1.18 to 3.20). Freedom from death, CVAs, and MIs was similar between the 2 groups (90.2% in the stenting group and 91.3% in the surgery group; RR for death, CVA, or nonfatal MI 1.12; 95% CI 0.61 to 2.06). Of those free from death, CVAs, and MIs, 11.7% in the stenting group and 2.4% in the surgery group underwent repeat revascularization (an absolute difference of 9.3%). Overall, 16.3% of the patients in the stenting group underwent additional revascularization compared with 2.8% in the surgery group (RR 5.88, 95% CI 2.58 to 13.40).

At 3 years, MACCEs occurred in 69 patients (28%) assigned to stent implantation, compared with 37 patients (14.6%) assigned to bypass surgery (RR 1.92, 95% CI 1.34 to 2.75). Freedom from death, CVAs, and MIs was similar in the stenting and surgical groups (88.2% in the stenting group and 89.3% in the surgery group; RR for death, CVAs, or nonfatal MIs 1.10; 95% CI 0.63 to 1.93). From 1 to 3 years, a similar number of patients in the 2 groups died or had CVAs or MIs (2.4% in the stenting group and 2.0% in the surgery group, RR 1.23, 95% CI 0.37 to 4.10), whereas repeat revascularization was performed more often after stenting than after surgery (5.7% in the stenting group and 2.0% in the surgery group, RR 2.88, 95% CI 1.02 to 8.12). The different clinical outcomes are illustrated by the Kaplan-Meier esti-

TABLE 3 Comparing Clinical Events Between PTCA and CABG in Patients With Multivessel Disease

Trial	Follow-Up	Number		Death	Q-MI	Repeat Revascularization
Balloon angioplasty versus CABG						
EAST[12]	3 yrs	CABG	194	6.2%	19.6%	13%
		PTCA	198	7.1%	16.6%	54%
RITA[13]	2.5 yrs	CABG	501	3.6%	5.2%	11%
		PTCA	510	3.1%	6.7%	38%
ERACI[14]	3 yrs	CABG	64	4.7%	7.8%	6.3%
		PTCA	63	9.5%	7.8%	37%
CABRI[15]	1 yr	CABG	513	2.7%	3.5%	6.5%
		PTCA	541	3.9%	4.9%	33.6%
BARI[16]	5 yrs	CABG	914	10.7%	19.6%	8%
		PTCA	915	13.7%	21.3%	54%
Involving proximal LAD						
Hannan et al[17]	3 yrs	CABG	15,873	10%	—	—
		PTCA	634	14%	—	—
Stent versus CABG						
SoS[3]	2 yrs	CABG	500	2%	8%	6%
		PTCA	488	5%	5%	21%
ERACI II[2]	1 yr	CABG	225	7.5%	6.6%*	4.8%
		PTCA	225	3.1%	2.3%*	16.8%
ARTS[4]	3 yrs	CABG	605	4.6%	5.0%	7.3%
		PTCA	600	3.7%	6.0%	29.2%
Involving proximal LAD						
ERACI II[18]	3.5 yrs	CABG	117	5%	11%*	3.4%
		PTCA	113	3.6%	8%*	27%
This study	3 yrs	CABG	253	4.3%	5.9%	4.8%
		PTCA	246	4.5%	5.7%	22%

*Figure shows the incidence of MI, including non-Q-MI.
PTCA = percutaneous transluminal coronary angioplasty; EAST = Emory Angioplasty Versus Surgery Trial; Randomized Intervention Treatment of Angina; ERACI = Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty Versus Coronary Artery Bypass Surgery in Multivessel Disease; CABRI = Coronary Angioplasty Versus Bypass Revascularisation Investigation; BARI = Bypass Angioplasty Revascularization Investigation; SoS = Stent or Surgery.

mates of event-free survival in the 2 original groups and in patients who survived for 3 years without CVAs or MIs (Figure 1). The number of patients with 3-vessel disease including the proximal LAD was different between the stenting group and the CABG group (29.3% vs 41.5%). However, the tendency of the RR for MACCEs was similar between patients with 2-vessel disease and those with 3-vessel disease. MACCEs for the patients with 2-vessel disease were 26.4% in the stenting group and 14.9% in the CABG group (RR for MACCEs 1.78, 95% CI 1.13 to 2.81), and MACCEs for the patients with 3-vessel disease were 31.9% in the stenting group and 14.3% in the CABG group (RR for MACCEs 2.24, 95% CI 1.26 to 3.98).

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The major findings of this study are that (1) the 3-year clinical survival of patients with multivessel coronary disease involving segment 6 was not statistically different between the stenting group and the CABG group; (2) the incidence of CVAs and MIs was similar in such patients between the stenting group and the CABG group during 3 years; and (3) the need for repeat revascularization was more frequent in the stenting group than the CABG group at 3 years. In the stent era, some clinical trials have shown that freedom from death, stroke, and MI was similar in patients with multivessel disease treated with stenting versus those treated with CABG.[1–4] The use of coronary stents has reduced the need for repeat revascularization compared with balloon angioplasty, although the rate remains higher than with CABG (Table 3). The present study shows that the use of coronary stents has a similar combined incidence of death, CVAs, and MIs for 3 years after randomization, even if patients with multivessel coronary disease have proximal LAD disease.

The main limitation of stent implantation compared with CABG is a greater incidence of repeat revascularization (22% vs 4.8%). The main cause of repeat revascularization during the initial hospitalization in the stenting group was stent thrombosis. From discharge to 1 year later, the rate of repeat revascularization in the stenting group was higher than in the CABG group because of restenosis (12.6% in the stenting group and 2.4% in the surgery group; an absolute difference of 10.2%). After 1 year, this tendency continued (5.7% in the stenting group and 2% in the surgery group; an absolute difference of 3.7%), but in a smaller proportion. The main limitation of stenting in such patients is the greater incidence of restenosis requiring repeat revascularization. In 51 patients who underwent repeat revascularization during 3 years in the stenting group, 25 patients (49%) had repeat revascularization for restenosis of the proximal LAD, but no patient had repeat revascularization because of restenosis that extended to the left main coronary artery. Drug-eluting stents have definitively been shown to dramatically reduce restenosis rates.[9,10] Further study should be done to compare stenting with

CABG for patients with multivessel coronary disease in the drug-eluting stent era. The ARTS II, which has just completed enrollment, may demonstrate the efficacy of drug-eluting stents in patients with multivessel coronary disease.[11] Bypass surgery is no longer the only option available to patients with multivessel coronary disease involving the proximal LAD.

This study is a substudy of the ARTS. The limited number of patients resulted in a lack of sufficient power, and patients recruited into the ARTS were very select, having suitable lesions for revascularization by percutaneous coronary intervention and CABG without severely impaired left ventricular function. In addition, clinical follow-up may have underestimated the incidence of restenosis after coronary stenting. However, this study demonstrates the long-term efficacy of stents for patients with multivessel coronary disease involving the proximal LAD.

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Chapter 24

Five-Year Clinical Effect of Coronary Stenting and Coronary Artery Bypass Grafting in Renal Insufficient Patients With Multivessel Coronary Artery Disease-Insights from ARTS Trial.

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Five year clinical effect of coronary stenting and coronary artery bypass grafting in renal insufficient patients with multivessel coronary artery disease: insights from ARTS trial

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KEYWORDS
Stent;
Coronary artery bypass;
Renal insufficiency

Aims To compare coronary stent implantation and bypass surgery for multivessel coronary disease in patients with renal insufficiency.
Methods and results In the ARTS trial, 142 moderate renal insufficient patients (Ccr $<$ 60 mL/min) with multivessel coronary disease were randomly assigned to stent implantation ($n = 69$) or CABG ($n = 73$). At 5 years, there was no significant difference between the two groups in terms of mortality (14.5% in the stent group vs. 12.3% in the CABG group, $P = 0.81$), or combined endpoint of death, cerebrovascular accident (CVA), or myocardial infarction (MI) (30.4% in the stent group vs. 23.3% in the CABG group, $P = 0.35$). Among patients who survived without CVA or MI, 18.8% in the stent group underwent a second revascularization procedure when compared with 8.2% in the surgery group ($P = 0.08$). The event-free survival at 5 years was 50.7% in the stent group and 68.5% in the surgery group ($P = 0.04$).
Conclusion At 5 years, the differences in mortality and combined incidence of death, CVA, and MI between coronary stenting and surgery did not reach statistically significant level. However, the occurrence of MACCE in the stent group was higher than in the CABG group, mainly driven by the higher incidence of repeat revascularization in the stent group.

Introduction

Renal dysfunction is a well known risk factor for adverse cardiac events after coronary revascularization. Renal dysfunction, even the mild renal dysfunction, is associated with both restenosis and mortality after percutaneous coronary intervention.[1,2] Coronary artery bypass grafting (CABG) is also associated with adverse outcome in patients with renal dysfunction.[3] Renal dysfunction is an important factor for calculating CABG risk scores, according to ACC/AHA guidelines, Cleveland clinic score, and Euro scores.[4–7] However, no randomized trial has compared the long-term clinical effect of coronary stenting vs. CABG in renal insufficient patents with multivessel coronary disease. We, therefore, investigated the clinical outcomes of renal insufficient patients in the ARTS trial.

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Methods

Study population

The Arterial Revascularization Therapies Study (ARTS) trial was a randomized trial comparing CABG and coronary stenting for the treatment of patients with multivessel coronary artery disease. Between April 1997 and June 1998, 1205 patients from 67 participating centres were randomized to either stent implantation ($n = 600$) or CABG ($n = 605$). Patients included had not previously undergone bypass surgery or angioplasty with at least two *de novo* lesions located in different major epicardial coronary arteries potentially amenable to either bypass surgery or stent implantation ($>$50% diameter stenosis in a vessel with a reference diameter of at least 2.75 mm). The agreement on the part of a surgeon and an interventional cardiologist that an equivalent degree of revascularization could be attained by either approach was required for entry into the study. Clinical results were analysed at short (30 days), medium (1 year), and long-term intervals (3 and 5 years). A detailed description of the protocol has been published previously.[8–10] The present study was a posthoc study, focusing on the renal dysfunction

in the ARTS trial. Renal dysfunction was classified by estimated creatinine clearance (Ccr) calculated by use of the Cockcroft–Gault formula:[11] Ccr (mL/min) = [(140 − age) × weight (kg)]/[serum creatinine (mg/dL) × 72]. Patients who had Ccr < 60 mL/min comprised the moderate renal insufficient group and patients who had Ccr ≥ 60 mL/min comprised the mild renal dysfunction and normal renal function group, according to the definition of National Kidney Foundation.[12] Patients with left main stem stenosis, impaired left ventricular function (left ventricular ejection fraction <30%), previous cerebrovascular accident (CVA), myocardial infarction (MI) within the week preceding randomization, neutropaenia, or thrombocytopaenia, or an intolerance or contraindication to acetylsalicylic acid or ticlopidine and patients who needed concomitant major surgery and severe hepatic or renal disease (worst Ccr level is 27.3 mL/min in enrolled patients) were not included in the study. Among 1205 patients, 1062 patients (88.1%) had their Ccr level before the revascularization. *Figure 1* shows the cumulative curve of Ccr in overall patients. Among 1062 patients, 142 patients had moderate renal dysfunction (Ccr < 60 mL/min), of which 69 were randomly assigned to undergo stenting and 73 to CABG. All patients gave written informed consent. Randomization did not take into account Ccr level. The aim of this study was to evaluate coronary stent implantation and bypass surgery for multivessel coronary disease in patients with renal insufficiency. To evaluate the interventional strategy in the renal insufficiency group more specifically, we also investigated the Ccr ≥ 60 mL/min group in the ARTS trial.

Data collection and endpoints

Angiographic data were adjudicated by an independent core laboratory (Cardialysis BV, The Netherlands). The study protocol required all patients to have follow-up clinic visits with an electrocardiogram (ECG) at 1, 3, and 5 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. The clinical events were defined as any of the following major adverse cardiac or cerebrovascular events (MACCE) within 5 years after randomization, defined as death, stroke, transient ischaemic attack, reversible ischaemic neurologic deficits, documented non-fatal MI, and repeated revascularization by percutaneous intervention or surgery. Deaths from all causes were reported. 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[13]) and either cardiac enzymes greater than five times the upper limit of normal or a ratio of peak serum creatinine kinase MB (CK-MB) to creatinine kinase (CK) greater than 0.1. From the eighth day onwards, either abnormal Q waves or enzymatic changes were sufficient for a diagnosis of MI.

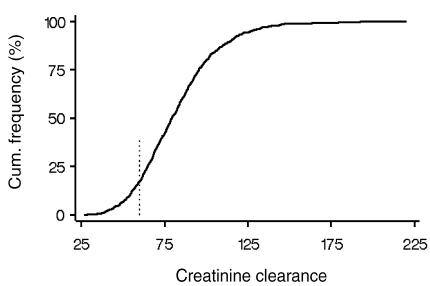


Figure 1 The cumulative curve of Ccr in the ARTS trial.

The primary endpoint was defined as the absence of any of the following MACCE within 5 years after randomization: death, CVA, documented non-fatal MI adjudicated by either new abnormal Q wave or pre-defined enzymatic changes, or repeat revascularization by coronary stenting or CABG.

Statistical analysis

Statistical analysis was performed with SAS 6.12 software (SAS Institute Inc.). Continuous variables were expressed as mean ± SD and compared with the unpaired Student's *t*-test. The Fisher exact test was used for categorical variables. Discrete variables were expressed as counts and per cent values and compared in terms of relative risks (RRs) with 95% confidence intervals (CI) calculated by the formula of Greenland and Robins.[14] All analyses were based on the intention-to-treat principle, and statistical tests were two-tailed. Cumulative event-free survival was calculated according to the Kaplan–Meier method and differences were assessed using the log-rank test. Ccr was analysed as a continuous value for the prediction of MACCE in univariate analysis. *P*-values <0.05 were considered statistically significant.

Results

Patient characteristics

Baseline and procedural characteristics were similar between patients assigned to stenting (stent arm) or CABG (CABG arm) within each group (*Table 1*). In the moderate renal insufficiency group (Ccr < 60 mL/min group), all patients allocated to stent implantation were treated with stents, whereas five patients allocated to bypass surgery were instead treated with stent implantation or medical treatment. In total, 100% of renal insufficient patients in the stent arm and 93.2% of those in the CABG arm received the assigned treatment.

Five year clinical outcome

Comparison between moderate renal dysfunction (the Ccr < 60 mL/min group) vs. mild renal dysfunction and normal renal function (the Ccr ≥ 60 mL/min group)

In the Ccr < 60 mL/min group, complete follow-up during 5 years was obtained in 100% patients assigned to stenting (stent arm) and in 97% assigned to CABG (CABG arm). In the Ccr ≥ 60 mL/min group, complete follow-up during 5 years was obtained in 99% patients assigned to stenting and in 98% assigned to CABG. *Table 2* displays the 5 year clinical results with respect to comparison between patients assigned to stent and CABG within each group. Five year mortality rate of the moderate renal insufficient group was 14.5% in the stent arm and 12.3% in the CABG arm. Those rates were higher than the group with mild renal dysfunction and normal renal function (7.6% in the stent arm and 7.1% in the CABG arm), but did not achieve significant differences in both arms: RR, 1.90; 95% CI 0.98–3.65; $P = 0.07$ in the stent arm and RR, 1.73; 95% CI 0.86–3.46; $P = 0.16$ in the CABG arm. However, the combined incidence of death, CVA, or MI was higher in patients with moderate renal impairment in both arms, stenting and CABG, when compared with patients with mild renal dysfunction and normal renal function (30.4 vs. 16.6% in the stent arm: (RR, 1.83; 95% CI, 1.22–2.77; $P = 0.01$ and 23.3 vs. 14.3% in the CABG arm: RR, 1.63; 95% CI, 1.02–2.62; $P = 0.05$). Regardless of the revascularization strategies, the occurrence of repeat revascularization was similar between the Ccr < 60 mL/min

Table 1 Patient characteristics

	Ccr < 60 mL/min group		Ccr ≥ 60 mL/min group	
	Stent ($n = 69$)	CABG ($n = 73$)	Stent ($n = 458$)	CABG ($n = 462$)
Male, *n* (%)	44 (64)	53 (73)	359 (78)	356 (77)
Age, (year ± SD)	70 ± 6	71 ± 6	59 ± 9	60 ± 9
Hypertension, *n* (%)	36 (52)	34 (47)	196 (43)	198 (43)
Diabetes, *n* (%)	15 (22)	11 (15)	84 (18)	65 (14)
Hypercholesterolaemia, *n* (%)	40 (58)	38 (52)	258 (57)	273 (59)
Family history, *n* (%)	21 (30)	31 (43)	191 (42)	192 (42)
Current smoking, *n* (%)	11 (16)	8 (11)	134 (29)	130 (28)
Unstable angina, *n* (%)	22 (32)	26 (36)	169 (37)	162 (35)
Ejection fraction (%)	61 ± 13	58 ± 13	61 ± 12	60 ± 13
Three vessel treatment, *n* (%)	23 (33)	26 (36)	141 (31)	159 (34)
Peripheral artery disease, *n* (%)	4 (5.8)	5 (6.8)	27 (5.9)	23 (5.0)
COPD, *n* (%)	4 (5.8)	5 (6.8)	22 (4.0)	22 (4.0)
Treated segments	2.5 ± 1.0	2.6 ± 0.8	2.7 ± 1.1	2.8 ± 0.8
Lesion type (B2/C)/lesion (%)	67	61	67	62
Stent/lesion	1.1 ± 0.6		1.1 ± 0.5	
IIb/IIIa inhibitor, *n* (%)	2 (3)		11 (2)	
CCr (mL/min)	52 ± 7	52 ± 6	91 ± 23	90 ± 22

Table 2 Clinical results

	Ccr < 60 mL/min group			Ccr ≥ 60 mL/min group		
	Stent ($n = 69$)	CABG ($n = 73$)	RR (95% CI)	Stent ($n = 458$)	CABG ($n = 462$)	RR (95% CI)
Death, *n* (%)	10 (14.5)	9 (12.3)	1.18 (0.51–2.72)	35 (7.6)	33 (7.1)	1.07 (0.68–1.69)
Cardiac death, *n* (%)	3 (4.3)	5 (6.8)	0.64 (0.15–2.69)	13 (2.8)	10 (2.2)	1.31 (0.56–3.05)
CVA, *n* (%)	8 (11.6)	4 (5.5)	2.12 (0.67–6.71)	13 (2.8)	14 (3.0)	0.94 (0.45–1.97)
MI, *n* (%)	6 (8.7)	8 (11.0)	0.79 (0.29–2.17)	35 (7.6)	28 (6.1)	1.26 (0.78–2.04)
Q-MI, *n* (%)	4 (5.8)	8 (11.0)	0.53 (0.17–1.68)	29 (6.3)	24 (5.2)	1.22 (0.72–2.06)
Death, CVA, MI, *n* (%)	21 (30.4)	17 (23.3)	1.31 (0.76–2.26)	76 (16.6)	66 (14.3)	1.16 (0.86–1.57)
Repeat revascularization, *n* (%)	20 (29.0)	7 (9.6)	3.02 (1.37–6.70)	136 (29.7)	37 (8.0)	3.71 (2.64–5.21)
RE-PTCA, *n* (%)	17 (24.6)	7 (9.6)	2.57 (1.14–5.81)	104 (22.7)	34 (7.4)	3.09 (2.14–4.45)
RE-CABG, *n* (%)	6 (8.7)	1 (1.4)	6.35 (0.78–51.4)	45 (9.8)	5 (1.1)	9.08 (3.64–22.7)
MACCE, *n* (%)	34 (49.3)	23 (31.5)	1.56 (1.03–2.37)	184 (40.2)	95 (20.6)	1.95 (1.58–2.41)

If a patient required repeated angioplasty and later required coronary-artery bypass grafting, the total count for 'CABG' and 'PTCA' at 5 years would reflect both events, not just the worst that occurred, but the count for the general variable 'repeat revascularization' would reflect only one event.

group and the Ccr ≥ 60 mL/min group with a higher repeat revascularization rate in the stent arms than that in the CABG arms (29.0 vs. 29.7% in the stent arm: RR, 0.98; 95% CI, 0.66–1.50; $P = 1.00$ and 9.6 vs. 8.0% in the CABG arm: RR, 1.20; 95% CI, 0.56–2.58; $P = 0.65$). The MACCE rate in the stent arms was higher than that in the CABG arm, mainly due to the higher incidence of repeat revascularization in both the Ccr < 60 mL/min group and the Ccr ≥ 60 mL/min group. However, the difference in rates of MACCE between the stenting and the surgery in the Ccr < 60 mL/min group was similar to the Ccr ≥ 60 mL/min group (Δ17.8 vs. Δ19.6%, respectively).

To assess the effect of renal insufficiency on outcome, Ccr was analysed as a continuous valuable for the prediction in MACCE. Ccr was a significant predictor for MACCE in the CABG group, but not in the stent group (RR, 0.986; 95% CI, 0.978–0.995; $P = 0.0015$ in the surgery group and RR, 0.996; 95% CI, 0.990–1.001; $P = 0.1288$ in the stent group).

Comparison of intervention in renal insufficient patients

In the moderate renal insufficient group, the overall 5 year mortality rate and the incidence of cardiac death were not statistically different between the stent and the CABG arms (RR of total death, 1.18; 95% CI, 0.51–2.72; $P = 0.81$ and RR of cardiac death, 0.64; 95% CI, 0.15–2.69; $P = 0.72$). Among 10 patients who died during 5 year follow-up in the stent arm, seven patients (70%) died of non-cardiac reasons. Among nine patients who died during 5 year follow-up in the CABG arm, four patients (44%) died of non-cardiac reasons.

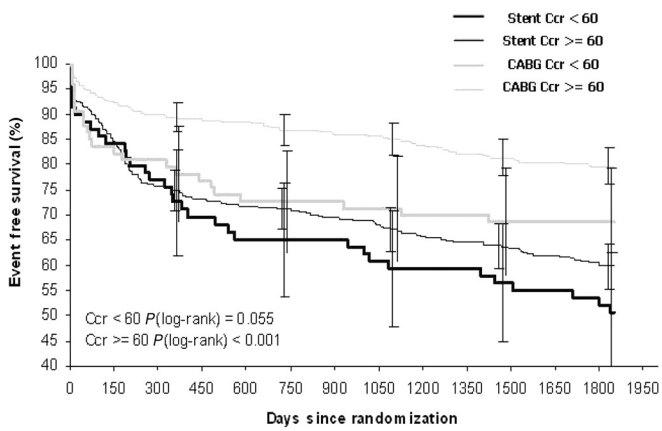
The combined incidence of death, stroke, or MI was also not statistically different between patients in the stent arm and in the CABG arm, although the actual rates were higher in the stent arm than in the CABG arm (30.4% in the stent arm vs. 23.3% in the CABG arm: RR, 1.31; 95% CI, 0.76–2.26; $P = 0.35$). However, the incidence of repeat revascularization was significantly higher in the stent arm

when compared with the CABG arm (29.0 vs. 9.6% RR, 3.02; 95% CI, 1.37–6.70; $P = 0.005$). Overall, MACCE occurred in 34 patients (49.3%) assigned to stent implantation when compared with 23 of patients (31.5%) assigned to bypass surgery (RR, 1.56; 95% CI, 1.03–2.37; $P = 0.04$). The different incidence of MACCE rate was driven by the higher incidence of repeat revascularization in the stent arm. The different clinical outcomes are illustrated by the Kaplan–-Meier estimates of event-free survival in the stent and CABG arm within each group (*Figure 2*).

Discussion

Renal insufficiency is associated with an increase in mortality and major adverse cardiac events after revascularization in a dose-dependent fashion.[1–3,15] In the present study, at 5 years after revascularization, patients with moderate renal insufficiency (Ccr $<$ 60 mL/min) and multivessel coronary disease had poor clinical outcomes for composite events of death, CVA, or MI when compared with mild renal dysfunction and normal renal function patients (Ccr $\geq$ 60 mL/min). Nevertheless, the rate of clinically driven repeat revascularization was similar between patients with moderate renal dysfunction and patients with normal renal function and mild renal dysfunction, regardless of the allocated strategy of revascularization. These results are comparable to those reported in previous retrospective studies.[1,2,15] However, in these studies and the present study, no follow-up angiographic assessment was performed. High angiographic in-stent restenosis rates have been documented in patients with end stage renal function, but the actual rate of restenosis in moderate renal insufficiency is still unknown.[16,17] In the present study, the rate of clinically driven repeat revascularization was comparable in patients with normal renal function and those with moderate renal dysfunction, despite a higher incidence of late cardiac events in this latter group, although we suspect that the patients with altered renal function are more prone to restenosis. Two factors may have contributed to this unexpected relatively low rate of intervention; First, as mentioned earlier, angiographic follow-up was not mandated by protocol. Secondly, a high incidence of silent ischaemia has been documented in these patients with renal dysfunction, a fact that may also explain the relatively low incidence of clinically driven intervention, particularly in the absence of mandated angiographic follow-up. It could be hypothesized that a high prevalence of silent ischaemia in renal insufficient patients may contribute to the comparable clinically driven repeat revascularization rate in spite of the high incidence of subsequent cardiac events when compared with patients with normal renal function.

This study also highlights that the 5 year mortality and composite rate of death, CVA, or MI did not reach a significantly statistical level between patients allocated to stenting or CABG in the moderate renal insufficiency group, although actual incidence of this rate in the stent arm was higher than that in the CABG arm. There are no precious reports comparing the clinical results of stenting vs. CABG for moderate renal insufficiency patients. However, some reports have compared outcomes after stenting and CABG in dialysis patients.[18–20] All these studies showed that patients with dialysis or severe renal insufficiency had better long-term survival after CABG than PCI. However, these results did not apply to our study. Dialysis and moderate renal insufficient patients are different medical



Patients at risk	0	1 year	2 years	3 years	4 years	5 years
Stent Ccr < 60	69	50	45	41	39	35
Stent Ccr >= 60	458	343	326	308	291	274
CABG Ccr < 60	73	57	53	52	50	50
CABG Ccr >= 60	462	413	401	393	376	368

Figure 2 The Kaplan–Meier estimates of event-free survival in the stent and CABG arms within the renal sufficient and insufficient groups. Error bars indicate 95% CI.

conditions. The limitations of coronary stenting for renal insufficient patients with multivessel disease are two-fold: a high incidence of repeat revascularization and the likelihood of renal function deterioration due to extensive use of contrast media in multivessel treatment. The ARTS trial was initiated in April 1997. It is relevant to consider the differences between the techniques used in this study and newly developed techniques for coronary revascularization such as off-pump CABG and new, minimally invasive approaches [21,22]. Similarly, important developments in percutaneous coronary intervention have taken place since the completion of recruitment in the ARTS trial. Drug-eluting stents have definitively been shown to dramatically reduce restenosis rates and the different incidence of repeat revascularization (surgery and coronary intervention) are likely to narrow with the advent of drug-eluting stents.[23–26] In addition, iso-osmolar, non-ionic contrast medium, aceltylcysteine, and pre-hydration may potentially prevent the renal dysfunction induced by contrast media.[27–29]

This study is a *post hoc* sub-study of ARTS trial. The moderate number of patients may limit conclusions due to the lack of statistical power. We had several restrictive inclusion criteria, including lesion characteristics which had to be suitable for both percutaneous and surgical revascularization, so that the tentative conclusion may be restricted to the population initially included in the trial. In addition, the exact aetiology of renal dysfunction and renal function at follow-up period were not evaluated in this study. However, this is the first randomized prospective study to compare the 5 years clinical outcomes of the stenting vs. CABG in moderate renal insufficient patients with multivessel coronary disease.

Conclusions

In this 142 moderate renal insufficient patients (Ccr $<$ 60 mL/min) prospective cohort, the difference in 5 year mortality and combined incidence of death, CVA, and MI between coronary stent and surgery did not reach a statistically significant level, although the actual event rates in the stent group were higher than in the CABG group. The occurrence of MACCE in the stent group was statistically higher than in the CABG group, mainly due to the higher incidence of repeat revascularization in the stent group. However, the difference of MACCE rate between the stent and the CABG in the Ccr $<$ 60 mL/min group was similar as compared to the CCr $\geq$ 60 mL/min group.

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Chapter 25

Sex differences and their impact on clinical outcome after percutaneous or surgical revascularisation: a report from the Arterial Revascularisation Therapies Study (ARTS).

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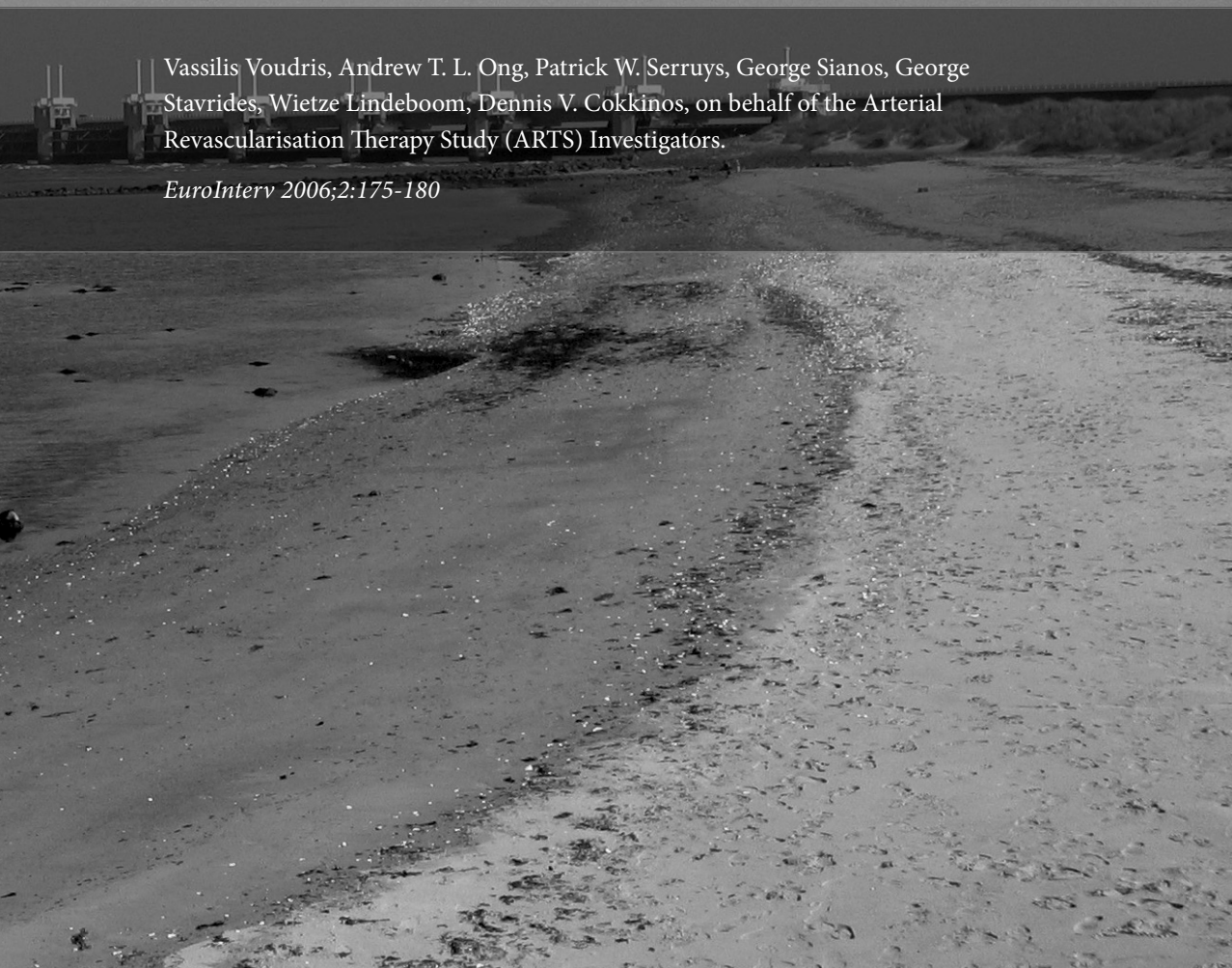

Sex differences and their impact on clinical outcome after percutaneous or surgical revascularisation: a report from the Arterial Revascularisation Therapies Study (ARTS)

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The authors have no conflict of interest to declare.

KEYWORDS
Multi-centre randomised trial, stent, multivessel disease, percutaneous coronary intervention, coronary artery bypass surgery.

Abstract

Aims: To determine whether women have an unfavorable outcome after coronary interventions compared with men, we evaluated patients undergoing revascularisation within the Arterial Revascularisation Therapies Study (ARTS).

Methods and results: We evaluated 1205 patients (23% women) with multivessel disease randomised to percutaneous or surgical coronary revascularisation. The in-hospital results, and clinical outcome at five years were evaluated. Women were older, with a higher prevalence of hypertension, hypercholesterolaemia, family history for coronary artery disease (all $p<0.001$), diabetes mellitus ($p=0.05$) and stable angina ($p<0.05$) than men, but had a lower incidence of history of myocardial infarction or smoking (both $p<0.001$). More major bleeding complications, even after adjusting for baseline clinical characteristics (OR 29.4, 95% CI: 5.3-500, $p<0.005$) were observed in women following percutaneous coronary intervention. During clinical follow-up freedom from major adverse cardiac and cerebrovascular events was similar in men and women, regardless of treatment strategy. Men assigned to bypass surgery had a better quality of life, but women reported more frequently angina.

Conclusion: The clinical outcome of women with multivessel disease undergoing coronary revascularisation was similar to that in men. However, women presented more bleeding complications before hospital discharge, and had less favourable assessment in specific domain of daily life at follow-up.

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Introduction

Cardiovascular disease is the leading cause of death in both women and men. Although the number of cardiovascular deaths has declined in men, it has actually increased in women over the past decade. Previous studies reporting the outcome of coronary revascularisation performed with bypass surgery or percutaneous intervention have reported higher rates of mortality and major complications in women[1-3]. The reasons for this sex difference were attributed to a smaller surface area and smaller size of coronary arteries, advanced age, more risk factors (diabetes mellitus, arterial hypertension), greater burden of comorbidity, and more acute coronary artery disease at presentation in women[4,5]. However most of these studies were performed before the introduction of innovative transcatheter revascularisation techniques, such as coronary artery stenting. Furthermore, women are less likely to receive left internal mammary artery grafts and to achieve complete revascularisation.

The Arterial Revascularisation Therapies Study (ARTS) was designed to compare Coronary Artery Bypass Grafting (CABG) and Percutaneous Coronary Intervention combined with stent implantation (PCI) for the treatment of patients with multivessel disease[6]. Overall, at one year PCI is less expensive than CABG and offers the same degree of protection against death, stroke, and myocardial infarction, but is associated with a greater need for repeated revascularisation. At five years there was no difference in mortality between CABG and PCI, but major adverse cardiac and cerebrovascular events were higher in the PCI group, driven by the increased need for repeat revascularisation[7]. The aim of this study was to determine whether women enrolled in the ARTS study have an unfavourable in-hospital and long-term clinical outcome after PCI or CABG interventions compared with men.

Methods

Patients

Between April, 1997 and June, 1998, 1205 patients with multivessel disease were randomised to either CABG (n=605) or PCI (n=600). The protocol of this study has been previously described[8]. All patients had clinical follow-up visits including an ECG at one and six months, one, two, three and five years. Additional information was obtained by telephone interview or via the referring physician, when needed. An independent committee adjudicated clinical events and ECGs.

Euro-Qol questionnaire

Health related quality of life was assessed at one and six months, one, two, and three year clinical follow-up using the Euro-Qol questionnaire, which allows patients to grade their general health status[9]. The questionnaire includes a visual/analogue scale (Euro-Qol thermometer) for patients to use in rating their overall status from 0 ("worst" imaginable health) to 100 ("best" imaginable health). The questionnaire also comprises five items (mobility, self-help, usual activity, pain or discomfort, and anxiety or depression); these ratings were then summarised (Euro-Qol summary) after being weighted to account for differences in the importance of the various items to the patient.

Statistical analysis

Statistical analysis was performed with SAS 6.12 software (SAS Institute Inc., Chicago, Illinois). Data included baseline patients' characteristics, information on coronary artery lesion characteristics, in-hospital results and outpatient clinical follow-up. The primary clinical analysis consisted of a comparison between the two groups according to gender. Categorical variables are presented as absolute numbers (percent) and were compared by the chi-square test or Fisher's exact test as appropriated. Continuous data, expressed as mean ± SD, were compared with the Student's t-test or Wilcoxon's test. All analyses were based on per protocol principle. Event free survival rate was estimated by the Kaplan-Meier method, and differences were assessed by the log rank test. The test for proportionality showed that the hazard was non-proportional, so logistic regression instead of Cox regression was used. A series of univariable logistic regression models with in hospital outcome or major adverse cardiac and cerebrovascular events at five years as dependent variable and sex as the independent variable was used for estimation of the effect of gender. If the effect of gender was statistically significant, a multivariate logistic regression was undertaken with outcome as dependent variable and sex, diabetes, hypercholesterolaemia, hypertension, body mass index, family history, smoking, silent ischaemia, stable angina, previous myocardial infarction as independent variables. The coefficients of the terms for sex were used to calculate Odds Ratios (OR) and their 95% Confidence Intervals (CI) for in hospital outcome and five-year major adverse cardiac and cerebrovascular events of men compared to women. Statistical significance was considered at a p value <0.05 (2-tailed).

Results

Of the 1,205 randomised patients with multivessel disease, 283 (23%) were women (PCI: 138; CABG: 145) and 922 (77%) men (PCI: 462; CABG: 460).

Clinical and angiographic characteristics

The clinical and angiographic characteristics of the men and women are shown in Table 1. Women were older than men ($p<0.001$), and had a higher incidence of hypercholesterolaemia, hypertension, family history for coronary artery disease (all $p<0.001$), diabetes mellitus ($p=0.05$) and stable angina ($p<0.05$), but previous or current smoking and history of myocardial infarction were present in a lower rate (both $p<0.001$). Although women were shorter and weighed less, the body mass index was similar to that of men.

Procedural characteristics

In patients assigned to PCI there were no differences between men and women in the number of segments diseased, lesions treated, stents implanted/patient, or the duration of PCI procedure (Table 2). Similarly, in patients assigned to CABG the number of diseased segments, distal anastomoses, arterial conduits implanted, left internal mammary use, and the duration of surgical procedure were the same in men and women.

Table 1. Baseline clinical and angiographic characteristics

	Men (n=922)	Women (n=283)	P
Age, (years)	59±10	65±8	<0.001
Body mass index	27.2±3.5	27.4±4.2	0.66
History, (%)			
– Myocardial infarction	46	35	<0.001
– PTCA	2	2	1.0
Peripheral vascular disease (%)	5	6	0.76
Transient ischaemic attack	1	0.7	1.0
Risk factors, (%)			
– Hypertension	40	59	<0.001
– Previously smoker	51	25	<0.001
– Current smoker	30	18	<0.001
– Family history	37	52	<0.001
– Diabetes mellitus	16	21	0.05
– Hypercholesterolaemia(> 200 mg/dl)	54	71	<0.001
Stable angina, (%)	57	64	<0.05
Number of diseased vessels, (%)			
– Two vessels	64	66	0.90
– Three vessels	33	34	0.87
Ejection fraction (%)	60±13	62±13	0.08

PTCA: Percutaneous Transluminal Coronary Angioplasty.

Table 2. Procedural Characteristics

Patients assigned to PCI	Men (462)	Women (138)	P
Number of segments diseased	2.6±1.0	2.6±0.9	0.65
Number of lesions treated	2.7±1.1	2.6±1.2	0.75
Number of stents/patient	2.8±1.2	2.9±1.3	0.85
Duration of PCI procedure (min)	91.3±44.1	91.3±46.1	0.99
Patients assigned to CABG	**Men (460)**	**Women (145)**	**P**
Number of segments diseased	2.6±1.1	2.5±0.8	0.16
Number of distal anastomoses	2.8±1.1	2.6±1.0	0.17
Number of arterial conduits	1.2±0.6	1.1±0.6	0.17
LIMA use	0.9±0.4	0.8±0.4	0.38

PCI: Percutaneous Coronary Intervention combined with stent implantation,
CABG: Coronary Artery Bypass Frafting, LIMA: Left Internal Mammary Artery.

In-hospital outcome

Women assigned to PCI had more bleeding complications than men (7.2% vs. 0.2%, p<0.001); however, no differences were observed in patients assigned to CABG treatment (2.8% in men vs. 1.4% in women, p=0.54). Bleeding complications remained higher in women even after adjusting for baseline clinical characteristics (OR 29.4, 95% CI 5.3 - 500, p<0.005). Sex adjusted OR for in hospital complications according to treatment strategy (PCI or CABG) is presented in Table 3.

Clinical follow-up

There was no effect of gender in the five-year's clinical outcome, according to treatment strategy (Figure 1). In patients assigned to CABG treatment the incidence of death was 10.1% in men and 7.2% in women (p= 0.48); in patients assigned to PCI 9.0% in men and 7.4% in women (p= 0.29). There were no differences in the incidence of major adverse cardiac and cerebrovascular events in men compared to women in patients assigned to CABG (OR 0.8, 95% CI 0.5-1.3, p= 0.38), or PCI (OR 0.9, 95% CI: 0.6 - 1.4, p=0.77). These results did not change when the hard end-points (death/myocardial infarction/cerebrovascular accident) were considered (CABG: OR 0.8, 95% CI 0.5-1.5, p= 0.57, PCI: OR 1.2, 95% CI 0.7-2.1,

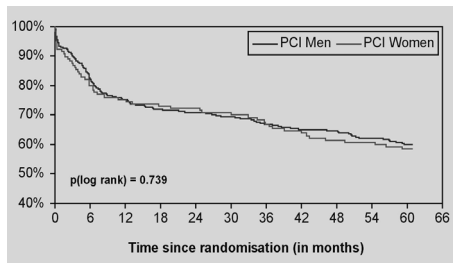

Figure 1 A. MACCE in PCI patients

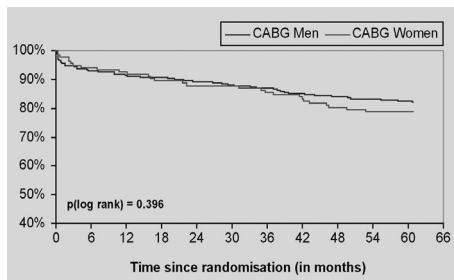

Figure 1 B. MACCE in CABG patients

Figure 1. Kaplan-Meier curves according to gender showing freedom from: (A) death/cerebrovascular accident/myocardial infarction or revascularisation in patients undergoing PCI; (B) death/cerebrovascular accident/myocardial infarction or revascularisation in patients undergoing CABG.
PCI: percutaneous coronary intervention combined with stent implantation, CABG: coronary artery bypass grafting.

Table 3. Odds Ratios of in-hospital complications for men compared to women, according to treatment strategy (PCI or CABG)

	PCI			CABG		
	OR	95% CI	P	OR	95% CI	P
In hospital outcome	0.6	(0.3 - 1.2)	0.14	1.8	(0.7 - 6.2)	0.29
MI	0.7	(0.2 - 2.6)	0.58	1.2	(0.4 - 4.3)	0.72
CVA	0.6	(0.1 - 12.5)	0.65	1.8	(0.3 - 34.9)	0.57
Major bleeding	29.4	(5.3 - 500)	0.001	1.5	(0.4 - 10.1)	0.58

PCI: Percutaneous Coronary Intervention combined with stent implantation, CABG: Coronary Artery Bypass Grafting, MI: Myocardial Infarction,
CVA: Cerebrovascular Accident.

p= 0.57). However CABG was associated with a lower incidence of major adverse cardiac and cerebrovascular events at five years, compared to PCI in both sexes (p<0.005). The sex adjusted odds ratios for five years major adverse cardiac and cerebrovascular event, according to treatment strategy is presented in Table 4.

Anginal status

At five years follow-up in patients undergoing an initial strategy of CABG, 13% of men compared to 24% of women (p<0.01) reported angina symptoms; in patients assigned to PCI, there were no differences in the incidence of angina (21% of men compared to 23% of women p= 0.71).

Quality of life

There were some differences in quality of life at three years, as assessed by the self-rated Euro-Qol questionnaire, among men and women. Men showed better quality of life (higher score on the Euro-Qol thermometer) compared to women (p<0.05) and favourable assessment (lower score on the Euro-Qol domain) in specific items such as mobility (p<0.001), self-help (p<0.005) or usual activity (p<0.01). The differences in quality of life according to treatment strategy are shown in Table 5. Men after CABG showed better quality of life and favourable assessment in specific domains such as "mobility" and "anxiety or depression" by three years. In patients allocated to PCI group the only difference was a favourable mobility in men compared to women.

Discussion

In the present study we analysed the in-hospital, and five-year clinical outcome, according to gender, in a large series of patients with multivessel disease undergoing after randomisation, PCI or CABG procedures in native coronary artery lesions. Women were older, had more risk factors for coronary artery disease, and were on stable angina; conversely, men had a higher incidence of history of myocardial infarction. Bleeding complications were significantly higher in women post-PCI (even after adjusting for baseline clinical characteristics), but there was no effect of gender at five year's major adverse cardiac and cerebrovascular events independent of treatment strategy. In patients assigned to CABG women reported angina more frequently during follow-up and men had a better quality of life, as expressed by Euro-Qol questionnaire.

Gender and PCI

A number of previous studies have examined the influence of gender on in-hospital outcomes after PCI. Overall, these studies have shown higher in-hospital mortality in women than in men, especially

Table 4. Odds ratios of major adverse cardiac or cerebrovascular events at five years for men compared to women, according to treatment strategy (PCI or CABG)

	PCI			CABG		
	OR	95% CI	P	OR	95% CI	P
5-years MACCE	0.9	0.6 - 1.4	0.77	0.8	0.5 - 1.3	0.38
Death	1.1	0.5 - 2.8	0.86	1.4	0.5 - 4.1	0.54
MI	1.4	0.7 - 3.2	0.44	0.6	0.3 - 1.3	0.17
CVA	0.8	0.3 - 2.2	0.58	0.6	0.3 - 1.9	0.39
revascularisation	1.0	0.6 - 1.5	0.92	0.7	0.4 - 1.4	0.32
– CABG	0.9	0.5 - 1.8	0.86	0.9	0.1 - 18.6	0.94
– re-PTCA	0.9	0.6 - 1.5	0.73	0.7	0.4 - 1.4	0.27

PCI: Percutaneous Coronary Intervention combined with stent implantation, CABG: Coronary Artery Bypass Grafting, MACCE: Major Adverse Cardiac or Cerebrovascular Events, MI: Myocardial Infarction, CVA: CerebroVascular Accident, PTCA: Percutaneous Transluminal Coronary Angioplasty.

Table 5. Quality of life among men and women at three years according to treatment strategy

	PCI			CABG		
Variable	Men	Women	P	Men	Women	P
Euro-Qol thermometer*	77±16	75±18	0.45	79±15	75±18	0.03
Euro-Qol summary*	86±16	83±19	0.08	86±20	82±20	0.02
Euro-Qol domain+						
Mobility	1.4±2.8	2.5±3.3	<0.001	1.4±2.8	2.1±3.2	0.01
Self-help	0.5±2.2	0.9±3.3	0.14	0.4±1.9	1.0±3.1	0.005
Usual activity	0.9±1.7	1.3±2.2	0.13	0.7±1.6	1.1±1.9	0.02
Pain	4.8±6.8	5.3±7.4	0.69	5.1±7.7	5.8±7.4	0.16
Anxiety	2.3±4.6	2.8±5.4	0.56	2.0±4.0	3.1±5.4	0.04

* High score on the Euro-Qol thermometer and the Euro-Qol summary indicates a good quality of life.

+ Low score of the Euro-Qol domain reflect a favourable assessment of each component.

PCI: Percutaneous Coronary Intervention combined with stent implantation, CABG: Coronary Artery Bypass Grafting.

in earlier series[10-12]. The higher incidence of in-hospital complications could be related to the fact that women were older, have smaller body mass index, and had higher prevalence of other co-morbid conditions. More recent studies have reported improved clinical outcomes for women who underwent elective PCI[3,13], due to advances in technology and improvement in revascularisation techniques.

Although the mortalty difference between men and women was attenuated after accounting for differences in baseline clinical characteristics, gender remained an important risk factor for vascular complications. Previous studies have shown that women had more bleeding complications, mainly at the access site when anticoagulation was used[14]. The excess vascular complications among women, however, may represent a clinically modifiable risk; careful attention to sheath size, heparin dosing, and rapid sheath removal have been demonstrated to lower risks of vascular complications[15]. The influence of gender on long-term clinical outcome following PCI has not been adequately assessed in previous studies. A pooled analysis of seven prospective stent trials including 7,171 patients (2,179 women and 4,992 men) with systematic angiographic and clinical follow-up demonstrated no differences in target vessel revascularisation one year after bare-metal stenting between men and women[16]. In the Dynamic Registry[3] one-year mortality and combined end-point of death/myocardial infarction/CABG were higher in women than in men; however after controlling for other risk factors, gender was not a significant predictor of death or death plus myocardial infarction at one year. Very recently, Lansky et al[17] reported higher unadjusted one-year rates of target vessel revascularisation in women compared to men treated with the paclitaxel-eluting stent in the TAXUS-IV trial, but in multivariate analysis, gender was not an independent predictor of revascularisation.

Gender and CABG

The frequency of CABG performed in women has increased over the past decade in association with a gradual ageing of the surgical population[18]. Many studies examining gender differences outcomes after CABG report a higher unadjusted post-operative mortality and morbidity for women compared with men. Edwards et al[19] analysed the data from the Society of Thoracic Surgeons National Cardiac Surgery database; they reported that women were older, presented more commonly for non-elective procedures, and had a higher prevalence of pre-operative comorbid conditions, such as diabetes, hypertension, and peripheral vascular disease. Guru et al[20] reported that women had a higher early mortality even in the current era with improved surgical techniques. Very recently Huynh et al[21] presented the results of the ROSETTA-CABG registry, with one-year clinical follow-up; women had a nearly three times greater probability than men to present a composite clinical event (death, non-fatal myocardial infarction, or unstable angina), and four times to require PCI during follow-up. However female gender was not independently associated with adverse cardiac outcomes by multivariate regression analysis. In another study[20] the risk-adjusted survival of women was worse than that of men in the first year after CABG, but their long-term mortality was similar to that of men. It has been reported that left internal mammary artery use and multiple arterial grafts were less frequently used in women during CABG[19,22]. However, when adjustments were made for left internal mammary artery graft use, it did not change the early or late mortality risk for women[20].

Quality of life following revascularisation and gender

Relief of angina, and improvement in quality of life represent the main benefits for both CABG and PCI and constitute the main indication for these procedures in most patients. In the BARI trial, there was a better functional status at one year among the patients undergoing CABG, but this difference had diminished after four years[23]. In the SoS trial[24] the relative benefits of CABG and PCI in the improvement of health status differ in men and women at one year after intervention. Although in men CABG was clearly superior to PCI in improving patients' health status, in women both procedures showed equal benefit at one year. In another study[25], in patients undergoing CABG the baseline and follow-up Duke Activity Status Index scores for women were significantly lower than those of men, even after correction for pre-operative risk factors. The explanation for the gender differences in recovery after revascularisation procedures could relate, in part, to the different social roles of women and men; women may feel greater disruption than men, when they cannot resume their roles upon returning home after CABG. Furthermore, women are more likely to be unmarried, to live alone, and to report a lower level of social support than men.

Study limitations

When interpreting our results a number of issues should be considered. The number of women studied was smaller compared to men, so the power to detect a significant difference was lower. This post-hoc analysis is based on a randomised clinical trial for which all patients had specific inclusion and exclusion criteria, potentially limiting generalisation. However, patients in a randomised clinical trial may be an ideal group for studying sex differences because the rigorous trial design ensures that the women and men are reasonably comparable. It must be recognised that Euro-Qol questionnaire was developed to estimate usefulness and may not be as sensitive as disease-specific instruments to analyse treatment results. Furthermore, because treatment group assignment was not blinded, the patients' knowledge of the treatment may have influence responses to the Euro-Qol questionnaire.

Conclusions

Women enrolled in the ARTS study were older and had more risk factors compared to men. The in-hospital outcome has identified an increased risk of bleeding complications in women treated with PCI. At five-years there were no gender specific differences in the incidence of major adverse cardiac and cerebrovascular events regardless of treatment therapy (PCI or CABG). However, quality of life differences indicate a role for more effective rehabilitation in women. The influence of gender in the era of drug-eluting stents and closure devices following PCI has to be defined.

Acknowledgement

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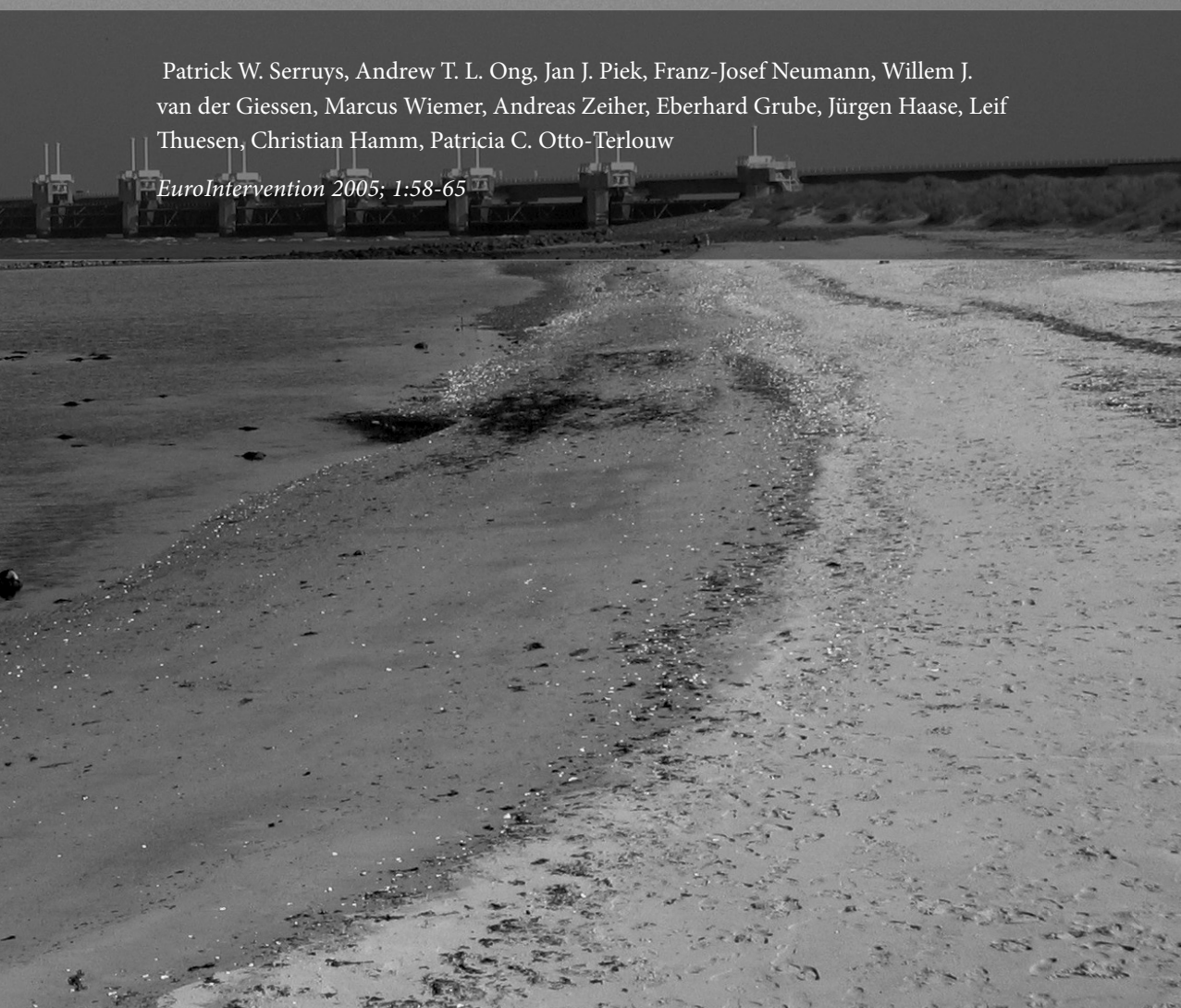
Chapter 26

A Randomized Comparison of a Durable Polymer Everolimus-Eluting Stent With a Bare Metal Coronary Stent: The SPIRIT First Trial.



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A randomized comparison of a durable polymer Everolimus-eluting stent with a bare metal coronary stent: The SPIRIT first trial

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KEYWORDS
Stent, eluting stent, everolimus, randomized trial.

Abstract

Background: Everolimus is a sirolimus analogue with similar efficacy in animal models, and has been previously successfully tested in humans using an erodable polymer.

Methods: This first-in-man single blind multi-centre randomized controlled trial assessed the safety and efficacy of everolimus eluting from a durable polymer on a cobalt chromium stent in patients with *de novo* native coronary artery lesions. Sixty patients were allocated to stent implantation with an everolimus-eluting stent (n=28) or an identical bare stent (n=32). Patients had either stable, unstable angina or silent ischaemia. Suitable lesions treated were single *de novo* native coronary lesions with 50-99% stenosis and could be covered by a 18 mm stent. The primary endpoint was in-stent late loss at 180 days, analysed on a per treatment basis. The major secondary endpoint was percent in-stent volume obstruction (%VO) as measured by intravascular ultrasound (IVUS) at 180 days. The clinical secondary endpoint was major adverse cardiac events (MACE) at 180 days.

Results: At 6 months, (matched pairs angiographic analysis), the in-stent late loss, percentage diameter stenosis and percentage of patients with binary restenosis were 0.10 mm, 16% and 0% respectively, in the everolimus arm (n=23), as compared with 0.87 mm, 39% and 25.9%, respectively in the bare stent arm (n=27, p<0.001 for late loss and diameter stenosis, p = 0.01 for restenosis). Significantly less neointimal hyperplasia was observed in the everolimus group compared to the bare stent group (10 ± 13 mm^3 vs 38 ± 19 mm^3, p<0.001) and similarly, less volume obstruction (8.0 ± 10.4% versus 28.1 ± 14.0%, p<0.001). A major adverse cardiac event occurred in 2 patients in the everolimus arm versus 6 in the bare stent arm.

Conclusion: Everolimus eluted from a durable polymer on a cobalt chromium stent effectively suppresses neointimal growth at 6 months compared to an identical bare stent.

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Introduction

Recent studies that have evaluated the local application of anti-proliferative drugs (sirolimus and paclitaxel) for the prevention of restenosis via a stent delivery system have shown that these therapies successfully inhibit the development of neointimal hyperplasia[1,2].

Everolimus is an effective anti-proliferative agent[3]. On a molecular level, everolimus forms a complex with the cytoplasmic protein FKBP12. In the presence of everolimus, the growth factor-stimulated phosphorylation of p70 S6 kinase and 4E-BP1 is inhibited. The latter proteins are key proteins involved in the initiation of protein synthesis. Since phosphorylation of both p70 S6 kinase and 4E-BP1 is under the control of mammalian Target Of Rapamycin (mTOR), this finding suggests that, like sirolimus, the everolimus-FKBP12 complex binds to and thus interferes with its function. Disabling mTOR explains the cell cycle arrest at the late G1 stage caused by everolimus and sirolimus.

The feasibility of using everolimus on a drug eluting stent was determined by the FUTURE I trial[4]. This trial utilized an S-stent and bioabsorbable polymer system (both Biosensors International, Singapore) and confirmed the safety of the everolimus-eluting stent at 6 and 12 months. At 6 months, a 7.7% Major Adverse Cardiac Event (MACE) rate was observed with no thrombosis and no late incomplete apposition. The efficacy was demonstrated by significant reduction of in-stent tissue proliferation at 6 months: both angiographic in-stent late loss and IVUS% neointimal volume were reduced by 87%. No angiographic in-stent binary restenosis was observed in the everolimus-eluting stent arm. The 12 month FUTURE I results showed sustained safety and efficacy with no new MACE events, no aneurysms, no late stent malapposition, and no thrombosis observed between 6 and 12 months. Minimal Lumen Area and Luminal Volume Index were maintained up to 12 months and no in-stent binary restenosis was observed up to 12 months.

The SPIRIT First clinical trial represents the first clinical evaluation of the Guidant XIENCE™ V Everolimus Eluting Coronary Stent System (XIENCE™ V Everolimus Eluting CSS), to investigate the potential benefits of the local application of everolimus in a durable polymer in combination with a thin strut cobalt chromium stent.

Methods

Patient selection

This randomized single-blind trial was performed at 9 medical centers and enrolled patients from December 2003 to April 2004. It was approved by the ethics committee at each participating institution, and all patients gave written informed consent.

Patients were eligible for the study if they were aged above 18 years and had received a diagnosis of stable or unstable angina or silent ischaemia. Additional eligibility criteria were the presence of a single primary *de novo* coronary lesion that was 3.0 mm in diameter as assessed by on-line QCA, that could be covered by an 18 mm stent, a stenosis of between 50-99% of the luminal diameter, and a Thrombolysis In Myocardial Infarction (TIMI) flow grade of 1 or more. Patients were not eligible for enrollment if they had an evolving myocardial infarction, stenosis of an unprotected left main coronary artery, an ostial location, located within 2 mm of a bifurcation, a lesion with moderate to heavy calcification, an angiographically visible thrombus within the target lesion, a left ventricular ejection fraction of less than 30%, were awaiting a heart transplant, or had a known hypersensitivity or contraindication to aspirin, heparin, clopidogrel, cobalt, chromium, nickel, tungsten, everolimus, acrylic and fluoro polymers or contrast sensitivity that could not be adequately pre-medicated.

The Everolimus-eluting stent

The Guidant XIENCE™ V Everolimus Eluting CSS is comprised of the Guidant MULTI-LINK VISION® Stent and delivery system, and a drug eluting coating. The Guidant MULTI-LINK VISION® Stent is a balloon expandable stent, which consists of serpentine rings connected by links fabricated from a single piece of medical grade L-605 cobalt chromium alloy.

Everolimus is blended in a nonerodable polymer (this drug layer was coated over another nonerodable polymer primer layer). This coating includes of acrylic and fluoro polymers, both approved for use in blood contacting applications. This layer of everolimus-polymer matrix with a thickness of 5-6 microns is applied to the surface of the stent and is loaded with 100 micrograms of everolimus per square centimeter of stent surface area with no top coat polymer layer. The stent is designed to release approximately 70% of the drug within 30 days after implantation.

Everolimus (Certican®, Novartis Corporation) has been evaluated in clinical trials in the US and Europe for use as an immunosuppressant following cardiac and renal transplantation[5]. Everolimus has received market approval in the European Union.

Study procedure

Following the confirmation of angiographic inclusion and exclusion criteria and prior to the procedure, patients were allocated through a telephone randomization service and assigned in a 1:1 ratio to either an everolimus eluting stent or bare metal stent. A single stent 3.0 mm in diameter, 18 mm long was used in the study.

Lesions were treated using standard interventional techniques with mandatory pre-dilatation and stent implantation at a pressure not exceeding the rated burst pressure. Due to packaging differences, physicians were not blinded to the device. Post-dilatation was allowed with a balloon shorter than the implanted stent. In the event of a dissection occurring at the edge of the implanted stent, it was recommended that a single additional bare Guidant MULTI-LINK VISION® stent be implanted as animal data only on single everolimus stent implantation were available at the onset of the study; these patients were *a priori* excluded from the per-treatment analysis but are part of the acute success population. IVUS was performed after angiographically optimal stent placement had been obtained and was repeated if additional post-dilatation was performed.

Intravenous boluses of heparin were administered according to local standard practice. Treatment with aspirin, at a minimum dose of 80 mg per day, was started at least 24 hours before the procedure and continued indefinitely. A loading dose of 300 mg of clopidogrel was administered 24 hours before the procedure, followed

by 75 mg daily for three months. Treatment with ticlopidine was permitted in case of clopidogrel hypersensitivity. Device success was defined as a final in-stent diameter stenosis of less than 50 percent by QCA using the assigned device. Clinical success was defined as the successful implantation of any device, with stenosis of less than 50 percent of the vessel diameter by QCA and no major cardiac events during the hospital stay.

Follow-up

Patients were evaluated at 30 days and 6 months. Further evaluations will be performed at 9 months and 1 year, with annual evaluations out to 5 years. At outpatient visits, patients were asked specific questions about the interim development of angina according to the Canadian Cardiovascular Society classification of stable angina. They were also monitored for MACE. Angiographic and IVUS evaluations were performed at 6 months, and will be repeated at 1 year. Prior to performing a follow-up angiogram, the physician was required to record in the source documents whether a revascularization (if required) was clinically indicated – defined as the presence of ischaemic symptoms and/or a positive functional ischaemia study.

Quantitative coronary angiography evaluation

Quantitative coronary angiography was performed using the CAAS II analysis system (Pie Medical BV, Maastricht, Netherlands). In each patient, the stented segment and the peri-stent segments (defined by a length of 5 mm proximal and distal to the stent edge) were analyzed. The following QCA parameters were computed: computer-defined Minimal Luminal Diameter (MLD), reference diameter obtained by an interpolated method, and percentage diameter stenosis. Binary restenosis was defined in every segment as diameter stenosis $\geq$50% at follow-up. Late loss was defined as the difference between MLD post-procedure and MLD at follow-up. Results are presented as matched pairs in the manuscript and as unmatched pairs in the Appendix. Unmatched pairs data is most commonly presented and utilises the mean QCA results of all projections obtained. Matched pairs data is more accurate as it compares the same views post-procedure and at follow-up and uses only QCA data of identical projections.

Intravascular ultrasound analysis

Post-procedure and follow-up stented vessel segments were examined with mechanical or phased array intravascular ultrasound using automated pullback at 0.5 mm per second. The coronary segment beginning 5 mm distal to and extending 5 mm proximal to the stented segment was examined. A computer-based contour detection program was used for automated 3-D reconstruction of the stented and adjacent segments. The lumen, stent boundaries and external elastic membrane (vessel boundaries) were detected using a minimum cost algorithm. The Stent Volume (SV) and Lumen Volume (LV) were calculated according to Simpson's rule. The intra-stent neointimal volume was calculated as the difference between SV and LV. The percentage obstruction of the stent volume was calculated as intra-stent neointimal volume/stent volume*100. Feasibility, reproducibility and inter- and intra-observer variability of this system have been validated *in vitro* and *in vivo*[6]. Incomplete apposition was defined as one or more stent struts separated from the vessel wall with evidence of blood speckles behind the strut on ultrasound, while late incomplete apposition was defined as incomplete apposition of the stent at follow-up which was not present post-procedure.

Study endpoints

The primary angiographic endpoint was in-stent luminal late loss, as determined by quantitative angiography. Secondary endpoints (QCA and IVUS) at 6 months and 1 year included the in-stent and in-segment late loss, angiographic binary restenosis rate, percentage diameter stenosis; and in-stent percentage volume obstruction. In-stent was defined as within the margins of the stent while in-segment was defined as located either within the margins of the stent or 5 mm proximal or distal to the stent. Late loss was calculated as the difference between the follow-up and post-procedure minimum luminal diameter. Secondary clinical endpoints were a composite of major cardiac events, including cardiac death, Q-wave or non-Q-wave myocardial infarction, clinically driven surgical or percutaneous revascularization of the target lesion (MACE) or vessel (Target Vessel Failure) at 30 days, 6 months, 9 months, and annually up to 5 years after the index procedure; and acute device, procedure and clinical success. All deaths that could not be clearly attributed to another cause were considered cardiac deaths. A non-Q-wave myocardial infarction was defined by an increase in the creatine kinase level to more than twice the upper limit of the normal range, accompanied by an increased level of creatine kinase-MB, in the absence of new Q waves on electrocardiography.

The endpoints were adjudicated by an independent clinical events committee. In addition, a data and safety monitoring board that was not affiliated with the study sponsor reviewed the data to identify any safety issues related to the conduct of the study.

Statistical analysis

The primary endpoint and all trial endpoints were analyzed on the per-treatment evaluable population which consisted of patients who had no bailout stenting and no major protocol deviations, as evaluated in a blinded manner. Acute success was analyzed on the entire patient population.

The sample size for the study was determined based on the primary endpoint of in-stent late loss at 180 days and on the following assumptions: a single comparison of active to uncoated; one-tailed t-test, unequal and unknown variances in the two groups being compared; α=0.05; true mean difference between the bare stent group and the treatment group of 0.48 mm. This assumption was made based on the results of the VISION Registry (mean late loss=0.83 mm)[7], SIRIUS trial (mean late loss=0.17 mm)[8] and TAXUS IV trial (mean late loss=0.39 mm)[9]. (Assume the true mean late loss for the treatment group is 0.35 mm, the difference between the bare stent group and treatment group is calculated as: 0.83 mm - 0.35 mm = 0.48 mm). The standard deviation was assumed to be 0.56 mm in the bare stent group and 0.38 mm in the treatment group (based on the results of the VISION Registry study and SIRIUS trial); approximately 20% rate of lost to follow-up or dropout; approximate-

ly 10% of patients with bailout stents. Given the above assumptions, 30 patients per arm (with the analysis of 22 evaluable patients per arm) will provide 95% power for comparison. Although the trial was not powered based on the major secondary endpoint, percent volume obstruction at 180 days, enrolling 30 patients per arm (analysis of 22 patients per arm) would provide more than 96% power.

Binary variables were compared using Fisher's Exact test. For continuous variables, means and standard deviations were calculated and groups compared using the Wilcoxon Rank-Sum test, except for the primary endpoint which was evaluated with a one sided *t*-test. Final 6-month results are presented in the manuscript, while the Appendix contains results that were available at the time that the 180-day report was prepared.

Results

Patient characteristics

Between December 2003 and April 2004, 28 patients were randomly assigned to receive the everolimus-eluting stent, and 32 were assigned to receive the bare stent. As defined in the protocol, all results (except acute success) are presented for the per-treatment population (27 patients in the everolimus group, and 29 patients in the bare stent group, Figure 1). In the everolimus group there was one bailout procedure, and in the bare stent group there were two bailout procedures and one major protocol deviation (the patient was on the heart transplant waiting list). With the exception of a significantly higher number of patients with hypertension requiring treatment in the everolimus group, the two groups were similar with respect to clinical variables examined (Table 1).

Table 1. Baseline characteristics of the per-treatment patient population and of each treatment group.*

	Everolimus stent (n = 27)	Bare stent (n = 29)	All patients (n = 56)
Age(yrs)	64 ± 10	61 ± 9	63 ± 9
Male gender (%)	70	76	73
Current smokers (%)	28	31	30
Diabetes (%)	11	10	11
Hypertension requiring medication (%)	70	41	55
Hyperlipidemia requiring medication (%)	70	76	73
Prior intervention (%)	19	7	13
Prior MI (%)	24	14	19
Stable angina (%)	78	79	79
Unstable angina (%)	19	14	16
Target vessel (%)			
Left anterior descending	48	45	46
Left circumflex	22	21	21
RCA	30	34	32
AHA / ACC Lesion Class (%)**			
A	0	10	5
B1	41	28	34
B2	59	62	61
C	0	0	0
Reference Vessel Diameter (mm ± SD)	2.61 ± 0.40	2.71 ± 0.28	2.66 ± 0.34
Lesion length (mm ± SD)	10.1 ± 2.6	10.9 ± 3.3	10.5 ± 3.0

* There were no significant differences between the treatment groups except for Hypertension Requiring Medication (P=0.04)

** AHA / ACC = American Heart Association / American College of Cardiology

FIGURE 1

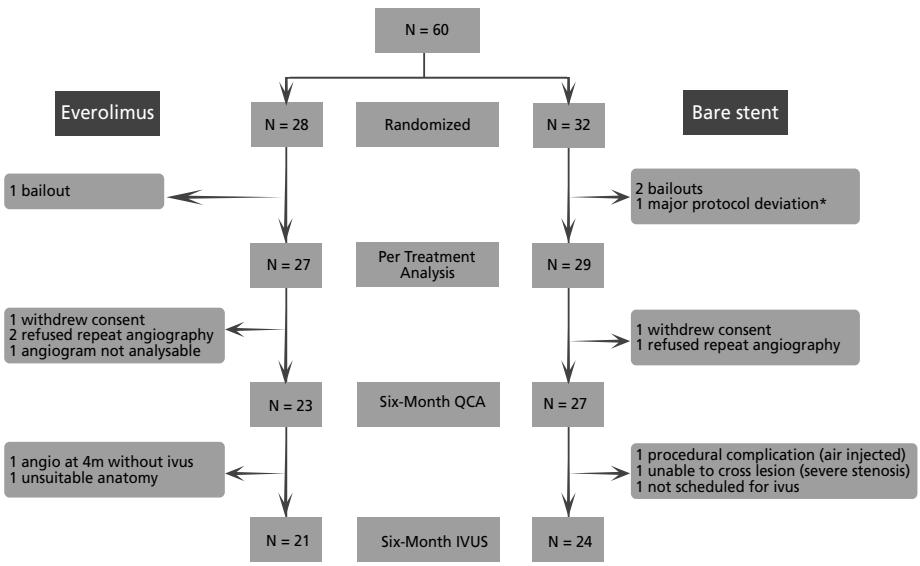

Fig. 1: Flowchart of patients

Procedural characteristics

The lesions in the two groups were treated similarly with the use of conventional techniques. Glycoprotein IIb/IIIa inhibitors, used at the investigators' discretion, were administered to 7.4% of the patients in the everolimus group and 3.4% of those in the bare stent group. The two groups did not differ significantly with respect to the rate of device success (96.4% in the everolimus group and 93.8% in the bare stent group) or clinical success (96.4% in the everolimus group and 100% in the bare stent group).

Quantitative coronary angiography analysis

Angiographic data at 6 months were available for 50 of the 56 analysable patients (89.3%). The mean reference diameter of the target vessel, the mean length of the lesion at baseline, the reference vessel diameter and mean MLD of the stented segment were similar in the two groups (Tables 1 and 2). At six months, with matched pairs analysis, the mean MLD of the stented segment was significantly greater in the everolimus group. The mean in-stent late loss, percentage of stenosis, and percentage of patients with 50 percent or more stenosis were 0.10 mm, 16%, and 0%, respectively, in the everolimus group, as compared with 0.87 mm, 39%, and 25.9%, respectively, in the bare stent group ($p<0.001$ for late loss and diameter stenosis, $p=0.01$ for restenosis). Figure 2 shows the cumulative frequency of stenosis immediately after the index procedure and at six months in each treatment group. Table 2 and Figure 3 show the results of sub-segmental quantitative angiographic analyses for matched pairs. The late luminal loss at both the proximal and the distal edges of the stent was less in the everolimus group than in the bare stent group ($p<0.01$ for proximal and $p=0.04$ for distal). The late luminal loss in the stented segment was significantly less in the everolimus group than in the bare stent group ($p \leq 0.001$).

Intravascular ultrasound evaluation

At six months follow-up, intravascular ultrasound evaluation showed no significant differences between the two groups with respect to the volume of the stent or the vessel volume (Table 3). Significantly

FIGURE 2

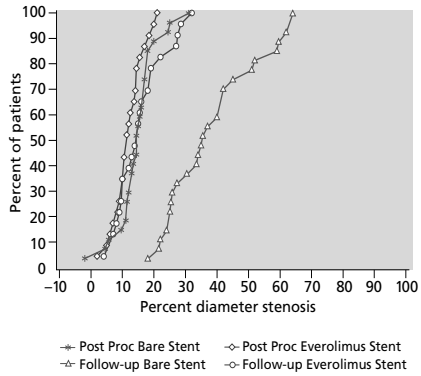

Fig. 2: Cumulative frequency of stenosis (in-stent) immediately after stenting and at six months

FIGURE 3

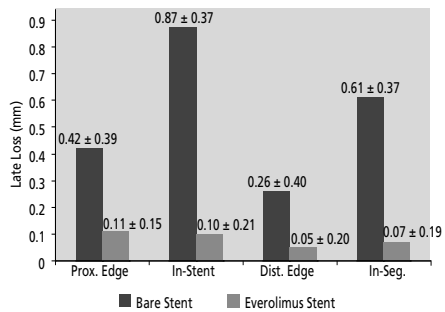

Fig. 3: Comparison of in-segment / in-stent late loss

Table 2. Results of sub-segmental quantitative coronary angiographic analysis (Matched Pairs).

	Proximal edge			In-stent			Distal edge			In-segment analysis		
	Everolimus- (n = 23)	Bare (n = 27)	P-value	Everolimus- (n = 23)	Bare (n = 27)	P-value	Everolimus- (n = 23)	Bare (n = 27)	P-value	Everolimus- (n = 23)	Bare (n = 27)	P-value
Reference Vessel Diameter (mm)												
After procedure	2.80 ± 0.33	3.04 ± 0.38	0.06*	2.71 ± 0.28	2.89 ± 0.35	0.11*	2.64 ± 0.30	2.80 ± 0.39	0.21*	2.65 ± 0.30	2.84 ± 0.41	0.10*
At 6 months	2.78 ± 0.32	2.67 ± 0.40	0.22*	2.70 ± 0.31	2.58 ± 0.37	0.25*	2.61 ± 0.37	2.46 ± 0.36	0.19*	2.61 ± 0.36	2.59 ± 0.36	0.89*
Minimal Luminal Diameter (mm)												
After procedure	2.56 ± 0.44	2.61 ± 0.45	0.79*	2.38 ± 0.25	2.45 ± 0.31	0.50*	2.23 ± 0.41	2.26 ± 0.45	0.77*	2.11 ± 0.35	2.14 ± 0.40	1.00*
At 6 months	2.45 ± 0.46	2.19 ± 0.49	0.04*	2.28 ± 0.33	1.58 ± 0.41	< 0.001*	2.18 ± 0.38	2.00 ± 0.45	0.21*	2.04 ± 0.40	1.54 ± 0.41	< 0.001*
Late Loss (mm)	0.11 ± 0.15	0.42 ± 0.39	<0.01*	0.10 ± 0.21	0.87 ± 0.37	< 0.001***	0.05 ± 0.20	0.26 ± 0.40	0.04*	0.07 ± 0.19	0.61 ± 0.37	< 0.001*
Diameter Stenosis (%DS)												
After procedure	9 ± 11	14 ± 9	0.07*	12 ± 5	15 ± 6	0.05*	16 ± 10	20 ± 10	0.16*	20 ± 8	24 ± 9	0.05*
At 6 months	12 ± 12	17 ± 17	0.26*	16 ± 8	39 ± 14	< 0.001*	16 ± 10	19 ± 14	0.82*	22 ± 11	41 ± 14	< 0.001*
Binary Restenosis Rates	4.3%	3.7%	1.00**	0.0%	25.9%	0.01**	0.0%	7.4%	0.49**	4.3%	33.3%	0.01**

* two-sided Wilcoxon rank sum test ** two-sided Fisher's Exact test *** One-sided t-test † Fisher's Exact test

Table 3. IVUS measurements at 6 month follow-up.

	Everolimus- (n = 21*)	Bare (n = 24*)	P-value
Vessel volume (mm^3)	291 ± 82	296 ± 73	0.64
Stent volume (mm^3)	134 ± 28	139 ± 33	0.69
In-stent neo-intimal volume (mm^3)	10 ± 13	38 ± 19	<0.001
Luminal volume (mm^3)	124 ± 32	100 ± 31	0.04
In-stent volume obstruction (%)**	8.0 ± 10.4	28.1 ± 14.0	<0.001

* This final table contains an additional 13 patients not included in the 180-day report prepared for the sponsor. In 8 patients (4 in each group), an imputed stent length of 18mm was used due to non-continuous pullback. In a further 5 patients (all bare stent group) results were unavailable at the time of the 180-day report. (see Appendix)

** In-stent volume obstruction = 100* (In-stent neo-intimal volume / Stent volume)

ess neointimal hyperplasia was observed in the everolimus-stent group compared to the bare-stent group (10 ± 13 vs. 38 ± 19 mm^3, p<0.001) and similarly, significantly less volume obstruction, (8.0 ± 10.4% versus 28.1 ± 14.0%, p<0.001). Figure 4 is a cumulative curve of percentage volume obstruction. No in-stent volume obstruction was detected in almost half of the patients in the everolimus-stent group, whereas in the bare stent group, some degree of obstruction by neointima was present in all patients (Figure 4). No evidence of an "edge effect," aneurysm formation, in-stent thrombosis, persistent dissection or late incomplete apposition were observed.

FIGURE 4

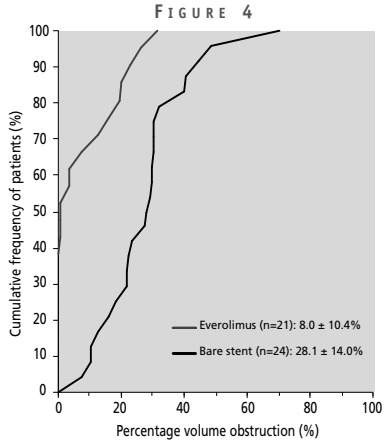

Fig. 4: Percentage in-stent volume obstruction versus cumulative frequency of patients. Values are expressed as mean ± standard deviation for each group.

Major adverse cardiac events

Major adverse cardiac events are listed in Table 4. There was one Q-wave myocardial infarction in the everolimus group in a patient who underwent additional revascularization for angina in a non-target vessel 18 days after the study procedure and suffered thrombosis of this non-study stent 12 days later. The everolimus stent was patent with no evidence of thrombus at the time of the thrombotic occlusion of the non study stent. One patient in the everolimus arm underwent a clinically driven target lesion revascularization at 3 weeks for symptomatic persistent dissection at the proximal edge left untreated at the time of the procedure. There were no clinically driven target revascularizations in the everolimus group for restenosis. There were six clinically driven target lesion revascularizations in the bare stent group, five were treated percutaneously for restenosis and the sixth by bypass surgery. No adverse effects were attributable to everolimus or the polymer coating of the stents.

Table 4. Hierarchical major adverse cardiac events at 180 days in per-treatment population*.

Event**	Everolimus stent n = 26	%	Bare stent n = 28	%
Cardiac death	0	0	0	0
Myocardial infarction				
Q-wave	1‡	3.8	0	0
Non-Q-wave	0	0	0	0
Reintervention				
Clinically driven TLR-CABG	0	0	1	3.6
Clinically driven TLR-PCI	1 §	3.8	5	17.9
Clinically driven TVR-CABG	0	0	0	0
Clinically driven TVR-PCI	0	0	0	0
Target vessel failure	2	7.7	6	21.4
Major adverse cardiac events	2	7.7	6	21.4

* One patient in each group withdrew consent after treatment
** No statistical significance was detected between groups for all endpoints tested.
‡ Q-wave MI due to thrombosis of a non-study stent in a non-target vessel.
§ Clinically driven TLR for persistent dissection proximal to the stent 3 weeks after the index procedure.

Discussion

The main finding of this randomized first-in-man study is that an everolimus-eluting stent coated with a durable polymer was associated with an in-stent angiographic late loss of 0.10 mm, significantly less than the corresponding bare cobalt chromium metal stent of 0.87 mm, which satisfied the primary endpoint of this trial and confirmed the efficacy of this system. Correspondingly, in-segment late loss was also significantly less in the everolimus-stent group.

Currently, two different drug-eluting systems (sirolimus and paclitaxel) are available. Although no published scientific comparative data is to date available, it appears that, from historical randomized trials, a difference of approximately 0.2 mm in-stent late loss exists between sirolimus and paclitaxel. Even if the impact of restenosis and MACE is currently unknown, some slight difference in restenosis rates and MACE can be expected. New devices should at least equal the incumbents in performance. This performance may be judged on late

loss, restenosis rate and / or the need for reintervention. With an in-stent late loss ranging from zero to 0.2 mm, it has been difficult to find a compound with the same efficacy, without resorting to the -limus family (Figure 5). With the sirolimus molecule being rather large and complex, it is therefore not surprising that major pharmaceutical companies have thoroughly explored its numerous analogues in order to develop a suitable competitor to sirolimus. The drug used in this study, everolimus differs from sirolimus by a substitution of a hydrogen radical/side-branch with a methyl sidechain.

FIGURE 5

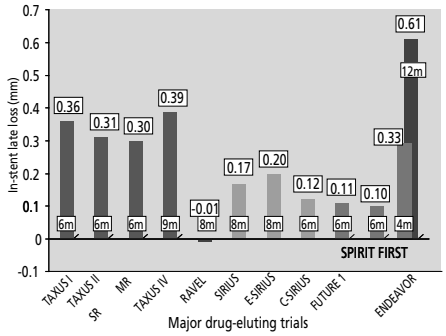

Fig. 5: Comparison of in-stent late loss from drug-eluting trials.

The reason for developing new compounds is to improve on the side effects of the existing compounds such as delayed healing with re-endothelialization and fibrin[11], early[12] and late stent thrombosis[13]. The success of the device lies in its three components - the drug, the polymer properties and the stent. The use of a sirolimus analogue is not in itself a guarantee of success since some of them have intrinsically, a potency in inhibition of up to 100 times less (e.g. tacrolimus), and some other analogues with equal *in vitro* inhibitory effects nevertheless fail to equally inhibit neointimal growth *in vivo*, because their duration of elution was suspected to be too short. However it has already been demonstrated that everolimus in clinical trials using a bioerodable polymer with a slower elution profile than sirolimus is effective in reducing late loss to below 0.2 mm[4]. Therefore the remaining challenge was to establish whether everolimus eluted from a durable polymer was also efficient and is addressed in this report.

Although the 6-month results are promising, one year angiographic and IVUS follow-up results are awaited to confirm the long-term results of this device in light of recent findings regarding an increasing late loss seen with other devices over time.

At the time of the publication of RAVEL, it was argued that the restenosis rate of the bare stent was excessively high at 26%. Similarly, in the present trial the restenosis rate in the bare stent arm was 25.9%. Nevertheless, it must be emphasized that in both cases these restenosis rates correspond to the value predicted and derived from multivariate analyses including as determinant parameters vessel size, MLD post, incidence of LAD disease and diabetics. Of interest, the late loss of the bare stent groups in RAVEL and this study were similar, corresponding to their restenosis rates. This is at variance with the VISION registry, and publications on stent strut thickness, but may be explained by the mismatch in stent size and reference diameter.

This study was powered for late loss and not for clinical events, and it was not surprising that the 3 fold reduction in events failed to be statistically significant. At the time of trial design, safety studies with overlapping eluting-stents in animal models had not been completed, requiring the use of bare stents for bailout. As a result of this confounder, these patients were *a priori* excluded from the per-treatment analysis. This study was however designed as a first in man trial with everolimus on an untested new durable polymer in combination with a cobalt chromium stent.

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Appendix

Sponsor: Guidant Corporation, Santa Clara, California, USA.

Principal Investigator: Patrick W. Serruys (The Netherlands).

Executive Committee: P.W. Serruys (Principal Investigator and Chairman, Rotterdam, The Netherlands); Gary Johnson (Vice President of Regulatory Affairs/Clinical Research, Guidant Corporation); Stan Fink (Director of Clinical Research USA, Guidant Corporation).

Data Safety Monitoring Board (DSMB) - J.G.P. Tijssen, Amsterdam, The Netherlands; F.W.A. Verheugt, Nijmegen, The Netherlands; W. Wijns, Aalst, Belgium.

Clinical Events Committee (CEC) - J. Vos, Amphia Ziekenhuis, Breda, The Netherlands; B.J.W.M. Rensing, Sint Antonius Ziekenhuis, Nieuwegein, the Netherlands; C. Hanet, Clinique Universitaire de Saint-Luc, Brussels, Belgium.

Data management - Angiographic and IVUS core laboratories: Cardialysis BV, Rotterdam, The Netherlands; Data Coordination Centre and Site Monitoring: Guidant Europe, Diegem, Belgium.

The following investigators and institutions participated in the SPIRIT First trial:

Clinical sites: J.J. Piek, Academisch Medisch Centrum, Amsterdam, The Netherlands (18 patients); F.J. Neumann, Herzzentrum, Bad Krozingen, Germany (14 patients); P.W. Serruys, Thoraxcentre, Erasmus Medical Centre, Rotterdam, The Netherlands (5 patients); M. Wiemer, HZ Herzzentrum, Bad Oeynhausen, Germany (5 patients); A. Zeiher, Uni. Klinikum Frankfurt, Frankfurt, Germany (4 patients); E. Grube, Heart Center Siegburg, Siegburg, Germany (4 patients); J. Haase, Red Cross Hospital, Frankfurt, Germany (4 patients); L. Thuesen, Skejby Sygehus, Aarhus, Denmark (4 patients); C. Hamm, Kerckhoff Klinik, Bad Nauheim, Germany (2 patients).

Table A2. Appendix: results of intra vascular ultra sound analysis as per 180-day progress report - Clinical investigation plan 02-350 The SPIRIT first clinical trial. Guidant Corporation, Data on file.

	Everolimus (n = 17)	Bare (n = 15*)	P-value
Vessel volume (mm^3)	299 ± 87	284 ± 77	0.76
Stent volume (mm^3)	138 ± 30	139 ± 39	1.00
In-stent neo-intimal volume (mm^3)	11.2 ± 14.0	41.4 ± 20.1	<0.001
Luminal volume (mm^3)	126 ± 35	98 ± 34	0.06
In-stent volume obstruction (%)	8.6 ± 10.7	29.0 ± 13.9	<0.001

Table A1. Appendix: results of sub-segmental quantitative coronary angiographic analysis (Unmatched Pairs) as per 180-day progress report - Clinical investigation plan 02-350 The SPIRIT first clinical trial. Guidant Corporation, Data on file.

	Proximal edge			In-stent			Distal edge			In-segment analysis		
	Everolimus (Post N=27 Fup N=23)	Bare (Post N=29 Fup N=26)	P-value	Everolimus (Post N=27 Fup N=23)	Bare (Post N=29 Fup N=26)	P-value	Everolimus (Post N=27 Fup N=23)	Bare (Post N=29 Fup N=26)	P-value	Everolimus (Post N=27 Fup N=23)	Bare (Post N=29 Fup N=26)	P-value
Minimal luminal diameter (mm)												
After procedure	2.49 ± 0.44	2.57 ± 0.39	0.44*	2.34 ± 0.26	2.42 ± 0.31	0.41*	2.18 ± 0.44	2.25 ± 0.42	0.67*	2.07 ± 0.37	2.14 ± 0.37	0.74*
At 6 months	2.45 ± 0.46	2.19 ± 0.50	0.05*	2.28 ± 0.33	1.58 ± 0.42	<0.001*	2.18 ± 0.38	1.99 ± 0.46	0.19*	2.04 ± 0.40	1.53 ± 0.41	<0.001*
Late loss (mm)	0.10 ± 0.17	0.38 ± 0.38	0.01*	0.10 ± 0.23	0.84 ± 0.36	<0.001***	0.07 ± 0.20	0.26 ± 0.41	0.14*	0.09 ± 0.20	0.60 ± 0.36	<0.001*
Diameter stenosis (%DS)												
After procedure	10 ± 10	15 ± 9	0.13*	12 ± 4	15 ± 6	0.02*	17 ± 10	19 ± 9	0.39*	21 ± 8	24 ± 8	0.14*
At 6 months	12 ± 12	18 ± 17	0.21*	16 ± 8	39 ± 14	<0.001*	16 ± 10	20 ± 14	0.67*	22 ± 11	41 ± 14	<0.001*
Binary restenosis rates	4.3%	3.8%	1.00**	0.0%	26.9%	0.01**	0.0%	7.7%	0.49**	4.3%	34.6%	0.01**

* Two-sided Wilcoxon rank sum test ** Two-sided Fisher's Exact test *** One-sided t-test

Chapter 27

One-Year Clinical Outcome of Various Doses and Pharmacokinetic Release of Paclitaxel Eluted From an Erodable Polymer - Insight in the Paclitaxel In-Stent Controlled Elution Study (PISCES).

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EuroInterv 2005; 1:165-172

One-year clinical outcome of various doses and pharmacokinetic release formulations of paclitaxel eluted from an erodable polymer - Insight in the Paclitaxel In-Stent Controlled Elution Study (PISCES)

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F. Litvack is an employee of Conor Medsystems. No other authors have a conflict of interest. Funding sources: Conor Medsystems

KEYWORDS
Stent, Paclitaxel, Elution release kinetics

Abstract

Aims: The one year clinical benefit of various doses and release durations of paclitaxel eluted from an erodable polymer has not been evaluated so far.

Methods and results: Conor paclitaxel-eluting stents have intra-stent wells in which drug and polymer are deposited. Stents with six different release formulations (dose: 10 µg or 30 µg, duration: 5, 10 or 30 days, direction: mural or bidirectional) were implanted in 6 patient cohorts. Clinical follow-up was conducted at 4 and 12 months. Quantitative angiography and IVUS were performed at 4 months, and additional angiographic and IVUS follow-up were performed for groups D5 (10µg/30days/mural) and D6 (30µg/30days/mural), as they had shown the most favorable results at 4 months. At one year, the lowest major adverse cardiac event rates were observed in the slow release (30 day) group (5.1% in D5 and 6.9% in D6). One-year in-stent late loss was 0.52±0.34 mm in D5 and 0.36±0.50mm in D6 (p=0.20) while neointimal area was 0.99±0.54 mm^2 in D5 and 0.77±0.92 mm^2 in D6 (p=0.42). Corresponding in-stent binary restenosis at one year was 0% and 5.6% respectively (p=0.36).

Conclusions: Patients who received the slow release formulation stent had better clinical outcome at one year than those who received the fast release formulation. However, the effect on neointimal suppression requires investigation in a larger population to determine whether the high dose formulation confers an additional clinical benefit.

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Introduction

Drug-eluting stents consist of a drug, a polymer, and a stent platform. Several drugs with durable or erodable polymers have been tested in clinical trials and show that drug-eluting stents significantly inhibit neointimal growth compared to bare metal stents[1-4]. However, the most effective drug dose and pharmacokinetic release formulation have not been evaluated thoroughly in humans.

The Paclitaxel In-Stent Controlled Elution Study (PISCES) has demonstrated that kinetic variations play a key role in the efficacy of a drug-eluting system[5]. At 4 months, the inhibition of in-stent neointimal hyperplasia was better in the slow release groups compared to the fast release groups. The present study evaluates (1) the one-year clinical outcome in all 6 groups and (2) neointimal growth in the two slow release groups, using serial quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS) analysis; in order to understand the long-term impact of drug dose and pharmacokinetic release.

Methods

Patient selection

The PISCES trial was a prospective, multi-center, sequentially enrolled, non-randomized, open-label trial in which patients were treated with a Conor paclitaxel-eluting stent in one of six different release formulations, and the results of each group was compared (Table 1). The study device and protocol have been described previously[5,6]. In brief, 191 patients with single *de novo* lesions with a reference diameter of 2.5-3.5 mm and a lesion length that could be covered by a single 17mm stent were enrolled. Conor drug-eluting stents were loaded with 10 or 30 µg of paclitaxel within a bioresorbable polylactide-co-glycolide (PLGA) matrix. The drug and polymer were deposited in the wells. The in-vitro drug release period was either 10 or 30 days. The PLGA polymer is fully erodable and neither polymer nor drug is retained in the stent after several months of implantation.

Follow-up and endpoints

The study protocol required all patients to have follow-up clinic visits with an electrocardiogram (ECG) at one, four and twelve months. An independent clinical event committee adjudicated clinical events and ECGs. Quantitative angiography and IVUS were performed at 4 months. Clopidogrel was discontinued per protocol at 6 months following stent implantation.

Additional angiographic and IVUS follow-up was performed at 12 months in groups D5 and D6 which showed the best results at 4 months (Figure 1)[5,6].

The safety endpoint of the present study is a composite of major adverse cardiac events (MACE) defined as cardiac death, Q-wave or non-Q-wave myocardial infarction, and target lesion revascularization (TLR) at 12 months. If the cause of death was undetermined, it was categorized as cardiac death. Myocardial infarction (MI) was diagnosed by a rise in the creatine kinase level to more than twice the upper normal limit with an increased creatine kinase-MB accompanied by new abnormal Q-waves in the surface electrocardiogram (Q-wave MI) or not (non-Q-wave MI). TLR was defined as revascularization of the stented and the peri-stent segments (5mm proximal and distal). Target vessel revascularization (TVR) was defined as revascularization due to narrowing (>50% diameter stenosis) of any portion of the target vessel outside the peri-stent segment but was not included as an event in the MACE rate.

The efficacy endpoints included the in-stent and peri-stent (in-stent + 5 mm proximal edge + 5 mm distal edge) angiographic late loss and binary restenosis rate as well as percent in-stent volume obstruction as determined by quantitative intravascular ultrasound (IVUS).

Quantitative Coronary Angiography (QCA) evaluation

The quantitative ultrasound and coronary angiographic (QCA) analyses were performed by an independent core laboratory that remained blinded to treatment allocation (Cardialysis, Rotterdam, The Netherlands). Quantitative coronary angiography was performed by means of the CAAS II analysis system (Pie Medical BV, Maastricht, The Netherlands). In each patient, the in-stent and peri-stent segments were analyzed. Binary restenosis was defined in every segment as diameter stenosis >50% at follow-up. Late loss was defined as the difference between MLD post-procedure and MLD at follow-up

Quantitative Intravascular Ultrasound (IVUS)

Post-procedure and follow-up stented vessel segments were examined with intravascular ultrasound (Cardio Vascular Imaging System, CVIS, Sunnyvale CA, U.S.A.) using an automated pullback at 0.5 mm per second. A computer-based contour detection program was applied using CUARD QCU analysis software (Cuard BV, Wijk Bij Duurstede, The Netherlands) for 3-D reconstruction of the stented and adjacent segments[7,8]. The intrastent neointimal area was calculated as the stent area minus lumen area, and plaque area outside the stent was calculated as the vessel area minus stent area. The percentage in-stent volume obstruction was calculated as intrastent neointimal volume/stent volume*100.

Table 1. Release formulations

	D1	D2	D3	D4	D5	D6
Paclitaxel dose (µg/17mm stent)	10	10	10	30	10	30
Duration of elution (days)	5	10	10	10	30	30
Direction of elution	Abluminal and luminal (bidirectional)	Abluminal and luminal (bidirectional)	Abluminal (mural)	Abluminal and luminal (bidirectional)	Abluminal (mural)	Abluminal (mural)
Key	10/5/b	10/10/b	10/10/m	30/10/b	10/30/m	30/30/m

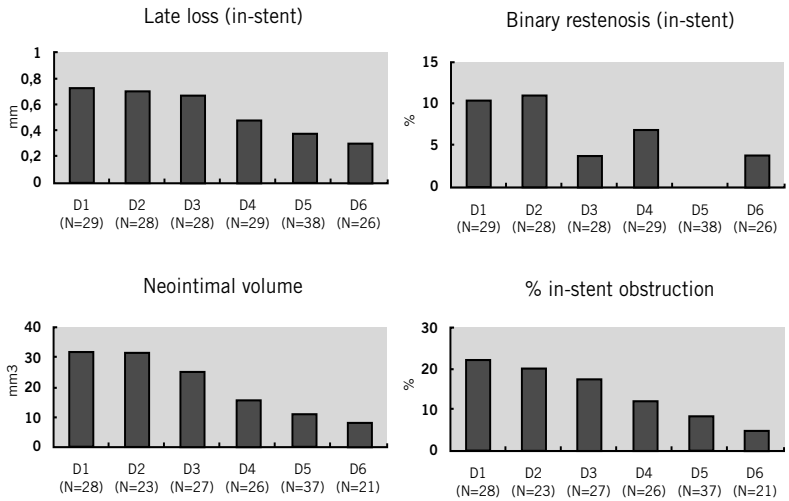

Figure 1: 4-month QCA and IVUS results.

Statistical analysis

The analyses of MACE, angiographic and IVUS parameters were per protocol based, in patients who received the allocated Conor paclitaxel-eluting stents. Continuous variables are expressed as mean±standard deviation. Discrete variables are presented as percentages. For patient demographics, the following tests were applied to calculate the differences among the six groups: F-test from an analysis of variance, two-sample t-test, likelihood ratio chi-square test, Fisher's exact test and Cochran-Mantel-Haenszel test. For QCA and IVUS parameters, continuous variables were compared between groups D5 and D6 with the Student t test, and comparisons between 4 months and 12 months within the same group were performed with a paired *t* test. The Fisher exact test was used for categorical variables. All statistical tests were two-tailed, and p values less than 0.05 were considered statistically significant.

Results

Patient and lesion characteristics

In the PISCES trial, 191 patients were enrolled. The investigational device could not be implanted in four patients. In total, 187 patients were treated with one of the six different formulations of paclitaxel-eluting Conor stents. The average age was 59.1±9.2 years and the prevalence of diabetes was 18.2% in the total population. The baseline demographic and angiographic data was similar among the six groups, except for the incidence of a positive smoking history (Tables 2 and 3).

Clinical events

Clinical follow-up was complete for all patients at one year (Table 4). At four months, the slow release groups had a relatively lower incidence of MACE compared to the fast release groups (2.6% in D5 and 3.4% in D6). This tendency did not change at one year (5.1% in D5 and 6.9% in D6; Figure 2). Between 4 months and 1 year, a MACE occurred in two patients in the slow release groups (D5 and D6): one patient in D5 suffered a non Q-MI due to a non-TVR (maximum CK level of 356 U/L), and one patient in D6 had diffuse in-stent restenosis (binary restenosis of 68%) at 4-month angiographic follow-up with a positive exercise tolerance test. This patient was placed on the waiting list for a repeat intervention. Two weeks after the angiography, she was admitted with a Q-wave MI (maximum CK level of 1687 U/L) and underwent re-catheterization which demonstrated total occlusion at the inlet of the stent. This patient was subsequently treated with a sirolimus-eluting stent. Notwithstanding this patient who had angiographic restenosis, a positive functional test for ischemia but delayed re-intervention at the 4 month follow-up, there were no instances of abrupt, delayed stent thrombosis in the PISCES patients.

Serial QCA analysis

A total of 50 patients (74%) in groups D5 and D6 underwent serial QCA analysis at 4 months and 1 year. The baseline and post-procedure QCA data were similar in the two groups (Table 4). At 4 months, in-stent late loss was not significantly different between

Table 2. Patient characteristics (per protocol)

	D-1 10/5/b N=30	D-2 10/10/b N=29	D-3 10/10m N=30	D-4 30/10/b N=30	D-5 10/30/m N=39	D-6 30/30/m N=29	P-Value comparing 6 groups	P-Value between D5 and D6
Age (mean±SD)	57.4±9.90	61.8±8.9	59.7±9.6	60.2±8.8	56.7±7.6	58.5±10.5	0.23	0.41
Male, %	60.0 (18/30)	72.4 (21/29)	76.7 (23/30)	60.0 (18/30)	82.1 (32/39)	69.0 (20/29)	0.28	0.21
Smoking, %	53.3(16/30)	86.2 (25/29)	76.7 (23/30)	73.3 (22/30)	89.7 (35/39)	72.4 (21/29)	0.01	0.06
Diabetes, %	16.7 (5/30)	17.2 (5/29)	23.3 (7/30)	13.3 (4/30)	10.3 (4/39)	31.0 (9/29)	0.31	0.03
Hypertension, %	40.0 (12/30)	62.1 (18/29)	63.3 (19/30)	56.7 (17/30)	35.9 (14/39)	62.1 (18/29)	0.08	0.03
Dyslipidemia, %	66.7 (20/30)	62.1 (18/29)	73.3 (22/30)	63.3 (19/30)	61.5 (24/39)	65.5 (19/29)	0.93	0.74
Prior MI, %	40.0 (12/30)	44.8 (13/29)	33.3 (10/30)	30.0 (9/30)	41.0 (16/39)	41.4 (12/29)	0.85	0.98
Prior CABG, %	3.3 (1/30)	3.5 (1/29)	0.0 (0/30)	0.0 (0/30)	2.6 (1/39)	6.9 (2/29)	0.59	0.39
Prior PCI	6.7 (2/30)	6.9 (2/29)	10.0 (3/30)	13.3 (4/30)	15.4 (6/39)	17.2 (5/29)	0.71	0.84

Table 3. Lesion and procedural characteristics (per protocol)

	D-1 10/5/b N=30	D-2 10/10/b N=29	D-3 10/10m N=30	D-4 30/10/b N=30	D-5 10/30/m N=39	D-6 30/30/m N=29	P-Value comparing 6 groups	P-Value between D5 and D6
Treated vessel								
LAD	50.0%	41.4%	56.7%	50.0%	48.7%	27.6%	0.30	0.08
LCX	16.7%	20.7%	13.3%	23.3%	23.1%	37.9%	0.30	0.28
RCA	33.3%	37.9%	30.0%	26.7%	28.2%	34.5%	0.94	0.58
ACC/AHA classification								
A/B1/B2	100.0%	100.0%	100.0%	100.0%	94.9%	96.6%	0.34	0.74
C	0.0%	0.0%	0.0%	0.0%	5.1%	3.4%	0.34	0.74
Angiographic features								
Reference vessel diameter, mm	2.76±0.40	2.70±0.52	2.82±0.43	2.64±0.43	2.73±0.41	2.70±0.41	0.71	0.79
Lesion length, mm	9.73±3.68	9.08±3.60	10.60±3.83	10.62±3.09	9.35±3.24	10.31±3.36	0.37	0.24
Minimal lumen diameter, mm	1.10±0.35	1.06±0.38	0.97±0.37	1.05±0.25	1.03±0.28	1.00±0.31	0.70	0.64
Diameter stenosis, %	60.32±9.57	61.02±11.54	65.72±11.77	59.89±7.77	62.05±8.19	63.17±9.63	0.21	0.61
Procedural characteristics								
Stent/patient	1.2±0.38	1.1±0.35	1.1±0.43	1.1±0.25	1.2±0.43	1.0±0.00	0.41	0.13
Stent length, mm	19.03±4.90	18.80±4.80	18.20±3.90	17.60±2.28	18.38±3.88	17.0±0.0 0	0.39	0.13
Stent diameter, mm	3.18±0.24	3.18±0.24	3.25±0.25	3.21±0.25	3.31±0.24	3.25±0.25	0.26	0.44

D5 and D6, although in-stent late loss was lower in D6 than in D5 (0.32±0.40 mm versus 0.40±0.32 mm respectively, p=0.43). From 4 months to 1 year, the late loss increased in both groups but the trend remained in favor of D6; no statistical difference between the two groups could be established although D6 showed a lower in-stent late loss at 1 year (0.52±0.34 mm in D5 and 0.36±0.50 mm in D6, p=0.20). Overall peri-stent binary restenosis at 1 year was observed in one patient in each group (3.1% in D5 and 5.6% in D6, p=1.00).

Serial IVUS analysis

A total of 45 patients (66%) underwent serial IVUS analysis at 4 months and 1 year. The IVUS results showed no statistical differences between groups D5 and D6 (Table 5). The percent in-stent obstruction at 1 year was 12.46±7.60 in D5 and 8.37±9.10 in D6 (p=0.12). However, in D5, the neointimal area increased significantly from 4 months to 1 year (delta=0.38mm^2, p=0.0003) whereas the difference between 4 months and 1 year in D6 failed to be significant (delta=0.21 mm^2, p=0.36, Figure 3).

At 4 months, significant expansive remodeling (an increase in the plaque area outside the stent) was observed in both groups (7.75±1.93 mm^2 vs 9.09±2.45 mm^2, p<0.0001 in D5; 8.04±1.76 mm^2 vs 8.95±1.67 mm^2, p=0.0015 in D6). Between 4 months and 1 year, a significant regression of the expansive plaque area outside the stent was observed in both groups (9.09±2.45 mm^2 vs 8.46±2.15 mm^2, p=0.045 in D5; 8.95±1.67 mm^2 vs 8.37±1.74 mm^2, p=0.0023 in D6).

Discussion

The main findings of this study are the following: first, the slow release (30 day) groups have better clinical outcomes at 1 year compared to the fast release (5 or 10 day) groups. Second, compared to the low dose (10 µg) group, the high dose (30 µg) group had lower late loss and neointimal volume at one year without sta-

Table 4. MACE (Patients with events, per protocol)

	D-1 10/5/b N=30	D-2 10/10/b N=29	D-3 10/10m N=30	D-4 30/10/b N=30	D-5 10/30/m N=39	D-6 30/30/m N=29
Post procedure ~ 4-month						
Cardiac death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)
Q-wave MI	1 (3.3%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	1 (2.6%)	1 (3.4%)
Non Q-wave MI	1 (3.3%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TLR	5 (16.7%)	4 (13.8%)	2 (6.7%)	1 (3.3%)	0 (0.0%)	1 (3.4%)
TVR	0 (0.0%)	1 (3.4%)	1 (3.3%)	0 (0.0%)	2 (5.1%)	1 (3.4%)
MACE	5 (16.7%)	5 (17.2%)	2 (6.7%)	2 (6.7%)	1 (2.6%)	1 (3.4%)
4-month ~ 12-month						
Cardiac death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Q-wave MI	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)
Non Q-wave MI	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)
TLR	0 (0.0%)	1 (3.4%)	2 (6.7%)	1 (3.3%)	0 (0.0%)	1 (3.4%)
TVR	0 (0.0%)	1 (3.4%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	1 (3.4%)
MACE	0 (0.0%)	1 (3.4%)	2 (6.7%)	1 (3.3%)	1 (2.6%)	1 (3.4%)
Post procedure ~ 12-month						
Cardiac death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)
Q-wave MI	1 (3.3%)	0 (0.0%)	0 (0.0%)	1 (3.3%)†	1 (2.6%)	2 (6.9%)
Non Q-wave MI	1 (3.3%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)
TLR	5 (16.7%)	5 (17.2%)	4 (13.3%)	2 (6.7%)	0 (0.0%)	2 (6.9%)
TVR	0 (0.0%)	2 (6.9%)	2 (6.7%)?	0 (0.0%)	2 (5.1%)	2 (6.9%)
MACE	5 (16.7%)	6 (20.7%)	4 (13.3%)	3 (10.0%)	2 (5.1%)	2 (6.9%)

*TVR was not included as an event in the MACE rate

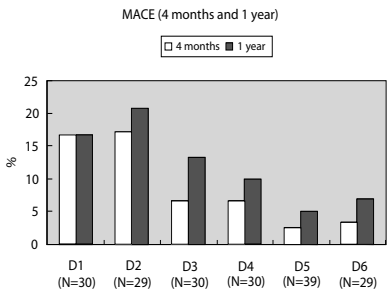

Figure 2: 4-month and 1-year MACE.

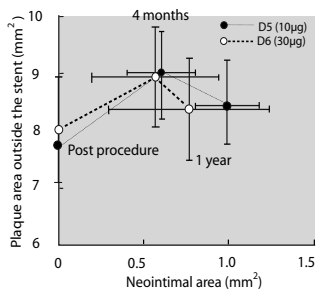

Figure 3. Correlation between neointimal area and peri-stent area over 2 years. Error bars indicate 95% CI.
P values for Neointimal area
D5: Between post procedure and 4 months: <0.0001
Between 4 months and 1 year: 0.0003
D6: Between post procedure and 4 months: 0.029
Between 4 months and 1 year: 0.36
P values for plaque area outside the stent
D5: Between post procedure and 4 months: <0.0001
Between 4 months and 1 year: 0.045
D6: Between post procedure and 4 months: 0.0015
Between 4 months and 1 year: 0.0023

tistically significant difference. Third, between 4 months and 1 year, modest neointimal growth continued in both the low and high dose groups without new instances of in-stent angiographic restenosis or target lesion revascularization, and this neointimal growth was statistically significant in the low dose group only. Fourth, plaque outside the stent increased during the first 4 months following Conor paclitaxel-eluting stent implantation, but by 1 year it had partially regressed in both the low and high dose groups.

Various drug elution processes have reported conflicting clinical results[3,9-12]. In the SCORE trial, QuaDDS stents with a total of 4000 μg paclitaxel and a durable acrylate polymer were found to have an unacceptable safety profile[9]. In the DELIVER trial, the Multi-Link PENTA stent with a coating of 45-150μg paclitaxel (a dose density of 3.0μg/mm^2 stent surface area) without a polymer showed no impact in reducing clinical revascularization or restenosis compared to bare metal stents, presumably due to the rapid elution of the drug[10]. In the ELUTES and ASPECT trials, the high-dose non polymer paclitaxel-eluting stent has the better outcomes compared to the low dose group[11,12]. In the TAXUS IV trial, a slow-release (7.5% at 30 days), polymer-based paclitaxel eluting stent with a total of 106 μg paclitaxel (a dose density of 1.0 μg/mm^2 stent surface area) eluted from a durable polymer showed significantly better inhibition of neointimal growth and clinical outcomes when compared to bare metal stents[3]. In the light of this study and other paclitaxel–eluting stent trials, the drug release profile is a key factor in the clinical efficacy, and drug-eluting stents with a slow release formulation seem to be more efficient. In the present study, the slow release groups demonstrate the best 1-year clinical outcomes, mainly due to better outcomes in the first 4 months. The drug and polymer are completely removed from the wells after several months, thus this novel drug-eluting stent may potentially preclude the chronic vessel reaction usually observed with a durable polymer and persistent drug on the stent[13,14]. Further, there were no instances of late stent thrombosis. Though more data from larger studies is required to draw definitive conclusions, these results support the hypothesis that complete drug elution and polymer resorbtion may confer safety benefits with respect to delayed thrombosis.

In this study, the expansive vessel remodeling observed at 4 months seems similar to the remodeling observed after implantation of Taxus polymeric paclitaxel-eluting stents[15]. The expansive vessel shrinkage observed at 1 year also suggests that the chronic vessel reaction to mechanical injury and biological reaction to the drug and polymer have subsided in that period of time.

However, the chronic vessel reaction inside the stent differs from the reaction observed behind the stent struts. Although this study showed a regression of tissue growth outside the stent between 4 months and 1 year, compaction of neointima was not observed in either the low dose or the high dose group over the same time period. The precise reason for this phenomenon is unclear. One might hypothesize that this could be a result of different tissue composition inside and outside the stent. The tissue growth inside the stent is composed of smooth muscle cells in a proteoglycan rich matrix, whereas the tissue growth behind the stent struts consists of several components: 1) intracellular matrix and cell proliferation such as smooth muscle cells and lymphocyte cells, 2) oedema due to mechanical injury and biological reaction against the drug, polymer and stent, and 3) growth or regression of existing atherosclerotic plaque. Thus, the direction of volumetric change (regression or expansion) from 4 months to 1 year may not be similar inside and outside the stent.

In this study, the actual late loss and neointimal area were smaller in the 30 μg group than in the 10 μg group. These differences were not statistically different and did not influence the clinical outcomes.

Table 5. Serial QCA analysis (post procedure, 4 months and 12 months)

	D5 (10/30/m) N=32	D6 (30/30/m) N=18	P-value
Pre			
Lesion length	9.39±3.37	10.04±2.80	0.49
RVD, mm	2.71±0.43	2.69±0.42	0.84
MLD, mm	1.05±0.29	1.02±0.33	0.73
DS, %	61.5±7.7	62.5±9.2	0.67
Post stenting			
In-stent			
MLD, mm	2.68±0.35	2.51±0.38	0.12
DS, %	12.4±6.5	13.6±6.2	0.56
In-peristent*			
MLD, mm	2.31±0.41	2.18±0.38	0.29
DS, %	22.3±9.1	23.5±8.9	0.65
4-month			
In-stent			
MLD, mm	2.28±0.32	2.19± 0.53	0.53
DS, %	19.9±9.3	21.7±9.7	0.63
Late loss, mm	0.40±0.32	0.32±0.40	0.43
Binary restenosis, %	0.0	5.6	0.36
In-peristent*			
MLD, mm	2.10±0.36	1.97±0.48	0.27
DS, %	25.3±8.7	29.9±13.6	0.20
Late loss, mm	0.21±0.29	0.21±0.39	0.95
Binary restenosis, %	0.0	5.6	0.36
12-month			
In-stent			
MLD, mm	2.16±0.34	2.15±0.65	0.93
DS, %	21.3±10.3	23.2±20.6	0.72
Late loss, mm	0.52±0.34	0.36±0.50	0.20
Binary restenosis, %	0.0	5.6	0.36
In-peristent*			
MLD, mm	2.01±0.35	1.94±0.61	0.69
DS, %	27.5±9.67	29.3±20.8	0.73
Late loss, mm	0.30±0.26	0.24±0.50	0.62
Binary restenosis, %	3.1	5.6	1.00

* In-peristent = In-stent + 5 mm proximal + 5 mm distal

The 10 μg paclitaxel dose may be sufficient to suppress neointimal growth in humans at least for a period of one year. It may also be argued that the sample size is too small to detect a biological difference between the low and the high dose.

In animal studies, paclitaxel polymer coated stents have been found to inhibit in-stent neointimal growth but with signs of delayed intimal healing at 28 days, such as fibrin deposition, inflammation and increased cellular proliferation. By 90 days, local toxicity associated with paclitaxel resolves but in-stent neointimal growth suppression is no longer present[16]. In humans following bare metal stent implantation, the neointima does not keep growing beyond 6 months and

Table 6. Serial IVUS analysis (post procedure, 4 months and 12 months)

	D5 (10/30/m) N=30	D6 (30/30/m) N=15	P-value
Post stenting			
Vessel area, mm^2	15.84±3.36	16.00 ±2.80	0.88
Stent area, mm^2	8.09±1.81	7.95±1.77	0.81
Plaque area outside the stent, mm^2	7.75±1.93	8.04±1.76	0.63
4-month			
Vessel area, mm^2	17.31±3.56	17.33±2.74	0.99
Stent area, mm^2	8.22±1.86	8.64±1.92	0.49
Lumen area, mm^2	7.61±1.87	8.08±1.82	0.43
Neointimal area, mm^2	0.61±0.57	0.57±0.74	0.81
Plaque area outside the stent, mm^2	9.09±2.45	8.95±1.67	0.85
% in-stent obstruction	7.49±6.92	6.21±7.39	0.57
12-month			
Vessel area, mm^2	16.74±3.56	16.73±3.02	0.99
Stent area, mm^2	8.21±1.84	8.36±1.83	0.80
Lumen area, mm^2	7.23±1.87	7.59±1.46	0.52
Neointimal area, mm^2	0.99±0.54	0.77±0.92	0.42
Plaque area outside the stent, mm^2	8.46±2.15	8.37±1.74	0.89
% in-stent obstruction	12.46±7.60	8.37 ±9.10	0.12

instead begins to regress due to the replacement of water-trapping proteoglycans (hyaluronan and versican) by decorin and type I collagen[17]. In this study, compaction of neointima was not observed and it is unknown whether neointimal tissue will keep growing or stop beyond one year. Further follow-up is warranted to evaluate the long-term efficacy of these devices and to find the best elution period and drug dose.

Limitations

At one year, 26% and 34% of the patients in the groups of D5 and D6 respectively did not undergo serial invasive QCA or IVUS follow-up evaluation. Following completion of patient enrolment, the protocol was subsequently amended to allow one year angiographic and IVUS follow-up, necessitating a new informed consent. Patients who did not undergo one-year angiography reported no anginal symptoms at one year. The sample sizes for groups D5 and D6 were insufficient to detect a difference in outcome between the low and high doses in the slow release formulation. However, they served as the basis for the development of a large randomized trial (the EuroSTAR trial) which is evaluating both doses (10 µg and 30 µg per 17mm stent) of slow-release paclitaxel using the reservoir-based technology on an ultra-thin cobalt-chromium stent in 270 patients.

Conclusions

The PISCES trial suggests that the pharmacokinetics of drug-eluting stents is important for both neointimal suppression and for clinical outcomes at 1 year. The slow release (30 day) formulation had better clinical outcomes compared to the fast release (5 or 10 day) formulation. The drug dose (10 µg or 30 µg) did not seem to influence the amount of neointimal suppression but the sample sizes in this pilot dose-finding study were insufficient to detect a beneficial difference in dose.

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Chapter 28

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CHAPTER 28:

SUMMARY AND CONCLUSIONS

This thesis in many ways summarises percutaneous coronary intervention as we know it today, that is, with a provisional stenting approach. More and more commonly, we choose a drug-eluting stent (DES) as the default stent. Twenty years have passed since stents were first used to maintain vessel patency following balloon angioplasty. **Chapter 2** provided a historical account of coronary artery stents, while **Chapter 3** looked at drug-eluting stents and current and future studies in progress.

The Impact of Unrestricted Use of Drug-Eluting Stents

In 2002, at the Thoraxcentre, a decision was made to implant drug-eluting stents in all patients suitable for stent implantation, irrespective of clinical or angiographic findings, and to research the efficacy and safety of these stents in untested patient populations. The original trials that led to the commercialisation of drug-eluting stents were performed in highly selected patients with simple lesions, to reduce the number of confounding factors. However, the patients studied in those trials make up only 20% of the typical patient population seen in a cardiac catheterisation laboratory. For the remaining 80%, it was extrapolated that these drug-eluting stents would be safe and efficacious, and that assumption required proving.

Therefore, all patients undergoing stent implantation were prospectively and consecutively enrolled into the RESEARCH registry (which enrolled from April 2002 to February 2003), and the T-SEARCH registry (from February 2003 onwards). The one year results of the RESEARCH registry have previously been reported. In **Chapters 5 and 6** we report the medium term results of the RESEARCH registry. At two years, despite a higher risk profile in the sirolimus-eluting stent (SES) treated group over the bare metal stent (BMS) treated group, the cumulative rate of major adverse cardiac events (MACE) was lower in the SES group compared to the BMS group, 15.4% versus 22.0% respectively, hazard ratio (HR) 0.68 (95% confidence interval (CI) 0.50 to 0.91); p = 0.01. This advantage was maintained at three years, with MACE rates of 18.9% vs 24.7% respectively, HR 0.73 (95% CI 0.56 to 0.96), p= 0.026. With regards to target vessel revascularization (TVR), the major driver of events, the two-year risk was also lower in the SES group as compared to the BMS group, 8.2% versus 14.8% respectively, HR 0.53 (95% CI 0.36 to 0.79); p= 0.002; while the 3-year risk was 7.5% versus 12.6%, HR 0.57 (95% CI 0.38 to 0.87); p= 0.01. This thus confirmed the superiority of sirolimus-eluting stents over bare stents.

In 2003, paclitaxel-eluting stents (PES) became the default drug-eluting stent, replacing SES. Having already proven the efficacy of SES, we now had the opportunity to compare the efficacy of two drug-eluting stents, PES and SES in **Chapter 4.** At one year, the cumulative incidence of MACE were similar, 13.9% in the PES group and 10.5% in the SES group (unadjusted HR 1.33 (95% CI 0.95-1.88), p=0.1).

We then corrected for baseline differences and that bought the adjusted hazard ratio to 1.16 (95% CI 0.81-1.64, p=0.4). The one year cumulative incidence of clinically driven TVR was similar, 5.4% versus 3.7% respectively (HR1.38 (95% CI 0.79-2.43, p=0.3)).

The Efficacy of Drug-Eluting Stents in Specific Patient and Lesion Subgroups

In this thesis, the specific subgroups not previously studied in the clinical trials pre-commercialisation were scientifically scrutinised and reported. In particular, diabetic patients were targeted in **Chapter 7**, and the different available devices were compared.

At one year, there were no differences in unadjusted outcomes by stent type (MACE rates of 20.4% for SES vs 15.6% for PES, p=0.12) or when adjusted for multivariate predictors (adjusted HR 0.68, 95% CI 0.37 to 1.24, p=0.21). Patients who required insulin had a significantly higher, crude MACE rates at 1 year compared with those who used oral agents, but this rate became non-significant after adjustment for independent predictors of outcome. In **Chapter 8**, patients who presented with an acute ST-elevation myocardial infarction treated with coronary stent implantation to maintain arterial patency were studied – again, comparison was made between sirolimus and paclitaxel eluting stents. At one year, no significant differences were seen between groups, with one year survival free of MACE of 90.2% for SES and 85% for PES (p = 0.16). Between 1 month and 1 year, the revascularisaton rate was low, being no reintervention in the SES group, and only 1.5% in the PES group, p=0.14. We cautioned against the use of bifurcation stenting in acute myocardial infarction, due to the potentially higher risk of stent thrombosis.

Chapter 9 reported the outcomes of patients in whom stent implantation was considered a procedure of last resort, performed on patients in whom the cardiac surgeons had declined to offer cardiac surgery and were instead revascularised percutaneously. In this high risk population, coronary stenting with drug-eluting stents was associated with a 30 day mortality rate of 1.2%, 6 month rate of 3.6% and 12 month mortality rate of 4.8%. These actual results were much lower than the predicted in-hospital mortality rates of between 7.8 ± 3.3% and 13.2 ± 11.1% calculated using the standard and logistic Euroscore methods respectively, suggesting that coronary stenting with drug-eluting stents is an attractive proposition for high-risk patients.

In the next few chapters, specific lesion subgroups were studied. With the advent of drug-eluting stents, longer and longer coronary artery segments were covered, given the dramatic reduction in restenosis rates. In **Chapter 10** we looked at the outcomes of patients who had received more than 64mm of continuous stents in a coronary artery, the so-called 'full-metal-jacket'. With a median of 79mm of stent (range 64-168mm), the one year TVR rate was 7.5% and the overall incidence of MACE was 18%, with no difference between SES and PES groups. **Chapter 11** reported excellent results of PES in saphenous vein grafts with low one year MACE rates of 7.5%. In **Chapter 12**, a comparison of the two drug-eluting

stent types and bare metal stents was made in chronic total occlusions, that is, lesions which had been completely blocked for at least 3 months. Here, we reported that at one year, the freedom from TVR was higher in the SES and PES groups compared with the BMS group (97.4% and 96.4% versus 80.8% respectively, p=0.01). This clearly demonstrated the efficacy of drug-eluting stents over bare stents for this condition.

The treatment of left main lesions, traditionally a surgical cohort, was looked at in **Chapter 13**, and a comparison made between bare metal and drug-eluting stents. Here, with a median follow-up of 503 days (range, 331 to 873 days), the cumulative incidence of MACE was lower in the DES cohort than in the BMS group (24% versus 45%, respectively; HR, 0.52 [95% CI, 0.31 to 0.88]; P=0.01). Total mortality did not differ; however, there were significantly lower rates of both myocardial infarction (4% versus 12%, respectively; HR, 0.22 [95% CI, 0.07 to 0.65]; P=0.006) and TVR (6% versus 23%,respectively; HR, 0.26 [95% CI, 0.10 to 0.65]; P=0.004) in the DES group. In the last of the subgroups looked at, bifurcation lesions were studied in **Chapter 14**. In this study, at six months, survival free of MACE was 93.7% for SES versus 85.8% for PES, p=0.05. Survival-free of target lesion revascularization (TLR) was 95.7% for SES versus 86.8% for PES, p=0.01. This study was not powered to determine the differences in TLR between stent type. Compared with historical data of bare metal stents, MACE rates were low.

Early and Late Stent Thrombosis

As with all new technologies, the initial overblown enthusiasm that accompanied the 'zero restenosis' cry was followed by intellectual reproach. As more patients were treated with drug-eluting stents, it became clear that some of these patients were experiencing a rare complication that was often sudden, acute in onset and potentially life threatening. This was stent thrombosis, a condition also seen with bare metal stents. Given that drug-eluting stents were known to inhibit neointima formation, hence the process of re-endothelialisation and healing, there was grave concern and uncertainty regarding its incidence with drug-eluting stents. From the comprehensive RESEARCH and T-SEARCH database at the Thoraxcentre, we were able to quickly and accurately report to the cardiology community that the incidence of early stent thrombosis (that occurring within the first 30 days of stent implantation) was no different between bare metal and the new drug-eluting stents (**Chapter 15**). This, in retrospect was correct, as the major determinants of early stent thrombosis were mechanical issues, and had nothing to do with the drug, or polymer in the early period. In the first 30 days after stent implantation, the incidence of angiographically proven stent thrombosis in the BMS, SES and PES groups were 1.2%, 1.0% and 1.0% respectively, p=0.9. Multiple potential risk factors were identified in most patients with ST. Bifurcation stenting in the setting of acute myocardial infarction was an independent risk factor for angiographic stent thrombosis in the entire population (odds ratio [OR] 12.9, 95% CI 4.7 to 35.8, p< 0.001). In patients with DES who had angiographic stent thrombosis, 30-day mortality was 15%,

whereas another 60% suffered a nonfatal myocardial infarction; no further deaths occurred during six months of follow-up. Including possible cases, the respective incidences were 1.4%, 1.5% and 1.6%.
With regards to late stent thrombosis (that occurring later than 30 days), the short paper of **Chapter 16** was the first to highlight to the medical community of the anecdotal consequence of stopping antiplatelet therapy following drug-eluting stent implantation. This report was followed by **Chapter 17**, which reported that the incidence of angiographically proven late stent thrombosis was at least 0.35% (95% confidence limits 0.17% to 0.72%) in patients treated with DES and importantly, it may also occur when patients are stable on antiplatelet monotherapy.

Cost-Effectiveness of Drug-Eluting Stents

A study into a new device is not complete without an assessment of its costs, as related to its benefit, expressed as the cost effectiveness of the new drug-eluting stent in comparison to the incumbent bare metal stent. Cost-benefit analyses using trial data pre-commercialisation showed that these stents were indeed cost effective. Using real world data from the RESEARCH registry (**Chapter 5**), we were able to demonstrate in **Chapter 18** that outside of trial situations, in a typical catheterisation laboratory, the unrestricted use of drug-eluting stents were not cost effective at the prices charged in 2002. Cost effectiveness was measured using the incremental cost effectiveness ratio per TVR avoided and was €29 373 at 1 year, and €22 267 at 2 years, when the cost effectiveness price is a ratio less than €10,000. Unique to a cost-effective analysis, we were able to use the formula to provide using contemporary pricing, a cost neutral price of €779 per drug-eluting stent when used in an unrestricted population.

Multi-vessel Stenting

Looking forward, it is important to test whether coronary artery stenting would be a viable alternative to coronary artery bypass surgery as a revascularisation strategy. The five year report of the ARTS trial, the largest randomised trial to compare coronary artery stenting to bypass surgery, importantly demonstrated no difference in mortality between the two groups (8.0% vs. 7.6% respectively; p=0.83; relative risk [RR], 1.05; 95% confidence interval [CI], 0.71 to 1.55). There was an increased need for revascularisation in the stenting group (30.3% versus 8.8%; $p < 0.001$; RR, 3.46;95% CI, 2.61 to 4.60), which resulted in a higher overall major adverse cerebral and cardiac event (MACCE) rate in the stenting group, 41.7% versus 21.8% compared to the CABG group ($p< 0.0001$; RR 1.91;95% CI, 1.60 to 2.28). This is reported in **Chapter 19**.
In **Chapter 20**, the ARTS II trial, a multicentre registry of multivessel disease patients treated with sirolimus-eluting stents, reported low one-year repeat revascularisation rates of 8.5%, and MACCE rates of 10.5%. When compared with the historical ARTS I surgery group the sirolimus treated groups

had similar overall outcomes at one year (RR 0.89 (0.65-1.23)). This led to the design of the SYNTAX trial (**Chapter 21**), a randomised trial comparing coronary artery bypass surgery to coronary artery stenting using paclitaxel-eluting stents in the highest risk group of patients – that is patients with left main disease and those with three vessel disease. Importantly for the SYNTAX trial, data from the preceding chapters from the RESEARCH and T-SEARCH registry were used in the trial design.
Subgroup analyses from the ARTS trial looked at the effect of stents in the proximal left anterior descending artery (**Chapter 23**) and reported that at 3 years, there was no difference in the combined incidence of death, stroke, and myocardial infarction in either group, but the need for repeat revascularization was more frequent in the group with stenting than in the group with coronary artery bypass grafting. In patients in the ARTS trial who had renal insufficiency (**Chapter 24**), those who underwent stenting had a lower 5-year freedom from MACCE as compared to those who underwent CABG, mainly due to the increased need for repeat revascularisation (50.7% versus 68.5% respectively, p=0.04. Finally, the effect of gender was studied in **Chapter 25**. At 5-years, the clinical outcome of women with multivessel disease undergoing coronary revascularisation was similar to that in men within their treatment groups. However, women presented more bleeding complications before hospital discharge in the stenting group.

New Drug-Eluting Stents

Having only discussed sirolimus and paclitaxel-eluting stents to date, new challengers have entered the horizon. The 6-month results of the SPIRIT FIRST trial were extremely positive, demonstrating that everolimus eluted from a durable polymer on a cobalt chromium stent effectively suppresses neointimal growth compared to an identical bare stent (**Chapter 26**). The 6 month primary endpoint results were as follows: in-stent late loss, percentage diameter stenosis and percentage of patients with binary restenosis were 0.10 mm, 16% and 0% respectively, in the everolimus arm (n=23), as compared with 0.87 mm, 39% and 25.9%, respectively in the bare stent arm (n=27, p<0.001 for late loss and diameter stenosis, p = 0.01 for restenosis). Finally, the PISCES trial, in which a new paclitaxel-eluting stent was studied, the effect of prolonged dosing and dose size was tested in a population that was sequentially enrolled (**Chapter 27**). Patients who received the slow release formulation stent had better clinical outcomes at one year than those who received the fast release formulation. However, due to the small sample size and non-randomized design of the trial, the effect on neointimal suppression require investigation in a larger population to determine whether the high dose formulation confers an additional clinical benefit over the low dose formulation. Importantly, this trial appeared to explain the failure of other drug-eluting stents and subsequently influenced the development of future devices.

Conclusion

Therefore, in conclusion, the last 5 years of drug-eluting stent use has revolutionised revascularisation of coronary arteries, with many patients now genuinely able to have the option of either percutaneous coronary intervention with drug-eluting stents or coronary artery bypass surgery as their preferred revascularisation strategy. We were able to reassure the medical community on the issue of stent thrombosis, as well as to guide it with regards to pricing. This thesis, through its thorough study of drug-eluting stents when used in a real world unrestricted population, has paved the way for newer studies, pushing the limits of coronary stenting, in particular left main and three vessel disease. Finally, as we move forward, this thesis ends with new participants, some of whom will succeed, and others that will fail, but all need to be studied and scrutinised.

SAMENVATTING EN CONCLUSIES

Dit proefschrift vat op vele manieren de status op het gebied van percutane coronaire interventie samen, zoals vandaag de dag uitgevoerd met provisional stenting. Sinds de introductie van de eerste coronaire stent zo'n 20 jaar geleden om de kransslagader langer open te houden, is de drug-eluting stent momenteel voor velen de stent van eerste keuze geworden. **Hoofdstuk 2** geeft een historisch overzicht van de ontwikkeling van coronaire stents, terwijl **Hoofdstuk 3** meer specifiek de drug-eluting stent en huidige en toekomstige studies beschrijft.

De impact van ongelimiteerd drug-eluting stent gebruik

In 2002 werd er in het Thoraxcentrum besloten om drug-eluting stents te gaan gebruiken in alle patiënten die in aanmerking kwamen voor stent implantatie in een patiëntenpopulatie zoals nog nooit eerder bestudeerd, zonder enige klinische of angiografische restricties, met als doel de veiligheid en effectiviteit van deze nieuwe stents te onderzoeken. De oorspronkelijke studies die leidden tot de commercialisering van drug-eluting stents werden uitgevoerd in zeer geselecteerde patiënten met eenvoudige laesies, om zo het aantal confounders zo klein mogelijk te houden. Desalniettemin waren deze patiënten slechts representatief voor zo'n 20% van de populatie zoals wordt gezien in de dagelijkse praktijk. Er werd echter zonder specifiek bewijs verondersteld dat de resultaten van deze studies geëxtrapoleerd konden worden naar de overige 80% van de patiënten.

Alle patiënten werden geïncludeerd in de RESEARCH registratie (inclusie van april 2002 tot februari 2003) en vervolgens in de T-SEARCH registratie (inclusie vanaf februari 2003). De 1-jaars resultaten van de RESEARCH registratie werden reeds eerder gepubliceerd. In **Hoofdstuk 5 en 6** rapporteren we over de middellange termijn resultaten van de RESEARCH registratie. Na 2 jaar was de cumulatieve incidentie van major adverse cardiac events (MACE) significant lager in patiënten behandeld met sirolimus-eluting stents (SES) dan in patiënten behandeld met bare-metal stents (BMS) (15.4% vs. 22.0%; hazard ratio (HR) 0.68 (95% betrouwbaarheidsinterval (CI) 0.50 – 0.91; p=0.01)), ondanks een hoger klinisch en angiografisch risicoprofiel in de met SES behandelde patiënten. Dit verschil bleef significant na 3 jaar, waar de incidentie van MACE 18.9% vs. 24.7% was in patiënten respectievelijk behandeld met SES en BMS. Wat betreft nieuwe revascularizaties in de index kransslagader (target vessel revascularization, oftewel TVR), de veroorzaker van het gros van de events, was het 2-jaars risico ook significant lager in de SES groep (8.2% vs. 14.8% respectievelijk; HR 0.53, 95% CI 0.36 – 0.79; p=0.002); terwijl het 3-jaars risico 7.5% vs. 12.6% (HR 0.57; 95% CI 0.38 – 0.87; p=0.01) was. Dit bevestigde de superioriteit van SES ten opzichte van BMS.

In 2003 werd de paclitaxel-eluting stent (PES) de stent van eerste keuze, en verving daarmee de SES. Gezien we de superioriteit van SES ten opzichte van BMS reeds bewezen hadden, hadden we nu de mogelijkheid tot het vergelijken van beide drug-eluting stents, SES en PES (**Hoofdstuk 4**). Na 1 jaar was

de cumulatieve incidentie van MACE gelijk in beide groepen (13.9% na PES implantatie en 10.5% na SES implantatie; HR 1.33, 95% CI 0.95 – 1.88; p=0.01). Vervolgens corrigeerden we voor de verschillen tussen beide groepen wat resulteerde in een HR van 1.16 (95% CI 0.81 – 1.64, p=0.4). De 1-jaars cumulatieve incidentie van klinisch gedreven TVRs was gelijk (5.4% voor PES en 3.7% voor SES; HR 1.38, 95% CI 0.79 – 2.43; p=0.3).

De effectiviteit van drug-eluting stents in specifieke patiënten en laesies

In dit proefschrift worden specifieke subgroepen van patiënten uitgebreid bestudeerd. Subgroepen van patiënten die nooit eerder werden bestudeerd in de klinische trials die hebben geleid tot commercialisering van de stents. Meer specifiek worden diabeten besproken in **Hoofdstuk 7**, en de verschillende beschikbare stents werden vergeleken. Na 1 jaar bleken er geen verschillen te bestaan in de ongecorrigeerde uitkomsten tussen SES en PES. De incidentie van MACE was 20.4% na SES en 15.6% na PES (p=0.12). Correctie voor onafhankelijke voorspellers resulteerde in een HR van 0.68 (95% CI 0.37 – 1.24; p=0.21). Insuline afhankelijke diabeten hadden een significant hogere incidentie van MACE op 1 jaar in vergelijking tot niet-insuline afhankelijke diabeten. Echter, dit verschil verloor haar significantie na correctie voor onafhankelijke voorspellers. In **Hoofdstuk 8** worden patiënten bestudeerd met acuut myocard infarct en opnieuw werd er een vergelijking gemaakt tussen patiënten behandeld met SES en PES. Na 1 jaar werden er geen significante verschillen gevonden tussen beide groepen, met een MACE vrije overleving van 90.2% na SES implantatie en 85% na PES implantatie (p=0.16). Tussen 1 maand en 1 jaar bleek de incidentie van revascularizaties laag te zijn (0% in de SES groep en 1.5% in de PES groep; p=0.14). Echter, we waarschuwden voor het gebruik van bifurcatiestenting in de setting van een acuut myocard infarct, gezien het mogelijk verhoogde risico op stent trombose.

Hoofdstuk 9 rapporteert over de uitkomsten van patiënten waarin stent implantatie werd gezien als behandeling van laatste keuze; patiënten afgewezen door thoraxchirurgen voor bypass chirurgie en om die reden percutaan werden behandeld. In deze hoog-risico populatie bleek de 30-dagen mortaliteit 1.2% te zijn, na 6-maanden 3.6% en na 12 maanden 4.8%. De incidentie van overlijden bleek veel lager dan de op basis van de standaard en logistische Euroscore methoden te verwachten sterftecijfers van respectievelijk 7.8±3.3% - 13.2±11.1% en suggereerden dat het gebruik van drug-eluting stents een aantrekkelijk alternatief was voor deze hoog-risico patiënten.

In de volgende hoofdstukken, worden patiënten met specifieke laesies bestudeerd. Samengaand met de ontwikkeling van drug-eluting stents werden de behandelde segmenten steeds langer, mede door de significant lagere restenose getallen. In **Hoofdstuk 10** keken we naar de uitkomsten van patiënten die meer dan 64mm aan continue stent lengte ontvingen in 1 specifieke coronair arterie, de zogenaamde "full-metal jacket". Met een mediane stent lengte van 79mm (spreiding van 64-168mm), was de 1-jaar TVR incidentie 7.5% en de incidentie van MACE 18%, zonder verschil tussen SES en PES. **Hoofdstuk 11** rapporteert over de uitstekende resultaten behorend bij het gebruik van PES in veneuze bypass graft met

een 1-jaar MACE incidentie van slechts 7.5%. In **Hoofdstuk 12**, waarin een vergelijking wordt gemaakt tussen de twee drug-eluting stents en BMS in chronisch totale occlusies (= compleet obstructieve laesies die reeds meer dan 3 maanden bestaan). We beschrijven dat na 1 jaar, de overleving vrij van TVR hoger is in de SES en PES groepen dan in de BMS groep (97.4% en 96.4% versus 80.8%, p=0.01). Dit geeft duidelijke de superioriteit aan van drug-eluting stents boven die van BMS voor deze specifieke laesies. De behandeling van patiënten met hoofdstam laesies, van oorsprong een chirurgisch cohort, en de relatieve effectiviteit van beide drug-eluting stents en BMS wordt beschreven in **Hoofdstuk 13**. Na een follow-up met een mediaan van 503 dagen (spreiding 331 – 873), was de cumulatieve incidentie van MACE lager in de drug-eluting stent groep dan in de BMS groep (respectievelijk 24% versus 45%, HR 0.52, 95% CI 0.31 – 0.88; p=0.01). Ondanks dat de mortaliteit gelijk bleek te zijn na beide behandelingen was er een significant lager risico op zowel myocard infarcten (respectievelijk 4% versus 12%, HR 0.22, 95% CI 0.07 – 0.65; p=0.006) als TVR (respectievelijk 6% en 23%, HR 0.26, 95% CI 0.10 – 0.65; p=0.004) in de drug-eluting stent groep. Tenslotte worden patiënten behandeld voor bifurcatielaesies bestudeerd in Hoofdstuk 14. In deze studie, op 6 maanden, was de MACE vrije overleving 93.7% na SES implantatie versus 85.8% na PES implantatie (p=0.05). De overleving vrij van revascularizatie door een significante vernauwing in de indexlaesie/stent (oftewel target lesion revascularization, TLR) was 95.7% na SES versus 86.8% na PES (p=0.01). Echter, de studie had onvoldoende statistische power om een verschil in TLR aan te tonen tussen beide stent types. In vergelijking met historische data over het gebruik van BMS was de incidentie van MACE laag.

Vroege en late stent trombose

Zoals met elke nieuwe technologie werd het overdonderende enthousiasme over de "0% restenose" gevolgd door een wat meer gematigde en intellectuele heroverweging. Naar mate er meer patiënten behandeld werden met drug-eluting stents werd het duidelijk dat sommige van deze patiënten een zeldzame complicatie doormaakten die meestal plots en onverwacht optrad en levensbedreigend kon zijn – stent trombose, een gebeurtenis die ook wel was beschreven na het gebruik van BMS. Aangezien drug-eluting stents hadden bewezen de groei van neointima weefsel te remmen, door in te grijpen op het proces van re-endothelializatie en genezing, ontstond er een ernstige bezorgdheid over het voorkomen van deze gebeurtenis na drug-eluting stent gebruik. Gebaseerd op data van de uitgebreide RESEARCH en T-SEARCH databases uit het Thoraxcentrum waren we in staat snel en accuraat aan de cardiologische gemeenschap te rapporteren dat de incidentie van vroege stent trombose (binnen 30 dagen na stent implantatie) niet verschillend was tussen BMS en de nieuwe drug-eluting stents (**Hoofdstuk 15**). Retrospectief gezien bleek dit correct, omdat de belangrijkste voorspellers van vroege stent trombose mechanische problemen bleken te zijn, die niks te maken hadden met het medicijn of de polymeer op de stent in de vroege periode. In de eerste 30 dagen na stent implantatie, bleek de incidentie van angiografisch aangetoonde stent trombose in de BMS, SES PES groepen respectievelijk 1.2%, 1.0%

en 1.0% te zijn (p=0.9). Meerdere mogelijke voorspellers voor stent trombose werden geïdentificeerd. Bifurcatiestenting in de setting van acuut myocard infarct bleek een onafhankelijke voorspeller van angiografische stent trombose in de gehele studiepopulatie (HR 12.9, 95% CI 4.7 – 35.8; p<0.001). In patiënten behandeld met drug-eluting stents die stent trombose ontwikkelden bleek de 30-dagen mortaliteit 15% en ontwikkelde 60% een acuut myocard infarct. Geen nieuwe patiënten stierven tot 6 maanden. Indien ook de mogelijke gevallen van stent trombose (dood zonder aanwijsbare oorzaak) werden meegenomen, was de incidentie 1.4% na BMS, 1.5% na SES en 1.6% na PES.
Wat betreft late stent trombose (na 30 dagen na stent implantatie) was het korte artikel uit **Hoofdstuk 16** het eerste dat de medische gemeenschap erop attendeerde op de anekdotische consequentie van het stoppen van plaatjesremmers na drug-eluting stent implantatie. Deze studie werd gevolgd door de studie uit **Hoofdstuk 17** waar wordt gerapporteerd dat de incidentie van angiografische late stent trombose 0.35% was (95% CI 0.17% - 0.72%) in patiënten behandeld met DES en dat stent trombose eveneens kan voorkomen op stabiel aspirine gebruik.

Kosten-effectiviteit van drug-eluting stents

Een studie over een nieuw product is niet compleet zonder de beoordeling van zijn kosten ten opzichte van zijn baten, uitgedrukt als de kosten-effectiviteit van de drug-eluting stent in vergelijking tot de BMS. Kosten-effectiviteitsanalyses gebaseerd op studie data voorafgaand aan de commercialisering bewees reeds dat deze stents kosten-effectief waren. Gebruikmakend van data uit de dagelijkse praktijk zoals beschreven in de RESEARCH registratie (**Hoofdstuk 5**) beschreven we in **Hoofdstuk 18** de situatie buiten de setting van een klinische trial, in een typisch catheterisatielab. Hierin bleek het gebruik van de drug-eluting stent niet kosten-effectief te zijn tegen de prijzen die gehanteerd werden in 2002. De kosten effectiviteit werd gemeten op basis van de kosten-effectiviteits ratio per vermeden TVR en was €29.373 na 1 jaar en €22.267 na 2 jaar, terwijl ratio van kosten effectiviteit onder de €10.000 lag. Uniek aan deze analyse was dat we in staat waren een formule te gebruiken met eigentijdse prijscalculatie. Een prijs van €779 per drug-eluting stent bleek kosten neutraal te zijn in onze populatie van ongeselecteerde patiënten.

Stenting voor meervatslijden

Vooruitkijkend in de toekomst is het belangrijk om te tested of het stenten van coronair arterien een haalbaar alternatief kan zijn voor bypass chirurgie. In de 5-jaars resultaten van ARTS studie, de grootste gerandomiseerde studie die bypass chirurgie vergeleek met stenting, toonde aan dat er geen verschil in mortaliteit was tussen beide groepen (8.0% vs. 7.6%, HR 1.05, 95% CI 0.71 – 1.55; p=0.83). Echter, de noodzaak tot nieuwe revascularizaties bleek aanzienlijk hoger in de groep behandeld met stenting,

30.3% ten opzicht van 8.8% in de bypass group (HR 3.46, 95% CI 2.61 – 4.60; p<0.001) wat vervolgens resulteerde in een hogere MACCE incidentie (een gecombineerd eindpunt van dood, stroke, myocard infarct, en nieuwe revascularizatie) in de stenting groep (41.7%) in vergelijking tot de bypass groep (21.8%, HR 1.91, 95% CI 1.60 – 2.28; P<0.0001) (**Hoofdstuk 19**).

In **Hoofdstuk 20**, rapporteren we een lage incidentie van nieuwe revascularizaties (8.5%) en MACCE (10.5%) in patiënten uit de ARTS-II studie, een multicenter registratie van patiënten met meervatslijden behandeld met SES. In vergelijking met het historische chirurgische cohort uit de ARTS-I studie resulteerde het gebruik van de SES in vergelijkbare resultaten op 1 jaar (HR 0.89, 95% CI 0.65-1.23). Dit laatste leidde tot het design van de SYNTAX studie (**Hoofdstuk 21**), een gerandomiseerde studie die bypass chirurgie vergelijkt met stenting met PES in patiënten uit de hoogste risico categorie, namelijk met hoofdstamlaesies en 3-vats lijden. Vernoemenswaardig is dat data uit de RESEARCH en T-SEARCH registraties werd gebruikt voor het design van deze trial.

In een subgroup analyse van de ARTS studie van patiënten met proximale hoofdstamlaeasies (**Hoofdstuk 23**) beschrijven we dat er na 3 jaar geen verschil was in de incidentie van het gecombineerde eindpunt van dood, stroke en myocard infarct tussen de twee groepen. Echter, de behoefte aan nieuwe revascularizaties bleef significant hoger na stenting. In patiënten uit de ARTS studie met nierinsufficiëntie (**Hoofdstuk 24**), bleken patiënten die waren behandeld met stenting een significant lagere 5-jaars overleving vrij van MACCE te hebben dan patiënten behandeld met bypass chirurgie; opnieuw met name door de verhoogde incidentie van revascularizatie na stenting (68.5% vs. 50.7 na bypass chirurgie; p=0.04). Ten slotte bestudeerden we de impact van geslacht op de resultaten van de ARTS studie in **Hoofdstuk 25**. Na 5 jaar bleek er geen verschil te zijn in de klinische uitkomsten van zowel mannen als vrouwen met meervatslijden behandeld met bypass chirurgie of stenting. Echter, vrouwen behandeld met stenting bleken een verhoogd risico op bloedingen te hebben voor ontslag uit het ziekenhuis.

Nieuwe Drug-Eluting Stents

Ondanks dat we tot nog toe enkel de resultaten van de SES en de PES besproken hebben is er inmiddels een verscheidenheid aan nieuwe stents op de markt gekomen. Zo waren de 6-maanden resultaten van de SPIRIT First studie zeer positief. De studie toonde aan dat everolimus, afgescheiden van een duurzame niet oplosbare polymeer op een cobalt chromium stent effectief was in het onderdrukken van neointima groei in vergelijking tot een BMS (**Hoofdstuk 26**). De resultaten op 6-maanden waren als volgt: in-stent late loss, percentage diameter stenose en het percentage van patiënten met binaire restenose waren respectievelijk 0.10mm, 16% en 0% in de everolimus arm (n=23) in vergelijking tot respectievelijk 0.87mm, 39% en 25.9% in de BMS arm (n=27; p<0.001 voor late loss en diameter stenose en p=0.01 voor restenose). Ten slotte werd het effect van een langdurigere afscheiding en dosisvariatie beschreven in de PISCES studie, waarin een nieuwe paclitaxel-eluting stent werd getest (**Hoofdstuk 27**). Patiënten die behandeld werden met de langzame afscheiding variant bleken een betere klinische uitkomst te hebben na 1 jaar dan patiënten behandeld met de variant met een veel vluggere afscheiding van paclitaxel. Echter, mede door de kleine studiepopulatie en het ongerandomiseerde design van de studie kon het effect op het remmen van neointima onderdrukking niet goed bestudeerd worden en is

een grotere studiepopulatie nodig om te bepalen of een hogere dosis samenhangt met een additioneel klinisch voordeel ten opzichte van de lage dosis. Niet onbelangrijk was echter dat de PISCES studie het falen van tal van nieuwe drug-eluting stents wist te verklaren en de studie beïnvloedde op die manier de ontwikkeling van tal van nieuwe producten.

Conclusie

We kunnen concluderen dat in de laatste 5 jaar het gebruik van drug-eluting stents heeft gezorgd voor een substantiële verbetering in de behandeling van patiënten met coronairlijden. Daarbij is de mogelijk tot het kiezen van een revascularizatie strategie naar voorkeur met bypass chirurgie of stenting steeds realistischer geworden.
We waren in staat om de medische gemeenschap enigszins gerust te stellen over het probleem van stent trombose, evenals enige richtlijn te geven met betrekking tot prijscalculaties. Dit proefschrift, met een diepgaande analyse van drug-eluting stents zoals gebruikt in de dagelijkse praktijk zonder enige restricties, heeft een weg gebaand voor nieuwe studies die de grenzen van het gebruik van drug-eluting stents aan de kaak stellen, zoals bijvoorbeeld bij hoofdstamlaesies en 3-vatslijden.
Gezien de tijd niet stil blijft staan eindigt dit proefschrift met nieuwe deelnemers. Sommigen zullen slagen, anderen zullen falen; maar allen zullen uitgebreid bestudeerd moeten worden.

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A little bit of my life in Rotterdam was spent at Cardialysis, whether it was for an investigators' meeting, or to present data, or simply to meet up with Professor. I would like to also thank the people in Cardialysis for the time they spent with me, in particular, Marie Angele and Gerrit Anne.

Away from the Thoraxcenter, there have been numerous other influential figures in my life to date. Cardiology, as I know it was first introduced to me by my father when I was 8 years old. One particular evening when my mother was in hospital having just given birth to my brother Adrian; he needed to do a ward round, and there was no better place to put me but in the Coronary Care Unit at the General Hospital in Kuala Lumpur and to get the nurses there to babysit me while he went and saw patients. As part of the entertainment, they hooked me up to the cardiac monitor, and I was soon able to see my electrocardiograph being printed out on the single channel printer. That was indeed a revelation. For my next experiment, I discovered that if I jumped up and down quickly, I could cause ventricular fibrillation (on paper, at least)!

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Finally, a little aside: Life works in funny ways. I was born in Malacca, an ex-Dutch colony formerly under the control of the Dutch East India Company (VOC) from 1641-1825. My grandmother's house is in Heeren Street (Heerenstraat), in Malacca. Along the way, I studied, worked and did my training in

Australia, which was discovered by the Dutchman Abel Tasman and for many years known as Hollandia Nova. I spent my interventional fellowship year in a country also discovered by Abel Tasman – New Zealand (Zeelandia Nova). And finally, for my PhD research, I ended up in the Netherlands. And now, I am back in Australia. See the connection? And so the journey continues, from the beginning until now, and beyond.

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ABSTRACT PRESENTATIONS

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