Unrestricted Utilization of Sirolimus-Eluting Stents in the "Real World". The *R*apamycin-*E*luting *S*tent *E*valuated *A*t *R*otterdam *C*ardiology *H*ospital (RESEARCH) registry

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Thesis

To obtain the degree of Doctor from the Erasmus University Rotterdam by command of the Rector Magnificus

Prof.dr. S.W.J. Lamberts

and according to the decision of the Doctorate Board
The public defense shall be held on

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Para Francine

Normally, it is important to look normal.
(Normalmente, é importante parecer normal)

Dr. Ivaldo Lemos

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Part 2 – Sirolimus-eluting stents: Limitations and Shortcomings

Chapter 1 Introduction and Overview of the Thesis

Introduction and Overview of the Thesis

In-stent restenosis has long been considered the main limitation hampering the long-term efficacy of coronary stenting. Although stent implantation itself has been associated with reduced rates of restenosis compared to balloon angioplasty, in-stent restenosis still persists in up to 40% of patients with complex presentations. Even though a number of "predictors" of restenosis are known and are helpful in characterizing "high-risk" populations, the incidence of restenosis remains largely unpredictable in an individual basis.[1-3] In addition to its relatively high rate in some subsets, the treatment of restenosis has been proven to be frequently challenging. In-stent restenosis in its more complex forms may re-occur in up to 80% of patients following percutaneous re-treatment with conventional techniques.[4] Moreover, although intracoronary brachytherapy has been shown effective in reducing the recurrence rate of in-stent restenosis, treatment failure still occurs in approximately 30% of cases after endovascular irradiation.

Recently, sirolimus-eluting stents implantation has been shown in feasibility studies [5-9] and in randomized trials [10-13] to markedly decrease restenosis in selected patients. In the early First-In-Man (FIM) study with 45 patients, no cases of restenosis were detected up to two years.[5-9] These results were further confirmed in the RAVEL trial (RAndomized study with the sirolimus-eluting Bx VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions),[10] where restenosis was also not detected after sirolimus-eluting stent implantation. Based on these findings, sirolimus-eluting stents received CE Mark approval in Europe in April 2002 and are since then commercially available for routine clinical use.

Although sirolimus-eluting stents have virtually abolished restenosis in the FIM [5-9] and RAVEL,[10] these studies have mainly included elective patients with relatively non-complex lesions. In the subsequent SIRIUS (SIRolImUS-eluting Bx velocity balloon expandable stent trial),[11] and E-SIRIUS [12] trials, which included patients with increased risk profiles, restenosis occurred in 8.9% and 5.9% of cases in the sirolimus groups respectively (compared to 36.3% and 42.3% of patients treated with conventional stents, respectively; $p<0.01$ for both).[11,12] Indeed, the effects of SES implantation in complex, unselected patients, such as those commonly treated in daily practice, remains largely unknown.

The purpose of this thesis was to comprehensively evaluate the impact of sirolimus-eluting stent implantation on the outcomes of patients treated in the "real world" of interventional cardiology. Sirolimus-eluting stents were utilized as the strategy of choice for all consecutive candidates to percutaneous revascularization, in a clinical scenario where virtually every patient, with any clinical or anatomical conditions, were considered potentially eligible. The relative benefits and limitations of this approach were evaluated in comparison with conventional approaches in use immediately prior to the introduction of sirolimus stents. The short- and long-term outcomes of several high risk subsets not included in the currently available randomized trials were evaluated in detail.

The safety and efficacy of unrestrictive utilization of sirolimus-eluting stents in the "Real World" were analyzed in the Part 2 of the thesis. The global impact of sirolimus-eluting stent implantation on the overall outcomes of a population of consecutive patients was described in Chapter 3. Subsequently, patients at high clinical risk of complications and patients with complex anatomical characteristics were examined in separate reports. Chapters 4, 5, and 6 evaluated the impact of sirolimus-eluting stents on the short- and long-term clinical outcomes and restenosis rates of patients with acute coronary syndromes. Chapter 7 described the relationship between sirolimus or conventional stent implantation on the mortality of patients with or without decreased renal function. Percutaneous intervention utilizing sirolimus-eluting stents for patient subsets most commonly considered for surgical revascularization was evaluated in Chapters 8 to 12: the effectiveness of sirolimus-eluting stent for chronic total occlusions was examined in Chapter 8 and for left main coronary artery disease in Chapters 9 and 10; for multivessel disease with left anterior descending artery involvement in Chapter 11; for chronic total occlusions in Chapter 12. Patients with very small vessels, patients with very long stented segments, and those with bifurcation stenting, cases at high risk for restenosis with conventional stenting, were studied in Chapters 13, 14, and 15 respectively. The merits of sirolimus-eluting stents for patients with previous failed percutaneous treatments were evaluated in Chapter 16 to 18: the effectiveness of sirolimus-eluting stent implantation for in-stent restenosis was detailed in Chapter 16 and compared to vascular brachytherapy in Chapter 17; sirolimus-eluting stent implantation for recurrent in-stent restenosis after brachytherapy was studied in Chapter 18.

Part 3 of this thesis examined the limitations and shortcomings of sirolimus-eluting stent implantation. Chapter 19 offered a morphological description and mechanistic analysis of a consecutive series of patients with post-sirolimus restenosis. Chapter 20 examined the incidence, as well as the predictors, of restenosis after sirolimus-eluting stents in complex patients, which statistical pattern of occurrence is further detailed in Chapter 21. The impact of over-dilatation of undersized sirolimus stents was studied in Chapter 22. Finally, Chapters 23 and 24 examined the costs and the balance between costs and effects of sirolimus-eluting stent implantation.

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Chapter 2 Drug-Eluting Stents for the Treatment of Coronary Disease – State of the Art.

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The Paris Course on Revascularization, EuroPCR Textbook 2004

Drug-Eluting Stents for the Treatment of Coronary Disease: State of the Art.

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Introduction

In-stent restenosis has long been considered the main complication limiting the long-term efficacy of coronary stenting. Although stent implantation itself has been shown to reduce restenosis compared to balloon angioplasty, in-stent restenosis still occurs in 10-40% of the patients. Although a number of "predictors" have been described and are helpful in characterizing "high-risk" populations, the occurrence of restenosis remains largely unpredictable for a particular patient.[1-3] Moreover, in-stent restenosis in its more complex forms may re-occur in up to 80% of patients following percutaneous re-treatment with conventional techniques.[4] Although intracoronary brachytherapy has been proven effective in reducing the recurrence rate of in-stent restenosis, treatment failure still frequenlty occurs. In a recent study, 60% of patients have been reported to experience at least one major cardiac event up to 4 years after endovascular irradiation.

A large body of evidence has been accumulated in an attempt to understand the processes involved in restenosis. The initial injury caused by the mechanical dilatation and stent implantation triggers a "normal" healing vascular response that ultimately leads to neointimal formation, which, when excessive, may re-narrow the vessel lumen (restenosis). An array of local reparative processes have been shown to occur after the initial vascular trauma, involving platelets, inflammatory cells, smooth muscle cells, endothelial cells, and the secretion of a number of growth factors and cytokines.[5,6]

Based on the accumulated knowledge about the cellular and molecular mechanisms of restenosis, an endless list "concepts", "strategies", devices, and drugs have been tested, and failed, to decrease restenosis.[7] More recently, however, drug-eluting stents have emerged as an effective therapeutic option to reduce the incidence of in-stent restenosis. The present chapter will focus on describing the current clinical and pre-clinical information available for drug-eluting stents, as well as the limitations and future research directions for these devices.

Rationale

A proposed explanation for the repeated failure of clinical pharmacological studies with systemically administered drugs is that these agents cannot reach sufficient tissue levels at the site of dilatation without increasing the risk of systemic side effects. In this regard, local administration offers advantages by applying the drug to the precise site of injury, therefore yielding very high concentration of the active agent with low or negligible systemic concentrations.

Utilizing the stent itself as the platform for local drug delivery is an appealing approach. Coronary stents have been extensively proven to be safe and effective in mechanically alleviating coronary obstructions, with predictable and stable short-term results in a wide range of clinical situations. By combining an agent with antiproliferative properties to a "conventional" metallic stent, one is able to preserve the mechanical scaffolding properties of stenting while the active agent is administered to the very spot of vascular injury, with no time delay, with high local doses, and with the potential to control the time (short- vs. long-course) and site (mural vs. luminal) of drug release, among other characteristics.

Table 1. Overview of possible anti-restenotic approaches for stent-based strategies

Anti-proliferative	Anti-thrombins	Immunomodulators	Migration inhibitors / ECM modulators	Promote healing / endothelialization
– Paclitaxel	– Hirundin	– sirolimus and analogs	– Halofuginone	– VEGF
– QP-2	– Iloprost	– tacrolimus	– Propyl hydroxylase inhibitors	– 17-β estradiol
– Vincristin	– Abciximab	– Biorest	– C-proteinase inhibtors	– Tkase inhibitors
– Methotrexate		– Mizoribine	– Metalloproteinase inhibitors	– BCP 671
– Angiopeptin		– Cyclosporin	– Batimastat	– Statins
– Mitomycin		– Biorest	– Probucol	– NO donors
– BCP 678		– Interferon γ1b		– EPC antibody
– Antisense c-myc		– Leflunomide		
– ABT 578		– Tranilast		
– Actinomycin-D		– Cyclosporin		
– RestenASE		– Corticosteroids		
– 1-chloro-deoxyadenosine		– Micophenolic acid		
– PCNA ribozyme		– Biphosphonates		
– Celecoxib				

The delivery vehicles

Coated stents have been subjected to extensive investigations long before being available for implantation in humans. The process of binding pharmacological agents to a metallic mesh has been early recognized to be challenging. The coating should be resistant to mechanical abrasion during the frequently laborious process of stent implantation, and should comply with a number of pharmacological practical requirements, such as drug release in a predictable (dose and time) way and suitability for sterilization. Furthermore, the coating itself should not induce an increased vascular reaction. It should be noted in addition that a potential universal coating is unlikely, and that different pharmacological agents may require different delivery vehicles. Currently, a variety of different formulations have been developed that provide appropriate stent coating for clinical use, including direct drug binding, and coatings with phosphorylcholine, nonerodable or bioabsorbable polymers, or ceramic layers.

The agents

The local agent should be one that inhibits the complex cascade of events that leads to neointimal 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 on the vascular reparative processes are all potential targets for therapeutic approaches aiming at reducing neointimal proliferation. A variety of potential candidates are available (Table 1) and an increasing number of clinical studies have been conducted to evaluate the efficacy of different eluting-stents.

It is important to recognize that the clinical effect of these devices is highly dependent on each one of the components of the complex platform/vehicle/agent, as well as the interactions among these elements. It is therefore unlikely that a drug-eluting stent "class-effect" might exist, due to the myriad of possible therapeutic combinations. Indeed, different drug-eluting stents have been shown to significantly vary in their ability to reduce restenosis. Indeed, several drug-eluting stents have been already shown ineffective, as summarized in Table 2.

Polymer-coated sirolimus- and paclitaxel-eluting stents have the largest clinical experience to date, with a total of 8 already completed randomized trials comparing the effect of these devices against conventional stents. Sirolimus-eluting stents are available for clinical use in Europe, Asia, and South America since 2002 and in the US since 2003. Polymer-coated paclitaxel-eluting stents have been commercialized in Europe, Asia, and South America since 2003 and are expected to be launched in the US in the beginning of 2004. The main clinical information derived from randomized trials and from other clinical studies including post-marketing registries are detailed below. In addition to sirolimus and paclitaxel stents, an increasing number of other drug-eluting stents have been tested in preliminary clinical trials with promising results and are summarized in the sections below.

Sirolimus

Sirolimus (Rapamycin; Rapamune®) is a naturally occurring macrocyclic lactone with a potent immunosuppressive action, which was approved by the US Food and Drug Administration for use in renal transplant recipients in September 1999. Sirolimus inhibits cellular proliferation by blocking cell cycle progression at the G1 to S transition. Its action is mediated by binding to an intracellular receptor, the FK506 binding protein (FKBP12). The complex rapamycin-FKBP12 then inhibits the activity of a key regulatory kinase denominated mammalian Target Of Rapamycin (mTOR). The inhibition of mTOR suppresses cytokine-driven (IL-2, IL-4, IL-7 and IL-15) T-cell proliferation. Its inhibition has several important effects, including the inhibition of translation of a family of mRNAs that code for proteins essential for cell cycle progression. The inhibition of mTOR prevents mitogen-induced downregulation of p27Kip1.[8,9] In addition, smooth muscle cell proliferation is shown to be inhibited by rapamycin-FKBP12 in p27Kip1(-/-) knockout mice, suggesting that neointimal inhibition may also operate via a pathway that is independent of p27Kip1.[8] Human neointimal tissue extracted during atherectomy exhibited a peculiar upregulation of FKBP12 at mRNA and protein levels, indicating the potential for sirolimus in preventing coronary restenosis.[10]

Table 2. Failed pharmacologic stent-based strategies to prevent restenosis

Trial	Agent	vehicle	Stent platform	reason for clinical failure
SCORE [47]	Taxol derivative QP2 (4000μg)	polymer sleeves	QuaDS-QP2 stent	excessive incidence of stent thrombosis and myocardial infarction possibly due to the polymer sleeves
DELIVER [38]	Paclitaxel (3μg/mm^2)	direct binding	Multi-link penta	lack of efficacy
ACTION [48]	Actinomycin-D (10 and 2.5μg/mm^2)	Polymeric coating	Multi-link tetra	lack of efficacy
BRILLIANT-EU [49]	Batimastat	Phosphorylcholine coating	BiodivYsio stent	lack of efficacy
PRESENT trials [50]	Tacrolimus (60 and 230μg)	Nanoporous ceramic coating	FlexMaster ceramic stent	lack of efficacy
EVIDENT [50]	Tacrolimus (352μg)	PTFE	PTFE-covered stent graft	lack of efficacy
IMPACT[51]	Micophenolic acid (14-day or 45-day release 3.3 μg/mm^2)	"Unicoat" polymer	Duraflex stent	lack of efficacy

Systemic and local administration of sirolimus in porcine models of restenosis have been shown to significantly reduce neointimal hyperplasia.[11,12] Sirolimus-eluting stents have been first implanted in patients with coronary disease in the pioneer First-In-Man experience, which included 45 patients with relatively non-complex *de novo* lesions treated between December 1999 and February 2000.[13-18] Patients were treated in São Paulo, Brazil (n=30), and Rotterdam, The Netherlands (n=15) and received sirolimus-eluting stents in 2 formulations. Both formulations contained 140 µg of sirolimus per cm^2, but with different delivery kinetics (fast-release formulation [<15-day drug release], or slow release formulation [>28-day drug release]). Angiographic *in-stent* restenosis was not detected in any case up to 2 years and only one case had a 52% diameter stenosis proximal to the stent.[13,18] Two-year intravascular ultrasound examination showed only minimal neointimal proliferation, with 6.3±5.5% percent intimal hyperplasia within the stent in the fast release group (São Paulo), 7.5±7.3% in the slow-release group (São Paulo), and 4.4±3.1% in the slow-release group Rotterdam.[13,18] Moreover, the 2-year event-free survival was 90.1%, with no major events occurring between 2 and 3 years.[16]

Four randomized trials comparing the outcomes of patients treated with sirolimus-stents and conventional bare stents have been concluded to date, and are summarized in Tables 3 to 7.[19-23] 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 included 238 patients with single non-complex de novo lesions. At six months follow-up, the angiographic restenosis rate of the treated group was zero, the loss in minimal lumen diameter was zero. The clinical outcomes were significantly better among patients treated with sirolimus stents, with 94% of patients being free of any major cardiac events at 1 year (compared to 71% in the bare stent group; p<0.01).[20] Recently, data from the RAVEL trial with a more prolonged follow-up period have shown maintenance of the initial results, with a 2-year event-free survival of 90%.[19]

The subsequent SIRolImUS-Eluting Bx Velocity™ Balloon-Expandable Stent (SIRIUS) trial, which randomized 1101 patients with *de novo* lesions to sirolimus or bare stents, confirmed the clinical efficacy of sirolimus-eluting stents.[21] In-stent binary restenosis (within the margins of the stent) was reduced by 91% (3.2% vs. 35.4%; p<0.01) and in-segment restenosis (including the stented portion and the 5mm segments proximal and distal to the stent) was reduced by 75% (8.9% vs. 36.3%; p<0.01).[21] At 9 months, the incidence of major adverse events was significantly lower in the sirolimus group (7.1% vs. 18.9%; p<0.01), mainly due to a decrease in the need of target lesion revascularization (4.1% vs. 16.6%; p<0.01). Prolonged follow-up data (up to 2 years) were recently presented and showed sustained benefit of sirolimus-eluting stent implantation in the SIRIUS trial.[24] The recently published E-SIRIUS trial has enrolled 352 patients with longer lesions and smaller vessels than the RAVEL and SIRIUS trials.[23] Nevertheless, the 8-month in-stent restenosis rate was 3.9% in the sirolimus and 41.7% in the bare stent group (p<0.01). Similarly, the incidence of in-segment restenosis (5-mm edges included) was significantly reduced (5.9% vs. 42.3%; p<0.01). The 9-month incidence of major cardiac events was 8% vs. 22.6% in the sirolimus and bare groups (p<0.01). Similarly, in the C-SIRIUS trial, which randomized 100 patients to sirolimus or conventional stenting, in-segment restenosis was not detected in any patient after sirolimus-eluting stent implantation.[22] Differently from the previous trials, in the C-SIRIUS direct stenting was allowed (at the discretion of the operator), which did not affect the incidence of restenosis (i.e. zero restenosis rate in patients treated with pre-dilatation or direct stenting). Intravascular ultrasound examination at follow-up further confirmed the marked neointimal inhibition after sirolimus-eluting stent implantation. In the RAVEL trial, the percent neointimal obstruction at 8 months was 1 ± 3% in the sirolimus group versus 29 ± 20% in the bare group (p<0.001).[25] Also, in the SIRIUS study, sirolimus-eluting stents were associated with a significant reduction of in-stent percent obstruction (3.1 % vs. 33.4%; p<0.001).[21]

Subgroup analysis of patients included in the RAVEL and SIRIUS have shown that the overall benefit of sirolimus-eluting stents was also observed across many subsets of patients and lesion types.[21,26] However, in the SIRIUS trial, post-sirolimus restenosis was significantly increased in diabetics, long lesions, and small vessels. Indeed, post-sirolimus restenosis has been shown to frequently occur in association with higher complexity characteristics.[27] The impact of sirolimus-eluting stents for the treatment of more complex lesions has been addressed in recently released studies evaluating some patient subgroups not enrolled in the early randomized trials (Table 8).

The Rapamycin Eluting Stent Evaluated At Rotterdam Cardiology Hospital study (RESEARCH) was a single-center registry which included patients treated with SES according to a non-restrictive inclusion criterion. Virtually all consecutive patient subsets were considered eligible. Long-term (12-month) outcomes of the first 508 patients with *de novo* lesions treated exclusively with SES were compared with 450 patients treated with bare stents in the period just prior to the introduction of drug-eluting stents.[28] Only 2 (0.4%) presented with thrombotic stent occlusion in the first month after the procedure, while the stent thrombosis rate in the bare stent group was 1.6% (p=0.1). There were no further thrombotic events up to one year. Sirolimus-eluting stents reduced by 38% the 1-year risk of major cardiac events (9.7% vs. 14.8%; p<0.01), mainly due to a risk reduction of 65% in clinically driven repeat intervention (3.7% vs. 10.9%; p<0.01). Importantly, approximately 68% of patients included in the registry would have been excluded from the earlier clinical trials (e.g. patients with previous coronary surgery, patients admitted with acute myocardial infarction, and those with multivessel stenting, among other characteristics).

Paclitaxel

Paclitaxel was originally isolated from the bark of the Pacific Yew. It is an antineoplastic agent that is currently used to treat several types of cancer, most commonly breast and ovarian cancer. Paclitaxel exerts its pharmacological effects through formation of numerous decentralized and unorganized microtubules. This

enhances the assembly of extraordinarily stable microtubules, interrupting proliferation, migration and signal transduction.[29,30] Unlike other anti-proliferative agents of the colchicine type, which inhibit microtubuli assembly, paclitaxel shifts the microtubule equilibrium towards microtubule assembly. It is highly lipophylic, which promotes a rapid cellular uptake, and has a long-lasting effect in the cell due to the structural alteration of the cytoskeleton.

Stent-based paclitaxel has been investigated by several groups, using different stent types and preparations (copolymer coatings for paclitaxel elution [31-35] or direct dip-coating of paclitaxel on a stainless steel stent).[36-39] Clinical studies utilizing direct dip-coating of paclitaxel stents are summarized in Tables 9 and 10. Contradictory clinical results have been obtained with these devices. While the European Evaluation of Paclitaxel Eluting Stent trial (ELUTES) [36] and the ASian Paclitaxel-Eluting stent Clinical Trial (ASPECT) [37] have shown a significant, dose-dependent reduction in restenosis with paclitaxel stents, the larger RX Achieve™ Drug-Eluting Coronary Stent System In the Treatment of Patients With De NoVo NativE CoronaRy Lesions (DELIVER-I) study failed in demonstrating the beneficial effect of these devices.

Clinical studies utilizing polymer-coated paclitaxel-eluting stents are summarized in Tables 3 to 7.[31-35] In total, more than 1,900 patients with de novo lesions have been enrolled in the TAXUS I,[32] II,[31] and IV trials [34,35] and randomized to paclitaxel or bare stents. A marked reduction in neointimal proliferation and binary restenosis was observed in the active groups, leading to 12-month target lesion revascularization rates that ranged from 0 to 6.8% with paclitaxel stents, which was significantly lower than in controls (TLR rates from 10.0 to 16.7%).[31,32,34,35] Multivariate analysis from patients included in the TAXUS IV trial [34,35] have identified several multivariate predictors of 9-month target lesion revascularization. Apart from utilization of bare stents (OR 4.58 [95% CI: 2.64, 7.95]; p<0.0001), other independent predictors were: diabetes (1.78 [95% CI: 1.10, 2.88]; p=0.02), increase in stent length (1.04 [95% CI: 1.01, 1.07]; p=0.006), decrease in acute gain (2.08 [95% CI: 1.11, 3.88]; p=0.02), and lesion angulation (0.98 [95% CI: 0.97, 0.99]; p<0.03). Polymer-coated paclitaxel-eluting stents were shown to be safe, with rates of subacute stent thrombosis similar to those seen in the bare stents (Table 7).

The WISDOM registry is a post-marketing registry conducted with the objective of evaluating unselected patients treated with paclitaxel stents in the "real world". Preliminary results of this multinational registry on approximately 1,000 patients have been presented in the AHA annual meeting in November 2003 and confirmed the 30-day safety of paclitaxel-eluting stents in more complex patients, with only 0.4% of patients presenting stent thrombosis.

Other Drugs

To date, sirolimus- and paclitaxel-eluting stents have the most extensive accumulated clinical experience and are the only drug-eluting stents commercially available for clinical use. However, a myriad of new devices have been recently tested and are currently in various stages of development for clinical use. New drug-eluting stents that have been already evaluated in preliminary clinical studies are summarized in Table 11. Several analogues of sirolimus have been investigated.

Limitations

A late "catch up" phenomenon has been described after implantation of a high dose (800 µg) paclitaxel derivative QP2-eluting stent, with the restenosis rate increasing from 13% at 6 months to 62% at 12 months.[40,41] However, long-term efficacy should be evaluated separately for each drug-eluting stent assembly, since a "class-effect" is unlikely for these devices and each platform/vehicle/agent complex should be evaluated separately. To date, the sirolimus-eluting stent has the largest body of long-term data available. The First In Man study has shown persistent positive results up to 2 and 3 years, without any evidence of late catch-up restenosis[16,18]. In the RAVEL[19] and SIRIUS[24] trials, no further events due to restenosis were observed up to 2 years. With paclitaxel, no rebound effect was seen from 6 to 12 months in TAXUS-I,[32] TAXUS II,[31] TAXUS IV,[34,35] ELUTES,[36] and ASPECT[37] trials.

In the RAVEL trial, stent malapposition (as observed by intravascular ultrasound) was more frequent at 6 months in sirolimus-eluting stent patients than in the control arm [25]. Moreover, in SIRIUS [42] late acquired stent malapposition was more commonly observed in the sirolimus group. However, in TAXUS-II [31] patients treated with bare stents or paclitaxel-eluting stents there were similar rates of late-acquired malapposition. Nevertheless, these observations of late malapposition by ultrasound have not been associated with any adverse events throughout the follow-up period in any of these studies.[25,31,42-44]. Also, late thrombotic stent occlusion was not seen to be more frequent in patients treated with sirolimus- or paclitaxel eluting stents, even after clopidogrel discontinuation.

The costs of currently marketed drug-eluting stents (i.e. sirolimus- and paclitaxel-eluting stents) have been perceived as a major limitation for a more widespread use of these devices. In an analysis from the RAVEL trial, the utilization of the sirolimus-eluting stent resulted in a mean additional procedural cost of €1,286, as compared to the control group based on costs in the Netherlands.[45] However, due to the decrease in re-interventions attributable to the sirolimus-eluting stent at the end of the first year of follow-up the estimated cost difference had decreased to 54 €. In other words, in the RAVEL trial the reduction of major event risk from 28.8% to 5.8% after sirolimus-eluting was accomplished at an extra cost of €54 per patient. Moreover, data from the the SIRIUS trial have shown that at 1 year the costs of sirolimus-eluting stent implantation were approximately US$ 300 higher per patient. In the SIRIUS, investigators have reported a ratio of approximately US$1700 per repeat revascularization avoided, which has been considered to compare favorably with other medical treatments for patients with cardiovascular disease.[46] Obviously, the cost and effect estimations derived from the RAVEL and SIRIUS trials cannot be directly extrapolated to other situations and formal analyses from other clinical scenarios are warranted.

Future Directions

As restenosis rates are still not "zero" in the real world of interventional cardiology, the search for and testing of new drugs will continue. Next to newer drugs and optimalization of the drug carrier, other methods are currently being investigated to locally treat the injured vessel wall. For example, stent-based delivery of adenoviral gene vectors was recently achieved *in vitro* and in carotid arteries of rats. Though stent-based local gene delivery has not entered the clinical arena yet, it will be possible very soon and give a lot of new opportunities to attack coronary artery disease and the problems of restenosis.

Another possibility to contain the detrimental effects of vessel wall injury after percutaneous interventions is to restore the integrity of the endothelial cell lining as soon as possible. This way, the attraction of inflammatory cytokines as well as activated platelets and macrophages can be limited.

The most logical way to accomplish this is endothelial cell seeding of the stent. The problems of sterilization, mechanical stretch during implantation and endothelial cell viability have been the major limitations in this approach. Recently, a method has been developed to coat a stent with antibodies to CD-34 receptors on progenitor endothelial cells. In this way circulating endothelial cells can be captured from the circulation and provide an early re-endotheliazation on the stent surface. After promising animal data showing a confluent layer of endothelial cells very early after stenting, clinical pilot trials are on-going.

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Table 3. Randomized trials comparing bare metal stents with polymer-coated sirolimus- or paclitaxel-eluting stents – Study characteristics

	Study groups	design	inclusion criteria	exclusion criteria	Antiplatelet
SIROLIMUS					
RAVEL [19,20,26]	– Polymer-coated sirolimus-eluting stent (n=120 pts) – Bare stent (n=118 pts)	randomized double-blind	– single *de novo* lesion – native vessel – lesion length < 18 mm – vessel diameter 3 - 3.5mm	– total occlusion, ostial – thrombus containing lesion – unprotected LMC with >50% stenosis – evolving myocardial infarction – left ventricular ejection fraction <30%	Aspirin lifelong Clopidogrel for 2 months
SIRIUS [21]	– Polymer-coated sirolimus-eluting stent (n=533 pts) – Bare stent (n=525 pts)	randomized double-blind	– single *de novo* lesion – native vessel – lesion length 15 - 30 mm – vessel diameter 2.5 - 3.5mm	– total occlusion, ostial, bifurcation – thrombus containing lesion – unprotected LMC with >50% stenosis – myocardial infarction < 48 hours – left ventricular ejection fraction <25% – multivessel stenting	Aspirin lifelong Clopidogrel for 3 months
E-SIRIUS [23]	– Polymer-coated sirolimus-eluting stent (n=175 pts) – Bare stent (n=177)	randomized double-blind	– single d*e novo* lesion – native vessel – lesion length 15 - 32 mm – vessel diameter 2.5 - 3.0mm	– total occlusion, ostial, bifurcation – thrombus containing lesion – unprotected LMC with >50% stenosis – evolving myocardial – left ventricular ejection fraction <25%infarction – multivessel stenting	Aspirin lifelong Clopidogrel for 2 months
C-SIRIUS [22]	– Polymer-coated sirolimus-eluting stent (n=50 pts) – Bare stent (n=50 pts)	randomized double-blind	– Single *de novo* lesion – Stable or unstable angina or documented silent ischemia – Lesion length 15 - 32 mm – Vessel diameter 2.5 - 3.0 mm	– total occlusion, ostial – Recent MI (< 24 hours) – Unprotected LM disease – Angiographic evidence of thrombus – LV ejection fraction < 25%	Aspirin lifelong Clopidogrel for 2 months
PACLITAXEL (polymer-coated)					
TAXUS I [32]	– Polymer-coated slow-release paclitaxel-eluting stent (n=31 pts) – Bare stent (n=30 pts)	randomized double-blind	– Single lesion, single stent – Restenotic or *de novo* lesions – lesion length ≤ 12 mm – vessel diameter 3.0 - 3.5mm	– total occlusion – acute myocardial infarction – left ventricular ejection fraction <30% – stroke < 6 months	Aspirin for at least 12 months Clopidogrel for 6 months
TAXUS II [31]	– Polymer-coated slow-release paclitaxel-eluting stent (n=131 pts) – Bare stent control for SR-paclitaxel (n=136 pts) – Polymer-coated moderate-release paclitaxel-eluting stent (n=135 pts) – Bare stent control for MR-paclitaxel (n=137 pts)	randomized double-blind	– Single lesion, single stent – Native vessel – *De novo* lesions – lesion length ≤ 12 mm – vessel diameter 3.0 - 3.5mm	– total occlusion – evolving myocardial infarction – unprotected LMC with >50% stenosis – left ventricular ejection fraction <30% – coronary intervention < 30days	Aspirin lifelong Clopidogrel for at least 6 months
TAXUS III [33]	– Polymer-coated slow-release paclitaxel-eluting stent (n=28 pts)	series of cases	– Single lesion, single stent – Native vessel – In-stent restenosis lesions – lesion length ≤ 30 mm	– total occlusion – evolving myocardial infarction – left ventricular ejection fraction <30% – stroke < 6 months	Aspirin lifelong Clopidogrel for 6 months
TAXUS IV [34,35]	– Polymer-coated moderate-release paclitaxel-eluting stent (n=662 pts) – Bare stent control for MR-paclitaxel (n=652 pts)	randomized double-blind	– Single de novo lesions – Length 10 - 28 mm – vessel diameter 2.5 -3.75mm	– total occlusion, ostial, bifurcation – Prior intervention in the target vessel < 9 months – myocardial infarction < 72 hours	Aspirin lifelong Clopidogrel for 6 months

Table 4. Randomized trials comparing bare metal stents with polymer-coated sirolimus- or paclitaxel-eluting stents – Patient characteristics

	diabetics (%)	AMI admission (%)	Multivessel disease (%)	LAD (%)	LM (%)
SIROLIMUS					
RAVEL [19,20,26]					
Sirolimus	16	0	NA	49	0
Bare stent	21	0	NA	51	0
SIRIUS [21]					
Sirolimus	25	0	42	44	0
Bare stent	28	0	41	43	0
E-SIRIUS [23]					
Sirolimus	19	0	NA	57	0
Bare stent	27	0	NA	56	0
C-SIRIUS [22]					
Sirolimus	24	0	NA	36	0
Bare stent	24	0	NA	40	0
PACLITAXEL (polymer-coated)					
TAXUS I [32]					
Paclitaxel	23	0	NA	55	0
Bare stent	13	0	NA	27	0
TAXUS II [31]					
Paclitaxel-SR	11	0	NA	40	0
Bare stent-SR	16	0	NA	44	0
Paclitaxel-MR	17	0	NA	42	0
Bare stent-MR	14	0	NA	52	0
TAXUS III [33]	14	0	25	36	4
TAXUS IV [34,35]					
Paclitaxel	23	0	NA	40	0
Bare stent	25	0	NA	41	0

Table 5. Randomized trials comparing bare metal stents with polymer-coated sirolimus- or paclitaxel-eluting stents – Procedural characteristics

	IIbIIIa (%)	ACC/AHA Lesion type C (%)	ISR Mehran Class III or IV [4] (%)	Chronic total occlusion (%)	stents/pt	bifurcation stenting (%)
SIROLIMUS						
RAVEL [19,20,26]						
Sirolimus	10.1	0	-	0	1.0 ± 0.3	0
Bare stent	9.5	0	-	0	1.1 ± 0.3	0
SIRIUS [21]						
Sirolimus	60	26	-	0	1.4 ± 0.7	0
Bare stent	59	21	-	0	1.4 ± 0.6	0
E-SIRIUS [23]						
Sirolimus	14	NA	-	0	*	0
Bare stent	18	NA	-	0	*	0
C-SIRIUS [22]						0
Sirolimus	58	30	-	0	1.38 ± 0.57†	0
Bare stent	48	16	-	0	1.66 ± 0.94	
PACLITAXEL (polymer-coated)						
TAXUS I [32]						
Paclitaxel	NA	0	NA	0	NA	0
Bare stent	NA	0	NA	0	NA	0
TAXUS II [31]						
Paclitaxel-SR	12	NA	0	0	‡	0
Bare stent-SR	13	NA	0	0	‡	0
Paclitaxel-MR	21	NA	0	0	‡	0
Bare stent-MR	24	NA	0	0	‡	0
TAXUS III [33]	NA	-	18	4	1.5±0.5	0
TAXUS IV [34,35]						
Paclitaxel	58	20	-	0	1.08 ±0.29	0
Bare stent	57	22	-	0	1.09 ±0.36	0

ISR=in-stent restenosis; MR=moderate release; NA=not available; SR=slow-release
* overlapping stents in 34% (sirolimus) vs. 31% (bare stent)
† $p<0.05$ vs. control
‡ One study stent was implanted in 93% of pacltaxel-SR patients and in 94% of the remaining groups

Table 6. Randomized trials comparing bare metal stents with polymer-coated sirolimus- or paclitaxel-eluting stents – Quantitative Angiography Analysis

	pre-procedure		post-procedure		Follow-up				
	RD (mm ± SD)	length (mm ± SD)	DS (% ± SD)	MLD (mm ± SD)	time (months)	DS (% ± SD)	MLD (mm ± SD)	Restenosis (%)	Late loss (mm ± SD)
SIROLIMUS									
RAVEL [19,20,26]*									
Sirolimus	2.60±0.54	9.56±3.33	11.9±5.9 ‡	2.43±0.41	6	14.7±7.0 ‡	2.42±0.49 ‡	0 ‡	-0.01±0.33 ‡
Bare stent	2.64±0.52	9.61±3.18	14.0±6.8	2.41±0.40	6	36.7±18.1	1.64±0.59	26.6	0.80±0.53
SIRIUS [21] †									
Sirolimus	2.79±0.45	14.4±0.58	16.1±9.7	2.38±0.45	8	23.6±16.4 ‡	2.15±0.61 ‡	8.9 ‡	0.24±0.47 ‡
Bare stent	2.81±0.49	14.4±0.58	16.2±8.5	2.4±0.46	8	43.2±22.4	1.60±0.72	36.3	0.81±0.67
E-SIRIUS [23] †									
Sirolimus	2.60±0.37‡	14.9±5.4	18.2±9.6	2.17±0.39	8	24.7±14.7 ‡	1.97±0.48 ‡	5.9 ‡	0.19±0.39 ‡
Bare stent	2.51±0.37	15.1±6.5	18.0±9.1	2.10±0.39	8	48.3±23.4	1.29±0.61	42.3	0.80±0.57
C-SIRIUS [22] *									
Sirolimus	2.65±0.30	14.5±6.3	6.1±9.1	2.53±0.30	8	20.5±10.3	2.15±0.35‡	2.3‡	0.09±0.31‡
Bare stent	2.62±0.35	12.6±5.2	5.6±10.6	2.50±0.28	8	47.8±24.5	1.39±0.69	52.3	0.79±0.74
PACLITAXEL (polymer-coated)									
TAXUS I [32] *									
Paclitaxel	2.99±0.46	10.70±3.27	6.12±9.49	2.95±0.34	6	13.56±11.77‡	2.60±0.49‡	0	0.36±0.48‡
Bare stent	2.94±0.52	11.89±4.93	9.84±7.06	2.87±0.43	6	27.23±16.69	2.19±0.65	10	0.71±0.47
TAXUS II [31] †									
Paclitaxel-SR	2.78±0.44	10.6±3.9	23.1±9.3	2.15±0.37	6	26.8±12.8‡	2.01±0.46‡	5.5‡	0.31±0.38‡
Bare stent-SR	2.77±0.49	10.5±4.1	21.2±8.4	2.23±0.43	6	35.1±15.1	1.70±0.49	20.1	0.79±0.45
Paclitaxel-MR	2.72±0.46	10.2±4.8	21.5±8.0	2.20±0.39	6	26.8±13.1‡	2.00±0.48‡	8.6‡	0.30±0.39‡
Bare stent-MR	2.73±0.45	10.7±4.1	22.0±9.0	2.20±0.40	6	37.1±17.8	1.66±0.56	23.8	0.77±0.50
TAXUS III [33] *§	2.84±1.25	13.61±6.36	16.9±7.6	2.41±0.46	6	26.9±18.6†	1.93±0.61	4.5	0.47±0.48
TAXUS IV [34,35] †									
Paclitaxel	2.76±0.48	14.4±6.7	19.1±9.5	2.26±0.48	9	26.3±15.5‡	2.03±0.55‡	7.9‡	0.23±0.44‡
Bare stent	2.79±0.48	14.4±7.1	19.1±9.9	2.29±0.49	9	39.8±18.5	1.68±0.61	26.6	0.61±0.57

* *In-stent* quantitative coronary angiography
† *In-segment* quantitative coronary angiography (includes the 5-mm proximal and distal edges)
‡ $p<0.05$ vs. control
§ excludes patients with restenosis in a bare stent or in a gap between the paclitaxel-eluting stents

Table 7. Randomized trials comparing bare metal stents with polymer-coated sirolimus- or paclitaxel-eluting stents – Clinical Outcomes

Study	Follow-up (months)	Death (%)	Myocardial infarction (%)	Target vessel revascularization (%)	Any event (%)	Stent thrombosis (%)
SIROLIMUS						
RAVEL [19,20,26]	12					
Sirolimus		1.7	3.3	0*	5.8*	0
Bare stent		1.7	4.2	22.9	28.8	0
SIRIUS [21]	9					
Sirolimus		0.9	2.8	3.8*	7.1*	0.4
Bare stent		0.6	3.2	15.8	18.9	0.8
E-SIRIUS [23]	9					
Sirolimus		1.1	4.6	4.0*	8.0*	1.1
Bare stent		0.6	2.3	20.9	22.6	0
C-SIRIUS [22]	9					
Sirolimus		0	2	4	4	0
Bare stent		0	4	18	18	2
PACLITAXEL (polymer-coated)						
TAXUS I [32]	24					
Paclitaxel		0	0	3	3	0
Bare stent		0	0	10	10	0
TAXUS II [31]	12					
Paclitaxel-SR		0	2.3	10.1*	10.9*	0.7 †
Bare stent-SR		1.5	5.1	15.9	22.0	0
Paclitaxel-MR		0	3.7	6.9*	9.9*	0 †
Bare stent-MR		0	5.2	19.1	21.4	0
TAXUS III [33]	12	0	3.6	21.4	29.0	0
TAXUS IV [34,35]	12					
Paclitaxel		1.4	3.5	6.8*	10.6*	0.6
Bare stent		1.2	4.6	16.7	19.8	0.8

* $p<0.05$ vs. control

† rates of angiographically documented stent thrombosis

Table 8. Sirolimus-eluting stents for complex subsets

	Design	Restenosis (%)		late loss (mm)	TVR (%)	
SIRIUS bifurcation [52] *§	Randomized: MV stenting + SB stenting (n=43 pts) vs. MV stenting + SB balloon (n=43 pts)	SES + SES (MV): SES+SES (SB): SES+balloon (MV): SES+balloon (SB):	6.0 24.0 6.2 18.7	0.27±0.47 0.52±0.60 0.14±0.24 0.27±0.38	SES+SES: SES+balloon:	11.1 4.5
Degertekin [53] † ||	Series of cases with ISR (n=16 pts)	13.3		0.26±0.67	6.3	
Sousa [54] ‡ ¶	Series of cases with ISR (n=25 pts)	4.0		0.16±0.42	0	
Saia [55] * ||	Series of cases with post-brachytherapy ISR (n=12 pts)	40		0.68±1.20	33.3	
RESEARCH AMI [56] *§	Series of cases with ST elevation AMI (n=96 pts)	0		-0.04±0.25	0	
RESEARCH *de novo* [28] ¶	Consecutive cases treated in 2 phases: bare stents (n=450 pts) vs. SES (n=508 pts)	-		-	Bare stent: SES:	10.9 3.7

ISR=in-stent restenosis; MI=myocardial infarction; MV=main vessel; SB=side branch; SES=sirolimus-eluting stent; TVR=target vessel revascularization
* angiographic follow-up at 6 months
† angiographic follow-up at 4 months
‡ angiographic follow-up at 12 months
§ clinical follow-up at 6 months
|| clinical follow-up at 9 months
¶ clinical follow-up at 12 months

Table 9. Clinical Studies with Dip-Coated Paclitaxel-eluting Stents – Study Design

	Study groups	design	inclusion criteria
ELUTES [36]	2.7 µg/mm^2 paclitaxel (n=37 pts) 1.4 µg/mm^2 paclitaxel (n=39 pts) 0.7 µg/mm^2 paclitaxel (n=39 pts) 0.2 µg/mm^2 paclitaxel (n=37 pts) Bare stent (n=38 pts)	randomized	*de novo* lesion native vessel single lesion
ASPECT [37]	3.1 µg/mm^2 paclitaxel (n=60 pts) 1.3 µg/mm^2 paclitaxel (n=58 pts) Bare stent (n=59 pts)	randomized	Single lesion lesion length <15 mm vessel diameter 2.5 - 3.5mm
DELIVER I [38]	3.0 µg/mm^2 paclitaxel (n=522 pts) Bare stent (n=519 pts)	randomized	Up to 2 native vessels treated (1 target and 1 non-target, with only 1 de novo lesion per vessel) lesion length <25 mm vessel diameter 2.5 – 4.0 mm
DELIVER II [39]	3.0 µg/mm^2 paclitaxel (n=1531 pts)	series of cases	One of the following: - 1 target lesion: length < 25 mm, chronic total or subtotal occlusion, restenotic, or in a bifurcation site - 1 target lesion: length > 25 mm, de novo, chronic total or subtotal occlusion, restenotic, or involving a bifurcation - 2 target lesions: length < 25 mm, de novo, chronic total or subtotal occlusion, restenotic, or in a bifurcation

CTO=chronic total occlusion; NA=not available; pts=patients

Table 10. Clinical Studies with Dip-Coated Paclitaxel-eluting Stents – Angiographic and Clinical Outcomes

	Restenosis (%)	Late loss (mm ± SD)	Clinical follow-up (months)	Death (%)	Myocardial infarction (%)	Target vessel revascularization (%)	Any event (%)	Stent thrombosis (%)
ASPECT [37] * †			6					
3.1 μg/mm^2 paclitaxel	4‡	0.29±0.72‡		0	3.4	1.7	10	5.1
1.3 μg/mm^2 paclitaxel	12‡	0.57±0.71‡		1.7	1.7	1.7	7	1.7
Bare stent	27	1.04±0.83		0	1.7	1.7	5	0
ELUTES [36] §			12					
2.7 μg/mm^2 paclitaxel	3.1	0.10±0.12 ‡		2.7	2.7	5.4	14	2.7
1.4 μg/mm^2 paclitaxel	13.5	0.47±0.11		0	0	10.3	10	0
0.7 μg/mm^2 paclitaxel	11.8	0.47±0.12		0	0	7.7	10	0
0.2 μg/mm^2 paclitaxel	20.0	0.72±0.12		0	0	5.4	5	0
Bare stent	20.6	0.73±0.12		0	0	15.8	18	2.6
DELIVER I [38] * ||			12					
3.0 μg/mm2 paclitaxel	16.7	0.43‡		0.2	1.4	6.2	7.5	0.4
Bare stent	22.4	0.56		0.8	1.0	6.8	9.4	0.4
DELIVER II [39]	-	-	6	2.3	4.9	9.6	15.7	-

* *In-segment* quantitative coronary angiography (includes the 5-mm proximal and distal edges)
† all stent thrombosis events occurred in patients on aspirin and cilostazol (instead of aspirin and ticlopidin/clopidogrel)
‡ p<0.05 vs. control
§ *In-stent* quantitative coronary angiography
|| available for 228 pts in the paclitaxel group and fro 214 controls

Table 11. Clinical studies with new drug-eluting stents

	design	inclusion criteria	Study groups	Restenosis (%)	Late loss (mm)
EVELOLIMUS					
FUTURE I trial [57]	randomized (2:1)	Single *de novo*	Bioabsorbable polymer-coated everolimus-eluting stent (n=27 pts)	0	0.11*
	single-blind	Length <18 mm, diameter 2.75 –4.0mm	Bare stent control for MR-paclitaxel (n=15 pts)	9.1	0.85
FUTURE II trial [57]	randomized (1:2)	Single *de novo*	Bioabsorbable polymer-coated everolimus-eluting stent (n=21 pts)	0	0.12*
	single-blind	Length <18 mm, diameter 2.75 –4.0mm	Bare stent control for MR-paclitaxel (n=43 pts)	19.4	0.85
17β-ESTRADIOL					
EASTER trial	series of cases	Single *de novo*, diameter 3.0 - 4.0 mm	Phosphorylcholine-coated estrogen-eluting stent (2.54 μg/ mm2) (n=30 pts)	6.6	0.31
DEXAMETHASONE					
STRIDE trial	series of cases	Single *de novo,* diameter 2.75 - 4.0 mm	BiodivYsioMatrix LO stent immersed in dexamethasone solution (15mg/ml) (n=71 pts)	13.3	0.45
ABT-578					
ENDEAVOR trial	series of cases	Single *de novo*, diameter 3.0 - 3.5 mm	Phosphorylcholine-coated Driver cobalt alloy stent (n=100 pts)	NA	0.20
Nitic Oxide drug-elution					
NOBLESSE trial	series of cases	Single *de novo*, diameter 2.75 - 3.5 mm	Bioabsorbable polyesteramide-coated Genic stent with oxigen free scavenger covalently bounded (n=45 pts)	9.5	0.69

*p<0.05 compared to controls

Chapter 3 Unrestricted Utilization of Sirolimus-Eluting Stents Compared to Conventional Bare Stent Implantation in the "Real World". The Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry

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Unrestricted Utilization of Sirolimus-Eluting Stents Compared to Conventional Bare Stent Implantation in the "Real World". The Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry

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Background: The effectiveness of sirolimus-eluting stents in unselected patients treated in the daily practice is currently unknown.
Methods and Results: Sirolimus-eluting stent implantation has been utilized as the default strategy for all percutaneous procedures in our hospital, as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. Consecutive patients with *de novo* lesions (n=508) treated exclusively with sirolimus-eluting stents (SES group) were compared to 450 patients who received bare stents in the period just before (pre-SES group). Patients in the SES had more frequently multivessel disease, more type C lesions, received more stents, and had more bifurcation stenting. At 1 year, the cumulative rate of major adverse cardiac events (death, myocardial infarction, or target vessel revascularization) was 9.7% in the SES group and 14.8% in the pre-SES group (HR 0.62 [95% CI 0.44–0.89]; p=0.008). The 1-year risk of clinically driven target vessel revascularization in the SES group and in the pre-SES group was 3.7% vs. 10.9% respectively (HR 0.35 [95% CI 0.21–0.57]; p<0.001).
Conclusions: Unrestricted utilization of sirolimus-eluting stents in the "real world" is safe and effective in reducing both repeat revascularization and major adverse cardiac events at one year compared to bare stent implantation.

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Introduction

In-stent restenosis has long been recognized as the main limitation of coronary stenting, with rates of as high as 50% in more complex subsets. Recently, sirolimus-eluting stent (SES) implantation has been proven to markedly reduce the incidence of angiographic restenosis and repeat revascularization in selected patients.[1-3] In the First-In-Man study, no cases of restenosis were detected in a series of 45 patients, with persistent neointimal inhibition demonstrated up to two years.[4] These findings have been further confirmed in randomized trials comparing SES with conventional bare stents.[2,3] In 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),[2] there were no cases of binary angiographic restenosis in patients treated with SES implantation. Similarly, in the SIRolImUS-eluting Bx velocity balloon expandable stent trial (SIRIUS),[3] restenosis occurred in 9% of cases in the SES group compared to 36% of patients treated with conventional stents (p<0.001).

Based on these findings, since the first half of 2002, SES have progressively received clinical approval by official regulatory agencies and are currently available for routine use in Europe, Asia, South America, and more recently the U.S. However, all clinical trials completed so far have included elective patients with relatively non-complex lesions. The effects of SES implantation in complex, unselected patients, such as those treated in daily practice, remains largely unknown. Notably, the occurrence of restenosis in a small, but relevant proportion of patients in the SIRIUS trial occurred mainly in patients with diabetes, small vessels, and long lesions,[3] characteristics frequently found in most series. Moreover, restenosis after SES implantation has been recently shown to occur in association with procedures with increased complexity.[5] The present study was therefore conducted to investigate the impact of sirolimus-eluting stents on the outcomes of patients treated in the "real world" of interventional cardiology, as compared to a strategy utilizing conventional bare stent implantation.

Methods

Study Design and Patient Population

The study protocol of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) has been described elsewhere.[6] Briefly, the RESEARCH is a single-center registry conducted with the main purpose of evaluating the safety and efficacy of sirolimus-eluting stent implantation for patients treated in daily practice. To include a patient population representative of the "real world", we have adopted since 16th April 2002 a policy of utilizing sirolimus-eluting stents (Cypher; Johnson & Johnson-Cordis unit, Cordis Europa NV, Roden, the Netherlands) as the default strategy for every percutaneous coronary intervention.

In the first 6 months enrollment, a total of 508 patients with de novo lesions were treated exclusively with SES and were included in the present report (SES

group) (72% of the 710 patients treated with stents in during the period). Patients treated with bare stents and SES in the same procedure (66 patients) and those treated only with bare stents (136 patients) were not included in the present report. At the initiation of the RESEARCH registry, SES were available in lengths of 8, 18, and 33 mm and diameters from 2.25 to 3.00 mm, but post-dilatation with larger balloons was allowed (0.5-mm larger balloons were utilized in 55% of cases where a 3.0-mm SES was used). However, unavailability of an appropriate SES size was still the reason for non-utilization of SES in 77% of cases. Moreover, 5% of cases were included in other study and were not enrolled in the RESEARCH. In the remaining patients not included, SES were not utilized because of for a variety of reasons, predominantly operator's personal choice.

Patients treated solely with SES were compared to a group of consecutive patients treated with bare stents for de novo lesions in the preceding 6 months (pre-SES group). In order to better match the vessel sizes treated in the 2 study groups, patients receiving bare metal stents larger than 3.5-mm were excluded from this analysis (n=176). This cutoff value (instead of 3.0-mm diameter stents) was chosen due to the post-dilatation policy applied in the SES group, which extended the utilization of SES to patients with 3.5-mm vessels by visual estimation. In addition, patients treated with bare stents smaller than 2.25 mm were not included (n=30). In total, 450 consecutive patients thereby comprise the pre-SES group (69% of all patients with de novo lesions treated with stents during the period). The present study population was consequently composed of a total of 958 patients divided into two sequential cohorts, primarily distinguished by the interventional strategy applied (bare stent 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.

Procedures and Post-Intervention Medications

All interventions were performed according to current standard guidelines[7] and the final interventional strategy was entirely left to the discretion of the operator. Angiographic success was defined as residual stenosis < 30% by visual analysis in the presence of TIMI 3 grade flow. Periprocedural glycoprotein IIbIIIa inhibitors and antithrombotic medications were used according to the operator's decision. All patients were advised to maintain lifelong aspirin. One-month clopidogrel treatment (75mg/d) was recommended for patients treated in the pre-SES phase. For patients treated with SES, clopidogrel was prescribed for 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.

Endpoint Definitions and Clinical Follow-up

The primary outcome was the occurrence of major adverse cardiac events, defined as 1) death, 2) non-fatal myocardial infarction, or 3) target vessel revascularization. Myocardial infarction was diagnosed by a rise in the creatine kinase level to more than twice the upper normal limit with an increased creatine kinase-MB. 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 angiographically documented as a complete occlusion (TIMI flow 0 or 1) or a flow limiting thrombus (TIMI flow 1 or 2) of a previously successfully treated artery.

Information about the in-hospital outcomes was obtained from an electronic clinical database for patients maintained in our institution and by review of the hospital records for those discharged to referring hospitals (patients were referred from a total of 14 local hospitals). Post-discharge survival status was obtained from the Municipal Civil Registries. All repeat interventions (surgical and percutaneous) and re-hospitalizations were prospectively collected during the follow-up. Questionnaires with information about anginal status and medication usage were sent to all living patients. The referring physicians and institutions were contacted whenever necessary for additional information.

During follow-up, coronary angiography was obtained as clinically indicated by symptoms or documentation of myocardial ischemia. Additionally, late angiographic evaluation was eventually obtained from "complex" patients in the SES group, typically with SES implanted in bifurcations, left main coronary, chronic total occlusions, very small vessels, long stented length (>36mm), and acute myocardial infarction (in total, 38% patients in the SES group had angiographic follow-up between 6 and 9 months). No angiographic re-study was performed in the pre-SES group. Due to the well-known effect of angiographic re-evaluation in increasing the incidence of repeat revascularization,[8] all re-interventions 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 analyzed. 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 non-invasive testing.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation (SD) and were compared using Student's unpaired t-test. Categorical variables were presented as counts and percentages and compared with the Fisher's exact test. All statistical tests were 2-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 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, years±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 MI, %	40	30	<0.01
Previous angioplaty, %	18	19	0.8
Previous 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 MI

Results

Baseline and Procedural Characteristics

Baseline and procedural characteristics are shown in Table 1 and Table 2. Overall, 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 frequenly used. Periprocedural administration of glycoprotein IIbIIIa inhibitors was more frequent in the pre-SES phase (33% vs. 19%; p<0.01). The angiographic success rate was similar in both groups.

Clinical Outcomes

Complete follow-up information was available for 99.1% of patients (mean follow-up period 405 days). There were no significant differences between the SES group and the pre-SES group in the incidence of major adverse cardiac events during the first month (3.0% vs. 4.2% respectively; p=0.3) (Table 3). Target vessel revascularization at 30 days was 1.0% (n=5) in the SES group and 2.2% (n=10) in the pre-SES group (p=0.2), which included emergency bypass surgery in 2 patients (0.4%) in the SES group and in 2 cases (0.4%) in the pre-SES group (p=1.0) and early "redo" target vessel revascularization (e.g. residual dissection or compromised side branch in patients with continuing symptoms) in 1 patient (0.2%) in the SES group and in 1 patient (0.2%) in the pre-SES group (p=1.0). In the remaining cases, 30-day repeat intervention was due to angiographically documented stent thrombosis in 2 patients (0.4%) in the SES group and in 7 patients (1.6%) in the pre-SES group (p=0.1). No further thrombotic stent occlusion was observed in the late follow-up.

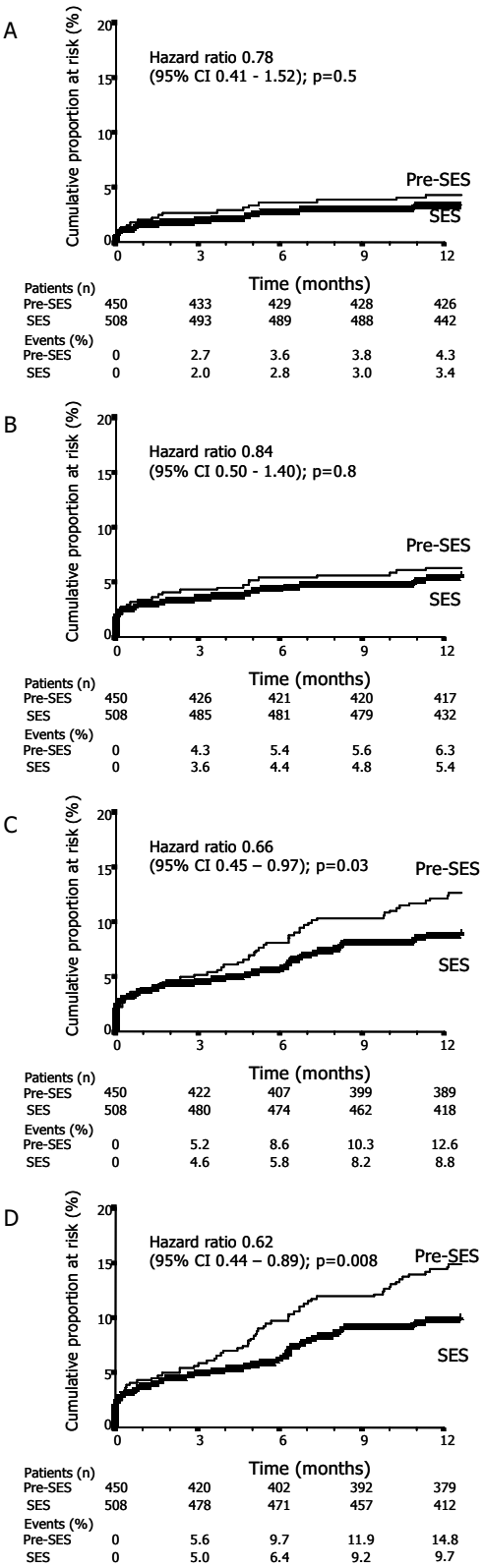

Figure 1 – One-year adverse events in patients treated with bare stents before the introduction of SES (Pre-SES group) and in patients treated exclusively with SES implantation (SES Group). Cumulative risk of death (A); death or myocardial infarction (B); death, myocardial infarction or target lesion revascularization (C); and death, myocardial infarction or target vessel revascularization (D).

Table 2. Angiographic and procedural characteristics of patients treated with conventional bare stents before the introduction of SES (Pre-SES group) and patients treated 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			
Type A, %	20	22	0.4
Type B1, %	32	31	0.7
Type B2, %	50	49	0.8
Type C, %	30	43	<0.01
Glycoprotein IIbIIIa 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±20	39±28.7	<0.01
Nominal stent diameter ≤2.5 mm, %	23	36	<0.01
Post-dilatation with a balloon ≥0.5 mm larger, %	19	55	<0.01
Angiographic success of all lesions,%	97	97	1.0

Table 3. 30-day outcomes of patients treated with conventional bare 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*
Death, %	2.0	1.6	0.6
Non-fatal myocardial infarction, %	1.6	0.8	0.4
Target lesion revascularization, %	1.8	1.0	0.4
Target vessel revascularization, %†	2.2	1.0	0.2
Any event, %	4.2	3.0	0.3
Stent thrombosis, %‡	1.6	0.4	0.1

*by Fisher's exact test
†Includes target lesion revascularization
‡Angiographically documented stent thrombosis requiring repeat intervention

At 1 year, the cumulative incidence of death and death or myocardial infarction was similar between both groups (Figure 1A and B). Patients treated with SES had significantly less death, myocardial infarction or target lesion revasculari-zation at 1 year than patients treated in the pre-SES phase (8.8% vs. 12.6% respectively; HR 0.66 [95% CI: 0.45–0.97]; p=0.03) (Figure 1C). Similarly, the 1-year cumulative risk of major adverse cardiac events (death, myocardial infarction or target vessel revascularization) was significantly reduced in the SES group (9.7% vs. 14.8% in the pre-SES group; HR 0.62 [95% CI 0.44–0.89]; p=0.008). The difference in out-comes between both groups was mainly due to a decrease in the need for target vessel revascularization in the SES group (5.1% vs. 10.9% in the pre-SES group; HR 0.49 (95% CI 0.29–0.82); p=0.007). Specifically, treatment with SES was associated with a marked reduction in clinically driven repeat interventions at 1 year (3.7% vs. 10.9% in the pre-SES group; HR 0.35 (95% CI 0.21–0.57); p<0.001) (Figure 2).

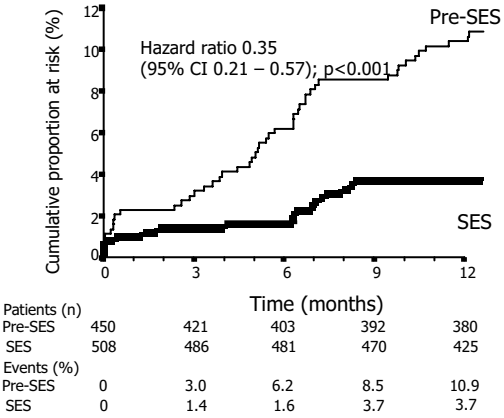

Figure 2 – One-year cumulative risk of clinically driven target vessel revascularization in patients treated with bare stents before the introduction of SES (Pre-SES group) and in patients treated exclusively with SES implantation (SES Group).

Predictors of Adverse Events

The impact of SES implantation on the risk of subsequent clinically driven target vessel revascularization in specific subsets is shown in Figure 3. Sirolimus-eluting stent implantation was associated with a risk reduction that ranged from 28% to 79% across the subgroups evaluated. However, the benefit of SES did not reach statistical significance in women (HR 0.59 [95% CI: 0.24–1.45]; p=0.25) and diabetics (HR 0.72 [95% CI: 0.30–1.77]; p=0.50). Patients treated with bifurcation stenting (HR 0.38 [95% CI: 0.13–1.13]; p=0.08) and patients receiving 33-mm or longer stents (HR 0.41 [95% CI: 0.16–1.03]; p=0.06) presented a strong trend to have better outcomes with SES implantation. In the other subgroups, SES utilization significantly decreased the need of repeat intervention (Figure 3). Importantly, the post-dilatation strategy applied in the present study did not influence the clinical benefit of SES implantation. The magnitude of the risk reduction was similar between patients treated with post-dilatation (HR 0.28 [95% CI: 0.13–0.62]; p=0.002) or without post-dilatation (HR 0.35 [95% CI: 0.18–0.70]; p=0.003).

Multivariate Cox proportional hazards analysis identified sirolimus-eluting stent utilization to be independently associated with a reduced risk of adverse clinical events (Table 4). After adjustment for other independent variables, SES significantly decreased the risk of clinically driven target vessel revascularization (adjusted HR 0.33 [95% CI 0.20–0.56]; p<0.01) and the risk of major adverse cardiac events (adjusted HR 0.55 [95% CI 0.38–0.80]; p<0.01).

Discussion

Sirolimus-eluting stent implantation has been shown to markedly decrease the incidence of in-stent restenosis in the context of randomized trials.[2,3] However, these studies have enrolled relatively non-complex patient populations referred for elective intervention. As a consequence, the findings from these studies cannot be directly extrapolated to many patients treated in the everyday practice, where complex, non-elective cases are the rule, rather than the exception. In the present study, sirolimus-eluting stents implantation was associated with a

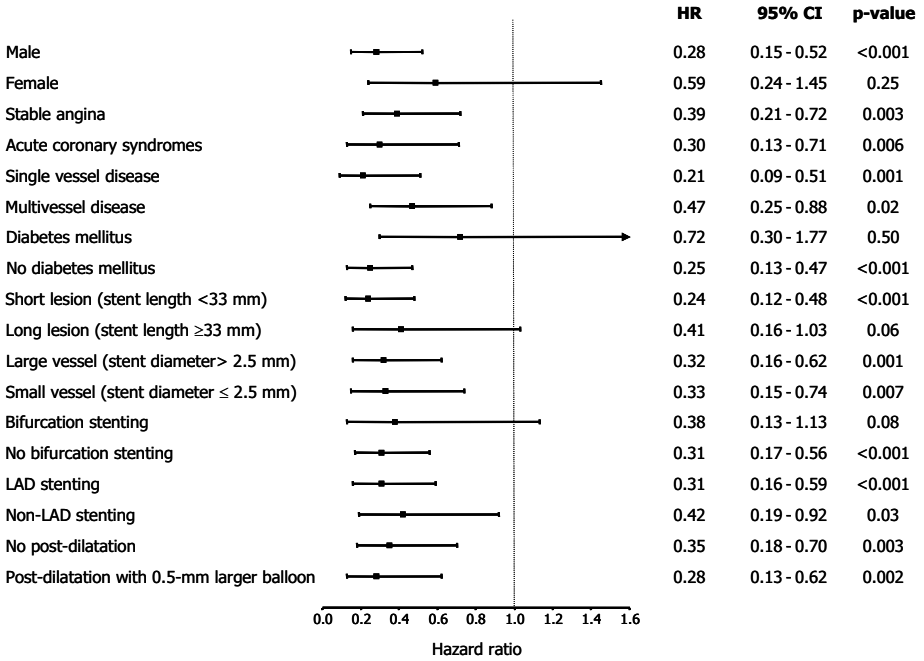

Figure 3. Hazard ratio of 1-year clinically driven target vessel revascularization (Cox proportional hazards models) in subgroups of patients according to baseline and procedural characteristics.

reduction in the rates of repeat revascularization and major adverse cardiac events at one-year in a consecutive, unselected cohort of patients. Sirolimus-eluting stent implantation resulted in a relative reduction of 51% in the overall rate of target vessel revascularization and of 65% in the rate of clinically driven target vessel revascularization.

Our series compared a strategy of unrestricted usage of sirolimus-eluting stents with conventional approaches utilizing bare stents in the pre-sirolimus-eluting stent "era". Although the two study groups were consecutively included over a total period of only one year, some important differences were noted in the interventional strategy applied. Patients in the sirolimus-eluting stent phase were treated with a less restrictive interventional approach, with a significant increase in the number and length of stents implanted, number of coronary segments dilated, bifurcation stenting, and decrease in the diameter of the stents. Possibly, this change in practice may reflect the early recognition by the operators that the acute results, even in this complex population, were maintained in medium-term. Also, it may reflect an attempt to accomplish more complete lesion coverage and ensure uniform drug-delivery over the entire diseased segment, since stent discontinuity and edge injury have been recently shown by our group to be associated with post-SES restenosis.[5] Moreover, the higher complex profile of patients treated with SES (e.g. high rates of multivessel disease, type C lesions, bifurcations) may translate a change in the decision-making process promoted by the availability of sirolimus-eluting stents in our institution. Although both study groups differed in some baseline and procedural characteristics, which may somewhat limit an unbiased comparison between them, it is worth noting that most, if not all, differences would be tradionally expected to increase the incidence of late complications in the SES-treated patients. Nevertheless, the treatment effect of sirolimus-eluting stents was significantly higher than bare stents, remaining virtually unaffected after adjustment for procedural characteristics.

The reduction of adverse events after sirolimus-eluting stent implantation in our series is lower than that observed in the RAVEL trial, where no binary angiographic restenosis was diagnosed.[2] The present findings more closely resembles those seen in the SIRIUS trial (75% reduction in clinically driven target lesion revascularization), in which patients with higher risk profiles were included.[3] Compared to the RAVEL study, the relative decline in effectiveness in the SIRIUS trial and in the RESEARCH study may have been related to the complexity of the procedures included. Although SES implantation markedly reduced the risk of subsequent revascularization in most subsets, the benefit of the new treatment did not reach statistical significance in some subgroups in our series. Indeed, the presence of diabetes and treatment of long lesions were shown to independently increase the incidence of complications. These findings highlight the need of further analyses with enlarged number of patients in order to fully estimate the clinical impact of SES in these patients. Also, whether the outcomes of higher risk subgroups can be improved with refinements in the procedural techniques remain to be established.

Importantly, the reduction of late complications was accomplished without any increase in unexpected sudden events. Our results extend the findings observed in an early report,[6] and show that sirolimus-eluting stent implantation in complex patients is safe, with no increase in acute device-related adverse events. The incidence (0.4%) and timing (within the first month) of documented thrombotic stent occlusion in the SES group was compatible with the current results with conventional bare metal stents. The utilization of IIbIIIa inhibitors and clopidogrel differed between both study groups. However, these differences did not significantly influence the clinical outcome in our study. Nevertheless, it should be noted that these agents were not uniformly used across the various patient subsets, being mainly used in cases at a higher risk of complications, which may have blunted the overall positive effect of these drugs.

Although restenotic lesions have been shown to be amenable to treatment by sirolimus-eluting stents,[9,10] the treatment of *de novo* lesions may be considered as the main field of application of the new device. In this regard, this study was conducted to evaluate the use of sirolimus-eluting stent as a prophylactic strategy in preventing, rather than treating, in-stent restenosis in the "real world".

Some patients have not been treated with the sirolimus-eluting stents during the time period of the study. However, in most instances, this was due to unavailability of large-diameter sirolimus-eluting stents. As large vessels have been shown to present a lower risk of restenosis,[3] it is quite possible that the non-inclusion of patients with larger vessels may have resulted in an underestimation of the overall treatment effect in the present report. The present study is a single-center experience from a tertiary referral center and lacks the obvious advantages of a multi-center, multi-national randomized study. Furthermore, it is unlikely that a randomized study will be conducted in the context in which this study was performed, with virtually no exclusion criteria.

Conclusions

This study demonstrates that unrestricted utilization of sirolimus-eluting stents in the "real world" is safe and effective in reducing the need of further revascularization and the incidence of major adverse cardiac events after one year, as compared to patients treated with bare stent implantation in the period immediately before.

Acknowledgments

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Chapter 4 Early Outcome After Sirolimus-Eluting Stent Implantation in Patients With Acute Coronary Syndromes

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Early Outcome After Sirolimus-Eluting Stent Implantation in Patients With Acute Coronary Syndromes

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Objectives: This study evaluated the early outcomes of patients with acute coronary syndromes (ACS) treated with sirolimus-eluting stents (SES).
Background: The safety of SES for patients at high risk for early thrombotic complications is currently unknown.
Methods: SES have been utilized as the device of choice for all percutaneous procedures in our institution, as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. After 4 months of enrollment, 198 patients with ACS had been treated exclusively with SES (64% of those treated in the period) and were compared to a control group composed by 301 consecutive patients treated with bare stents in the same time period immediately prior. The incidence of major adverse cardiac events (MACE) during the first month was evaluated (death, non-fatal MI, or re-intervention).
Results: As compared to controls, patients treated with SES had more primary angioplasty (95% vs. 77%; p<0.01), more bifurcation stenting (13% vs. 5%, p<0.01), less previous MI (28% vs. 45%; p<0.01), and less IIb/IIIa inhibitor utilization (27% vs. 42%; p<0.01). The 30-day MACE rate was similar between both groups (SES: 6.1% vs. controls: 6.6%; p=0.8), with most complications occurring during the first week. Stent thrombosis occurred in 0.5% of SES patients and in 1.7% of controls (p=0.4). At multivariate analysis, SES utilization did not influence the incidence of MACE (OR 1.0 [95% CI: 0.4 –2.2]; p=0.97).
Conclusions: Sirolimus-eluting stent implantation for patients with acute coronary syndromes is safe, with early outcomes comparable to bare metal stents.

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INTRODUCTION

Percutaneous intervention has been increasingly demonstrated to reduce the risk of adverse events in patients with acute coronary syndromes (ACS) (1,2). Several technical and medical advancements have all contributed to improve the results of angioplasty in this population. However, patients with acute coronary disease still present a higher risk for early events than chronic stable patients, possibly due to an increased propensity for thrombotic complications in the first days after the intervention (3-5).

Sirolimus-eluting stent (SES) implantation has been demonstrated to virtually abolish in-stent restenosis in elective patients with relatively simple lesions (6,7). Notably, the reduction of in-stent restenosis with SES was achieved without compromising the high acute success rates currently accomplished with bare stents. However, the impact of SES for unselected complex cases is presently not known. Sirolimus has been described to decrease endothelial function *in vitro* (8) and to affect platelet physiology (9-11). Moreover, impaired local vascular healing with delayed endothelization and late fibrin persistence has not been ruled out after SES implantation (12,13). Therefore, evaluation of the safety of SES in patients with increased risk for early thrombotic events is warranted.

The aims of this study were to investigate the impact of SES implantation on the occurrence of early adverse events (30 days) in a consecutive series of unselected patients with acute coronary syndromes enrolled in the RESEARCH (Rapamycin-Eluting Stent Evaluation At Rotterdam Cardiology Hospital) registry.

METHODS

The RESEARCH registry

The sirolimus-eluting stent (Cypher™; Johnson & Johnson - Cordis unit) received Conformité Européenne (CE) mark approval in April 2002, since then being commercially available for routine use in Europe. From 16th April 2002, it has been our policy to utilize the SES as the device of choice for every percutaneous coronary intervention performed in our institution, as part of the RESEARCH registry. The RESEARCH is a single-center registry conducted with the aims of evaluating the impact of SES implantation in the "real world" of interventional cardiology. All consecutive procedures were included, without any specific anatomical or clinical restriction. Additionally, a control group was formed by all patients treated with percutaneous interventions in the period immediately prior. Therefore, the control and the RESEARCH groups are constituted by 2 sequential cohorts, primarily defined by the interventional strategy applied (conventional bare stent or SES implantation respectively).

All procedures were performed according to standard interventional techniques except by the utilization of SES as the device of choice during the RESEARCH period (at the initiation of the RESEARCH registry, SES were available in diameters from 2.25 to 3.00 mm and lengths of 8, 18, and 33 mm). Glycoprotein IIb/IIIa inhibitors were given at the discretion of the operator. Postprocedural antiplatelet regimen consisted in of aspirin lifelong and clopidogrel 75mg/d for 1 month (control group and patients treated with bare stent only) or 3 months (patients treated with SES). Prolonged clopidogrel

prescription (6 months) was recommended for patients treated with SES and least one of the following characteristics: multiple SES (>3 stents), total stented length >36mm, chronic total occlusion, bifurcations, and in-stent restenosis.

During the RESEARCH period, according to the actual SES utilization, 3 subgroups were a priori expected: 1) patients treated only with SES, 2) patients in whom both a SES and a non-SES device were utilized at the index procedure, and 3) patients treated without implantation of any SES. The specific reasons for non-utilization of SES were registered on a lesion-per-lesion basis.

The RESEARCH registry was designed with the primary objective of evaluating the effectiveness of SES implantation, as compared to the control population. Effectiveness in both groups was measured by the survival time during which patients remain free of major adverse cardiac events (MACE) after 1 year of follow-up. Additionally, the following secondary objectives have also been predefined: 1) short-term (30-day) safety in patients with acute coronary syndromes, 2) survival free of MACE at 6-month follow-up, 3) cost-effectiveness analysis at 6 months and 1 year, 4) anginal status and medication usage at 6 months and 1 year, and 5) quality of life and work status at 6 months and 1 year.

In the present study we report on the 30-day outcomes patients with ACS treated with SES implantation, as compared to the control population. This study 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. Written informed consent was given by every patient.

Acute Coronary Syndrome Substudy

In the present report, we evaluated the 30-day outcomes of all 198 consecutive patients with unstable angina or acute myocardial infarction (MI) treated exclusively with SES during the first 4 months of the RESEARCH registry (from 16th April 2002 to 15th August 2002). This group represents 64% of all procedures performed in patients with ACS in the period (n=311 patients). Patients receiving both bare stents and SES in the same procedure (32 patients; 10%) and those treated without SES implantation (81 patients; 26.0%) were not included in the present analysis. Among patients not included, non-utilization of SES was due to unavailability of an appropriate SES size (diameter or length) in 73% of cases, inclusion in other study in 5%, and impossibility to cross the lesion with the SES in 1%. In the remaining 21%, SES were not utilized due to a variety conditions related to operator's personal choice or other "medical/technical issues" (for instance, balloon dilatation instead of stent implantation in small coronary branch, mechanical thrombectomy without stent implantation for vessels with a high thrombotic burden, or heparin-coated stents due to contraindication for antiplatelet therapy). A Control Group for comparison was constituted by 301 consecutive patients with ACS treated with bare stent implantation during the last 4 months (from 16th December 2001 to 15th April 2002) prior the initiation of the RESEARCH registry (94% of all patients treated in the period). Patients with unstable angina were categorized according to the Braunwald classification (14). Procedures performed in the first 24 hours of an acute MI were classified as rescue or primary angioplasty, if preceded or not by (failed) intravenous thrombolysis respectively. Patients treated after 24 hours but before discharge of an episode of myocardial infarction were classified as post-MI unstable angina (Braunwald Class C).

Endpoint Definitions and Follow-up

Major adverse cardiac events were defined as: 1) death, 2) non-fatal myocardial infarction, or 3) repeat target lesion or vessel revascularization. A definite diagnosis of myocardial infarction required an increase in the creatine kinase level to more than twice the upper normal limit with an increased level of creatine kinase MB (7). Target lesion revascularization (TLR) was defined as any surgical or percutaneous re-intervention motivated by a significant luminal narrowing within the stent or in the 5-mm distal or proximal peristent segments. Target vessel revascularization (TVR) was defined as any re-intervention driven by lesions located in the treated vessel even beyond the target lesion limits. Additionally, we analyzed the incidence of stent thrombosis, defined as any angiographically documented thrombotic occlusion (TIMI flow 0 or 1) or flow limiting thrombus (TIMI flow 1 or 2) occurring after the procedure (after removal of the guiding catheter) in an artery previously treated with angiographic success (TIMI flow 3 immediately after stent placement and percent in-lesion diameter stenosis$\leq$30%).

All procedures were performed in a tertiary cardiology center. As ruled by the local medical system organization, the majority of hospitalized patients treated in this tertiary facility were referred from other peripheral hospitals, to where they were discharged shortly after the procedure, unless a periprocedural complication occurs and/or specialized surveillance was required. In total, patients have been referred from a group of 14 local hospitals. Post-procedure medical care was performed at the discretion of the site of origin. Cardiac enzymes were measured serially after the procedure for all in-hospital patients maintained in our hospital. In most of the peripheral hospitals, cardiac markers were not collected routinely, unless a post-procedure myocardial infarction was suspected. For elective outpatient cases, it has been our practice to discharge the patients after a mean period of observation of 3 ± 1 hours (unpublished data), provided no post-procedural complications had occurred (access site hemostasis was routinely performed with a femoral closure device whenever possible). As a result of these policies for in- and outpatient cases, serial cardiac markers were only not available for patients in whom the likelihood of post-procedure myocardial infarction was judged to be low. Such policy has been supported by evidence from studies with large population cohorts showing that minor asymptomatic enzymatic elevation has no impact on either short- or long-term prognosis (15,16) and therefore is highly unlikely to influence the post-procedural medical conduct.

In-hospital outcome information was obtained by means of an electronic clinical database for patients maintained in our hospital after the procedure and by review of the hospital records for those discharged to secondary hospitals. During the follow-up, recordings of all repeat interventions (surgical and percutaneous) and re-hospitalizations were prospectively collected in a

dedicated database. Long-term survival status was assessed by written inquiries to the Municipal Civil Registries at 30 days, 6 months and 1-year after the procedures. Questionnaires were sent at 6 months and 1 year to all living patients with information regarding post-discharge anginal status, medication usage, and the occurrence of clinical events. Furthermore, a psychological questionnaire was sent and included forms with the SF-36 quality of life (17), the HADS anxiety and depression score (18) and the Type D personality score (19). The referring physician and institutions as well as the general practitioners were directly approached whenever necessary for additional information. For patients who went abroad, an effort was made to contact the local civil registries of their new residencies. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored.

Table 1 – Baseline and procedural characteristics of patients treated with bare stents versus patients treated with SES.

	Bare Stent (n=301)	SES (n=198)	p-value
Age, years ± SD	60±12	62±11	0.21
Male sex, %	75	68	0.10
Diabetes, %	12	18	0.07
Hypercholesterolemia	48	49	0.93
Current smoking, %	38	38	0.85
Hypertension, %	63	63	0.93
Previous MI, %	45	28	<0.01
Previous angioplasty, %	18	21	0.56
Previous coronary surgery, %	10	9	0.64
Coronary artery disease, %			0.12
Single-vessel disease	44	51	
Multivessel disease	56	49	
Unstable angina, %	68	68	1.0
Braunwald classification, %*			
Class I to III-A	5	4	0.61
Class I and II-B	45	42	0.65
Class III-B	21	22	0.78
Class I and II-C	14	9	0.23
Class III-C	15	22	0.12
Acute MI, %	32	32	1.0
Cardiogenic shock †	13	13	1.0
Rescue angioplasty †	23	5	<0.01
Primary angioplasty †	77	95	<0.01
Peak CKMB, UI/L±SD ‡	317±256	217±236	0.04
IIBIIIA inhibitor, %	42	27	<0.01
Vessel treated, %			
LMC	3	4	0.60
LAD	58	59	0.85
LCx	31	29	0.69
RCA	39	36	0.64
Bypass	6	5	0.84
Lesion type A/B1, %	42	44	0.71
Lesion type B2/C, %	78	78	1.0
Number of treated segments (±SD)	1.8±0.9	1.8±0.9	1.00
Total stented length, mm±SD	28±13	29±15	0.30
Bifurcation stenting	5	13	<0.01
Angiographic success all lesions, %	97	96	0.48

*relative to the number of patients with unstable angina; total sum may not result 100% due to rounding
†relative to the number of patients with acute MI
‡Upper limit of normal = 24 UI/L
SES=sirolimus-eluting stent; MI=myocardial infarction; LMC=left main coronary; LAD=left anterior descending artery; LCx=left circumflex artery; RCA=right coronary

Data Management and Statistical Analysis

All consecutive procedures were included in the control group and in the RESEARCH, utilizing a dynamic registry design as previously described by Rothman and Greenland (20). For each patient, the time until the first MACE was computed (person-time). Any eventual repeat percutaneous intervention acts then as a new index procedure and the person-time contributes again to the cohort. A patient can therefore contribute to one, two, or more person-time. This design is of particular interest in a study like the RESEARCH, which intends to evaluate 2 consecutive cohorts treated with coronary angioplasty. If re-entry is not allowed, the second group (in the present case, treatment with SES) is consequently emptied from cases with treatment for restenotic lesions. This design therefore permits the inclusion of patients with in-stent restenosis in both study periods, allowing the evaluation of the impact of each particular re-intervention on the subsequent outcomes. In view of the small applicability of this concept (person-time analysis) for short-term evaluations, no calculations with person-time units were performed in the current Acute Coronary Syndrome Substudy.

Discrete variables were presented as percentages and compared by Fisher's exact tests. Continuous variables were presented by their means and standard deviations and compared by Student's T test or 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 survival and MACE-free survival among the different groups. Multivariate independent predictors of 30-day outcomes were evaluated by logistic regression. All baseline and procedural characteristics presented in Table 1 were tested, and a final multivariate model was constructed by backward deletion of the least significant variables. All tests were two-tailed and a p value < 0.05 was considered as significant.

RESULTS

Baseline and Procedural Characteristics

Clinical and procedural characteristics of the 499 patients included in the present report are depicted in Table 1. As compared to the controls, patients treated with SES had more frequently primary angioplasty (95% vs. 77%; p<0.01), more bifurcation stenting (13% vs. 5%; p<0.01), less previous MI (28% vs. 45%; p<0.01), and less glycoprotein IIb/IIIa inhibitor utilization (27% vs. 42%; p<0.01) (Table 1). Also, peak creatine kinase MB was lower for acute MI patients treated with SES (217±236 UI/L vs. 317±256 UI/L; p=0.04) (Table 1). Procedural angiographic success was achieved in all attempted lesions in a similar proportion of cases in the SES and the control groups (96% vs. 97% respectively, p=0.48)(Table 1).

30-day Outcome

The 30-day outcomes of the SES and control groups are shown in Table 2. Complete follow-up information was available for all patients in the SES group and for all except 1 patient in the control group (99.7%). There were no differences in the incidence of adverse events between patients treated with bare stents and those treated with SES (30-day MACE rate 6.1% vs. 6.6%, respectively;

p=0.8), with most complications occurring in the first week after the procedure (Figure 1). Stent thrombosis occurred in 1 patient (0.5%) in the SES group and in 5 patients (1.7%) in the control group (p=0.4) (Table 2). We performed a multivariate analysis to determine independent predictors of MACE at 30 days. Figure 2 shows the 4 significant predictors of 30-day MACE identified in the final model. The presence of multivessel disease (OR 4.4 [95% CI: 1.8-10.8]; p<0.01), cardiogenic shock (OR 3.9 [95% CI: 1.2-12.8]; p=0.02), and acute MI at presentation (OR 3.3 [95% CI: 1.4-7.6]; p<0.01) were associated with an increased risk of MACE, while right coronary angioplasty (OR 0.4 [95% CI: 0.2-0.9]; p=0.04) was related to a decrease in the odds of early adverse events. When forced into the model, SES utilization (OR 1.0 [95% CI: 0.4–2.2]; p=0.97) did not predict the occurrence adverse events, with virtually no influence in the predictive strength of model (Figure 3).

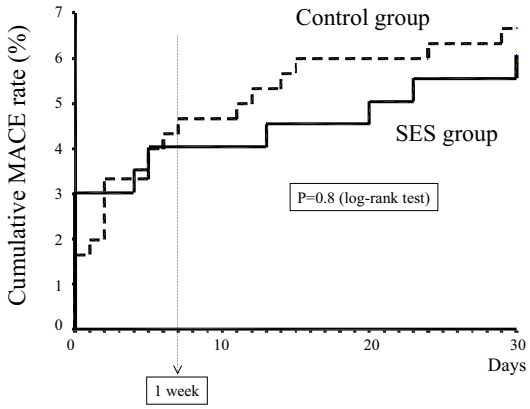

Figure 1 – Cumulative MACE rate (death, non fatal MI, or re-intervention) during the first month for controls (bare stent) and patients treated with sirolimus-eluting stents. Note that > 50% of events occurred during the first week in both groups.

DISCUSSION

In this study we analyze for the first time the impact of sirolimus-eluting stent implantation on the early outcomes of patients with acute coronary syndromes. As compared to conventional bare stents, utilization of SES in unselected patients with acute MI or unstable angina was observed to be safe at 30 days, with similar rates of procedural success and early adverse events.

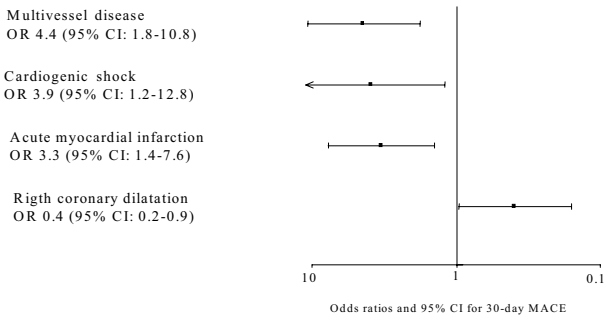

Figure 2 – Multivariate independent predictors of 30-day MACE (death, non fatal MI, and re-intervention) derived from the final logistic regression model. The odds ratios are shown on logarithmic scale together with their 95% confidence interval.

Patients treated with SES differed in some aspects from that included in the control group. Control patients presented more rescue angioplasty for failed thrombolysis (instead of primary angioplasty), which could have increased the risk of events in this group. Conversely, SES patients were more frequently treated for bifurcation lesions, a well-known risk factor for periprocedural complications (21,22). Moreover, glycoprotein IIb/IIIa inhibitors were less commonly used in patients treated with SES, which may have posed these patients to a higher procedural risk (23). It seems unlikely that the lower utilization of IIb/IIIa blockers in these group could be explained by a lower risk profile perceived during the procedure since both the control and SES populations were equally composed predominantly by patients with acute MI or high grade unstable angina, with no significant difference in their diabetic status. Nevertheless, after adjusting for baseline and procedural differences, the type of stent used, either bare or SES, was not significantly associated with the occurrence of early adverse events.

Recently, sirolimus has been reported to reduce endothelium-dependent relaxation in vitro in a porcine model, although the authors did not ruled out an effect of the drug vehicle (8). Additionally, sirolimus has been described to increase platelet aggregation and secretion in transplant recipients (11). However, recent studies have demonstrated that this drug efficiently blocks the synthesis of Bcl-3, a regulatory protein expressed when platelets adhere to collagen via integrin $\alpha_{IIb}\beta_{III}$ (9,10,24). Regardless of these contradictory laboratory findings, SES were not associated with clinically relevant device-related complications in our series, with no modification of the risk profile for procedural failure or event occurrence.

Patients treated with SES presented a similar timing of post-procedural complications as compared to controls, with most events occurring in the first days after the procedure, a typical pattern previously reported after bare stent implantation (4,5). In this context, a relatively delayed hazardous effect of the drug leading to an increase in "late" thrombotic complications after the first week was not observed in our patients.

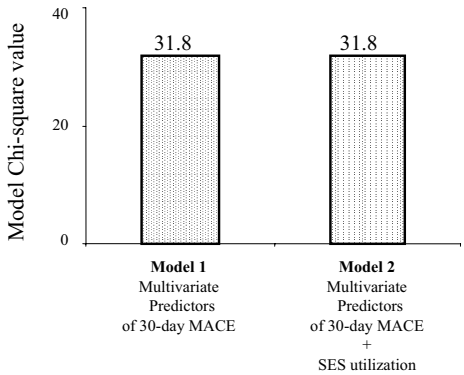

Figure 3 – Predictive strength (Chi-square values) for 30-day MACE (death, non fatal MI, and re-intervention) of multivariate models. Model 1 is the final model selected in the logistic regression and included the variables displayed in Figure 2. The forced inclusion of SES utilization (model 2) did not enhance the predictive strength of the model, as reflected by the negligible change in the Chi-square values.

STUDY LIMITATIONS

The present investigation suffers from the inherent limitations of a non-randomized trial, which explains some unbalance in the baseline characteristics among the treatment groups. However, the study population is representative of the "real world" of interventional cardiology, with findings more readily applicable to the daily clinical practice. Post-procedure cardiac markers were not collected routinely for all patients (available for 42% of controls and 46% of patients in the SES subgroup [p=NS]). This was justified by the fact that high grade enzymatic elevations, those with proven prognostic impact (15,16), rarely occur "unnoticed" in asymptomatic patients. When comparing pts with and without post-procedure enzymes collected, 30-day death rate was 7.1 % vs. 0 % ($p<0.001$) and re-intervention rate was 4.7% vs. 0% ($p<0.001$), reflecting the low risk nature of patients for whom cardiac markers were not measured. Similarly, the relatively low frequency of utilization of IIbIIIa inhibitors in our study reflects the current practice of administration of these drugs in several countries worldwide (25). Risk stratification was based mainly on clinical characteristics. Although laboratorial tests are known to add important prognostic information, the validated Braunwald classification for unstable angina applied in the present study provides a powerful clinical tool for individual risk assessment (14).

CONCLUSIONS

Sirolimus-eluting stent implantation for acute coronary syndromes was safe, with early outcomes comparable to conventional bare metal stents. Maintenance of the excellent short-term results already achieved with the current techniques is crucial for the validation of SES as a useful strategy in treatment of complex cases. Further evaluation in the context of randomized trials is warranted to confirm the present findings.

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Chapter 5 Sirolimus-eluting stent implantation in ST-elevation acute myocardial infarction: a clinical and angiographic study

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Sirolimus-eluting stent implantation in ST-elevation acute myocardial infarction: a clinical and angiographic study

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Background—Sirolimus-eluting stents (SES) have recently been proven to reduce restenosis and reintervention compared
with bare stents. Safety and effectiveness of SES in acute myocardial infarction remain unknown.
Methods and Results—Since April 16, 2002, a policy of routine SES implantation has been instituted in our hospital, with
no clinical or anatomic restrictions, as part of the RESEARCH (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital) registry. During 6 months of enrollment, 96 patients with ST-elevation acute myocardial infarction underwent percutaneous recanalization and SES implantation; these patients comprise the study population. The incidence of major adverse cardiac events (death, nonfatal myocardial infarction, reintervention) was evaluated. Six-month angiographic follow-up was scheduled per protocol. At baseline, diabetes mellitus was present in 12.5% and multivessel disease in 46.9%. Primary angioplasty was performed in 89 patients (92.7%). Infarct location was anterior in 41 (42.7%) of the cases, and 12 patients (12.5%) had cardiogenic shock. Postprocedural TIMI-3 flow was achieved in 93.3% of the cases. In-hospital mortality was 6.2%. One patient (1.1%) had reinfarction and target lesion reintervention the first day as a result of distal dissection and acute vessel occlusion. During follow-up (mean follow-up of 218±75 days), 1 patient died (1.1%), no patient had recurrent myocardial infarction, and there were no additional reinterventions. No early or late stent thromboses were documented. At angiographic follow-up (70%), late loss was -0.04±0.25mm, and no patient presented angiographic restenosis.
Conclusions—In this study, sirolimus-eluting stent implantation for patients with ST-elevation acute myocardial infarction was safe without documented angiographic restenosis at 6 months.

Circulation. 2003;108:1927-1929

Routine stent implantation has been shown to have a better procedural success rate and clinical outcome than bal-loon angioplasty in patients presenting with acute myocardial infarction (AMI).1 However, in-stent restenosis and vessel reocclusion remain significant clinical problems limiting the long-term success of percutaneous treatment.[1,2]

Sirolimus-eluting stents (SES) have been proven to virtually abolish in-stent restenosis in elective patients with relatively simple lesions,[3] with persistent neointimal growth inhibition up to 2 years.[4] Recently, we have demonstrated that the 30-day outcomes of SES implantation for patients with acute coronary syndromes were similar to those of a control population treated with bare stents.[5] Nevertheless, no specific information is presently available regarding the safety of these new devices in patients with AMI. Furthermore, the long-term clinical efficacy of SES for AMI is unknown. The rationale of the present study is therefore to evaluate the short- and midterm clinical and angiographic outcomes of SES implantation in a consecutive series of patients treated during the acute phase of AMI.

Methods

Patient Population

Since April 16, 2002, SES implantation (Cypher; Johnson & Johnson, Cordis Europa NV, Roden, the Netherlands) has been instituted as the default strategy for all percutaneous coronary interventions performed at our institution as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry, which has been described elsewhere.[5] All clinical situations and lesion morphologies were considered eligible. After 6 months of enrollment, 96 consecutive patients within 12 hours of an episode of AMI underwent mechanical reperfusion of the infarct-related artery with SES implantation; these patients comprise the present study population.

Procedure

Except for SES utilization, all procedures were performed according to standard techniques, and the final interventional strategy was left to the discretion of the operator. Weight-adjusted heparin was administered to achieve an activated clotting time of >300 seconds, or 200 to 250 seconds when platelet glycoprotein IIb/IIIa inhibitor was used. Postprocedural antiplatelet regimen consisted of lifelong aspirin use and 75 mg clopidogrel per day for 3 months. Prolonged clopidogrel prescription (6 months) was recommended for patients with at least one of the following characteristics: multiple SES (>3 stents), total stent length >36 mm, bifurcations, or in-stent resteno-sis. The local ethics committee approved the study protocol, and informed consent was obtained from all patients.

Definitions and Follow-Up

Patients were evaluated for the occurrence of death, reinfarction (clinical symptoms or new electrocardiographic changes, associated with re-elevation of the creatine kinase and creatine kinase MB levels of >1.5 times the previous value if within 48 hours, >3 times the upper normal limit if after 48 hours),[2] and target lesion revascu-larization (surgical or percutaneous reintervention motivated by a significant stenosis located within the stent or in the 5-mm segments proximal or distal to the stent). Information regarding repeat inter-ventions was prospectively collected in the local 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. To evaluate the incidence of restenosis after SES implantation for AMI, angiographic follow-up was scheduled at 6 months for all living patients. Binary restenosis was defined as a stenosis diameter >50% within the stent or in the 5-mm segments proximal or distal to the stent. Late loss was defined as the difference between the minimal luminal diameter immediately after the procedure and at follow-up.

Statistical Analysis

Continuous variables are expressed as mean±SD. Discrete variables are presented as count and percentages. Event-free survival curves were estimated according to the Kaplan-Meier method. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored.

Results

At baseline, mean age was 57±12 years. Twelve patients (12.5%) had diabetes mellitus, 10 (10.4%) had had a previous myocardial infarction, and 45 (46.9%) presented multivessel disease. Six patients (6.2%) had prior coronary angioplasty, and 1 (1%) had prior coronary bypass surgery. Mean creatine kinase level was 2685±2869 IU/L. Average time from the onset of symptoms to the beginning of the procedure was 3.6±2.9 hours. Primary angioplasty was performed in 89 patients (92.7%) and rescue angioplasty after failed thrombolysis in the remaining 7 (7.3%). Cardiogenic shock was diagnosed in 12 patients (12.5%). Periprocedural glycoprotein IIb/IIIa inhibitor (abciximab) was used in 45 patients (46.9%). Infarct location was anterior in 41 cases (42.7%). Overall, 104 culprit lesions were identified (in 8 patients, we found 2 different lesions anatomically and clinically related to the development of the AMI). The lesions were located in the left main in 2 cases (1.9%), the left anterior descending in 51 (49.0%), the left circumflex in 10 (9.6%), and the right coronary in 41 (39.4%). Before the procedure, TIMI flow 0 to 1 was present in 60.6% of the cases. Postprocedural TIMI-3 flow was achieved in 93.3%. Clopidogrel was prescribed for 3 months in 54% of patients and for 6 months in the remaining cases. Complete follow-up was available for 99% of the patients at 218±75 days. A total of 6 deaths occurred during the index hospitalization (6.2%). In 1 case, death occurred as a result of brain death in a patient with prolonged out-of-hospital resus-citation. The other 5 cases were all admitted in cardiogenic shock; 3 of them died the same day of the procedure as a result of progressive hemodynamic deterioration. The other 2 patients died of overwhelming sepsis at days 23 and 86 after a prolonged, stormy course. One additional death (1.1%) resulting from heart failure occurred during follow-up, shortly after hospital discharge, in a 77-year-old patient with 3-vessel disease, who was admitted with a large inferoposterior myocardial infarction and cardiogenic shock. In none of these cases, death occurred as an unexpected, sudden episode that could be attributable to stent thrombosis. Target lesion reintervention was necessary in 1 patient (1.1%) the same day as the procedure as a result of distal dissection, acute vessel occlusion, and reinfarction. There were no further cases of reinfarction or repeat intervention after discharge (Figure). Also, no early or late stent thromboses were documented. Six-month angiographic follow-up was obtained in 62 patients (70%). The angiographic outcomes are shown in the Table. Late loss was -0.04±0.25 mm, and there were no cases of binary restenosis.

Table 1. Quantitative coronary analysis in patients with acute myocardial infarction treated with sirolimus-eluting stent.

	Pre-procedure	Post-procedure	Follow-up*
Reference diameter, mm	2.73 ± 0.59	2.80 ± 0.47	3.04 ± 0.49
Minimum lumen diameter, mm	0.34 ± 0.50	2.54 ± 1.31	2.59 ± 0.42
Diameter stenosis, %	86 ± 21	14 ± 12	15 ± 11
Lesion length, mm	16.9 ± 9.9	-	-
Late loss, mm	-	-	-0.04 ± 0.25
Binary restenosis, %	-	-	0

* related to 62 patients with 6-month angiographic follow-up

Discussion

The present study is the first report on SES implantation for patients with ST-elevation AMI. The main finding is that, in these patients, SES implantation appears highly effective in preventing neointimal proliferation and restenosis, with re-sults similar to those observed in a randomized trial for relatively simple lesions.[3] Primary percutaneous coronary intervention has been dem-onstrated to be more effective than thrombolytic therapy for the treatment of AMI.[6] However, although consistently reduced by stent utilization, recurrent ischemia, restenosis, and reocclusion of the infarct-related artery occur in sizable proportions, increasing clinical events and healthcare costs.

In the Stent PAMI (Stent Primary Angioplasty for Myocar-dial Infarction) trial, 6-month restenosis and target vessel revascularization rates were 20.3% and 7.7%, respectively.[2] In the CADILLAC (Controlled Abciximab and Device Inves-tigation to Lower Late Angioplasty Complications) trial, the corresponding values were 22.2% and 8.9%, and reocclusion of the infarct-related artery 5.7%.[1] In this context, the absence of restenosis and reinterventions by SES as found in our study could further improve clinical outcomes, although this hypothesis should be tested in dedicated randomized trials.

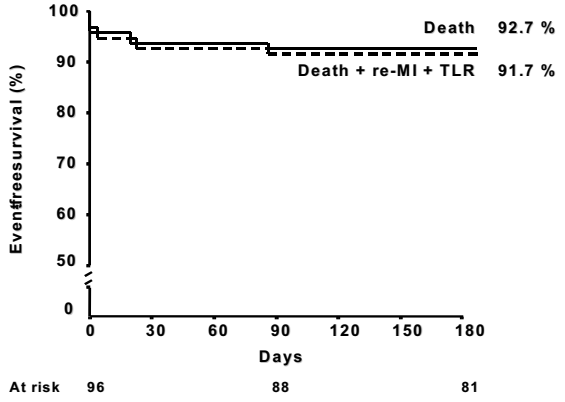

Figure 1. Kaplan-Meier curves for survival, and survival free from myocardial infarction (MI) and target lesion revascularization (TLR). It is evident the almost complete overlap of the curves, motivated by the very low incidence of recurrent myocardial infarction and reinterventions.

Previous preclinical laboratory data suggested that siroli-mus could decrease endothelial function in vitro,7 enhance agonist-induced platelet aggregation,[8] and delay vascular healing.[9] Altogether, these features can potentially increase the risk of thrombotic complications and adversely affect the outcome after SES implantation, especially in very suscepti-ble patients such as those treated during the acute phase of myocardial infarction. However, the clinical significance of these preliminary findings remains elusive. Indeed, we re-cently demonstrated the safety of SES for patients with acute coronary syndromes, although AMI at presentation was still associated with an increased risk of adverse events at follow-up.[5] The present study, with the very low event rate and the absence of episodes of acute and subacute thrombosis, confirms the safety of SES utilization, specifically in patients with AMI.

In this prospective, single-center registry of SES implan-tation in AMI, all the limitations inherent to this particular study design apply, and the patient number was relatively small. Notably, however, given the unrestricted inclusion criteria, this cohort of patients accurately reflects the daily practice in the "real world" of interventional cardiology, and therefore the results are extended to virtually all patients with AMI as a result of occlusion of native coronary vessels.

Conclusions

Routine SES implantation during mechanical reperfusion of AMI is safe and associated with no evidence of late luminal loss and restenosis at 6 months. Larger studies are necessary to confirm these findings and to evaluate the impact of SES implantation on clinical events for patients with AMI.

Acknowledgments

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Chapter 6 Short- and Long-Term Clinical Benefit of Sirolimus-Eluting Stents Compared to Conventional Bare Stents for Patients With Acute Myocardial Infarction

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Short- and Long-Term Clinical Benefit of Sirolimus-Eluting Stents Compared to Conventional Bare Stents for Patients With Acute Myocardial Infarction

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Objectives: To investigate the clinical outcomes of patients with ST-elevation myocardial infarction treated with sirolimus-eluting stents or conventional bare stents.
Background: The clinical impact of sirolimus-eluting stent implantation for patients with ST-elevation myocardial infarction is currently unknown.
Methods: Primary angioplasty was performed with sirolimus-eluting stents in 186 consecutive patients with acute myocardial infarction, who were compared with 183 patients treated with bare stents. The incidence of death, re-infarction, and repeat revascularization was assessed at 30 and 300 days.
Results: Post-procedure vessel patency, enzymatic release, and the incidence of short-term adverse events was similar in the sirolimus and bare stents (30-day rate of death, re-infarction, or repeat revascularization: 7.5% vs. 10.4% respectively; p=0.4). Stent thrombosis was not diagnosed in any patient in the sirolimus group and occurred in 1.6% of patients treated with bare stents (p=0.1). At 300 days, treatment with sirolimus-eluting stents significantly reduced the incidence of combined adverse events (9.4% vs. 17%; HR 0.52 [95% CI 0.30–0.92]; p=0.02), mainly due to a marked reduction in the risk of repeat intervention (1.1% vs. 8.2%; HR 0.21 [95% CI 0.06–0.74]; p=0.01).
Conclusions: Sirolimus-eluting stents were not associated with an increased risk stent thrombosis and were effective in reducing the incidence of adverse events at 300 days in unselected patients with ST-elevation acute myocardial infarction referred for primary angioplasty, compared to conventional bare stents.

J Am Coll Cardiol. *in press*

Introduction

Routine stent implantation has been advocated for patients with acute myocardial infarction referred for primary angioplasty, with superior results compared to balloon dilatation (1-3). However, the late clinical efficacy is still hampered by the occurrence of in-stent restenosis and the need for repeat intervention.

Sirolimus-eluting stents have proven effective in reducing late restenosis compared to conventional stenting in elective patients (4-6). We have recently shown in a relatively small consecutive series of cases that sirolimus-eluting stent implantation in patients with acute myocardial infarction was safe and associated with an extremely low (zero) incidence of angiographic restenosis at 6 months (7). However, the clinical benefit of sirolimus-eluting stents in comparison to conventional stent implantation remains currently unknown. We therefore evaluated the long-term clinical outcomes of a large series of patients with acute myocardial infarction treated with primary angioplasty utilizing sirolimus-eluting stents or conventional metal stents.

Methods

Since April 2002, sirolimus-eluting stent (SES) implantation (Cypher; Johnson & Johnson-Cordis unit, Cordis Europa NV, Roden, the Netherlands) has been utilized as the strategy of choice for patients treated with percutaneous intervention in our institution (8). Up to January 2003, a total of 186 consecutive patients with ST-elevation acute myocardial infarction have been treated with primary angioplasty utilizing exclusively sirolimus-eluting stents and were included in the present report. The first 89 patients of the present series were included in an angiographic substudy, of which the results have been reported previously (7). A control group for comparison was composed of 183 consecutive patients with ST-elevation acute myocardial infarction treated with conventional bare stents in the period immediately prior to the introduction of sirolimus-eluting stents. The following bare metal stents were used: BX Sonic or BX Velocity in 53% (Cordis, Johnson & Johnson Company, Warren, New Jersey), Multi-Link Penta in 22% (Guidant Corp., Santa Clara, California), Multi-Link Tetra in 6% (Guidant Corp., Santa Clara, California), R-Stent in 6% (Orbus Medical Technologies, Ft. Lauderdale, Florida), and other stents in 12%. In both study phases, all patients were enrolled regardless of the clinical or anatomical presentation, including patients admitted with cardiogenic shock (defined as persistent systolic blood pressure <90 mm Hg, or the need of vasopressors or intra-aortic balloon pumping required to maintain blood pressure >90 mm Hg with evidence of end-organ failure and elevated left ventricular filling pressures). Therefore, the total study population comprised all 369 consecutive patients with ST-elevation acute myocardial infarction undergoing primary angioplasty with either bare stents or sirolimus-eluting stents in the 2 study phases respectively. Patients

with angioplasty after failed thrombolytic therapy were excluded from the present analysis. This study protocol was approved by the local ethics committee and written informed consent was given by every patient.

The final interventional strategy, as well as the utilization of periprocedural glycoprotein IIbIIIa inhibitors and antithrombotic medications, was entirely left to the discretion of the operator. Baseline and post-procedure antegrade flow were evaluated off-line according to the TIMI criteria (9) by cardiologists blinded to the stent group and to the clinical outcomes. Clopidogrel was recommended for at least one month in the control group. In the SES group, clopidogrel was prescribed for 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, bifurcation stenting, and in-stent restenosis.

Table 1. Baseline and procedural characteristics of patients treated with bare stents or SES implantation.

	Bare stents (n=183)	SES (n=186)	P-value
Male, %	79	75	0.4
Age, years±SD	57±12	60±12	0.04
Diabetes, %	12	11	0.9
Current smoking, %	47	46	0.8
Previous myocardial infarction, %	24	14	0.03
Previous angioplasty, %	9	7	0.4
Previous bypass surgery,%	3	2	0.3
Coronary disease			0.3
Single-vessel, %	48	55	
Double-disease, %	29	27	
Triple-vessel, %	24	18	
Cardiogenic shock, %	10	13	0.3
Time from symptom onset to angioplasty, hours±SD	3.0±2.7	3.2±1.9	0.6
Infarct-related vessel			0.3
Right coronary artery,%	30	37	
Left anterior descending, %	57	53	
Left circumflex artery,%	10	8	
Left main coronary, %	1	2	
Bypass graft, %	2	-	
TIMI flow baseline			0.7
Grade 0/I, %	73	73	
Grade II, %	15	17	
Grade III, %	13	10	
TIMI flow after angioplasty			0.5
Grade 0/I, %	4	2	
Grade II, %	17	15	
Grade III, %	79	83	
Number of stents±SD	1.7±1.0	1.9±1.2	0.03
IIbIIIa inhibitor, %	56	37	<0.01
Clopidogrel prescription, months±SD	2.1±1.5	3.7±2.1	<0.01
Peak CK, IU/L±SD*	3957± 5135	3126± 3126	0.1
Peak CK-MB, IU/L±SD†	319± 230	296± 255	0.5

CK=creatine kinase; SD=standard deviation; SES=sirolimus-eluting stents
* Upper limit of normal 199 U/L
† Upper limit of normal 23 U/L

Patients were prospectively followed-up for the occurrence of major adverse cardiac events: 1) all-cause death, 2) non-fatal myocardial infarction, or 3) target vessel revascularization. Re-infarction was diagnosed by recurrent symptoms and/or new electrocardiographic changes in association with re-elevation of the creatine kinase and creatine kinase MB levels of >1.5 times the previous value, if within 48 hours, or >3 times the upper normal limit, if after 48 hours from the index infarction (1,7). Target vessel revascularization was defined a repeat intervention (surgical or percutaneous) 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 flow 0 or 1) or a flow limiting thrombus (TIMI flow 1 or 2) of a previously successfully treated artery. Routine angiographic follow-up was obtained only for patients treated with sirolimus-eluting stents enrolled during the first 6 months; results of this subanalysis have been previously reported (7).

Continuous variables were presented as mean±standard deviation and were compared using Student's unpaired t-test. Categorical variables were presented as counts and percentages and compared with the Fisher's exact test. Survival free of adverse events was estimated using the Kaplan-Meier method and differences between curves were evaluated by the log-rank test. Cox proportional hazards models were used to assess risk reduction. Multivariate analyses were performed to identify independent predictors of long-term major adverse cardiac events. Baseline and procedural characteristics associated with the incidence of adverse events at univariate analysis (p-value for selection ≤ 0.2) were tested for their multivariate predictive value (tested variables: SES utilization, diabetes, cardiogenic shock, multivessel disease, culprit vessel, pre-procedure TIMI flow, post-procedure TIMI flow, current smoking). The final model was built by backward stepwise variable selection with an entry and exit criteria set at the P=0.05 and P=0.1 levels respectively.

Results

Baseline characteristics were similar between both study groups, except by an older age and a lower incidence of previous myocardial infarction in the sirolimus group (Table 1). Procedural characteristics differed between both groups in terms of the utilization of IIbIIIa inhibitors (sirolimus: 37% vs. bare stents: 56%; p<0.01) and the number of stents implanted (sirolimus: 1.9±1.2 vs. bare stents: 1.7±1.0; p=0.03). As defined by the study protocol, the duration of clopidogrel prescription was longer for patients with sirolimus stents (Table 1).

There were no significant differences in the 30-day outcomes between patients treated with sirolimus or bare stents (Table 2). Stent thrombosis was diagnosed in 3 patients (1.6%) treated with bare stents and was not detected in the SES group (p=0.1) (Table 2).

At 300 days, there were no differences between both study groups in the incidence of death and death or re-infarction (Table 2). However, the incidence of 300-day major adverse events was significantly lower in the sirolimus stent group compared to the bare stent group (9.4% vs. 17% respectively; hazard ratio 0.52 [95% confidence interval 0.30–0.92]; p=0.02) (Table 2; Figure), mainly due to a marked reduction in the risk of repeat intervention (1.1% vs. 8.2% respectively; HR 0.21 [95% CI 0.06–0.74]; p=0.01). A multivariate analysis was

performed to adjust for baseline and procedural imbalances between the study groups (Table 3). Sirolimus-eluting stent utilization was identified as independent predictor of 300-day death, re-infarction, or repeat revascularization (HR 0.53 [95% CI 0.29–0.95]; p=0.03).

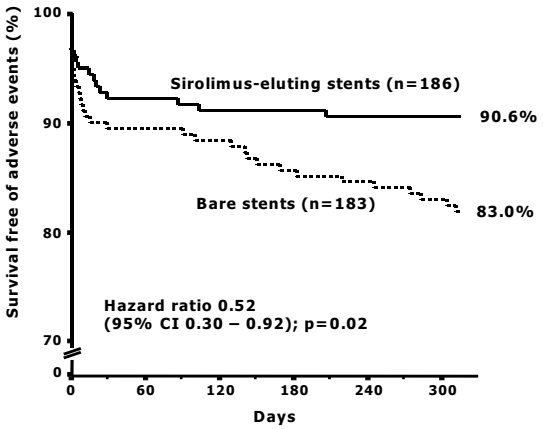
Table 2. Kaplan-Meier estimates of 30-day and 300-day adverse events.

	Bare stents (n=183)	SES (n=186)	P-value
30-day outcomes			
Death, %	5.5	5.9	1.0
Death or non-fatal re-infarction, %	7.1	6.5	0.8
Target vessel revascularization, %	4.4	1.1	0.1
Any event, %	10.4	7.5	0.4
Stent thrombosis, %*	1.6	0	0.1
300-day outcomes			
Death, %	8.2	8.3	0.8
Death or non-fatal re-infarction, %	10.4	8.8	0.5
Target vessel revascularization, %	8.2	1.1	<0.01
Any event, %	17.0	9.4	0.02

SES=sirolimus-eluting stents
*Angiographically documented stent thrombosis

Discussion

The main finding of the present study was that sirolimus-eluting stent implantation was effective in reducing the incidence of adverse events at 300 days in unselected patients with ST-elevation acute myocardial infarction, compared to conventional bare stenting. Furthermore, the risk of subacute thrombosis within the first 30 days did not appear higher compared with bare metal stents. Sirolimus-eluting stents were associated with a relative reduction of 48% in the risk of death, re-infarction, or repeat intervention and a relative reduction of 79% in the risk of repeat intervention at 300 days.



Survival free of re-infarction or target vessel revascularization in the sirolimus-eluting stent and conventional stent groups.

In our series, reperfusion treatment with sirolimus-eluting stents was associated with similar rates of vessel patency, enzymatic release, and 30-day complications compared to bare stents. The death rate and the incidence of death or re-infarction were similar in both study groups, but somewhat higher than those reported in randomized trials with selected patients (1,2). These findings most probably reflect the unrestrictive inclusion criteria of our series (10), which frequently enrolled patients not included in randomized studies, like for instance, cardiogenic shock, multivessel disease, and unprotected left main lesions. Importantly, stent thrombosis has not been identified in any patient treated with sirolimus stents and occurred in 3 controls (1.6%), with no statistical difference between the groups. Although the incidence of stent thrombosis in the bare stent group was at a somewhat higher range, our results in this group was not discrepant from historical series with conventional stents (1,2,11-13).

Coronary stenting for the treatment of acute myocardial infarction has been limited by the need of late repeat intervention, which has been reported to occur in approximately 9% of cases at 6 months, ranging from 3.6% to 22.7% (1-3). The incidence of repeat intervention after conventional stenting in our series (8.2%) was in line with these previous figures. Conversely, patients treated with sirolimus-eluting stent implantation had clearly a reduced risk of re-intervention at 10 months. Of note, between 30 days and 10 months, no additional patient was referred for repeat revascularization, which is consistent with the lack of angiographic restenosis after sirolimus stent implantation, as previously shown in a subset of patients from the present population (7).

Table 3. Multivariate predictors of 300-day major adverse cardiac events.

	Hazard ratio	95% confidence interval	P-value
SES utilization	0.53	0.29–0.95	0.03
Cardiogenic shock	3.31	1.72–6.34	<0.01
Culprit vessel left main coronary	6.05	1.60–22.87	<0.01
Culprit vessel left anterior descending	2.02	1.10–3.71	0.02
Post-procedure TIMI flow			<0.01
Grade 0/I (reference)	1.00	-	
Grade II	0.29	0.11–0.76	
Grade III	0.17	0.07–0.40	
Current smoking	0.57	0.31–1.02	0.06

SES=sirolimus-eluting stents
*Angiographically documented stent thrombosis

The peri- and post-procedural antiplatelet therapeutic scheme differed between patients treated with bare or sirolimus stents in our series. Patients in the sirolimus group received less glycoprotein IIbIIIa inhibitors but had a longer clopidogrel prescription time. However, none of these characteristics were identified as independent predictors influencing the outcomes of patients. The impact of clopidogrel and IIbIIIa inhibitors on the long-term clinical outcomes of patients with ST elevation acute myocardial infarction still remain to be established (2,14,15).

Conclusions

Sirolimus-eluting stent implantation for unselected patients with ST elevation acute myocardial infarction was associated with similar procedural and 30-days outcomes compared to bare stents, but markedly reduce the risk of major adverse events and repeat intervention at 10 months. By providing effective mechanical reperfusion with similar results to the current therapeutic standard, and decreasing the incidence of late complications, sirolimus-eluting stents appeared as an attractive

approach for this patient admitted with acute myocardial infarction. The promising results of the present study warrant further confirmation in the context of a randomized trial.

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Chapter 7 Impact of Baseline Renal Function on Mortality After Percutaneous Coronary Intervention With Sirolimus-Eluting Stents or Bare Metal Stents

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Impact of Baseline Renal Function on Mortality After Percutaneous Coronary Intervention With Sirolimus-Eluting Stents or Bare Stents

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Background: Renal impairment is an important predictor of mortality after percutaneous coronary intervention and may increase the restenosis rate. However, the relationship between restenosis and the risk of death in patients with renal impairment remains unclear. We evaluated the incidence of repeat revascularization and mortality in patients with or without renal impairment treated with sirolimus-eluting stents or bare stents.

Methods and Results: A total of 1080 consecutive patients treated during a period of 1 year had available data to calculate the baseline creatinine clearance. Patients were treated with bare stents (first 6 months; n=543) or sirolimus-eluting stents (last 6 months; n=537) and grouped according to the presence or absence of renal impairment (creatinine clearance <60ml/min). Patients with renal impairment had a higher mortality at 1 year (7.6% vs. 2.5%; hazard ratio 3.14 [95% CI: 1.68 – 5.88]; p<0.01), with no differences in mortality between the bare and sirolimus groups (hazard ratio 0.91 [95% CI: 0.49 – 1.68]; p=0.8). The incidence of target vessel revascularization was significantly reduced by sirolimus stents in patients without renal impairment (hazard ratio 0.59; [95% CI 0.39 – 0.90]; p=0.01) and in patients with decreased renal function (hazard ratio 0.37; [95% CI 0.15 – 0.90]; p=0.03).

Conclusions: SES implantation reduce clinical restenosis in patients with renal impairment compared to conventional stenting. However, this benefit was not paralleled by a reduction in the risk of death in this population. It seems unlikely that restenosis could contribute as a factor influencing the increased mortality of patients with impaired renal function.

Submitted for publication

Introduction

Chronic kidney disease has been shown to strongly increase the risk of short- and long-term adverse events in patients with atherosclerotic disease.[1-14] The impact of this association is further maximized by its rising prevalence, which is expected to more than double between 1998 and 2010.[13] In face of its growing frequency and the increased recognition of renal dysfunction as a powerful risk factor for future cardiovascular complications, the American Heart Association has recently released a scientific statement highlighting the clinical importance of this condition for the management of patients with coronary disease.[13] Unfortunately, the treatment of atherosclerotic heart disease in patients with renal impairment is often problematic due to the presence of multiple co-morbidities and to frequent limitations in drug prescription. Moreover, neither surgical nor percutaneous revascularization have been shown to eliminate the increased risk of patients with renal impairment.[4-6,9,10,12]

Patients with renal failure have previously shown to have higher mortality rates even after successful percutaneous coronary intervention.[4,5,10] Whether the occurrence of late restenosis contributes to the increased risk of death in this population remains unkown.[4,10] Dialysis patients have been reported to present high rates of angiographic restenosis after percutaneous intervention.[15] However, observational studies without angiographic re-evaluation have failed to shown an increase in clinical restenosis in patients with renal failure.[5,9] Moreover, previous reports have shown conflicting results regarding the impact of coronary stents on the outcomes of patients with renal impairment.[4,5,10]

Sirolimus-eluting stents (SES) have proven to markedly decrease neointimal growth and in-stent restenosis in comparison with conventional stents, with an impressive reduction in the risk of subsequent repeat revascularization.[16-19] However, all clinical trials conducted to date excluded this subset of patients with impaired renal function and, as a consequence, the impact of SES implantation on the outcomes of this subset of patients is currently unknown. The present study aimed therefore to evaluate the impact of baseline renal function on the 1-year mortality of patients treated with either conventional bare stents or sirolimus-eluting stents.

Methods

Patient Population and Procedures

Since April 2002, sirolimus-eluting stent implantation (Cypher; Johnson & Johnson-Cordis unit, Cordis Europa NV, Roden, the Netherlands) has been adopted as the default interventional strategy for all patients treated in our institution, as described elsewhere.[19,20] For comparison, a control group was composed of all consecutive patients treated with conventional bare stents in the period prior the introduction of sirolimus-eluting stents.[19,20] From October 2001 until October 2002 (6-month enrollment for both the pre-sirolimus and the sirolimus phases), a total of 1262 consecutive non-dialysis patients were treated with bare stents or sirolimus eluting-stents in the 2 study periods. From these, 1080 patients (86%) had pre-procedure serum creatinine measured in our institution and compose the present study population (bare stent group=543 patients; sirolimus-eluting stent group=537 patients).

All interventions were performed utilizing standard techniques and the final strategy was left at the operators' choice. Angiographic success was defined as residual stenosis < 30% by visual analysis with TIMI 3 antegrade flow. Periprocedural glycoprotein IIbIIIa inhibitor utilization was left to the discretion of the operator. All

patients were advised to maintain lifelong aspirin. Clopidogrel was prescribed for at least for 1 month in the bare stent group. For patients treated with sirolimus-eluting stents, clopidogrel was recommended for 3 months, unless for those with at least one of the following characteristics (in which case clopidogrel was maintained for at least 6 months): multiple SES implantation (>3 stents), total stented length >36 mm, chronic total occlusion, bifurcation, and in-stent restenosis. The study was approved by the local ethics committee and written, informed consent was obtained from every patient.

Clinical Follow-up and Endpoints

In-hospital clinical information was retrieved from an electronic database for patients maintained in our hospital and by review of the hospital records for those discharged to referring hospitals. Post-discharge survival status was obtained from the Municipal Civil Registries. Repeat revascularization procedures (surgical or percutaneous) and re-hospitalizations were prospectively collected during the follow-up. Patients were directly approached and/or the referring physicians and institutions were contacted whenever necessary for additional information.

The primary endpoint of the present study was all-cause mortality at 1 year. The incidence of target vessel revascularization was assessed to evaluate the anti-restenotic effect of sirolimus-eluting stents in comparison with bare stents. Target vessel revascularization was defined as a re-intervention (surgical or percutaneous) to treat any lesion located in the same epicardial vessel treated at the index procedure.

Renal Function Evaluation

The closest creatinine values before the procedure were used to calculate baseline creatinine clearance according to the formula proposed by Cockcroft and Gault: creatinine clearance (ml/min)=(140 - age) x weight (kg) ÷ 72 x serum creatinine (mg/dl) (x 0.85 for women).[21] Renal impairment was defined as a calculated creatinine clearance below 60 ml/min, a cutoff value previously proposed by the National Kidney Foundation - Kidney Disease Outcome Quality Initiative Advisory Board to identify patients with moderate renal impairment [11] and the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention.[13]

Table 1. Baseline and procedural characteristics of patients with or without renal impairment treated with bare stents or SES

	Normal renal function		Renal impairment		
	Bare stent (n=451)	SES (n=443)	Bare Stent (n=92)	SES (n=94)	p-value*
Male, %	79	73	48	50	<0.01
Age, years±SD	59±11	59±10	72±8	72±9	<0.01
Height, cm±SD	174±8	173±9	167±10	167±9	<0.01
Weight, kg±SD †	84±13	82±14	71±11	70±11	<0.01
Hypercholesterolemia, %	56	58	51	62	0.9
Hypertension, %	36	39	49	50	<0.01
Current smoking, % †	37	31	20	17	<0.01
Diabetes, %	14	18	20	20	0.2
Insulin-dependent diabetes	4	5	9	6	0.1
Non insulin-dependent diabetes	10	13	11	14	0.7
Previous MI, %	39	33	39	31	0.8
Previous bypass surgery, %	7	9	25	21	<0.01
Previous percutaneous intervention, % †	21	27	25	31	0.2
Clinical presentation					0.1
Stable angina, %	47	50	55	38	
Unstable angina, %	34	35	35	47	
Acute myocardial infarction, %	19	16	10	15	
Coronary vessel disease					<0.01
1-vessel disease, %	49	48	36	33	
2-vessel disease, %	36	34	29	31	
3-vessel disease, %	16	19	35	36	
Vessel treated					
Right coronary artery, %	39	39	32	28	0.02
Left anterior descending, %	57	57	52	63	0.9
Left circumflex artery, %	34	31	33	33	1.0
Left main coronary, %	4	2	5	5	0.2
Bypass graft, %	3	3	12	11	<0.01
Treatment of ISR (at least 1 lesion), % †	4	10	6	13	0.2
Number of stents implanted per pt,±SD ‡	1.9±1.1	2.1±1.4	2.1±1.4	2.4±1.6	<0.01
Angiographic success for all lesions, %	97	97	98	98	0.8
Periprocedural IIbIIIa inhibitor, % †	39	17	29	21	0.5
Statin at discharge, %	66	65	59	62	0.2
ACE inhibitor at discharge, %	30	25	26	28	1.0
Clopidogrel prescription, months±SD ‡	3.0±2.1	4.2±2.0	3.0±1.8	4.1±2.0	0.9
Serum creatinine, mg/dl±SD	0.9±0.8	0.9±0.2	1.3±0.4	1.3±0.4	<0.01
Creatinine clearance, ml/min±SD	101±29	98±25	49±9	50±9	<0.01

ISR=in-stent restenosis; pt=patient; SD=standard deviation; SES=sirolimus-eluting stents

* for the comparison between patients with normal renal function and patients with renal impairment pooled over stent type group

† p<0.05 for bare stents vs. sirolimus-eluting stents pooled over renal function group

‡ p<0.01 for bare stents vs. sirolimus-eluting stents pooled over renal function group

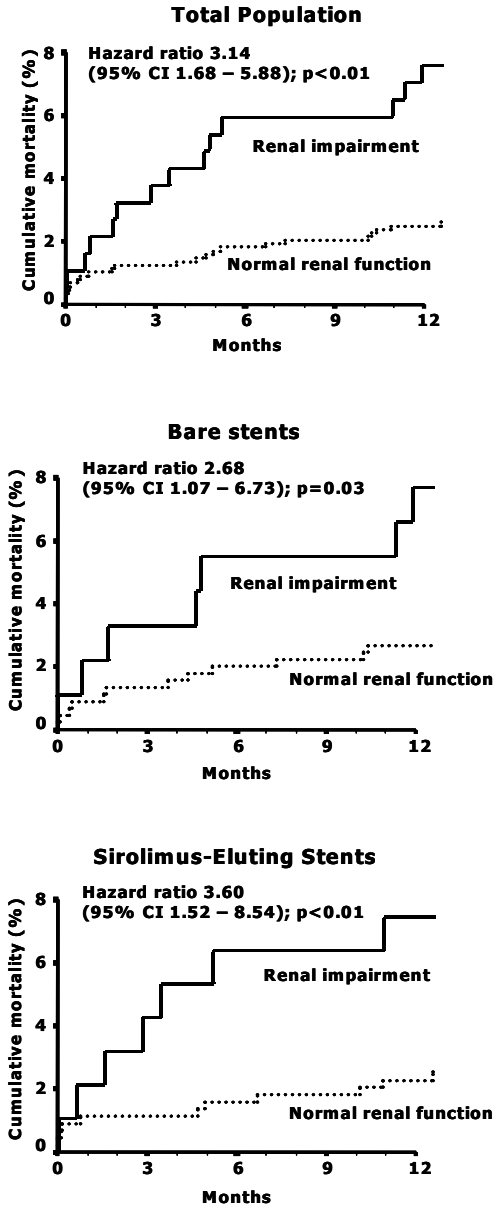

Figure 1. Incidence of all-cause death for patients with or without renal impairment. Top panel: total study population pooled over stent type. Mid panel: patients treated with bare stents. Lower panel: patients treated with sirolimus-elutings stents.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation (SD) and were compared using Student's T-test. Categorical variables were presented as counts and percentages and compared with the Fisher's exact test. The unadjusted cumulative incidence of death and target vessel revascularization was evaluated by the Kaplan-Meier method. Cox proportional hazards models were utilized to examine the effect of renal impairment, sirolimus-eluting stent implantation and the interaction between stent type vs. renal function on the clinical endpoints. In order to adjust for baseline differences between the study groups, all variables associated with the clinical endpoints at univariate analyses (p-value for selection ≤ 0.2) were tested in multivariate analyses to identify independent predictors of 1-year mortality (tested variables: sex, acute myocardial infarction at admission, triple vessel disease, hyphercholesterolemia, current smoking, diabetes, angiographic success, statin prescription, left anterior descending stenting, left main coronary stenting, bypass graft stenting, renal function impairment) and target vessel revascularization (tested variables: previous bypass surgery, acute myocardial infarction at admission, triple vessel disease, hyphercholesterolemia, current smoking, diabetes, left main coronary stenting, bypass graft stenting, number of stents implanted, treatment of in-stent restenosis, SES utilization). The final models were built by backward stepwise variable selection with a p-value <0.05 used as a criterion for both entry and removal of variables. All reported p values were two-tailed and a p-value <0.05 was regarded as significant.

Results

Baseline and procedural characteristics

From the 543 patients treated with bare stents, a total of 92 patients had renal dysfunction at baseline (17%), and among the 537 patients treated with sirolimus-eluting stents, renal dysfunction was present in 94 patients (18%). Table 1 summarizes the baseline and procedural characteristics of patients with normal renal function or renal impairment, according to the type of stent utilized. Pooled over the stent type utilized, patients with renal impairment were older and more frequently female; had more hypertension, previous coronary surgery, triple-vessel disease, bypass graft stenting, and a higher number of stents implanted per procedure. Also, patients with a lower clearance had lower weights and heights, and were less likely to smoke and to have received stent in the right coronary artery. Overall, in patients with or without renal impairment, the average serum creatinine was 0.9 ± 0.2 mg/dl vs 1.3 ± 0.4 mg/dl respectively (p<0.01), and the average creatinine clearance was 99 ± 27 mg/min vs 49 ± 9 mg/dl respectively (p<0.01).

Pre-procedure baseline characteristics between patients treated with sirolimus-eluting stents or bare stents were similar, except for a lower frequency of current smokers and a higher rate of previous percutaneous intervention and treatment of restenotic lesions in patients receiving sirolimus stents (Table 1). The average creatinine clearance was similar between patients treated with sirolimus or bare stents. In the sirolimus group, utilization of IIbIIIa inhibitors was lower and the number of stents implanted per procedure was higher (Table 1). Clopidogrel utilization was longer in the sirolimus group as per the pre-defined treatment protocol. There were no differences with regard to the post-procedure prescription of statin between the sirolimus and bare groups.

1-year mortality

Clinical follow-up data was available for 99.4% of patients (median follow-up period 421 days; interquartile range: 391 – 459 days). When all patients were pooled together, regardless of SES or bare stent utilization, the unadjusted risk of death at 1 year was significantly higher in patients with renal impairment than in patients with normal renal function (7.6% vs. 2.5% respectively; hazard ratio 3.14 [95% CI: 1.68 – 5.88]; p<0.01) (Figure

1). Similarly, when analysed separately, baseline renal impairment significantly increased the risk of death in patients treated with either bare stents or sirolimus-eluting stents (Figure 1). When evaluated irrespective of renal function, patients treated with bare stents or sirolimus-eluting stents had similar 1-year mortality rates (3.6% vs. 3.2% respectively; hazard ratio 0.91 [95% CI: 0.49 – 1.68]; p=0.8) (Figure 2). The interaction factor for the relationship of the effect of renal impairment and stent type on the risk of death was not significant (p-value for the interaction = 0.7).

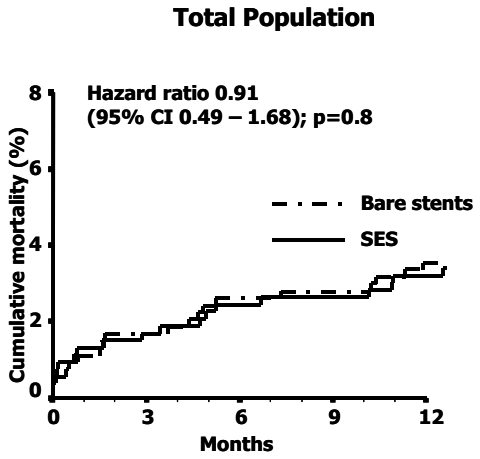

Figure 2. Unadjusted 1-year incidence of all-cause death for patients treated with bare stents vs. sirolimus-elutings stents polled over renal function.

At multivariate analysis, female sex (adjusted hazard ratio 2.00 [95% CI: 1.04 – 3.85]; p=0.04), renal impairment (adjusted hazard ratio 2.15 [95% CI: 1.10 – 4.28]; p=0.03), acute myocardial infarction (adjusted hazard ratio 3.00 [95% CI: 1.54 – 5.86]; p<0.01), and triple-vessel disease (adjusted hazard ratio 2.75 [95% CI: 1.44 – 5.22]; p<0.01) were identified as independent predictors of 1-year mortality (Table 2). The utilization of sirolimus-eluting stents had no influence in the risk of death at 1 year (adjusted hazard ratio 1.10 [95% CI: 0.59 – 2.07]; p=0.8) (Table 2).

Repeat revascularization

Overall, sirolimus-eluting stent significantly reduced the incidence of target vessel revascularization at 1 year compared to bare stent implantation (unadjusted hazard ratio 0.54 [95% CI 0.37 – 0.79]; p<0.01). Sirolimus-eluting stent implantation was effective in reducing the risk of target vessel revascularization both in patients without (unadjusted hazard ratio 0.59; [95% CI 0.39 – 0.90]; p=0.01) and in patients with renal impairment (unadjusted hazard ratio 0.37; [95% CI 0.15 – 0.90]; p=0.03). At multivariate analysis, sirolimus-eluting stent utilization remained as an important factor reducing the risk of repeat revascularization (adjusted hazard ratio 0.43; [95% CI 0.29 – 0.64]; p<0.01). Importantly, the presence of renal impairment did not significantly influence the risk of target vessel revascularization (adjusted hazard ratio 1.22; [95% CI 0.79 – 1.88]; p=0.4). Other independent predictors of 1-year target vessel revascularization are presented in (Table 2).

Table 2. Independent multivariate predictors of 1-year all-cause mortality and repeat revascularization

	Hazard ratio	95% confidence interval	p value
1-year mortality			
Female sex	2.00	1.04 – 3.85	0.04
Renal impairment	2.15	1.10 – 4.28	0.03
Acute myocardial infarction	3.00	1.54 – 5.86	<0.01
Triple-vessel disease	2.75	1.44 – 5.22	<0.01
Sirolimus-eluting stent utilization	1.10	0.59 – 2.07	0.8
1-year target vessel revascularization			
Renal impairment	1.22	0.79 – 1.88	0.4
Sirolimus-eluting stent utilization	0.43	0.29 – 0.64	<0.01
Current smoking	0.56	0.36 – 0.88	0.01
Treatement of in-stent restenosis	3.29	2.05 – 5.28	<0.01
Number of stents implanted	1.23	1.09 – 1.38	<0.01

Discussion

The main finding of the present study was that impaired renal function significantly increases 1-year mortality after percutaneous coronary revascularization, regardless of the use of sirolimus-eluting stents or conventional bare stents. Despite the clear anti-restenotic effect of sirolimus-eluting stents, which markedly reduced the incidence of target vessel revascularization compared to bare stents, mortality rates in patients with and without renal dysfunction were similar in both treatment strategies.

Impaired renal function has been previously shown to negatively influence survival rates after percutaneous intervention.[4-6,9,10,12] Although patients with renal impairment are well-known to have an increased prevalence of associated risk factors, it has been identified in our series and in previous reports to be an important independent predictor of mortality. A number of inflammatory, procoagulant, and atherogenic markers have been described in patients with renal impairment,[22-29] which may potentially accelerate disease progression and account for a higher tendency to acute events. Some of these factors have been previously associated with an increased risk of late restenosis.[15,30,31] Accordingly, patients with end-stage renal failure have been shown to present increased levels of fibrinogen and higher rates of restenosis than non-dialysis patients.[15] It has been hypothesized that the high incidence of restenosis could possibly contribute to the increased mortality seen in patients with renal impairment.[4,10] Our results challenge this concept by demonstrating that the strikingly reduction of clinical restenosis after sirolimus-eluting stents is not paralleled by any reduction in mortality among patients with renal impairment.

Even though drug-eluting stents did not decrease the mortality risk following coronary intervention, the reduction of restenosis represent an important therapeutic achievement for the clinical management of patients with renal impairment. In our series, sirolimus-eluting stents decreased the risk of repeat revascularization in patients with renal impairment by more than half of the risk seen with bare stents. The marked reduction in the risk of repeat revascularization may shift the focus of clinical attention after percutaneous intervention from restenosis prevention towards the institution of more aggressive disease-modifying strategies.

Although the present study suffers from the limitations related to its non-randomized nature, both study groups (bare and sirolimus groups) had comparable baseline characteristics. Creatinine clearance was calculated, as it has been shown to correlate well with actual values[21] and provide a better estimate of renal function than serum creatinine alone.[32] Complete data for pre-procedure creatinine clearance calculation were available for 86% of patients, which may introduce a selection bias in the analysis. Nevertheless, patients excluded from this study due to missing creatinine clearance data had an 1-year mortality rate of approximately 5.5%, which is intermediate between patients with and without renal impairment, indicating that the excluded cases may have a similar proportion of both groups of renal function.

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Chapter 8 Effectiveness of the Sirolimus-eluting Stent in the Treatment of Patients with a Prior History of Coronary Artery Bypass Graft Surgery

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Coronary Artery Disease. *In press*

Effectiveness of the Sirolimus-eluting Stent in the Treatment of Patients with a Prior History of Coronary Artery Bypass Graft Surgery

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Objective: Percutaneous coronary intervention in patients with a history of previous coronary artery bypass grafting (CABG) is associated with an increased rate of subsequent adverse events compared to those without prior CABG. We evaluated the impact of utilizing the sirolimus-eluting stent (SES) in this high risk population.
Methods: Since April 2002, SES implantation was utilized as the default strategy for all percutaneous procedures in our hospital. Consecutive patients with a history of previous CABG and *de novo* lesions (n=47) treated exclusively with SES, were compared to 67 patients who received bare stents in the 6 month period just before SES introduction.
Results: There were no significant differences between SES and bare stent with respect to baseline clinical or lesion characteristics. The only difference between the groups related to the nominal diameter of stent utilized, which was smaller in the SES group than the bare stent group (maximum diameter of SES available was 3.0mm). At 1 year, the cumulative incidence of death, myocardial infarction, or target vessel revascularization was significantly lower in the SES group than the bare stent group (8.5% versus 30.3%, HR 0.37 [95% CI 0.15-0.91]; p=0.03)
Conclusions: The utilization of sirolimus-eluting stents for percutaneous intervention in patients with previous coronary surgery is associated with a significant reduction in the 1-year incidence of major adverse cardiac events.

Coronary Artery Disease. *In press.*

Introduction

More than 300,000 people undergo coronary artery bypass graft (CABG) surgery every year in the U.S. alone, yet CABG is not a definitive therapy and patients continue to have considerable cardiovascular morbidity and mortality. Recurrence of ischemia and angina relates to either progression of native vessel atherosclerosis, or failure of the bypass grafts themselves. Indeed, angiographic studies have shown that by 10-12years, 75-79% vein grafts are occluded or severely diseased.[1,2] Furthermore, studies have also suggested that following bypass implantation, atherosclerosis within the native vessels may actually progress more rapidly compared to vessels in the same patient which were not grafted.[3,4] In the large Coronary Artery Surgery Study (CASS) of more than 9,500 patients, angina recurred in 24% within the first year and in 40% by the sixth year.[5] Therefore, an increasing number of people with a history of previous CABG are being considered for further revascularization.

Repeat CABG surgery is associated with a higher mortality than the first operation.[6,7] Percutaneous revascularization is therefore an attractive alternative strategy. However, following PCI, patients with prior CABG have been shown to have an increased combined risk of death and myocardial infarction.[8-13] They have a higher risk profile than those without previous CABG, tend to be older, and have more extensive vessel disease. Furthermore, intervention with stent implantation within venous bypass grafts themselves, is associated with a high subsequent rate of restenosis of 37-53%.[14,15] Drug-eluting stents have been shown to be highly successful in reducing restenosis in native coronary disease in a select patient population.[16,17] This study evaluates the sirolimus-eluting stent (SES) for percutaneous intervention in patients with previous CABG, compared to both those without prior CABG, and those treated in the preceding 6 months with bare stents.

Methods

From April 2002, all percutaneous coronary intervention at our centre was done with a policy of SES usage, irrespective of clinical presentation or lesion morphology, further details of the methodology are described elsewhere.[18,19] All procedures were performed with standard interventional techniques except with the use of SES as the device of choice. SES were available in lengths between 8mm and 33mm, and diameters of between 2.25-3.0mm. All patients were treated with long-term aspirin therapy and received a loading dose of 300mg clopidogrel followed by a daily dose of 75mg for at least 3 months. The procedural utilization of glycoprotein IIb/IIIa inhibitor therapy and distal protection devices was at the discretion of the operator.

The current study cohort comprises of 47 patients with a previous history of CABG who were treated for *de novo* lesions solely with SES. A control group (n=66) comprised of patients who had been treated similarly in the preceding 6-months though with bare stents. The protocol was approved by the local ethics committee an all patients signed a written informed consent.

Patients were followed up and evaluated for major adverse cardiac events (MACE), defined as: 1) death, 2) myocardial infarction (AMI), or 3) repeat target vessel revascularization. The diagnosis of myocardial infarction required an elevation of creatine kinase levels to 2X upper limit of normal, together with a rise in creatine kinase-MB. Target vessel revascularization (TVR) was defined as a reintervention in the treated vessel.

MACE-free estimates were calculated with the Kaplan-Meier method. Hazard ratios of adverse events were calculated by Cox proportional hazard models. A $p<0.05$ was considered as significant.

Results

Baseline patient demographics and procedural data are presented in table 1. There were no significant differences between the 2 groups treated with either bare stents or SES, except in the mean nominal diameter of stent utilized, which was smaller in the SES group.

Intervention within native coronary arteries only, occurred in 59.9% of the bare stent group, and 63.8% of the SES group. The angiographic success rate in both groups was high at >97%. Table 3 presents the Kaplan-Meier estimates of the rate of major adverse cardiac events of the two groups at 1 year. There is a significantly lower rate of events in the SES group, predominantly related to a reduced need for repeat target vessel revascularization (Table 2; Figure).

Table 1: Baseline patient demographics

	Bare stent n=66	SES group n=47	p value
Male sex (%)	66.7	70.3	0.5
Mean age (years)	69 ± 11	68 ± 9	1.0
Current smoker (%)	16.7	10.6	0.4
Diabetes mellitus (%)	19.7	21.3	1.0
Previous MI (%)	47.7	31.9	0.2
Previous PCI (%)	39.4	42.6	0.9
Multivessel disease (%)	95.5	91.5	0.5
Clinical presentation			0.2
Stable angina (%)	48.5	63.8	
Unstable angina (%)	43.9	34.0	
Acute MI (%)	7.6	2.1	
GP IIb/IIIa inhibitor	36.4	21.3	0.1
Treated vessel			
Left anterior descending (%)	34.8	42.6	0.4
Left circumflex (%)	33.3	29.8	0.8
Right coronary artery (%)	27.3	17.0	0.3
Left main coronary (%)	15.2	10.6	0.6
Bypass graft (%)	40.9	36.2	0.7
Mean number of stents	2.1 ± 1.4	1.9±0.9	0.7
Mean stent diameter (mm)	3.3 ± 0.6	2.8±0.3	<0.01
Stented length per patient (mm)	35.1±24.7	32.6±22.1	1.0
Angiographic success (%)	98.5	97.9	1.0

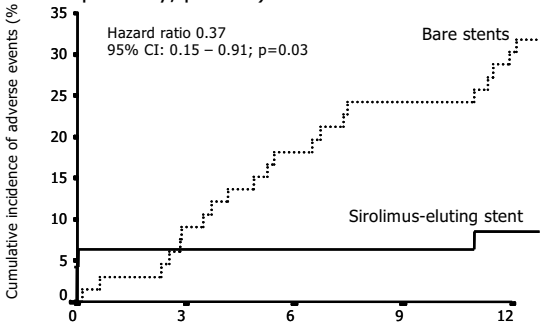
Table 2: Kaplan-Meier estimates of 1-year major adverse events

	Bare stents	SES	HR	95% CI	p-value
Death, %	6.1	2.1	0.34	0.04 – 3.09	0.3
Death or myocardial infarction, %	10.6	6.4	0.80	0.24 – 2.71	0.7
Target vessel revascularization, %	23.0	2.1	0.23	0.07 – 0.80	0.02
Any event, %	30.3	8.5	0.37	0.15 – 0.91	0.03

Discussion

Previous data show that percutaneous intervention with bare stents in patients with a history of previous CABG, is associated with an increased rate of MACE compared to those without prior CABG. [8-13] This relates, at least in part, to the association of this group of patients with an adverse risk profile as patients tend to be older, and have a higher prevalence of diabetes, and multivessel disease. [8-13] Moreover, this increase in MACE is evident whether patients are being treated in the context of either stable angina, or an acute coronary syndrome. [8-13] However, we have demonstrated that in a consecutive series of patients with previous CABG treated with PCI and stent implantation, the utilization of the sirolimus-eluting stent significantly reduces the rate of MACE compared to those treated with bare metal stents.

It is 20 years since Douglas et al demonstrated the feasibility of PCI in patients with a history of CABG. [20] More recently, the AWESOME randomized trial and registry demonstrated that at three years, the overall survival of patients with previous CABG and medically refractory angina, was similar whether treated with either PCI or re-do CABG. [21] Moreover, when given the choice of PCI or re-do CABG, the majority of patients preferred the former option. The Investigators concluded that PCI may be the preferred revascularization strategy.In the present study, 40.9% in the bare stent group, and 36.2% of the SES group underwent intervention within at least one bypass graft. Compared to native vessels, percutaneous revascularization of diseased saphenous vein grafts is hampered by an increased rate of adverse events thereby contributing to the worse outcome of post-CABG patients. Procedural complications may relate to distal embolisation of friable material within the graft, and at follow-up, grafts are subject to an increased rate of restenosis. Historically, results of balloon-only therapy were disappointing. [22-24] In one study of 454 patients, procedural success was 90%, with a 5-year MACE-free survival of only 26%. [24] Subsequently, a randomized trial demonstrated the benefit of stenting over balloon angioplasty. At 6-months, the rate of survival free from either death, myocardial infarction, repeat CABG, or TLR was 73% in the stented group versus just 58% in the balloon-only group (p=0.03). [15] However, the angiographic restenosis rate remained high (37% versus 46% respectively, p=0.24).



Cumulative incidence of major adverse events

The major limitation of PCI has always been the development of instent restenosis and subsequent need for repeat revascularization. In particular, restenosis rates utilizing bare stents within saphenous venous bypass grafts range between 37-53%. [14,15] Intervention solely within native vessels was undertaken in 59.9% of the bare stent group, and 63.8% of the SES group. The type of native vessel disease manifested in a population with a history of previous CABG can be difficult to effectively treat percutaneously; lesions may be ostial, or chronically occluded, or the disease may be diffuse and the arteries small and calcified. These features, together with the increased prevalance of diabetes in these patients, tend to increase the risk of developing restenosis.[25,26]

Studies evaluating the SES have demonstrated low rates of restenosis compared with bare stents when used in relatively simple lesions. [16,17] The current study evaluated the results of PCI in a high risk population with a history of previous CABG. Both cohorts were comparable with respect to baseline clinical and lesion characteristics, and all procedures were carried out as a consecutive series, in a single center by the same operators. The only difference between the groups was a significantly smaller mean nominal diameter of stent utilized in the SES group. This is likely to reflect the fact that the maximum nominal diameter of SES available was 3.0mm [27] (though post-dilatation was freely allowed) which is often small

particularly within venous bypass grafts. A smaller stent (associated with a smaller minimal lumen diameter) is more likely to be associated with subsequent restenosis [28] which might have tended towards an increased need for target vessel revascularization in the SES group. However, at 1 year, those treated with SES had a significantly lower rate of MACE compared to those patients treated with bare stent implantation, predominantly related to a reduction in the need for repeat target vessel revascularization.

Our study accurately reflects the "real world" practice of interventional cardiology, and clearly demonstrates the applicability of the sirolimus-eluting stent in reducing the subsequent rate of adverse events at one year, in a high risk population with a history of previous coronary artery bypass graft surgery.

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Chapter 9 Effectiveness of sirolimus-eluting stent for treatment of left main coronary artery disease

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The present study reports on the clinical outcome of 31 consecutive patients with left main coronary artery disease treated with a sirolimus-eluting stent. The implantation of this stent was associated with aboli-tion of post-discharge fatal events and percutaneous reintervention.

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Several trials have reported on the safety and fea-sibility of stent implantation to treat left main (LM) coronary disease, with favorable procedural and long-term results.[1–4] However, restenosis remains the major complication limiting late outcome after percu-taneous intervention. In patients treated with LM stenting, the occurrence of restenosis has been partic-ularly associated with hazardous clinical manifesta-tions.[5] In this viewpoint, although percutaneous inter-vention has increasingly been reported as a possible therapeutic alternative, surgical revascularization re-mains the most appropriate therapy.[6] The sirolimus-eluting stent (SES) (Cypher, Johnson & Johnson– Cordis, Miami, Florida) has recently proved its effi-cacy to reduce restenosis [7] in selected populations. Importantly, by maintaining all mechanical properties, the late benefit observed with the SES was accom-plished without compromising the excellent proce-dural and acute results already obtained with conven-tional metallic stents. Currently, the impact of SES implantation on patients with LM disease is unknown. We evaluated the efficacy of the SES on the short- and long-term clinical outcomes in 31 patients treated for LM disease.

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Since April 16, 2002, SES implantation has been adopted as the default strategy for all patients treated in our institution as part of the Rapamycin Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. Briefly, the RESEARCH is a single-center registry whose aim is to evaluate the efficacy of SES implantation in the "real world" of interventional cardiology. All consecutive patients were enrolled irrespective of clinical presentation and lesion characteristics, and the incidence of major ad-verse cardiac events was evaluated during follow-up. At 6 months after enrollment, a total of 563 consec-utive patients were treated solely with SES. Of these, 31 patients (5.5%) were treated for LM artery disease and formed the present study population. In our institution, patients with LM disease are routinely treated with surgical revascularization. Therefore, patients enrolled in this study were divided into 3 groups: (1) 5 patients treated within the acute phase of myocardial infarction, (2) 17 elective patients who were refused surgical treatment due to high preoperative risk (n = 9) or to patient's preference for percutaneous treat-ment (n = 8), and (3) 9 patients with bailout stenting for LM dissection that occurred during angioplasty (4 had dissection induced by the guiding catheter, 1 due to wire exit, and 3 due to proximal left anterior de-scending stenting) or during conventional diagnostic procedures (1 patient). The protected LM segment was defined by the presence of a patent coronary artery bypass graft (n = 11). LM dilatation was performed with implantation of a 3.0-mm SES in all patients (largest diameter available at the time of this study). Use of glycoprotein IIb/IIIa agents was left to the operator's discretion. All patients were receiving long-term doses of aspirin (>75 mg/day) and received a loading dose of 300 mg of clopidogrel, followed by a 75-mg daily single dose for 6 months. Patients' informed written consent was obtained in accordance with the rules of the institutional ethics committee that approved the study.

In-hospital outcome information was retrieved by means of an electronic clinical database for patients maintained in our hospital after the procedure and by review of the hospital records for those discharged to secondary hospitals. After discharge, recordings of all repeat interventions (surgical and percutaneous) and repeat hospitalizations were prospectively collected in a dedicated database. Follow-up information was ob-tained by regular outpatient evaluation, by phone contact, or by mail.

Clinical outcomes were evaluated by the incidence of major adverse cardiac events, defined as death, myocardial infarction, or any target vessel revascular-ization, either surgical or percutaneous. Deaths were classified as either cardiac or noncardiac. Deaths that could not be classified were considered to be cardiac related. Procedural success was characterized by Thrombolysis In Myocardial Infarction grade flow 3 and residual in-lesion stenosis $\leq$30%. Clinical success was defined by the summation of procedural success in the absence of major in-hospital events.

Discrete variables are presented as counts and per-centages. Continuous variables are expressed as mean ± SD.

Baseline clinical and procedural characteristics of the study group are listed in Table 1. Overall, unpro-tected LM disease was present in 20 patients (65%). Four patients with acute myocardial infarction were admitted with cardiogenic shock (80%). Intra-aortic balloon pump or left

ventricular assistance devices were used in patients with either hemodynamic com-promise (n = 5) or in elective patients deemed to have a very high procedural risk (n = 3).[8] Postdilatation after SES deployment (with 3.5- to 4.5-mm balloons) was performed in 24 patients (77%). The distal LM bifurcation was treated in 15 patients (48%); in these patients, both the parent and side branch vessels re-ceived a SES. Segments other than the LM segment were treated in 19 patients (61%).

Table 1. Baseline clinical and procedural characteristics (n=31)

	Acute myocardial infarction (n=5)	Bail out stenting (n=9)	Elective (n=17)
Age (years)	64±9	65±16	65±9
Men	3 (60%)	4 (45%)	10 (59%)
Hypercholesterolemia	3 (60%)	5 (56%)	12 (70%)
Treated diabetes mellitus	1 (20%)	3 (33%)	7 (41%)
Treated systemic hypertension	0 (0%)	3 (33%)	13 (76%)
Prior myocardial infarction	0 (0%)	3 (33%)	7 (41%)
Prior angioplasty	0 (0%)	2 (22%)	6 (35%)
Prior coronary bypass	0 (0%)	1 (11%)	10 (59%)
Clinical presentation			
Stable angina pectoris	-	6 (67%)	17 (100%)
Unstable angina	-	3 (33%)	0 (0%)
Lesion location			
Ostial	2 (40%)	6 (67%)	5 (29%)
Body	2 (40%)	0 (0%)	1 (6%)
Bifurcation	1 (20%)	3 (33%)	11 (65%)
Stents per patient	3±2.3	4.5±1.9	2.8±1.6
Direct stenting	3 (60%)	9 (100%)	5 (29%)
IIb/IIIa inhibitors	4 (80%)	5 (56%)	5 (29%)
Cardiogenic shock	4 (80%)	0 (0%)	0 (0%)
Hemodynamic assist			
Intra aortic balloon	4 (80%)	1 (11%)	0 (0%)
Left ventricle assist device	0 (0%)	0 (0%)	3 (18%)
Minimal luminal diameter (mm±SD), pre	1.31± 0.32	1.66±0.65	1.12±0.45
Minimal luminal diameter (mm±SD), post	2.95±0.03	2.67±0.48	2.71±0.60
Reference vessel diameter (mm±SD), post	2.94±0.34	3.18±0.51	3.22±0.60

Table 2 lists the clinical outcomes for patients with acute myocardial infarction, bailout stenting, and elective angioplasty. The incidence of in-hospital major cardiac events was 60%, 22%, and 12% in the 3 groups, respectively. The in-hospital mortality rate in patients with acute myocardial infarction was 60%, in the bailout group 11%, and in elective patients, the rate was 0%. All 3 deaths in the acute myocardial infarction group occurred in patients admitted in cardiogenic shock (2 presented with a totally occluded LM seg-ment). In-hospital repeat revascularization occurred in only 1 patient. This patient had been successfully treated for LM dissection, but developed cardiac tamponade after the procedure and underwent surgical pericardial drainage, during which time he received a venous graft to the first obtuse marginal branch.

Postdischarge complete clinical follow-up is reported in Table 3 and was available for all living patients, except for 1 patient (who could not be contacted). Mean follow-up was 5.1 months (range 3.3 to 6.9). There were no postdischarge deaths, myocardial infarctions, or percutaneous revascularizations. One patient underwent elective minimally invasive coronary bypass (total target vessel revascularization rate of 4%). Initially, this patient had an SES implan-tation for iatrogenic dissection of the LM segment. This patient's nontreated vessel (chronic, totally occluded left anterior descending artery) underwent elective revascularization 1 month later.

Table 2. In-hospital events (n=31)

	Acute MI (n=5)	Bailout stenting (n=9)	Elective (n=17)
Deaths	3 (60%)	1 (11%)	1 (6%)
Myocardial Infarction	0 (0%)	0 (0%)	2 (12%)*
Percutaneous revascularization	0 (0%)	0 (0%)	0 (0%)
Coronary bypass	0 (0%)	1 (11%)	0 (0%)
Major cardiac events	3 (60%)	2 (22%)	2 (12%)

*Both cases with non-Q wave infarction (patient-1 with peaked Creatine kinase MB 185U/I, patient-2 with 36U/I)

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Recently, several studies have demonstrated that stenting of the LM artery may be a safe and effective alternative to the surgical approach in carefully selected patients.[1,3,4] Although the in-hospital success rates are extremely acceptable, the death rate increases gradually for nearly 6 months after the index procedure, and thereafter reoccurrence of major cardiac events is mainly attributed to progression of atherosclerosis.[5] Solving restenosis apparently is the key to improving the long-term outcome in these patients. The SES has thus far displayed reduced restenosis rates and a reduced need for reintervention.[9,10]

The extremely high in-house mortality rate in the myocardial infarction group mirrors the fatal risk of patients having LM disease in this clinical scenario. Our findings agree with previous studies reporting in-hospital mortality rates of acute myocardial infarction due to LM lesions of 55% to 80%.[11,12] The major finding of this report is the absence of fatal events in all patients discharged from the hospital; this study highlights the outstanding performance of the SES. The 0% rate of percutaneous reintervention reinforces the efficacy of the SES.

Table 3. Post-discharge events (mean follow-up 5.1 ± 1.8 months, n=27)

	Acute MI (n=2)	Bailout stenting (n=8)	Elective (n=17)
Deaths	0 (0%)	0 (0%)	0 (0%)
Myocardial infarction	0 (0%)	0 (0%)	0 (0%)
Percutaneous revascularization	0 (0%)	0 (0%)	0 (0%)
Coronary bypass	0 (0%)	1 (12%)	0 (0%)
Major cardiac events	0 (0%)	1 (12%)	0 (0%)

In the present study, post– high-pressure dilatations with larger balloons were used to optimize stent-to-wall apposition, and overcame the 3-mm width availability of the SES. It is not known whether this (sometimes extreme) postdilatation will affect the elution properties and compromise the polymer's performance. Furthermore, by spreading the struts widely apart, the amount of drug per square millimeter of artery may be reduced and thus impair the efficacy of the SES. However, in this study, the rate of out-of-hospital clinical events was extremely low. Thus, the discrepancy between stent and postdilatation balloon size does not appear to be of clinical significance.

Further investigation to confirm this is warranted. This was a single-center observational study, and our results may have been confounded by unmeasured factors. However, the 0% follow-up mortality rate warrants clinical recognition. The importance of our findings is supported by the fact that our study popu-lation was representative of the real world of patients who undergo percutaneous coronary intervention, thus denoting the everyday practice of an interventional cardiologist.

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Chapter 10 Elective Sirolimus-Eluting Stent Implantation for Left Main Coronary Artery Disease – 6 Month Angiographic Follow-up and 1 Year Clinical Outcome

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Catheter Cardiovasc Interv. *In press*

Elective Sirolimus-Eluting Stents for Left Main Coronary Disease – 6-Month Angiographic Follow-up and 1-Year Clinical Outcome

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The effectiveness of sirolimus-eluting stent (SES) implantation in patients treated electively for left main (LM) stenoses has not been yet ascertained. The present study reports on the clinical and angiographic outcome of 16 consecutive patients treated electively for de novo stenoses in the LM. The impact of SES implantation on major adverse cardiac events (MACE) was evaluated. Mean age was 65±11 years. Unprotected LM was present in 9(56%), and 8 patients (50%) received stents extending into both the left anterior descending and circumflex arteries for stenoses of the distal left main bifurcation. In-house mortality and reintervention rate was zero. One patient developed a non-Q wave myocardial infarction related to the index procedure. At one-year clinical follow-up there were no deaths or further myocardial infarctions, one (6%) patient required target lesion revascularization (TLR). A total of 12 patients (75%) underwent 6-month angiographic follow up with a late lumen loss of 0.04±0.65mm, and one focal restenosis (8% of patients). Elective SES implantation for LM disease was associated with zero mortality and a very low incidence of additional major adverse events at 1 year.

Catheter Cardiovasc Interv. *In press*

Introduction

A number of studies have reported on the safety and feasibility of left main (LM) coronary artery stenting, with various degrees of success depending on the particular clinical scenarios under which the patient was treated(1-4). More widespread use of this approach is hampered by the potentially fatal consequences of in-stent restenosis in this situation. Thus, the treatment of choice in most centers remains surgical revascularization based on trials conducted in the early 1980s(5).

Accumulating data have repeatedly confirmed that sirolimus-eluting stent implantation has been associated with unparalleled results in reducing restenosis rates(6) and neointimal hyperplasia formation(7). In this study we report the angiographic and clinical outcomes of 16 consecutive patients, scheduled for percutaneous treatment of de novo LM stenoses.

Materials and methods

The present study population comprised 16 consecutive patients undergoing elective angioplasty for LM de novo stenoses. The LM was considered protected if there was a patent coronary artery bypass graft to the left anterior descending or circumflex coronary arteries. All patients were treated with the largest available diameter SES (3mm), at the time of the study. Additional dilatation with largest balloons was used if necessary. Use of glycoprotein IIb/IIIa agents was left to the operator's discretion. All patients were on chronic aspirin (>75mg daily) and received a loading dose of 300mg clopidogrel followed by a 75mg daily single dose for 6 months. The patients' informed written consent was obtained in accordance with the rules of the Institutional Ethics Committee, which approved the study. The analysis, interpretation, and submission for publication of this study were conducted independently of the trial sponsor.

A detailed description of the RESEARCH registry has been provided elsewhere(8). Briefly, the RESEARCH is a single-centre registry, which aims to evaluate the efficacy of SES (Cypher™; Cordis Europa NV, J&J, Roden, NL). All consecutive patients were enrolled irrespective of clinical presentation and lesion characteristics, and the incidence of major adverse cardiac events (MACE) was evaluated during the follow-up.

In-hospital outcome information was retrieved by means of an electronic clinical database for patients maintained in our hospital after the procedure and by review of the hospital records for those discharged to their referring physicians. After discharge, recordings of all repeat interventions (surgical and percutaneous) and re-hospitalizations were prospectively collected in a dedicated database. Living patients were evaluated at our outpatient clinic department, by telephone interviews, or by mail. Clinical follow-up was obtained in all 16 patients.

We evaluated the incidence of death, myocardial infarction, or any repeat vessel revascularization, either surgical or percutaneous. Target lesion revascularization (TLR) was defined as either surgical or percutaneous reintervention driven by significant (>50%) luminal 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. All patients had a successful procedure as characterized by Thrombolysis in Myocardial Infarction (TIMI) flow 3 and residual in-lesion stenosis≤30%. In addition, the patients were invited to have a follow-up angiographic evaluation at 6-months. The binary restenosis rate, was defined as >50% diameter stenosis occurring in the segment inside the SES or within the 5-mm proximal or distal edges.

Discrete variables are presented as counts and percentages. Continuous variables are shown as mean ± SD.

Results

Patients' baseline and procedural characteristics are presented in table 1. Mean age was 65±11 years, 11 (69%) were male and 7 (44%) had diabetes. Overall, 9 (56%) of the patients were treated for unprotected LM disease and 10 (63%) had a LM lesion involving the distal bifurcation. Of these, 8 (50%) received SES in both the left anterior descending and the circumflex artery. In three patients deemed to be at very high procedural risk, a left ventricular assist device (tandem heart®) was used successfully. The mean number of stents used per patient was 2.9±1.6. Three patients (19%) received SES in segments other than the LM, including a vein graft. In 13 patients (81%) dilatation with larger diameter balloons was used to overcome the undersized 3.0mm stent.

Table 1. Baseline and procedural characteristics of patients with LM disease treated electively with SES implantation.

Pt#	Age	Clinical presentation	Risk factors	Previous MI	Previous PCI	Unprotected LM	Lesion location	Bifurcation stenting	Largest diameter balloon used	Direct stenting
1	78	SA-III	HC	No	No	Yes	Distal	"crush"*	Yes	No
2	64	SA-II	HT	Yes	No	No	Distal	No	Yes	Yes
3	83	SA-III	No	No	No	Yes	Distal	T-stent	No	No
4	69	SA-III	DM	No	No	Yes	Body	T-stent	Yes	Yes
5	75	SA-II	HC	Yes	No	Yes	Distal	T-stent	No	No
6	50	SA-III	CS	No	No	Yes	Distal	No	Yes	Yes
7	65	SA-II	HC	No	No	No	Ostial	No	Yes	Yes
8	50	SA-III	CS-DM	No	Yes	Yes	Ostial	No	Yes	Yes
9	61	SI	DM	No	Yes	Yes	Distal	T-stent	Yes	No
10	56	SA-IV	HT	No	No	Yes	Distal	T-stent	Yes	Yes
11	68	SA-III	DM	No	No	No	Ostial	No	Yes	No
12	59	SA-III	DM	Yes	No	No	Ostial	No	No	No
13	48	SA-IV	DM	No	Yes	Yes	Distal	"crush"	Yes	No
14	56	SA-III	DM	Yes	Yes	No	Distal	Kissing stent	Yes	No
15	68	SA-III	CS	Yes	Yes	No	Distal	No	Yes	No
16	75	SA-III	HC	No	No	No	Ostial	No	Yes	No

* "crush" is defined when the stent of the side branch is firstly deployed being almost in parallel position with the stent in the main vessel. The second stent is situated in the parent vessel ensuring coverage of the side branch ostium. The stent in the main vessell is then deployed, crushing the proximal part of stent at the side branch. If necessary, further kissing balloon inflations were performed.
UA=unstable angina ; SA=stable angina ; SI=silent ischemia ; CS=current smoker ; DM=diabetes mellitus

One patient developed a non-Q wave infarction, in hospital, with a peak creatine kinase of 875 U/l (MB fraction of 125 U/l). This patient was a diabetic female (patient #15), with a distal LM stenosis protected by a left internal mammary artery (LIMA). After optimizing the bifurcation with kissing balloons there was a small dissection distal to the stent in the left anterior descending artery. The operator accepted the result and the patient went to the ward painfree.

Complete clinical follow-up information was available for all patients. Mean duration of follow-up was 11.8±1.5 (range 10-15) months and is summarized in table 2. There were no cases of acute, subacute or late thrombosis, or death. One patient required TLR, for proximal edge restenosis. This patient was a diabetic male, with LM ostial stenosis protected by a patent LIMA (patient#12). The stenosis was very heavily calcified as indicated by the fact that the cutting balloon ruptured, and was stented with a 3X18mm and 3X8mm SES. Post dilatation was done with a 4.0mm balloon and the post-procedure diameter stenosis was 43%. Follow-up intracoronary ultrasound revealed an underexpansion of the stent, due to severe calcification at the ostium.

Six-month angiographic follow-up was obtained in 12 (75%) patients. Quantitative coronary angiographic analysis is presented at table 3. The late lumen loss was 0.04 ± 0.65mm. There was one patient with recurrent restenosis, which represents an 8% angiographic restenosis rate at 1 year.

Table 2. In-hospital and 1-year clinical outcome in patients treated electively for LM disease with SES implantation

	In-hospital events	Late outcome
Deaths, %	0	0
Myocardial infarction, %	1(6%)	0
Reintervention		
Percutaneous revascularization	0	1(6%)
Coronary bypass	0	0
Cumulative incidence of MACE*	1(6%)	1(6%)

*MACE=major adverse cardiac events

Discussion

To our knowledge this is the first consecutive series of patients treated electively for LM stenoses with SES. In this study we have shown that elective SES implantation in patients with LM stenoses was associated with total absence of death, and low incidences of reintervention and restenosis. Park et al, have reported that treatment of LM bifurcation is technically demanding and associated with a 28% angiographic restenosis rate(9). However, in more than half of the patients in the present study, both the parent and the side branch vessel received SES in the distal bifurcation. Among these 73% underwent follow-up angiography with no evidence of restenosis. We had only one case of restenosis. This diabetic patient had a very complex procedure in the ostium of the LM and the stent was clearly underexpanded. The largest reported series of LM stenting so far, had rates of death, target lesion revascularization and restenosis of 7.4%, 16.7% and 21.1% respectively(3). In addition, the mortality rate in published data ranges from <10% in protected to 30% with unprotected LM stenting(10). This explains why patients with LM stenoses continue to be considered primarily as candidates for surgery.

Table 3. Quantitative coronary angiography

	Index procedure		Follow-up
	Pre	Post	
Reference diameter, mm±SD	2.92±0.66	3.45±0.66	3.24±0.57
Minimum luminal diameter, mm±SD	1.19±0.49	2.83±0.73	2.97±0.66
Acute gain, mm±SD		1.65±0.43	
Late loss, mm±SD			0.04±0.65
Restenosis rate, %			1 (8%)*

* Related to 12 patients with 6-month angiographic follow-up

Thus far, the outstanding results of SES implantation have been reported in the context of randomized trials. Moreover, in these studies LM stenoses were excluded. We have recently reported zero percent post discharge mortality rate in a very complex patient population that

received SES in the LM segment(11).The zero percent mortality rates underline the efficacy of SES implantation and further corroborate the remarkable results reported thus far with this device. The results are particularly impressive given that there was a 44% incidence of diabetes in the study population. The very low late loss of on 0.09mm is also of note in this setting. These data suggest that the use of SES may be expanded to the treatment of LM stenoses with extremely favorable results. However, a word of caution is in order. It is critically important to insure that the SES size chosen can be expanded to the appropriate diameter for the LM, which is generally greater than 3 mm and often 4-5 mm in diameter, since stent under deployment and the resulting risk of thrombosis can be rapidly fatal in this setting.

Randomized trials to specifically compare LM stent implantation with coronary artery bypass surgery have until now been avoided to due to logistic considerations, prohibitive sample size and cost requirements. However, taking into account the impact of SES on restenosis, percutaneous intervention with the SES may now be a safe and effective alternative to bypass surgery for this group of patients. The time for a multicenter, randomized trial of SES versus bypass surgery for LM stenoses may have arrived.

This is a single center observational study with a limited number of patients and it is possible that our results are confounded by unmeasured factors. Moreover the 75% angiographic follow-up rate somewhat limits confidence in the angiographic evaluation. Although small, this is the first series of patients that have been electively treated with SES in the LM segment. The 12% overall MACE rate is very encouraging, and the total absence of fatal events warrants recognition.

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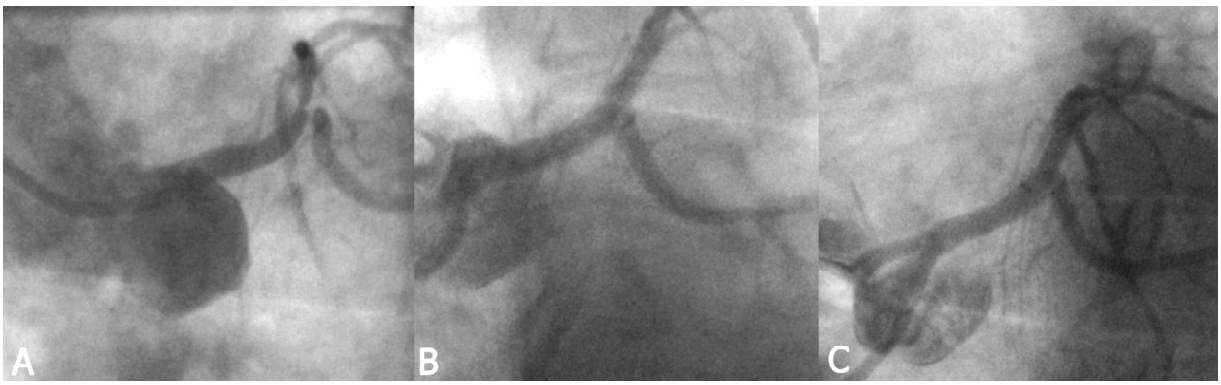

Unprotected LM stenosis involving the distal bifurcation (A). T-stenting with a 3X8mm cypher™ in the circumflex and a 3X18mm in the left anterior descending artery (B). Six-month follow-up angiography, with no restenosis (C).

Chapter 11 Elective Sirolimus-Eluting Stent Implantation For Multivessel Disease Involving Significant LAD Stenosis. One-Year Clinical Outcomes of 99 Consecutive Patients - The Rotterdam Experience

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Catheter Cardiovasc Interv. *In press*

Elective Sirolimus-Eluting Stent Implantation For Multivessel Disease Involving Significant LAD Stenosis. One-Year Clinical Outcomes of 99 Patients - The Rotterdam Experience

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The aim of this study was to evaluate the effectiveness of sirolimus-eluting stent (SES) implantation for patients with multivessel disease, that included left anterior descending artery (LAD) treatment. Since April 2002, SES has been utilized as the device of choice for all interventions in our institution, as part of the Rapamycin Eluting Stent Evaluated At Rotterdam Hospital (RESEARCH) registry. In the first 6 months of enrolment, 99 consecutive patients (17.6% of the total population) were treated for multivessel disease involving the LAD. The impact of SES implantation on major adverse cardiac events (MACE) was evaluated.

All the patients received SES in the LAD. Additional stent implantation in the right coronary artery (RCA), the left circumflex (LCx), or in all three major vessels was attempted successfully in 32 (32%), 51 (52%) and 16 (16%) of the treated patients respectively. During a mean follow-up of 360 ± 59 days (range 297 to 472 days) we had one death, one non-Q myocardial infarction and 8 patients required subsequent intervention. The event-free survival of MACE at one year was 85.6%.

Sirolimus-eluting stent implantation for multivessel disease in a consecutive series of patients is associated with low incidence of adverse events. The reported results are related predominantly to the reduction in repeat revascularization.

Catheter Cardiovasc Interv. *In press*

Introduction

The widespread use of percutaneous treatment for multivessel disease has been limited by the need for repeat revascularization(1-3). Indeed, the restenosis rate may be quite high, on a per-patient basis, since multilesion stenting is performed. Additionally, the ERACI II investigators have shown higher revascularization rates (27%) when the LAD was involved(4). Thus, in patients with multivessel disease the dominant form of revascularization remains bypass surgery.

The SES has recently proven its efficacy in reducing restenosis(5) in single de novo lesions. Importantly, the late benefit observed with SES was accomplished without compromising the excellent procedural and acute results already obtained with conventional metallic stents. The aim of the present study was to determine whether utilization of SES for a consecutive series of patients with multivessel stenoses and LAD involvement would be correlated with a reduced incidence of major events.

Methods

Study design and patient population

The RESEARCH study is a single center registry, which aims to evaluate the efficacy of SES (Cypher™; Cordis Europa NV, J&J, Roden) implantation. A detailed description of this study has been provided elsewhere(6,7). The SES was utilized as the device of choice in all patients treated, irrespective of clinical presentation or lesion characteristics. From 16th April 2002 until 15th October 2002 a total of 563 patients were treated solely with SES. In the present study, we report on 99 consecutive patients (17.6%) without previous bypass surgery treated electively with SES implantation in the left anterior descending (LAD) territory, together with stenting in the left circumflex (LCx) and/or right coronary artery (RCA) territories (i.e. revascularization of multivessel stenoses involving the LAD). Routinely, in our hospital, an experienced interventional cardiologist and a cardiothoracic surgeon discuss all patients referred for revascularization. When both agree on equivalence of revascularization then the patient is treated percutaneously in the first instance. The patients' informed written consent was obtained in accordance with the rules of the Institutional Ethics Committee, which approved the study. The analysis, interpretation, and submission for publication of this study were conducted independently of the trial sponsor.

Procedures, definitions and follow-up

The final interventional strategy was left entirely to the operator's judgment. Angiographic success rate defined as residual stenosis <30% by visual estimation in the presence of TIMI 3 flow. Peri- and post-procedural antithrombotic medications were used at the operator's discretion. The coronary arteries were subdivided into 15 segments according to the American Heart Association/American College of Cardiology (AHA/ACC) criteria(8). All patients were on chronic aspirin (>75mg daily) and received a loading dose of 300mg clopidogrel followed by a 75mg daily single dose for at least 3 months. Patients considered to be at higher thrombotic risk due to lesion complexity had a total of 6 months clopidogrel (multiple SES implantation [>3 stents], total stent length >36mm, chronic total occlusion, and bifurcations)(6).

We evaluated the incidence of MACE: death, myocardial infarction (MI), or repeat revascularization. Myocardial infarction was documented by a rise in the creatine kinase level of more than twice the upper limit with an increased creatine kinase-MB. Cardiac markers were measured serially for all patients maintained in our institution. Among those discharged to their community hospitals, cardiac markers were collected only if a post-procedural MI was suspected.

Consequently, enzymatic assessment was not available for all patients, but for those whom the likelihood of post-procedure MI was high. Target lesion revascularization (TLR) was defined as either surgical or percutaneous reintervention driven by significant (>50%) luminal narrowing either within the stent or the 5mm borders proximal and distal to the stent. Target vessel revascularization was defined as any reintervention in the treated vessel.

Table 1. Baseline and procedural characteristics in 99 patients treated with SES for multivessel disease involving the LAD

Age, years ± SD	64 ± 11
Male, %	66
Treated diabetes, %	25
Treated hypertension, %	51
Treated hypercholesterolemia, %	68
Current smoking, %	24
Previous MI, %	31
Previous PCI, %	19
Stable angina, %	58
Unstable angina, %	42
LCx treated (including LAD), %	52
RCA treated (including LAD), %	32
Triple vessel treatment, %	16
Glycoprotein IIbIIIa inhibitor, %	25
ACC/AHA lesion type*, n=293 lesions	
Type A, B1, %	38
Type B2, C, %	62
Number of implanted stents per patient ± SD	3.5 ± 1.5
Total stented length per patient, ± SD	62.6 ± 32.1
Nominal stent diameter utilized, mm ± SD	2.6 ± 0.3

LAD=left anterior descending, MI=myocardial infarction, LCx=left circumflex, RCA=right coronary artery

In-hospital outcome information was retrieved by means of an electronic clinical database for patients maintained in our hospital after the procedure and by review of the hospital records for those discharged to secondary hospitals. After discharge, recording of all repeat interventions (surgical and percutaneous) and re-hospitalizations was performed prospectively in a dedicated database. Living patients were evaluated at our outpatient clinic department, by telephone interviews, or by mail contact.

Statistical analysis

Continuous variables were expressed as mean ± SD and discrete variables as counts and percentages. Event-free survival distribution was estimated according to the Kaplan-Meier method. Patients lost to follow-up (n=2) were considered at risk until the date of last contact, at which point they were censored.

Results

Baseline and procedural characteristics are depicted in table 1. The mean age of our cohort was 64 ± 11 years, 42 patients (42%) were treated for unstable angina, diabetes was present in 25 patients (25%), and 31 (31%) had previous myocardial infarction. Overall, we had 15 patients (15%) treated for at least one chronic total occlusion (> 3-month duration) and 5 patients (5%) with in-stent restenosis. As was indicated by the study protocol, all patients received SES in the LAD. Among the 99 patients treated, 46 (46%) received SES in the proximal LAD, 56 (56%) in the middle LAD, 7 (7%) in the distal and 24 (24%) were treated in any of the diagonal branches. Additional SES stenting was undertaken in the RCA, LCx, and in both vessels 32 (32%), 51 (52%), 16 (16%) respectively. Overall, 295 lesions were treated (2.9±1.1 lesions per patient) with a mean stent utilization of 3.5±1.5 per patient; a total of 20 patients (20%), received more than 5 stents.

One patient died in-hospital following a complicated procedure with emergent bypass surgery due to left main stem dissection. Additionally, there was one post-procedure non-Q wave myocardial infarction [peaked creatine kinase 567U/I (MB fraction: 62U/I)].

Clinical follow-up was available for all but 2 patients (98%). Clinical outcomes at 30 days and 9-months are presented in table 2. Follow-up at 9 months was available for 100% of the patients and the cumulative incidence of MACE was 10%.

Table 2. 30-day and 9-month cumulative incidence of adverse events of patients treated with SES for multivessel disease involving the LAD.

	30-day	9-month
Death, %	1	1
Non-fatal myocardial infarction*, %	1	1
TLR, %	1	4
TVR, % (including TLR)	1	8
SES thrombosis†, %	0	0
Overall incidence of adverse events, %	3	10

* non-Q wave myocardial infarction [peaked creatine kinase 567U/I (MB fraction: 62U/I)].
†Angiographically documented SES thrombosis requiring reintervention The average follow-up was 360 ± 59 days (range 297 to 472 days).

There were no cases of acute or subacute thrombosis (angiographically documented stent thrombosis requiring repeat intervention). No further patients died or had MI. Overall 8 patients (8%) required subsequent revascularization. Among these, 4 patients (4%) had TLR. Two patients, originally treated for chronic total occlusion, had focal in-stent restenosis in the overlapping segment of two SES. The third had an underexpanded stent at the ostium of the RCA (which was heavily calcified) and had additional cutting balloon dilatation. The fourth patient had a TLR due to restenosis at the proximal edge of the SES. A further 4 patients (4%) had percutaneous reintervention in an untreated segment due to progression of atherosclerosis. The survival rate free of events at one year was 85.6% (Figure 1).

Discussion

In the present study, we report a low incidence of adverse events in patients treated with SES in a scenario of multivessel stenting, involving the LAD. This reduction is related to the reduced rates of repeat revascularizations presented in this study, predominantly to the reduction of target lesion reintervention. To our knowledge this is the first study reporting a freedom from revascularization of 92% at one year in patients with multivessel stenting. Although the utilization of stents in the ARTS, ERACI II and SOS trials was very high, freedom from revascularization was 79%, 83.2% and 79% respectively(1,9,10). The event-free survival rate reported in the ARTS trial within the stent group was 73.8%. The 85.6% survival rate reported in this study warrants further evaluation. The absence of death or myocardial infarction during the follow-up period is noteworthy. The majority of the patients (87%) were treated with dual anti-thrombotic

therapy (aspirin combined with clopidogrel) for six months. Moreover, statins as adjunctive medication were widely used (89%). We hypothesize that this aggressive treatment in combination with the use of drug-eluting stent might be related with this observation.

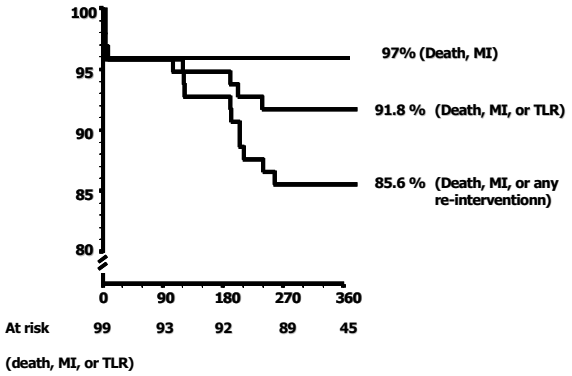

Figure 1. Event-free survival curves of 99 patients treated with SES for multivessel disease and LAD involvement.

The fact that 2 out of 4 TLR events were located in overlapping SES segments merits further investigation. It is unknown if the elution properties are compromised in overlapping sites, although preliminary results of overlapping SES from the RESEARCH population suggest a higher late luminal loss in this specific site but with no restenosis. We have recently reported that SES discontinuity and edge injury are related with post SES-restenosis(6). Therefore, when treating multivessel stenoses, complete lesion coverage is mandatory to ensure a homogeneous drug release over the entire diseased segment. This explains the high number and length of SES, compared to the aforementioned trials, used in the present study. The impact of SES in restenosis is of great clinical importance, and enhances the encouraging results presented thus far. The ARTS II trial is consequently undergoing to investigate the outcomes and costs of SES implantation for multivessel disease. The evolution in interventional cardiology has been tremendous. The domination of bypass surgery for multivessel disease was based on the historical results comparing angioplasty versus bypass surgery reported in the 1980s and 1990s. The future management of patients with multivessel disease needs to take into account the current evidence.

Limitations

This is an observational subanalysis of a single centre study with a limited number of patients and it is possible that our results are confounded by unmeasured factors. No comparison with other invasive modalities (e.g. conventional stenting and surgery) was reported. Knowing the outcomes of multivessel patients treated with these strategies(1,4,10), the relatively limited number of cases in our series (99 patients) precluded any attempt to comparatively evaluate, with enough statistical power, surgery or bare stent implantation with sirolimus-eluting stents. In the ARTS II trial, a sample size of 600 patients was calculated to guarantee a power of at least 90% to test the hypothesis that sirolimus-eluting stents were at least as effective as surgery(11). Only 16% of the patients were treated for triple-vessel disease. Therefore, the very low incidence of adverse events reported in this study, may not be applicable for larger groups of patients with triple-vessel disease. However, this is the first series of consecutive patients treated with SES in a multivessel setting and the 85.6% one-year event-free survival rate warrants recognition.

Conclusions

Sirolimus-eluting stent implantation for patients with multivessel disease involving the LAD is associated with low incidence of adverse events at one year, particularly of subsequent revascularization.

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Chapter 12 Significant Reduction in Restenosis Following the Use of Sirolimus-Eluting-Stents in the Treatment of Chronic Total Occlusions

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J Am Coll Cardiol. *In press*

Significant Reduction in Restenosis Following the Use of Sirolimus-Eluting-Stents in the Treatment of Chronic Total Occlusions

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Objectives: To assess sirolimus-eluting stent (SES) implantation for the treatment of chronic total occlusions (CTO).
Background: Long-term results following percutaneous coronary intervention (PCI) in the treatment of CTO`s is hindered by a significant rate of restenosis and re-occlusion. In the treatment of relatively simple non-occlusive lesions, SESs have shown dramatically reduced restenosis rates compared with bare stents (BMS), but whether these results are more widely applicable is unknown.
Methods: From April 2002, all patients at our institution were treated with SES as the device of choice during PCI. During the first 6-months, 563 patients were treated solely with SES, with treatment of a de novo CTO in 56 (9.9%). This CTO cohort was compared with a similar group of patients (n=28) treated in the preceding 6-month period with BMS.
Results: At 1 year, the cumulative survival-free of major adverse cardiac events was 96.4% in the SES group versus 82.8% in the BMS group, $p<0.05$. At 6-months follow-up, 33 (59%) patients in the SES group underwent angiography with a binary restenosis rate (>50% diameter stenosis) of 9.1% and in-stent late loss of 0.13 ± 0.46mm. One patient (3.0%) at follow-up was found to have re-occluded the target vessel.
Conclusions: The use of SESs in the treatment of chronic total coronary occlusions is associated with a reduction in the rate of major adverse cardiac events and restenosis compared to bare stents.

J Am Coll Cardiol. *In press*

Introduction

Chronic total occlusions (CTO) are common, and found in approximately one third of patients with significant coronary disease who undergo angiography. [1,2] Percutaneous intervention (PCI) of CTOs accounts for 10-15% of all angioplasties; however, following successful recanalization, there is an increased rate of subsequent restenosis and re-occlusion compared to non-occlusive stenoses. [3,4] Although several randomized trials demonstrated the efficacy of stent implantation over balloon-only angioplasty; even with stents, there remains a significant rate of both restenosis (32-55%) and re-occlusion (8-12%). [5-9]

In the treatment of relatively simple lesions, sirolimus-eluting stents (SES) markedly reduce the restenosis rate, with continued benefit documented up to 2 years follow-up. [10,11] Whether these results can be extrapolated to more complex lesions such as CTO`s, has yet to be determined. We sought to evaluate the effectiveness of the SES in a consecutive series of patients with at least one de novo CTO compared to a similar series treated with bare stents (BMS).

Methods

Patient population

Commencing in April 2002, all PCI at our institution was done solely with SESs, irrespective of clinical presentation or lesion morphology, these patients comprise the RESEARCH registry (further details of the methodology are described elsewhere). [12,13] Those deemed at an increased risk of restenosis (including the CTO population), were considered for 6-month angiographic follow-up. SES were available in lengths between 8mm and 33mm, and diameters 2.25mm to 3.0mm. In the first 6-months, 563 patients were treated, including 56 (9.9%) with successful revascularization of at least one CTO. These patients make up the present study cohort; all received 6-months dual anti-platelet therapy with clopidogrel in addition to aspirin. As pre-determined by the RESEARCH protocol, this study cohort of patients 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. Both groups were treated by the same operators utilizing standard techniques; the only difference being the type of stent. 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 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 at least 1-months` duration, [9] 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 either utilizing antegrade filling via collaterals, or assessment of the retrograde collateral filling. This was achieved by catheterizing both the left and right coronary arteries, and making a simultaneous injection to delineate the distance between the site of occlusion and the most proximal part of the vessel filled retrogradely.

Follow-up

Patients were followed up prospectively and evaluated for survival-free of major adverse cardiac events (MACE) using questionnaires and telephone enquiries. MACE was pre-defined 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.

Table 1: Baseline patient demographics

	Bare stents (n=28)	SESs (n=56)	p-value
Mean age (years)	59.8±11.1	60.2±10.0	0.9
Male sex (%)	85.7	71.4	0.2
Current smoker (%)	35.7	26.8	0.5
Diabetes mellitus (%)	7.1	14.3	0.5
Hypertension (%)	39.3	39.3	1.0
Hypercholesterolemia (%)	57.1	55.4	1.0
Previous MI (%)	46.4	55.4	0.6
Previous PCI (%)	21.4	12.5	0.3
Previous CABG (%)	0	0	-
IIb/IIIa inhibitor (%)	25.0	21.4	1.0
Multivessel disease (%)	60.7	46.3	0.3
PCI in at least one additional (non-occluded) major vessel (%)	28.6	42.6	0.2

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

Table 2: Baseline procedural characteristics

	Bare stents (n=29)	SESs (n=56)	p value
Target vessel			0.06
LAD (%)	27.6	51.8	
LCX (%)	27.6	25.0	
RCA (%)	44.8	23.2	
Mean length of occlusion (mm), (range)	12.7 (2.4-31.8)	11.3 (4.0-32.1)	0.5
Bifurcation stenting (%)	17.9	14.3	1.0
Mean number of stents implanted	1.8	2.0	1.0
Mean stent diameter (mm)	3.03±0.56	2.75±0.26	<0.001
Mean stent length (mm)	23.3±9.3	23.9±9.2	0.7
Total stented length (mm), (range)	41.8 (18 - 112)	45.2 (8 – 117)	0.7
Post-procedure QCA data			
Reference diameter (mm)	2.37±0.50	2.35±0.46	0.9
Minimal lumen diameter (mm)	2.18±0.49	2.06±0.48	0.3
Diameter stenosis (%)	10.4	11.6	0.6

LAD=left anterior descending artery; LCX=circumflex artery, RCA=right coronary artery; QCA=quantitative coronary angiography

Angiographic analysis

Quantitative analysis in those SES patients with follow-up angiography was undertaken in three coronary segments: in-stent (encompassing the entire length of stented segment), and the 5-mm proximal and distal edge segments either side of the in-stent segment. The target lesion comprised the in-stent plus the proximal and distal edge segments. Binary restenosis was defined as >50% diameter stenosis within the target lesion. Late lumen loss was calculated from the difference in minimal lumen diameter between post-procedure and follow-up.

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.

Results

The baseline patient and lesion characteristics of the two groups are presented in tables 1 and 2. One patient in the BMS group underwent successful recanalization and stent implantation in two CTO`s, thereby making a total of 29 lesions in this group. Mean length of occlusion could be determined in 45 (80.0%) of the SES group and 17 (62.1%) of the BMS group. There was no significant difference between the groups with respect to the post-procedural quantitative angiography, however, the mean diameter of stent utilized was greater in the BMS cohort.

There were no in-hospital major adverse events. Clinical follow-up data was obtained in 100% of both groups. There were no deaths or AMI in either group, with all events related to TVR. At one year, the cumulative survival-free of MACE was 96.4% in the SES group compared to 82.8% in the BMS group, p<0.05 (Figure 1). One patient in each group had a re-occlusion (1.8% SES group versus 3.6% BMS group, p=NS).

Table 3. Post-procedural and 6-month follow-up quantitive angiographic data for the sirolimus-eluting stent (n=33)

	Proximal 5mm	In-stent	Distal 5mm
Post-procedure			
Mean diameter (mm)	2.82 ± 0.66	2.58 ± 0.55	2.10 ± 0.64
MLD (mm)	2.43 ± 0.51	2.04 ± 0.45	1.75 ± 0.53
% diameter stenosis	14.1	12.9	21.8
6 month follow-up			
MLD (mm)	2.33 ± 0.90	1.91 ± 0.68	1.81 ± 0.75
% diameter stenosis	20.1	21.9	18.2
Lumen loss (mm)	0.10 ± 0.80	0.13 ± 0.46	-0.06 ± 0.54

MLD=minimal luminal diameter

At 6-months, 33 (58.9%) patients in the SES group underwent follow-up angiography, (none in the BMS group). The binary restenosis rate was 9.1%: one occlusion, one stenosis at the ostium of a side branch following T-stenting, and the third at the distal outflow of the SES. The patient with occlusion underwent bifurcation T-stenting following successful recanalization of a heavily calcified left anterior descending artery. At follow-up, the artery had re-occluded, and there was new akinesis of the left ventricular anterior wall. This patient with occlusion was managed with medical therapy; the other 2 patients with restenosis underwent percutaneous revascularization.

Discussion

Previous studies have demonstrated the importance of revascularization of CTO`s, with improvement in anginal symptoms, exercise capacity, and left ventricular function. [14-16] In addition, successful recanalization reduces the subsequent need for bypass surgery, the rate of AMI, and importantly, long-term evaluation has shown a 10-year survival advantage of 73.5% following successful PCI compared to 65.1% in those with unsuccessful PCI. [4,17]

To our knowledge this is the first report regarding the efficacy of SES in CTO`s, a subset of patients previously excluded from other protocols and, importantly, at increased risk of developing restenosis after conventional stent implantation. [3] Of the patients who underwent follow-up angiography, both the in-stent and proximal 5mm segments analysed showed an encouraging late loss of 0.13 ± 0.46mm and 0.10 ± 0.80mm respectively. The

distal 5mm actually showed an overall benefit, with enlargement of the vessel (late loss -0.06 ± 0.54mm).

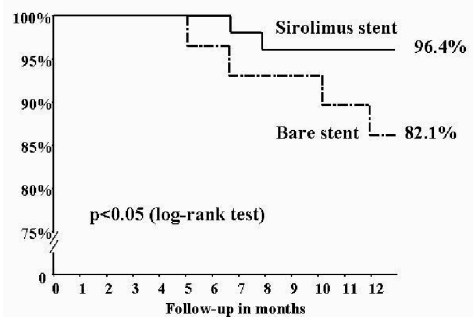

Figure 1: Kaplan-meier curves for survival-free of MACE (defined as death, acute myocardial infarction, or target vessel revascularization)

In addition to the angiographic data, the clinical follow-up is very encouraging with no death or myocardial infarction. Importantly, there were no significant differences in baseline demographics between the SES and BMS groups, and all procedures were carried out in the same centre by the same operators. The restenosis rate for BMS is inversely related to the post-procedural MLD and the number of stents utilized. [18] In the current study, although the mean diameter of stent used was significantly greater in the BMS cohort (related to a maximum available SES diameter of 3.0mm), with free utilization of post-dilatation, the post-procedural MLD was not significantly different between the 2 groups. All events in both groups related to TVR, and at one year, there was a significantly higher rate of survival-free of MACE of 96.4% in the SES group versus 82.8% in the BMS group.

Four major randomized trials have demonstrated the efficacy of stent implantation over balloon-only angioplasty in the treatment of CTO`s, reducing the 6-month restenosis rate from 68-74% to 32-55%. [5-8] Compared to this historical data, our study suggests that the SES confers a marked further advantage with a significantly lower binary restenosis rate of 9.1% ($p<0.05$). Figure 2. In addition, we had only one patient (3.0%) with vessel re-occlusion, compared to rates of between 8-12% in the same published trials utilising BMS. A recent study of the clinical results of 376 patients discharged from hospital without an adverse event following successful intervention of a CTO showed, at one year follow-up, a MACE-rate of 12.2%; [19] our results are therefore quite remarkable, with a MACE-free survival rate of 96.4%.

Limitations

This study evaluated only a small cohort of patients and angiographic follow-up was not obtained in all, so additional patients with silent re-occlusion cannot be excluded. However, those who did not undergo repeat angiography were all symptomatically well at follow-up. In addition, despite the discrepancy in follow-up angiography rates between the two groups which might have biased the results towards more revascularization in the SES group, the MACE rate remained statistically significant with a beneficial effect in favor of the SES. The study was not randomized, and used a retrospective comparitive population, however the same operators and interventional techniques were utilized.

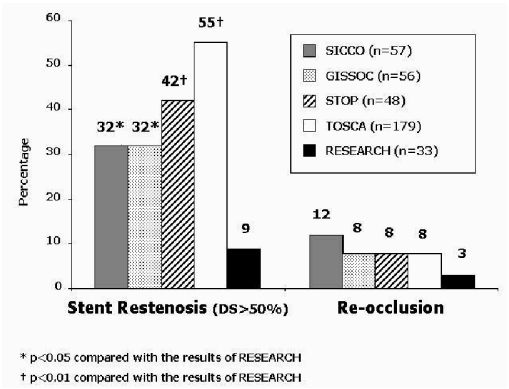

Figure 2: The percentage binary restenosis rate (>50% diameter stenosis), and re-occlusion rate of RESEARCH compared with published data from the patients treated with stent implantation in the randomized trials SICCO,[5] GISSOC,[6] STOP,[7] and TOSCA.[8]

Conclusions

The use of SESs in the treatment of complex patients with CTO`s is associated with a reduction in the rate of major adverse cardiac events and restenosis compared to bare stents.

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Chapter 13 Treatment of Very Small Vessels With 2.25-mm Diameter Sirolimus-Eluting Stents From the RESEARCH Registry

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Treatment of Very Small Vessels With 2.25-mm Diameter Sirolimus-Eluting Stents From the RESEARCH Registry

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A total of 91 patients were treated with 2.25-mm sirolimus-eluting stents (SES) for 112 lesions, which were compared to lesions treated with SES ≥2.5-mm diameter in the same procedure (n=109). The reference diameter was 1.88±0.34 mm and 2.52±0.57 mm respectively (p<0.01). At follow-up, the late late loss was 0.07±0.48 mm for 2.25-mm SES vs. 0.03±0.38 mm for larger SES (p=0.5) and the binary restenosis rate was 10.7% vs. 3.9% respectively (p=0.1). The 12-month target lesion revascularization rate was 5.5%. In conclusion, 2.25-mm SES were associated with low rates of clinical and angiographic late complications.

Am J Cardiol. *in press*

Implantation of 2.25-mm sirolimus-eluting stents in very small vessels of an unselected patient population treated in the "real world" was associated with low rates of restenosis and a reduced incidence of target lesion revascularization.

The role of coronary stenting for small coronary vessels is not defined, with several randomized trials comparing stents with balloon angioplasty presenting contradictory results.[1-6] Recently, sirolimus-eluting stents have strikingly reduced restenosis compared to conventional stents in 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) [7] and in the SIRolImUS-Eluting Bx Velocity Balloon-Expandable Stent (SIRIUS) trial.[8] In both studies, sirolimus-eluting stent implantation has been associated with a marked treatment effect on target lesion revascularization across the entire spectrum of vessel sizes in the included population. However, the RAVEL and SIRIUS trials were restricted to relatively large vessels (minimum stent diameter available was 2.5 mm). In a post-hoc analysis of patients enrolled in RAVEL,[9] sirolimus-eluting stents effectively inhibited neointimal proliferation independently of vessel size. Conversely, in the SIRIUS trial, patients in the lower strata of vessel diameter presented higher rates of in-stent restenosis.[8] The rationale of the present study was, therefore, to evaluate the clinical and angiographic outcomes after implantation of sirolimus-eluting stents dedicated to the treatment of very small vessels.

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Since 16th April 2002, sirolimus-eluting stent (SES) implantation (Cypher; Johnson & Johnson-Cordis unit, Cordis Europa NV, Roden, the Netherlands) has been utilized as the default strategy in our institution, as part of the RESEARCH (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital) study.[10] At 6 months enrollment, a total of 91 consecutive patients (16% from the total population in the period) had been treated with 2.25-mm diameter SES for 112 *de novo* lesions. Among these 91 patients, 60 patients had also lesions treated with SES ≥2.5 mm diameter (n=109 lesions) (average stent diameter in these lesions 2.9±0.2 mm). The angiographic outcomes of lesions treated with larger SES were utilized as a reference for comparison with lesions treated with 2.25-mm SES.

Table 1. Baseline and follow-up clinical characteristics of patients treated 2.25-mm diameter sirolimus-eluting stents (n=91 patients).

Men	56 (62 %)
Age (years ± SD)	64±12
Diabetes mellitus	24 (26 %)
On insulin	9 (10 %)
Systemic hypertension	51 (56 %)
Current smoking	21 (23 %)
Previous myocardial infarction	29 (32 %)
Previous percutaneous intervention	23 (25 %)
Previous coronary bypass surgery	10 (11 %)
Acute coronary syndrome	34 (37 %)
Multivessel coronary disease	66 (72 %)
12-month follow-up	
Death	2 (2.2 %)
Death + myocardial infarction	3 (3.3 %)
Target lesion revascularization	5 (5.5 %)
Any major adverse cardiac event	7 (7.7 %)

Sirolimus-eluting stents were available in diameters of 2.25, 2.50, 2.75, and 3.00 mm. The interventional strategy applied was entirely left to the discretion of the operator, including the choice of the most appropriate stent size. On-line quantitative coronary analysis guidance was available for all cases and is routinely used in our institution. This protocol was approved by the hospital ethics committee and written informed consent was obtained from every patient.

Major adverse cardiac events were defined as death, non-fatal myocardial infarction, or target lesion revascularization. Myocardial infarction was diagnosed by a rise in the creatine kinase level of more than twice the normal limit with increased MB fraction. Target lesion revascularization was defined as any re-intervention to treat a stenosis within the stent or in the 5-mm distal or proximal segments adjacent to the stent. All living patients were considered eligible for 6-month angiographic follow-up. Binary angiographic restenosis

was defined by diameter stenosis ≥50% at follow-up angiography. Late loss was calculated by the difference between the minimal luminal diameter after stenting and at follow-up.

Continuous variables were presented as mean±standard deviation and compared using Student's t-test. Categorical variables were presented as counts and percentages and compared with the Fisher's exact test. All statistical tests were 2-tailed. A p-value <0.05 was considered significant.

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Baseline clinical characteristics are shown in Table 1. Angiographic findings of lesions treated with 2.25-mm SES and lesions treated with larger diameter stents in other vessel segments are presented in Table 2. Lesions treated with 2.25-mm SES's were more frequently located at secondary branches, non-proximal segments, and ostial lesions, and had significantly smaller reference diameters (1.88±0.34 mm vs. 2.52±0.57 mm; p<0.01). Angiographic follow-up (7.1±1.3 months) was available for 62 patients (70% of eligible patients) and 151 lesions. Late loss was similar between both lesion groups (0.07±0.48 mm for 2.25-mm SES vs. 0.03±0.38 mm for larger SES; p=0.5), as illustrated in Figure 1.

Table 2. Angiographic characteristics of lesions treated with sirolimus-eluting stents of larger diameters and lesions treated with 2.25-mm diameter sirolimus-eluting stent.

	Larger SES (n=109)	2.25-mm SES (n=112)	P
Treated coronary arteries			<0.01
Left anterior descending	35 (32 %)	18 (16 %)	
Diagonal	2 (2 %)	33 (30 %)	
Left circumflex artery	22 (20 %)	15 (13 %)	
Obtuse marginal or intermedius	12 (11 %)	21 (19 %)	
Right coronary artery	30 (28 %)	8 (7 %)	
other branches	8 (7 %)	17 (15 %)	
Proximal location	34 (31 %)	11 (10 %)	<0.01
Ostial location	21 (19 %)	47 (42 %)	<0.01
Pre-procedure			
Reference diameter (mm±SD)	2.52±0.57	1.88±0.34	<0.01
Minimal luminal diameter (mm±SD)	0.82±0.53	0.57±0.37	<0.01
Diameter stenosis (%±SD)	67.8±18.5	69.4±19.1	0.5
Lesion length (mm±SD)	15.8±9.8	12.3±9.3	0.02
Post-stenting			
Minimal luminal diameter (mm±SD)	2.23±0.62	1.74±0.35	<0.01
Diameter stenosis (%±SD)	16.5±12.8	15.9±10.9	0.7
Follow-up*			
Minimal luminal diameter (mm±SD)	2.18±0.64	1.61±0.57	<0.01
Diameter stenosis (%±SD)	20.4±16.7	25.1±24.0	0.2
Late loss (mm±SD)	0.03±0.38	0.07±0.48	0.5
Binary restenosis (%)	3.9	10.7	0.1

SD=standard deviation; SES=sirolimus-eluting stent
*Refers to 62 patients (70% of eligible patients) with angiographic follow-up at 6 months (76 lesions in the larger SES group and 75 lesions in the 2.25-mm SES group)

Binary restenosis was identified in 8 lesions (10.7%) treated with 2.25-mm SES's and in 3 lesions (3.9%) treated with larger SES's (p=0.1). From the 8 restenotic lesions in 2.25-mm SES's, 3 (38%) occurred in stents implanted at the vessel ostium. Similarly, from the 3 restenotic lesions treated with larger SES's, 1 lesion (33%) was ostial. Restenosis rates for non-ostial lesions were 6.7% in the 2.25-mm SES group (n=45 lesions with angiographic follow-up) and 3.0% in the larger SES group (n=66 lesions) (p=0.4). All restenoses occurred within the stent.Follow-up clinical information was complete for 90 patients (99%) at an average of 258±92 days (Table 1). There were 2 in-hospital deaths (both in patients admitted with myocardial infarction and cardiogenic shock). Non-fatal ST-elevation myocardial infarction was diagnosed in one patient (creatine phosphokinase elevation 2.8 times the upper normal limit), and occurred in the same day of the index procedure due to thrombotic occlusion of a 2.25-mm SES implanted in the distal left anterior descending artery. A distal edge dissection was seen by intravascular ultrasound examination and treated with implantation of another 2.25-mm SES overlapping the previous stent. This patient was asymptomatic after 7 months, with widely patent SES's at angiographic evaluation. There were no other cases of stent thrombosis or myocardial infarction. Target lesion revascularization was performed in other 4 patients to treat restenosis occurring after 2.25-mm SES implantation (overall target lesion revascularization rate 5.5%) and the major adverse cardiac event rate was 7.7%.

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The main findings of this study were that implantation of very small (2.25-mm) sirolimus-eluting stents for *de novo* lesions was associated with markedly low lumen loss and restenosis rates. The reduced incidence of restenosis was translated in a very low need for repeat target lesion revascularization at 12 months (5.5%).

Small vessel size has been shown to be an important independent predictor of restenosis after percutaneous intervention.[11] Currently, the best interventional approach for patients small coronary vessels is unclear, even though a number of strategies have been tested in several randomized trials.[1-6] In the present report, implantation of 2.25-mm sirolimus-eluting stents strikingly inhibited neointimal proliferation in vessels with an average reference diameter of 1.88 mm, which is consistently smaller than the vessel size of all randomized studies published to date, ranging from 2.23 mm to 2.55 mm (Figure 2).[1-6] Although SES were implanted in very small vessels in our study, the late lumen loss (0.07 mm) was clearly smaller than after conventional stenting in previous series (1.12 mm to 0.54 mm).[1-6] Moreover, the late loss observed after 2.25-mm SES was similar to the late loss in previous trials with larger sirolimus-eluting stents, even

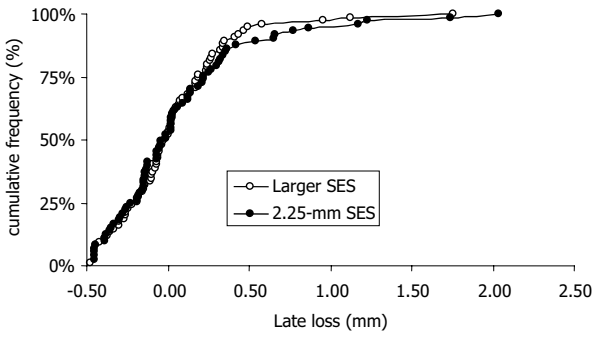

Figure 1. Cumulative frequency of late loss in lesions treated with 2.25-mm SES and lesions treated with larger stents (≥2.5 mm).

when considering only vessels in the lowest tercile of vessel size included in these studies (Figure 2).[8,9]

It is worth noting that restenosis was relatively common after treatment of ostial lesions. Placement of drug-eluting stents at ostial lesions may constitute a challenging technical problem in accomplishing complete lesion scaffolding. Indeed, we have recently shown that post-sirolimus-eluting stent restenosis is commonly associated with a discontinuity in stent coverage, which may be of particular concern for ostial (and bifurcation) lesions.[12] Drug-eluting stents especially designed for these lesions may be needed to improve the outcomes in this setting.

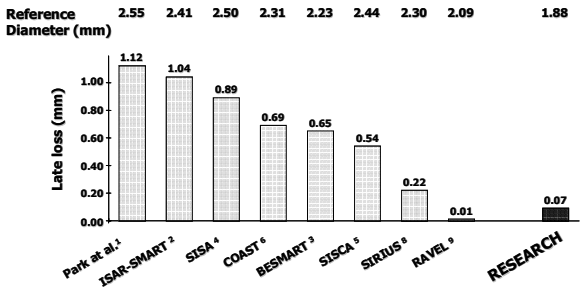

Figure 2. Reference diameter and late loss in the stent arm of randomized trials comparing stenting vs. balloon angioplasty for small vessels, in the SIRIUS and RAVEL trials (lowest vessel size range), and in the RESEARCH registry (2.25-mm SES).

This study presents several limitations related to its limited sample size and its non-randomized nature. Lesions treated with 2.25-mm SES showed a trend towards a greater incidence of binary restenosis and a larger late lumen loss compared to SES of larger diameters. Although not reaching statistical significance, our findings were in line with the recent SIRIUS trial, which identified small vessel size as a independent risk factor for restenosis after sirolimus-eluting stent implantation.[8] The present results warrant further investigation of the angiographic outcomes of 2.25-mm SES in studies including a larger number of patients. Although the present study lacks a true control group, this limitation is partially overcome by the comparison of vessels treated with the 2.25-mm SES with those treated with larger stents in multi-lesion procedures. A higher rate of angiographic follow-up (70% in this study) would be desirable to fully evaluate the angiographic outcomes. However, it should be noted that the present study enrolled an unselected cohort of consecutive patients treated in the daily practice, and that not consenting with angiographic follow-up was not an exclusion criterion. Obviously, this scenario differs substantially from that of randomized trials and limits the compliance to angiographic re-study. Importantly, all eligible patients for whom angiographic re-evaluation was not obtained remained event-free throughout the follow-up period.

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Chapter 14 Very Long Sirolimus-Eluting Stent Implantation for de novo Coronary Lesions

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Long length stenting has a poor outcome when bare metal stents are utilized. The safety and efficacy of the sirolimus-eluting stent (SES) in long lesions has not yet been evaluated. Therefore, the aim of the present study was to evaluate the clinical and angiographic outcomes of SES implantation over a very long length coronary artery segment. Since April 2002, all patients treated percutaneously at our institution received SES as the device of choice as part of the RESEARCH (Rapamycin Eluting Stent Evaluated At Rotterdam Cardiology Hospital) registry. During the RESEARCH registry, stents were available in lengths of 8, 18, and 33 mm. The present report included a pre-defined study population composed by patients treated with >36mm long stented segments. Patients had a combination of at least 2 overlapping stents in a minimum length of 41mm (i.e. one 33-mm SES overlapping an 8-mm SES) to treat native *de novo* coronary lesions. The incidence of major cardiac adverse events (death, non-fatal myocardial infarction, and target lesion revascularization) was evaluated. The study population is composed of 96 consecutive patients (102 lesions). Clinical follow-up was available for all patients at a mean of 320 days (range 265-442 days) In total, 20% of long-stented lesions were chronic total occlusions, mean stented length per lesion was 61.2±21.4mm (range 41mm-134mm). Angiographic follow-up at 6 months was obtained in 67 patients (71%). Binary restenosis rate was 11.9% and in-stent late loss was 0.13± 0.47mm. At long-term follow-up (mean 320 days), there were 2 (2.1%) deaths and the overall incidence of major cardiac events was 8.3%. As a conclusion, SES implantation appears safe and effective for *de novo* coronary lesions requiring multiple stent placement over a very long vessel segment.

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Treatment of complex coronary artery stenosis with a long segment of bare metal stent (BMS) is associated with high restenosis rates and poorer clinical outcome[1-7]. Therefore, in contrast to shorter lesions, stent placement for diffusely diseased coronary segments is commonly avoided. The efficacy of the sirolimus-eluting stent (SES) implantation has been recently evaluated in the context of two large randomized trials. The RAVEL trial [8] (Randomized Study with the Sirolimus- Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions) included only single lesions covered by an 18mm long stent and had a zero restenosis rate. In the SIRIUS trial[9] (US Multicenter, Randomized, Double-Blind Study of the Sirolimus-Eluting Stent in De Novo Native Coronary Lesions) relatively long stent placement was allowed (maximum of 2 overlapping 18-mm long SES) and the restenosis rate was 9.2%. The efficacy of SES implanted over a total coronary length > 36 mm has not been tested to date. In the present study, we sought to evaluate the outcomes of patients receiving overlapping stents implanted over a length >36 mm to treat native *de novo* coronary lesions.

METHODS

Since April 16, 2002, it has been our policy to utilize the SES (Cypher™; Cordis Europa NV, Roden, The Netherlands) as the device of choice for every percutaneous coronary intervention (PCI) performed in our institution, as part of the RESEARCH registry. Further details of the methodology has been previously described[10].

Study group and Stent Implantation: During the RESEARCH registry, SES were available at lengths of 8, 18, and 33 mm. The present report included a pre-defined study population composed of patients treated with stented segments >36 mm long. Therefore, due to the availability of stent lengths, all included patients had a combination of at least 2 overlapping stents in a minimum length of 41 mm (i.e. one 33-mm SES overlapping a 8-mm SES Patients receiving SES to treat in-stent restenotic lesions were excluded from the present analysis. Also, lesions with angiographically visible gaps between stents were not included in this study. During 6 months of enrollment, 96 consecutive patients (102 lesions) fulfilled the above criteria and composed the present study population. The stented length was based on the cumulative length of the individual adjacent stents. All procedures were performed according to standard interventional techniques except with the utilization of SES as the device of choice. However, the final interventional strategy was entirely left at the discretion of the operator (angiographic success defined as <30% residual diameter stenosis by visual assessment in the presence of TIMI-3 antegrade flow). All patient received aspirin lifelong and clopidogrel 75 mg/day for six months. Glycoprotein IIb/IIIa inhibitors were given at the discretion of the operator. The hospital ethics committee approved the study protocol and written informed consent was obtained from all patients.

Definitions and Follow-up

All patients were evaluated for the occurrence of major cardiac adverse events, defined as death, myocardial infarction, target lesion revascularization (TLR) and target vessel revascularization (TVR). In-hospital outcome information was retrieved by means of an electronic clinical database for patients maintained in our hospital after the procedure and by review of the hospital records for those discharged to secondary hospitals. After discharge, recordings of all repeat interventions (surgical and percutaneous) and re-hospitalizations were prospectively collected in a dedicated database. Follow-up information was obtained by regular

outpatient evaluation, by phone contact, or by mail. Myocardial infarction was documented by a rise in the creatine kinase level of more than twice the upper limit with an increased creatine kinase-MB. Cardiac markers were measured serially for all patients maintained in our institution. Among those discharged to their community hospitals, cardiac markers were collected only if a post-procedural MI was suspected. Consequently, enzymatic assessment was not available for all patients, but for those whom the likelihood of post-procedure MI was high[10]. TVR was defined as either surgical or percutaneous reintervention driven by significant (>50%) luminal 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. All living patients at 6 months were considered eligible for angiographic follow-up. Binary restenosis was defined as diameter stenosis > 50% within the stent or in the 5-mm segments proximal or distal to the stent. Late loss was defined as the difference between the post- procedure minimal luminal diameter and at follow-up.

Statistical Analysis

Discrete variables are presented as counts and percentages. Continuous variables are presented as mean ± standard deviation and compared by Student's T test.

Table 1. Demographics and procedural data (96 pts; 102 lesions)

Age (years)	64±12
Male (%)	62
Diabetes (%)	18
Current smoking (%)	26
Hypercholesterolemia (%)	57
Hypertension (%)	45
Previous myocardial infarction (%)	32
Previous Balloon Angioplasty (%)	19
Target vessel	
Left anterior descending artery (%)	47
Left circumflex artery (%)	9
Right coronary artery (%)	44
Chronic Total Occlusion (%)	20
Direct stenting (%)	53
Primary angioplasty,(%)	8
Glycoprotein IIb/IIIa inhibitor use (%)	31
Number of stents (per lesion)	2.66±0.9 (2-6)
Stented length (per lesion), (mm [range])	61.2±21.4 (41-134)
Mean nominal stent diameter (mm, [range])	2.82 ± 0.24

RESULTS

Baseline and procedural characteristics of the 96 patients (102 lesions) are presented in Table 1. Approximately half of lesions were located in the left anterior descending coronary artery (47%) or in the right coronary artery (44%). The mean number of stents per lesion was 2.66 ± 0.9 (range 2 to 6 stents) and the average stented length was 61.2 ± 21.4 mm. Angiographic success rate was 97%. Follow-up coronary angiography was performed in 67 patients (71% of eligible cases) (Table 2). Binary restenosis (diameter stenosis >50%) was identified in 8 lesions (11.9%). Among the 8 lesions (8 patients) with binary restenosis, 5 occurred within the stent, 1 in the proximal and 2 in the distal 5-mm adjacent vessel segment. All post-SES restenosis were focal and less than 10mm in length. Among these 8 patients, 4 were asymptomatic and did not undergo repeat revascularization. Complete clinical follow-up was available for all patients at an average of 320 ± 67.4 days (range: 265-442 days) and is summarized in Table 3.

Two patients died. One patient died during the in-hospital period after emergent bypass surgery for procedure related to left main stem dissection, caused by the guiding catheter. The second was admitted in cardiogenic shock due to post infarction unstable angina. He had 3-vessel disease but the treatment was restricted to the culprit lesion. In total, six 2.25-mm diameter SES were implanted in the LAD/diagonal bifurcation. The patient died suddenly 43 days after the procedure. Although there is no clear evidence, subacute stent thrombosis cannot be rule out in this case. Non-fatal myocardial infarction occurred in one patient. He developed, no-reflow phenomenon after stent placement which was resolved after intracoronary adenosine and nitropruside infusion. At 6 months follow-up angiography, the patient was asymptomatic with patent long stented segment.

Table 2: Quantitative coronary angiography post-procedure and at 6-months for patients with follow-up data (n=67).

	Proximal 5mm	In-stent	Distal 5mm
Post-procedure			
RD (mm)	3.17±0.55	2.68±0.51	2.45±0.51
MLD (mm)	2.76±0.54	2.17±0.47	1.94±0.53
Diameter stenosis, (%)	12	18	20
6-month follow-up			
RD (mm)	3.30±0.61	2.82±0.59	2.63±0.62
MLD (mm)	2.74±0.58	2.04±0.64	2.12±0.60
Diameter stenosis (%)	17	27	19
Late lumen loss (mm)	0.02±0.52	0.13±0.47	-0.16±0.47

MLD=Minimal lumen diameter ; RD=Reference diameter

Two patients underwent emergent bypass surgery for left main dissection. One patient died in-hospital as mentioned above, and the other had been successfully treated for left main dissection, but developed cardiac tamponade after the procedure and underwent surgical pericardial drainage, during which he received a venous graft to the first obtuse marginal branch.

A total of 4 patients were successfully treated with repeat PCI electively for focal restenotic lesions. Overall MACE-free survival was 91.7% at 320 days follow-up.

DISCUSSION

We report that the use of long length of SES implantation for de novo coronary lesions is associated with a low rate of major adverse cardiac events, mainly due to a reduced incidence of target lesion revascularization. In particular, SES demonstrated effective suppression of neointimal hyperplasia with a late lumen loss of 0.13 mm which is substantially lower than that of major published studies with bare metal stents for long segments, ranging from 0.79 to 1.41 mm[1,3-5]. Accordingly, the restenosis rate observed after SES was strikingly lower. It is noteworthy that the average stented length in our study was at least 10 mm longer than in previous series with bare metal stents.

Longer stented segment length using bare metal stents is an independent predictor of restenosis and adverse events [1]. Long stenting is frequently associated with prolonged intra-coronary manipulation due to multiple and overlapping stent placement, which may lead to injury to the vessel wall integrity. Moreover, the greater metal density may be potentially associated with a higher degree of local vascular injury, which altogether may

increase the risk of cardiac events and restenosis. Indeed, the incidence of late complications has been reported to be directly proportional to the total length of stents implanted. Previously, Schalij et. al reported a 25% incidence of major adverse events for patients treated with bare metal stents in a mean stented length of 45mm [6]. In the Additional Value of NIR Stents for Treatment of Long Coronary Lesions (ADVANCE)[3] Study, the reported MACE was 23%. The present results are reassuring, since the relatively low incidence of adverse events (8.3%) presented in our series occurred in association with a markedly long length of SES implanted (average 61 mm).

Table 3. 320—day major adverse cardiac events (n=96)

Death, n (%)	2 (2.1)
Non-fatal myocardial infarction, n (%)	1 (1.0)*
Target vessel revascularization, n (%)	6 (6.2)
percutaneous intervention	4 (4.2)
coronary artery bypass graft surgery	2 (2.1)†
Any major adverse cardiac event , n (%)	8 (8.3)

* non-Q wave myocardial infarction [CPK 567U/I (MB: 62U/I)].
†One of 2 patients who underwent emergency CABG for left main stem dissection died in hospital.

Among 5 patients (7.4%) with in-stent restenosis, only 1 focal in-stent restenosis was seen in the overlapped stented segment. Furthermore, consistent with previous reports regarding angiographic pattern of restenosis of SES[11], all our restenosis were focal and therefore easy to treat with repeat PCI. Since all patients with angiographically visible gaps between stents were excluded from the present analysis, incomplete lesion coverage was not identified as a possible mechanism of restenosis in any case.

There have been concerns that the risk for thrombosis might increase after implantation of long length of stent. In the current study, no documented thrombotic stent occlusion was observed, although we cannot rule out stent thrombosis in the patient that died suddenly 43 days after the index procedure. There is no consensus for the period of clopidogrel prescription following SES implantation especially after treatment of complex lesions. Although, no late thrombotic events were diagnosed after clopidogrel discontinuation in our series (i.e. after 6 months), additional studies are warranted for further evaluate the best antiplatelet scheme for these patients.

Several limitations are note-worthy due to evaluation of a small cohort of patients without direct comparative control group. Angiographic follow-up could not be obtained in all patients. However those who did not have control follow-up angiography were all uneventful. Post-procedure cardiac markers were not collective routinely for all patients (available for 46 patients [46%] in the study group). This was justified by the fact that high-grade enzymatic elevations, those with proven prognostic impact, rarely occur undetected in asymptomatic patients.

Conclusions

Sirolimus eluting stent implantation appear safe and effective treatment for de novo coronary lesions requiring multiple stent placement over a very long vessel segment.

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Chapter 15 Multi-lesion "Culotte" and "Crush" bifurcation stenting with sirolimus-eluting stents: long-term angiographic outcome

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Multi-lesion "Culotte" and "Crush" bifurcation stenting with sirolimus-eluting stents: long-term angiographic outcome

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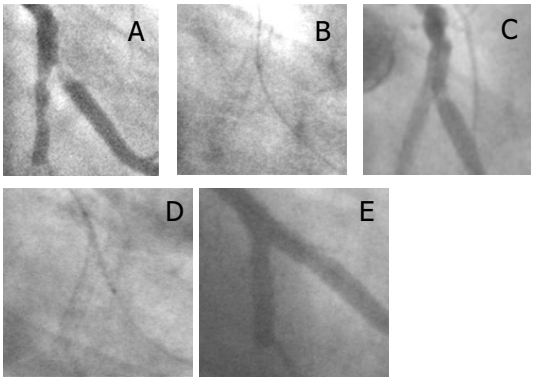

Figure 1. (A) left coronary angiogram (caudal right anterior oblique projection) showing diffuse disease with distal occlusion of the left circumflex artery and severe ostial stenosis in first obtuse marginal branch. **(B)** stent deployed covering the origin of the first marginal branch. A guidewire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

Case report

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

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

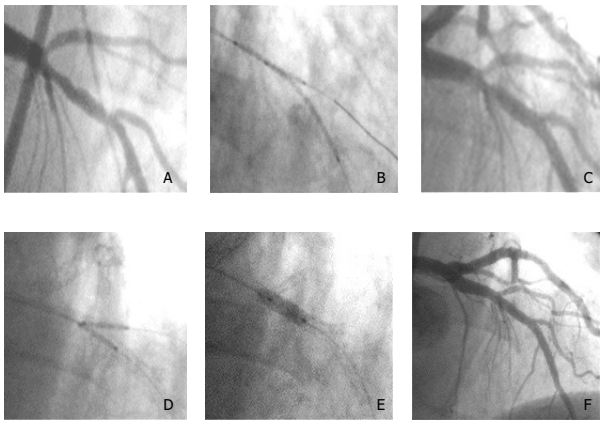

Figure 2. (A) left anterior descending artery (cranial right anterior oblique projection) presenting a long stenosis in its mid portion, involving the origin of the first and second diagonal branches. **(B)** "Crush" stenting: a 2.25 X 8mm sirolimus-eluting stent and a 3 X 33mm sirolimus-eluting-stent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

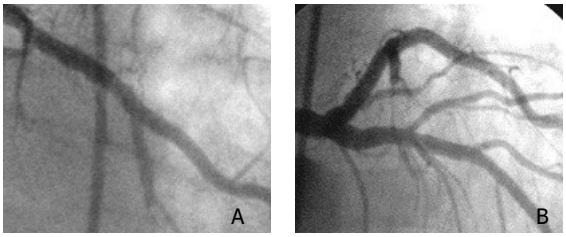

Figure 3. (A) Angiographic follow-up of the LCx – OM ostial lesions. No restenosis has occurred. **(B)** Excellent result after 6 months angiographic follow-up of the LAD.

Two PT Graphix Intermediate 0.014" guidewires were inserted in the LAD and second diagonal branch. A "crush" stent implantation was performed: a 2.25 X 8mm sirolimus-eluting stent and a 3 X 33mm sirolimus-eluting-stent (Cypher; Johnson & Johnson-Cordis unit) were concomitantly positioned in the second diagonal and mid LAD respectively (figure 2b). The 2.25 X 8mm sirolimus-eluting stent was deployed (12 atm) with its proximal portion partially placed through the LAD (figure 2b). Importantly, the LAD-diagonal stent was implanted while the undeployed 3 X 33mm sirolimus-eluting-stent was already positioned in the LAD in the site of its future implantation (covering the origin of the diagonal branch) (figure 2b). Subsequently, the balloon-catheter was retrieved from the diagonal branch and the LAD stent was deployed (22 atm) (figure 2b). After implantation of the LAD stent, a residual stenosis was noted in the proximal stent edge together with ostial compromise of the first diagonal branch, possibly due to plaque shiftening towards its origin (figure 2c). Additional "crush" stenting was performed to treat the LAD- first diagonal bifurcation (figure 2d). Following the same strategy as describe above, a 2.25 X 8mm sirolimus-eluting stent (Cypher; Johnson & Johnson-Cordis unit) was implanted in the first diagonal (12 atm) with its proximal portion partially deployed in the LAD (Figure 2d) while an undeployed 3 X 8mm sirolimus eluting-stent was already placed in the LAD (along the diagonal ostium) (figure 2d). The LAD stent was then deployed (20 atm) covering the ostium of the first diagonal branch (figure 2d). A small gap between the two LAD stents was noted and a 3 X 8mm sirolimus-eluting stent (Cypher; Johnson & Johnson-Cordis unit) was implanted (20 atm) to accomplish complete lesion coverage (figure 2e). Final high-pressure post-dilatation (22 atm) was performed in the mid LAD (Maverick balloon 3.0 X 9mm; Boston Scientific). Care was taken to inflate the balloon inside the stented area in order to avoid vessel injury in the non-stented edges. Excellent final angiographic result was achieved with TIMI 3 grade flow and minimal residual stenosis in all treated lesions (figure 2f).

The patient was included in the RESEARCH (Rapamycin Eluting-Stent Evaluated At Rotterdam Cardiology Hospitals) registry and agreed to undergo late angiographic follow-up [2]. After 208 days the patient remained asymptomatic and a stress test was negative. No adverse events had occurred. At coronary angiography, the right coronary artery was unchanged. All stents were widely patent with no angiographic evidence of stenosis (figure 3a and 3b).

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Chapter 16 Restenosis Rates Following Bifurcation Stenting with Sirolimus-Eluting Stents for De Novo Narrowings

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Restenosis Rates Following Bifurcation Stenting with Sirolimus-Eluting Stents for De Novo Narrowings

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The percutaneous treatment of coronary bifurcation stenoses is hampered by an increased rate of subsequent restenosis. The present study reports on the outcomes of a consecutive series of unselected patients with de novo bifurcation stenoses, treated with sirolimus-eluting stent implantation in both the main vessel and side branch. At 6 months, the incidence of major adverse cardiac events was 10.3% (one death and 5 target lesion revascularizations), with no episodes of acute myocardial infarction or stent thrombosis.

Percutaneous coronary intervention of bifurcation lesions is associated with lower procedural success rates, [1] and an increased subsequent rate of major adverse cardiac events (MACE) and restenosis. Various techniques and strategies have been applied in attempt to improve outcomes including kissing balloon dilatation, and the use of stent implantation in both branches.[2] The use of adjunctive atherectomy was found to be not advantageous in the CAVEAT I trial.[3] Although there was an improved initial angiographic result with less residual stenosis, this was at the expense of a higher rate of side branch occlusion and acute myocardial infarction. In the long-term, results of angioplasty in bifurcations have been hampered by problems of restenosis particularly following stent implantation within the side branch.[4, 5] Recently sirolimus-eluting stents (SESs) have demonstrated dramatically reduced restenosis rates in patients with relatively simple lesions.[6, 7] We sought to investigate the safety and efficacy of SES in a consecutive series of unselected patients with de novo bifurcation lesions enrolled in the RESEARCH (Rapamycin-Eluting Stent Evaluation At Rotterdam Cardiology Hospital) registry. [8]

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Since April 2002, SES implantation (Cypher™, Johnson & Johnson- Cordis unit) was adopted as the default strategy for all patients treated in our institution, as part of the RESEARCH registry.[8] Briefly, this single-centre registry, aims to evaluate the efficacy of SES implantation in the "real world" of interventional cardiology. All consecutive patients were enrolled irrespective of clinical presentation and lesion characteristics, and the incidence of MACE was prospectively evaluated during the follow-up. At 6-months, a total of 563 consecutive patients were treated solely with SES. Among these, 58 (10.3%) patients with de novo bifurcation lesions were treated with SES implantation in both the main and side branches, and compose the present study population. The patients' informed written consent was obtained in accordance with the rules of the Institutional Ethics Committee, which approved the study.

All procedures were performed with standard interventional techniques except with the use of SES as the device of choice. The strategy of bifurcation stenting employed, and the use of kissing balloon dilatation post-procedure was at the operators' discretion. One of 4 methods of stenting was used: T-stenting, culotte stenting, kissing stents, or the `crush` technique. T- and culotte stenting have been previously described.[5, 9] Kissing stents involved simultaneous implantation of the stents within both branches, with the proximal edges alongside each other thereby bringing forward the point of divergence. The `crush` technique involves positioning both stents, with the proximal part of the side branch stent lying well within the main vessel, whilst ensuring that the edge of the stent in the main vessel is more proximal than the side branch stent. The side branch stent is deployed first, and the balloon and wire carefully withdrawn. The main vessel stent is then deployed thereby crushing the proximal part of the side branch stent.[10] SESs were available in diameters from 2.25mm to 3.00mm and lengths from 8mm to 33mm. During the procedure, intravenous heparin was given to maintain an activated clotting time ≥250 seconds. All patients received lifelong aspirin, with clopidogrel for 6-months. The use of glycoprotein IIb/IIIa inhibitors was at the discretion of the operator.

Clinical and angiographic follow-up was performed at 6-months. Major adverse cardiac events (MACE) were pre-defined as death, myocardial infarction, or target lesion revascularization. The diagnosis of myocardial infarction 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.

Coronary angiograms were obtained in multiple views after intracoronary injection of nitrates. For the main branches, three coronary segments were subjected to quantitative angiography: in-stent, proximal edge, and distal edge segment. The in-stent analysis encompassed

the length of all stents used during the procedure. The proximal and distal edge segment included up to 5mm from the proximal and distal edge of the total segment treated with the study stents, respectively. For the side branches, 2 segments were analysed: in-stent and distal edge 5mm segment. Quantitative coronary angiographic (QCA) analysis was performed using the Cardiovascular Angiography Analysis System II (CAAS II) (Pie Medical, Maastricht, The Netherlands). The reference vessel diameter, minimal lumen diameter and percent diameter stenosis were measured at pre-, post-procedure and follow-up. The late loss was calculated as the difference between the minimal lumen diameter post procedure and that at follow-up. Binary restenosis was defined as the presence of >50% diameter stenosis within the target lesion.

Table 1 Baseline Clinical Characteristics (n=58)

Age (years)	63 ± 10
Men	42 (72%)
Hypertension	26 (45%)
Hypercholesterolemia	35 (60%)
Diabetes mellitus	16 (28%)
Current smoker	16 (28%)
Previous myocardial infarction	22 (38%)
Previous coronary angioplasty	5 (9%)
Previous coronary artery bypass surgery	3 (5%)
Number of coronary arteries significantly narrowed	
1	15 (26%)
2	28 (48%)
3	15 (26%)
Acute coronary syndrome	18 (31%)

Values are presented as the numbers (relative percentages) or mean value ± SD.

Fifty-eight patients with 65 bifurcation lesions were included in this study. Baseline patient characteristics are summarized in table 1. The lesion characteristics and stenting technique utilized are documented in table 2. At 6-months, the survival-free of MACE was 89.7%. One patient died following bifurcation stent implantation of the left main stem for an acute myocardial infarction. He was admitted in cardiogenic shock, and despite the use of abciximab and intra-aortic balloon pump support, died shortly after the procedure due to left ventricular failure. There were no episodes of acute or subacute stent thrombosis, and no patient had a myocardial infarction. Target lesion revascularization was undertaken in 5 patients (8.6%) as outlined below.

Table 2. Procedural and Lesion Characteristics (n = 65 lesions)

Coronary artery treated with bifurcation stenting	
Left anterior descending / diagonal	39 (60%)
Left circumflex / obtuse marginal	16 (25%)
Right coronary / posterior descending	4 (6%)
Left main stem – left anterior descending / circumflex	6 (9%)
Stenting technique	
T-stenting	41 (63%)
Culotte stenting	5 (8%)
Kissing stenting	2 (3%)
Crush stenting	17 (26%)
Kissing balloon dilatation after stenting	20 (31%)
Glycoprotein IIb/IIIa inhibitor use	20 (31%)

Values are presented as the numbers (relative percentages).

Table 3 Quantitative Coronary Angiography

	Proximal	In-stent	Distal
Main branch (n = 44)			
Reference diameter (mm)	N/A	2.64	N/A
Minimal lumen diameter (mm)			
Pre-procedure	N/A	0.64	N/A
Post-procedure	2.39	2.19	1.86
6-month follow-up	2.26	2.07	1.85
Diameter stenosis at 6-month (%)	28.3	22.9	25.4
Late lumen loss (mm)	0.12	0.12	0.01
Restenosis rate (%)	2.3	6.8	0
Side branch (n =44)			
Reference diameter (mm)	…	1.99	N/A
Minimal lumen diameter (mm)	…		
Pre-procedure	…	0.61	N/A
Post-procedure	…	1.80	1.57
6-month follow-up	…	1.49	1.47
Diameter stenosis at 6-month (%)	…	31.0	21.9
Late lumen loss (mm)	…	0.31	0.09
Restenosis rate (%)	…	13.6	0

Values are presented as mean values or relative percentages

Of 65 lesions, 6-month angiographic follow-up was performed in 44 lesions. The binary restenosis rate was 22.7% (10 of 44 lesions). QCA data are presented in Table 3. Angiographic restenosis occurred in 4 lesions within the main branch (1 in the proximal segment; 3 in the in-stent segment), yielding a restenosis rate of 9.1%. Angiographic restenosis occurred in 6 of the side branches, all within the in-stent segment. Of these 6 restenoses, 5 occurred at the ostium of side branch following the use of T-stenting (figure 1). All 4 patients with a restenosis within the main vessel, and 1 patient with a restenosis at the ostium of a side branch, underwent percutaneous target lesion revascularization with new drug-eluting stent implantation. Directional coronary atherectomy was additionally used in 1 patient. The remaining 5 patients, all with ostial side branch restenoses were asymptomatic and treated with medical therapy alone.

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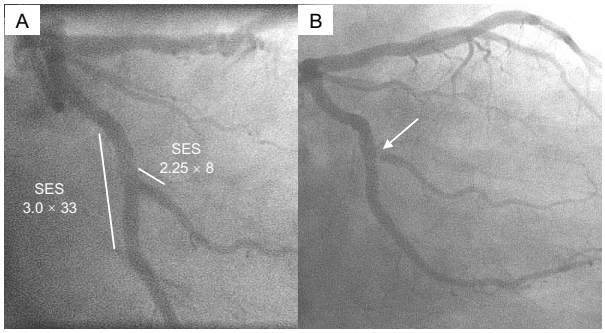
The major findings of this study of bifurcation stenting are the following: 1) SES implantation in both the main and side branches is feasible and associated with a low procedural complication rate, and no episodes of stent thrombosis. 2) The target lesion revascularization rate of 8.6% is seemingly diminished as compared to historical controls. 3) Angiographic restenosis rates of the main and side branches are 9.1% and 13.6%, with an overall restenosis rate of 22.7%. 4) Five of the 6 restenoses occurring in the side branch were located at the ostium following T-stenting technique.

Drug-eluting stent deployment in both vessels to treat bifurcation lesions may raise theoretical concerns that it could result in a propensity to stent thrombosis. When we treat bifurcation lesions with sirolimus-eluting stents using the culotte, kissing, or crush stenting techniques, there are some overlapping stent struts, where the higher concentration of sirolimus may induce endothelial function impairment and thus be associated with an increased rate of stent thrombosis. Although these stenting techniques were applied in 37% of the lesions treated, no stent thrombosis was reported during the follow-up period, implying that sirolimus has a wide safety margin.



A 3.0 x 33mm sirolimus-eluting stent (SES) was implanted in the circumflex artery, and a 2.25 x 8mm SES was implanted in the side branch (obtuse marginal) with T-stenting technique (A). At 6-months angiographic follow-up, restenosis occurred at the ostium of the side branch (arrowhead) (B).

Several strategies have been advocated to treat bifurcation lesions with PCI, such as deployment of stents in both vessels, stenting in one branch with balloon angioplasty in the other, and mechanical debulking. The published reports regarding the subsequent need for target lesion revascularization utilizing bare stents range from 17% to 53%, [5,11,12] thus the rate of 8.6% in our study is therefore very favorable. In addition, the rate observed in the current study may underestimate the true beneficial treatment effect of SES as explained below.

Five of the 6 restenoses in the side branch occurred at the ostium following T-stenting. When we apply T-stenting, stent positioning must be extremely accurate to ensure complete coverage of the side branch ostium. This is particularly difficult / impossible to achieve when the angle between the 2 branches is much $<90^{\circ}$. Restenosis at this site may therefore be mainly a reflection of incomplete coverage. The restenosis rate in the side branch following T-stenting was 16.7% (5 of 30 lesions), whilst that following the other stent techniques was 7.1% (1 of 14 lesions). The present study is limited because the choice of strategy was non-randomized, and there is no comparison with alternative strategies such as the use of stent implantation in the main vessel alone, with balloon-only angioplasty of the side branch. In addition, the sample size was relatively small, and any difference between the different techniques was not statistically significant. However, our results suggest that it seems wise to ensure the complete coverage of the ostium with SES using stenting techniques other than T-stenting. The "crush" technique is technically easier and quicker to do than a culotte, but further data with longer follow-up from a larger population is needed to fully determine the efficacy of these techniques.

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Chapter 17 Effectiveness of Sirolimus-Eluting Stent Implantation for Coronary Narrowings <50% in Diameter

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Effectiveness of Sirolimus-Eluting Stent Implantation for Coronary Narrowings <50% in Diameter

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Am J Cardiol. *In press.*

The long-term efficacy of percutaneous coronary intervention for mildly obstructive coronary narrowings is limited by the occurrence of restenosis, limiting the applicability of this therapy for these lesions. The present study reports on a consecutive series of 20 patients treated with sirolimus-eluting stent implantation for 23 angiographically mild de novo lesions, (defined as a diameter stenosis <50% by quantitative coronary angiography). At a mean follow-up of 399 ± 120 days, the survival-free of major adverse events was 95%, with no patient requiring target lesion revascularization.

Mildly obstructive coronary lesions do not cause anginal symptoms and ischemia per se. However, non-flow limiting lesions such as these can be associated with plaque rupture and erosion, potentially leading to acute myocardial infarction or sudden death.[1-6] Recent focus has been given to the development of novel technologies designed to detect regions of plaque thought to be at most risk, though the currently available information is limited by the lack of understanding of the natural progression of plaques. Previous data have shown that stent implantation for narrowings <50% stenosed, are subject to a not insignificant rate of adverse events at 1 year of 17%, particularly related to the need for repeat revascularization for restenosis.[7] The present report is an observation of the clinical outcomes of a first series of consecutive patients with angiographically mildly narrowed coronary arteries treated by sirolimus-eluting stent implantation.

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From April 2002, the sirolimus-eluting stent (SES) (Cypher™; Johnson & Johnson – Cordis) was utilized as the device of choice for every percutaneous coronary intervention performed in our institution, irrespective of clinical presentation or lesion morphology. Further details of the methodology are described elsewhere.[8,9] In brief, this single-centre registry was conducted with the aim of evaluating the impact of SES implantation in the "real world" of interventional cardiology.

During the first 6-months, 20 patients were treated solely with SES, for 23 angiographically mild, intermediate, or ambiguous lesions (4% of the total population treated). In order to exclude characteristics known to limit the angiographic determination of lesion severity, all of the following criteria had to be met: 1) the lesion was de novo 2) diameter stenosis by on-line quantitative coronary angiography (QCA) was <50%, 2) non-ostial location, 3) no visible angiographic thrombus, 4) not located in a diffusely diseased segment (as assessed by visual analysis).

The diagnostic approach to evaluate the clinical significance of the lesions utilizing invasive and / or non-invasive investigations, and the decision to proceed to stent implantation, was left at the operator's discretion. Patients were maintained on long-term aspirin medication, together with clopidogrel which was given for a minimum of 3 months. The protocol of the Registry 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. Written informed consent was obtained from every patient.

Coronary angiograms were obtained in multiple projections after intracoronary nitrate administration. Quantitative analyses were performed with the Cardiovascular Angiography Analysis System II (CAAS II; Pie Medical, Maastricht, The Netherlands) using validated edge-detection techniques. The empty tip of the angiographic catheter was utilized for image calibration. Lesion measurements were performed in the "worst" view with the end diastolic frame selected for analysis.

Patients were followed up prospectively and evaluated for survival free of major adverse cardiac events (MACE) using questionnaires and telephone enquiries when necessary. MACE was pre-defined as: 1) death, 2) non-fatal myocardial infarction, or 3) repeat target lesion revascularization. A definite diagnosis of myocardial infarction required an increase in the creatine kinase level to more than twice the upper normal limit, together with an increased level of the creatine kinase MB fraction. Target lesion revascularization was defined as any surgical or percutaneous re-intervention motivated by a significant luminal narrowing within the stent or in the 5-mm proximal or distal peri-stent segments. In the present cohort treated for angiographic mild lesions, follow-up data were obtained in all patients.

Discrete variables were presented as percentages and compared by Fisher's exact tests. Continuous variables were presented as means and standard deviations and compared by Student's T test. All tests were two-tailed and a p value < 0.05 was considered as significant.

The mean age of the patients was 54 ± 9 years, and 17 (85%) were men. Risk factors were diabetes mellitus in 1 patient (5%), hypercholesterolemia in 12 (60%), current smoking in 8 (40%), hypertension in 7 (35%). There was a history of previous acute myocardial infarction in 5 (25%), and prior coronary angioplasty in 6

(30%), no patient had undergone coronary artery bypass surgery. Of the 20 patients, 7 (35%) were treated for at least one additional severely stenotic lesion (>50% diameter stenosis) during the same procedure. Clinical presentation was stable angina pectoris in 12 (60%) and unstable angina pectoris in the remaining 8 (40%). The 23 lesions were treated with implantation of 26 SESs, with direct stent implantation in 21 lesions (91%). Glycoprotein IIb/IIIa inhibitor therapy was used in 4 patients (20%). The decision to treat was based on a good history of stable angina pectoris in 5 patients (25%), a positive thallium scan in 3 patients (15%), presentation with an acute coronary syndrome (with ECG changes and / or troponin elevation) thought to relate to the target lesion in 4 patients (20%), IVUS examination documenting a minimum lumen area <4.0mm^2 in 4 patients (20%), a fractional flow reserve ≤0.75 in 3 patients (15%), and a positive methergine test in 1 patient (5%).

The mean lesion length was 10.8 ± 4.7mm, and mean reference diameter 2.70 ± 0.60mm. Minimal luminal diameter increased from 1.66 ± 0.43mm at baseline, to 2.42 ± 0.59mm post-procedure (p<0.01). Pre-procedure diameter stenosis decreased from 39 ± 8% (range 14 – 49%) to 14 ± 10% (range 0 – 35%) (p<0.001). Mean diameter of stent was 2.9 ± 0.2mm with a mean length of 14.5 ± 7.5mm.

One patient had a peri-procedural non-Q wave myocardial infarction, with an elevation of creatine kinase 1-3x the upper limit of normal together with a rise in creatine kinase-MB fraction (maximum creatine kinase 532U/l, upper limit of normal 169U/l). Review of the final procedural angiogram showed dissection of the distal left anterior descending artery with TIMI II flow; this probably related to preceding difficult wire passage in a very tortuous part of the vessel. Follow-up angiography at 6-months showed that the dissection had healed with TIMI III distal flow. In-hospital, the survival-free of MACE was 1/20 (95%).

After a mean follow-up period of 399 ± 120 days (median 428 days) all patients were alive and free of myocardial infarction, and there were no further interventions in any mild lesion treated with SES. In total, 7 patients underwent control angiography at 6-months with no evidence of restenosis in any of the mild lesions. One patient, treated for a mild lesion of the left anterior descending artery, underwent angioplasty to a diagonal branch at follow-up. Review of the index procedure showed that the diagonal lesion had previously been present but not treated. The survival-free MACE was 95%.

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Our findings indicate that SES implantation for coronary narrowings with a diameter stenosis of <50% by quantitative angiography, is safe and associated with a very low incidence of adverse events at 1 year. Our results resemble those observed in the RAVEL trial, in which no patient had repeat revascularization after treatment of relatively "simple" lesions with SES.[10] Accordingly, mildly obstructive lesions do not generally present a "complex" morphology, and percutaneous therapy is usually not technically challenging. Indeed in our series, direct stent implantation was successful in 91% lesions.

The present study is observational, and limited by the small number of patients evaluated, and its non-randomized, non-controlled nature. Although the majority of our patients were treated on the basis of an evidence-based indication such as the IVUS assessment or fractional flow reserve, some were treated in the absence of objective ischemia (n=5). The use of SESs has been associated with evidence of delayed re-endothelialization raising concerns regarding a propensity to stent thrombosis which is associated with significant morbidity. Thus far, the published data from several SES trials show a rate of acute / subacute thrombosis that is comparable to that of bare metal stents. The decision as to whether to proceed to percutaneous coronary intervention for angiographically mild lesions, in the absence of documented ischemia, is a dilemma that is frequently encountered in current clinical practice. None of our patients had an episode of stent thrombosis, however the, albeit small, risk must be taken into account before proceeding to SES implantation in the absence of an evidence-based indication.

Evaluation of lesion severity by intracoronary measurements has been advocated to discriminate between patients who should receive invasive treatment from those in whom further treatment should be deferred.[11-17] Accordingly, the rate of subsequent events and need for target lesion revascularization has been shown to be low (4.4% at one year) if IVUS examination demonstrates a minimum lumen area of ≥4.0mm^2. [11] In addition, patients with an abnormal fractional flow reserve (<0.75) have been reported to present a higher risk for future complications than those with normal measurements.[15,16] In our series, stent implantation was undertaken in 7 patients (35%) following either IVUS examination showing a minimum lumen area <4.0 mm^2, and/or a fractional flow reserve of ≤0.75. However, such historical algorithms were produced when angioplasty was carried out with bare metal stents, and rely heavily on the prohibitively high incidence of adverse events following an eventual percutaneous treatment, which has been found to be around 17% at 1 year.[7,15] Even after following these algorithms, patients with "normal" findings at lesion assessment, who have been considered to be at "low risk" if left untreated, at one year, the rate of adverse events may still be as high as 11%.[12] Our results suggest that by altering the risk / benefit ratio of stent implantation versus deferred invasive therapy, the introduction of drug-eluting stents into clinical practice may potentially change the current treatment algorithms for patients with mild to moderate lesions. In addition, if the propensity to accelerated plaque progression or vulnerability to plaque rupture or erosion could be better evaluated, this might enable localization of areas of coronary artery plaque which could benefit most from stabilization with stent implantation. Although the present study did not specifically address this issue, this may broaden the applicability of percutaneous coronary intervention with drug-eluting stent implantation.

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Chapter 18 Clinical and Angiographic Outcomes After Over-Dilatation of Undersized Sirolimus-Eluting Stents With Largely Oversized Balloons. An Observational Study

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Catheter Cardiovasc Interv. *In press*

Clinical and Angiographic Outcomes After Over-Dilatation of Undersized Sirolimus-Eluting Stents With Largely Oversized Balloons. An Observational Study

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Purpose: To assess the safety and effectiveness of sirolimus-eluting stent (SES) post-dilatation with largely oversized balloons.
Methods: We evaluated the clinical outcome of 68 consecutive patients enrolled in the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry that underwent percutaneous coronary intervention with SES implantation and further post-dilatation with balloons >1mm larger than the stent nominal size. Angiographic follow-up was either scheduled for selected subgroups or clinically-driven.
Results: Overall, 75 lesions were treated. The procedure was successful in 98.5% of the cases. One patient (1.5%) underwent emergency coronary bypass surgery for acute vessel occlusion. During 10.1±1.7 months follow-up, 3 patients (4.5%) died, 1 (1.5%) had acute myocardial infarction, and 4 patients (6%) had target vessel revascularization. At angiographic follow-up, loss index was 0.13±0.34 and restenosis rate 7.7%.
Conclusions: Although not routinely recommended in every patient, sirolimus-eluting stent post-dilatation with largely oversized balloons appears a safe and effective strategy for selected patients.

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INTRODUCTION

Stent-based local drug delivery is a relatively new concept developed to prevent neointima hyperplasia growth and restenosis following coronary angioplasty and stenting (1). While the stent, with its mechanical properties, prevents elastic recoil and negative vessel remodeling, the drug bound on its surface exerts an inhibitory action toward smooth muscle cells proliferation and migration, the most important determinants of in-stent restenosis (ISR).

Sirolimus-eluting stents (SES) have been shown in randomized trials to virtually abolish in-stent restenosis in selected patients with *de novo* lesions (2). The revolutionary results obtained in the first studies have encouraged, in a few pioneer centers, the routine utilization of these new devices, with the double aim to give the best treatment available to all patients and, at the same time, to assess the efficacy of SES in more complex clinical subsets of patients and lesions, such as those found in the daily practice (3).

Several intravascular ultrasound (IVUS) studies have shown that optimal stent deployment was rarely achieved with angiographically-guided angioplasty alone (4-6). The major effect of these studies was the introduction of routine high pressure stenting (5,7). Moreover, stent post-dilatation with larger balloons has become common practice after the documentation of the frequent mismatch between the angiographic and the real vessel diameter (8-10), and the very low incidence of in-stent restenosis observed in the MUSIC study with IVUS-guided stent deployment (11). The choice to post-dilate a stent depends on many factors: operator's habit, attempt to improve suboptimal angiographic results, IVUS-guided stenting. In the AVID study, which evaluated the effects of IVUS-guided stent, additional balloon dilatation based on IVUS findings was performed in 43% of the patients (12). Similarly, in the CRUISE study, after IVUS examination the operators decided to use oversized balloons in 34% of the patients (13). This strategy has been proven to be safe with bare stents, and was not reported to hamper the efficacy of drug-eluting stents in the RAVEL trial (2), where it was allowed in order to achieve a less than 20% residual diameter stenosis.

In daily practice, based on angiographic or intravascular ultrasound findings, extreme over-dilatation with balloon >1mm larger than the stent nominal size might be required in selected cases to achieve a good procedural result. Moreover, temporary limited availability of properly sized stents could be related to local laboratory or manufacturers' problems. In the SES, sirolimus is blended in a 5-µm-thick layer of nonerodable polymer. Appropriate drug delivery depends on the polymer integrity and on the proper spacial distribution of the stent struts. Extreme post-dilatation of the stent could impair the effectiveness of SES in different ways: by enhancing tissue proliferation in response to greater vessel injury (14), by altering the mechanical properties of the stent, by disrupting the polymer coating, and by increasing the distance between the stent struts, therefore reducing local drug distribution.

In the present study, we evaluated the clinical and angiographic outcomes of 68 patients treated with SES implantation in which a post-dilatation with largely oversized balloons was performed.

METHODS

SES implantation was adopted as the default strategy for all patients undergoing PCI at our institution, as part of the RESEARCH (Rapamycin-Eluting Stents Evaluated At Rotterdam Cardiology Hospital) Registry (3). The SES was available in limited lengths (8, 18, and 33mm) and diameters (2.25, 2.5, 2.75 and 3.0mm). In a four months period from June to October 2002, 68 consecutive patients underwent

SES implantation and further post-dilatation with balloons >1mm larger than the stent nominal size and comprise the present study population.

All procedures were performed according to standard techniques and the final interventional strategy, as well as periprocedural adjunctive medications and intravascular ultrasound utilization, was left to the operator's discretion. All patients were pre-treated with aspirin and clopidogrel. Aspirin was maintained lifelong and at least 3 months of clopidogrel treatment was recommended thereafter. Prolonged clopidogrel prescription (6 months) was recommended for patients treated with SES and at least one of the following characteristics: multiple SES (>3 stents), total stented length >36 mm, chronic total occlusion, bifurcations, and in-stent restenosis. The study protocol was approved by the institutional ethics committee and written informed consent was obtained from all patients.

A procedure was considered successful when residual stenosis was < 30% by quantitative coronary analysis together with TIMI flow 3. During follow-up, coronary angiograms were obtained as clinically indicated by symptoms or positive ischemic tests. In addition, follow-up angiograms were scheduled for patients with SES implantation to treat in-stent restenosis, bifurcations, left main, chronic total occlusions, very small vessels (SES diameter 2.25mm), long stent length (>36mm), and acute myocardial infarction. Post-SES binary restenosis at follow-up was defined as >50% diameter stenosis occurring in the segment inside the SES or within 5-mm segment proximal or distal to the stent. Acute gain was defined as the difference between minimal luminal diameter (MLD) post- and MLD pre-procedure. Late loss was calculated as the difference between the MLD immediately after the procedure and the MLD at six months. Loss index was defined as the ratio between late loss and acute gain. The incidence of major adverse cardiovascular events (MACE), defined as death, myocardial infarction or target vessel revascularization (TVR), was evaluated. A definite diagnosis of MI required an increase in the creatine kinase (CK) level to more than twice the upper normal limit with an increased level of CK-MB.

Target lesion revascularization (TLR) was defined as any surgical or percutaneous re-intervention motivated by a significant luminal narrowing within the stent or in the 5-mm distal or proximal peristent segments. Target vessel revascularization (TVR) was defined as any re-intervention driven by lesions located in the treated vessel beyond the target lesion limits.

Discrete variables are reported as counts and relative percentages. Continuous variables are expressed as mean ± standard deviation.

RESULTS

Baseline clinical characteristics of the 68 patients are shown in table 1. Around 15% of the patients had diabetes mellitus, and 56% multivessel coronary disease. Notably, 23.5% of the patients presented acute myocardial infarction. Overall, 75 lesions were treated with 101 sirolimus-eluting stents, with an average stent length per lesion of 26.9±18.0 mm. Among the lesions, 7 (9.3%) were in the left main, and 9 (12%) in a saphenous vein graft. Chronic total occlusions (> 3 months) accounted for 24% of the procedures. Nominal stent diameter was 3.0 mm in 98 cases, 2.75 mm in 2, and 2.5 in 1. Further stent post-dilatation was performed with a 4.0 mm balloon in 70 lesions, and with 4.5 mm balloon in the remaining 5. Average inflation pressure was 15.9 ± 3.6 atm. Nominal balloon to artery ratio was 1.31±0.29. IVUS was used in 21 patients (30.8%). In 85.3% of the cases, the SES was implanted to treat a de novo lesion, in 9.3% to treat in-stent restenosis, and in 4% to treat a guiding catheter-induced vessel dissection (table 2). Glycoprotein IIb/IIIa inhibitors were used in 38.2% of the patients. The procedure was successful in 67 patients (98.5%). One patient developed diffuse distal vessel dissection after post-dilatation of the 3x18 mm SES with a 4x15 mm balloon, inflated up to 12 atmospheres, and underwent successful emergency CABG.

Table 1. Baseline patient characteristics (n=68)

Age, years	60±10
Men	45 (66.2%)
Risk Factors	
Current smoker	24 (35.3%)
Diabetes mellitus	10 (14.7%)
Family history of coronary heart disease	32 (47.1%)
Clinical Presentation	
Silent ischemia	3 (4.4%)
Stable angina pectoris	30 (44.1%)
Unstable angina pectoris	19 (27.9%)
Acute myocardial infarction	16 (23.5%)
Multivessel coronary disease	38 (55.9%)
Previous myocardial infarction	21 (30.1%)
Previous coronary bypass	9 (13.2%)
Previous percutaneous coronary intervention	17 (25%)

Table 2. Angiographic and procedural characteristics

Lesions, n	75
Target coronary artery	
Left anterior descending	21 (28.0%)
Left circumflex artery	6 (8.0%)
Right coronary artery	32 (42.7%)
Left main	7 (9.3%)
Saphenous vein graft	9 (12.0%)
Lesion type	
De novo	64 (85.3%)
In-stent restenosis	7 (9.3%)
Early re-intervention	1 (1.3%)
Guiding catheter injury/dissection	3 (4.0%)
Lesion type (AHA/ACC classification)	
Type A/B1	22 (29.3%)
Type B2/C	53 (70.7%)
Thrombus-containing lesions	16 (21.3%)
Moderate/severe calcifications	9 (12.0%)
Ostial lesions	23 (30.7%)
Bifurcation stenting	4 (5.2%)
Chronic total occlusions	18 (24%)
Glycoprotein IIb/IIIa inhibitors*	26 (38.2%)
Stent per lesion, n	1.35 ± 0.65
Stents length per lesion, mm	26.9 ± 18.0

*percentage relative to the number of patients (68)

Clinical follow-up was available for 67 patients (98.5%). During an average follow-up of 10.1±1.7 months, 3 (4.5%) patients died, 1 (1.5%) had acute myocardial infarction, and 4 patients (6%) had a TVR, of which 3 were TLR (4.5%). Overall MACE rate was 12.0%. One patient was admitted with acute large infero-posterior myocardial infarction and cardiogenic shock, which was irreversible despite positioning of intra-aortic balloon pump. A second patient died 5 months after the procedure because of end-stage renal failure. The cause of death of the third patient, who died 141 days after the revascularization procedure, is unknown: he was 75 years old, diabetic, with 3 vessel disease and moderate aortic valve stenosis, and had received a SES in the proximal right coronary artery. One patient had a small periprocedural myocardial infarction (CK max=346 UI/L,

MB=73 UI/L). The angioplasty was performed in a saphenous vein graft, which was totally occluded due to in-stent restenosis. Among the 4 target vessel re-interventions, only 1 was motivated by restenosis. The remaining were 1 case of emergency bypass surgery, already described, 1 early (5 days) percutaneous re-intervention caused by incomplete ostial coverage of the rigth coronary artery during the index procedure, and one case of in-stent re-dilatation driven by IVUS diagnosis of stent undersizing despite the absence of angiographic restenosis (the patient was symptomatic and presented angiographic restenosis in another lesion located distally in the same vessel, a saphenous vein graft). There were no episodes of early or late stent thromboses.

Table 3. Paired quantitative angiographic analysis.

	Baseline	Post	Follow-up
RD, mm	3.18±0.63	3.36±0.40	3.43±0.46
MLD, mm	0.68±0.62	2.88±0.42	2.66±0.77
Diameter stenosis, %	77±22	14±9	20±21
Lesion length, mm	20.1±14.1	-	-
Acute gain, mm	-	2.22±0.73	-
Late loss*, mm	-	-	0.24±0.61
Loss index	-	-	0.13±0.34
Binary restenosis*, %	-	-	7.7%

MLD=minimal luminal diameter; RD=reference diameter
*including one total re-occlusion

Angiographic follow-up was obtained in 34 patients for 39 lesions after 210±29 days (range 156-309 days). As previously specified, the reasons for repeat catheterization were: elective follow-up because the patient was included in selected subgroups in 32 cases (72.7% of the 44 patients scheduled for 6-months angiography), and clinically-driven re-catheterization in 2 patients. At baseline, mean reference diameter was 3.21 ± 0.58mm, MLD 0.86 ± 0.61mm, percent diameter stenosis 72 ± 21%, and lesion length 17.9 ± 11.5 mm. Paired quantitative coronary analysis for patients with angiographic follow-up is shown in table 3. Late loss was 0.24 ± 0.61 mm, with 76% of the cases in the range between –0.5 and +0.5 mm. Loss index was 0.13 ± 0.34. Overall, post-SES binary restenosis was observed in 3 lesions (7.7%): 2 were proximal edge restenosis, and in one patient the vessel was occluded approximately 30 mm proximally to the target lesion.

DISCUSSION

The present study shows that post-dilatation of SES with largely oversized balloons is relatively safe and associated with good angiographic results.

IVUS studies have demonstrated that incomplete stent deployment may occur in a considerable number of patients even with high-pressure techniques (6,15). Optimal stent expansion plays a key role in the prevention of stent thrombosis (4). Moreover, previous studies have shown that residual percent diameter stenosis after stent implantation is directly related to the development of restenosis (16,17). Similarly, in-stent minimal lumen cross sectional area measured by IVUS is inversely related to restenosis (18). All together, these findings provide the rationale to pursue optimal stent expansion. This outcome is often achieved by performing stent post-dilatation with balloons oversized with respect to the nominal stent size. Over-dilatation with balloons >0.25 mm larger has been shown to improve lumen gain and possibly reduce the need for target vessel revascularization, without increasing complications (9,10,19). However, in one study IVUS examination revealed that even with this strategy no stent reached its nominal size (19). Thus, it is commonly believed that post-dilatation with balloons up to 0.5 mm larger than the stent nominal size can be safely accomplished in most of the cases. Conversely, dilatation with balloons >0.5 mm larger than the stent nominal size is a rare procedure. In clinical practice, this extreme post-dilatation is performed in selected patients, commonly when the operator has the perception, based on angiographic or IVUS findings, that the stent implanted is markedly undersized relatively to the vessel diameter. In other situations this choice could be driven, in a bail-out procedure, by unavailability of the proper size of stents. In both cases, this strategy should be regarded as an extreme solution, not free from potential complications. Possible stent structure distortion and disruption must be taken into account, as well as the chance of extensive intimal dissection and vessel wall rupture. When the same strategy is applied with drug-eluting stents, further possible shortcomings should be considered. In fact, the success of drug-eluting stents depends critically on the achievement of the appropriate local drug concentration, which warrants potent antiproliferative effects and preserved vascular healing. The elution profile/release kinetics of the drug depend on the biological properties of the drug and of the coating matrix (1). Apart from the potential mechanical damages to the stent, excessive SES post-dilatation could impair their antiproliferative properties by damaging the polymer coating. Moreover, by increasing the distance between the drug-carrying stent struts, over-dilatation could decrease local sirolimus concentration to a sub-optimal or ineffective level. The results of the present study suggest that these potential risks do not have an evident impact on the the favorable clinical and angiographic outcome of SES, although some negative influence cannot be ruled out in single cases (20). In our series, extreme SES post-dilatation was not associated with an high rate of acute complication, although one patient had to be referred for emergency coronary surgery. The clinical outcome at mid-term follow-up was favorable, and the 12% incidence of MACE appears very satisfactory if we consider the unselected nature of the population analyzed, which included 24% of the patients with acute myocardial infarction. Notably, 9% of the lesions treated were in the left main and 12% in a saphenous vein graft. Moreover, at angiographic follow-up, restenosis was observed in a very limited number of patients. Although only 50% of the patients underwent repeat catheterization, the selection criteria of these patients ("complex" lesions and symptomatic patients) would have been expected to increase the chance of finding restenotic lesions, thus indirectly confirming the very positive results obtained. Remarkably, almost one fourth of the lesions were chronic total occlusions, condition traditionally associated with higher restenosis rates (21,22). Indeed, the loss index of the present series (0.13 ± 0.34), compares favorably with the historical series of the BENESTENT trial (0.46 ± 1.39), the BENESTENT II Pilot study (0.41 ± 1.18), and the MUSIC study (0.45 ± 0.33) using bare stents (table 4) (11).

In conclusion, angiographically or intravascular-guided post-dilatation of SES with largely oversized balloons

could be considered an extreme solution for stent undersizing. Although careful case by case evaluation in these situations is necessary, this strategy appears relatively safe and does not seem to impair the effectiveness of sirolimus-eluting stents.

Table 4. Angiographic findings compared to the MUSIC trial (11).

	MUSIC	SES overdilatat.
Reference diameter pre, mm	3.09±0.49	3.18±0.63
Reference diameter post, mm	3.40±0.54	3.36±0.40
Reference diameter at 6 months, mm	3.04±0.51	3.43±0.46
Minimum lumen diameter pre, mm	1.13±0.34	0.68±0.62
Minimum lumen diameter post, mm	2.90±0.36	2.88±0.42
Minimum lumen diameter at 6 m., mm	2.12±0.67	2.66±0.77
Diameter stenosis pre, %	63±10	77±22
Diameter stenosis post, %	15±6	14±9
Diameter stenosis at 6 m., %	30±17	20±21
Nominal balloon/artery ratio	1.20±0.15	1.31±0.29
Maximal inflation pressure	15.8±3.33	15.9±3.6
Acute gain, mm	1.79±0.39	2.22±0.73
Late loss, mm	0.78±0.56	0.24±0.61
Loss index	0.45±0.33	0.13±0.34

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Chapter 19 Routine Sirolimus-Eluting Stent Implantation for Unselected In-Stent Restenosis: Insights From the Rapamycin Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) Registry

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Heart. *In press*

Routine Sirolimus-Eluting Stent Implantation for Unselected In-Stent Restenosis: Insights From the Rapamycin Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) Registry

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Objective: To assess the effectiveness of routine sirolimus-eluting stent (SES) implantation for unselected patients with in-stent restenosis (ISR), and to provide preliminary information about the angiographic outcome for different lesion subgroups and for different ISR patterns.
Patients: We evaluated 44 consecutive patients (53 lesions) without previous brachytherapy that were treated with SES for in-stent restenosis at our institution. Routine angiographic follow-up was obtained at 6 months and the incidence of major adverse cardiac events was evaluated.
Results: At baseline, 42% of the lesions were focal, 21% diffuse, 26% proliferative, and 11% total occlusions. Small vessel size (reference diameter <2.5mm) was present in 49%, long lesions (>20mm) in 30%, treatment of bypass grafts in 13%, and bifurcation stenting in 18%. At follow-up, post-SES restenosis was observed in 14.6%. No restenosis was observed in focal lesions. For more complex lesions, restenosis rates ranged 20-25%. At 1-year follow-up, the incidence of death was 0%, myocardial infarction 4.7%, and target lesion revascularisation 16.3%. Target lesion revascularisation due to restenosis was performed in 11.6%.
Conclusions: Routine sirolimus-eluting stent implantation is highly effective for focal in-stent restenosis and appears to be a promising strategy for more complex patterns of restenosis.

Heart. *In press*

INTRODUCTION

Despite major advances in the field of percutaneous coronary interventions (PCI), long-term outcome is still limited by the occurrence of in-stent restenosis (ISR), which has been reported to occur in 10 to 50% of the patients in several series.[1] Furthermore, treatment of ISR is frequently a challenging clinical problem, with recurrent restenosis being reported in up to 80% in the most complex cases.[2] Currently, vascular brachytherapy is the only strategy proven to be more effective for the treatment of ISR than other conventional approaches.[3][4][5][6][7] However, post-brachytherapy recurrent restenosis has been reported to occur in 17% to 32% of patients at 1 year.[3][4][5][6][7] Moreover, despite the relative improvement in outcomes, brachytherapy has not been extensively adopted as routine therapy in many centers, mostly due to logistic and technical limitations.

Sirolimus-eluting stents (SES) have been shown in randomized trials to virtually abolish in-stent restenosis in selected patients with *de novo* lesions.[8][9] Moreover, prolonged (up to 2 years) inhibition of the proliferative response has been documented in two series of patients with non-complex lesions.[10][11] Due to the potent antiproliferative and antimigratory effects of the drug on vascular smooth muscle cells and the clinical efficacy demonstrated for *de novo* lesions, SES implantation has been recently tested in two preliminary studies to treat in-stent restenosis.[12][13] In one study with 25 relatively non-complex cases, zero recurrent binary restenosis was observed after SES.[13] In the other study, among 16 patients with more complex lesions, repeat in-stent restenosis was observed in 20% of cases.[12] However, due to the limited number of patients in both reports, the outcome in patients with complex lesion morphology, a condition commonly seen in daily practice, is currently unclear.

In the present study, we evaluated the clinical and angiographic outcomes of 44 consecutive patients treated with routine SES implantation for in-stent restenosis with a broad range of morphological lesion patterns.

METHODS

Patient population and Procedures

Since the 16th of April 2002, SES implantation has been adopted as the default strategy for all patients undergoing PCI at our institution, as part of the RESEARCH (Rapamycin-Eluting Stents Evaluated At Rotterdam Cardiology Hospital) Registry.[14] Fourty-four consecutive patients without previous brachytherapy were treated for in-stent restenosis during a 6-month enrolment period and comprise the present study population. No patient with in-stent restenosis was treated in the same period exclusively with other percutaneous devices (e.g. bare metal stents, cutting balloon) or with brachytherapy and therefore excluded from this report. The study protocol was approved by the hospital ethics committee and written informed consent was given by every patient.

The CYPHER^{TM} sirolimus-eluting stent (Cordis Europa NV, Roden, NL) was utilized in all patients. The stents were available in lengths of 8, 18 or 33mm and in diameters of 2.25, 2.5, 2.75 and 3.0mm. All procedures were performed according to standard techniques and the final interventional strategy was left to the operator's discretion. Complete lesion coverage was recommended, as well as a small region of overlap of adjacent stents when treating lesions that required more than one stent. Periprocedural adjunctive medications were left to the

discretion of the operator. All patients were pre-treated with aspirin and clopidogrel. Aspirin was maintained lifelong and at least 3 months of clopidogrel treatment was recommended thereafter.

Table 1. Baseline patient characteristics

Patients	44
Age, years±SD	63±13
Men	73%
Risk Factors	
Current smoker	27%
Hypercholesterolemia*	68%
Systemic hypertension	48%
Diabetes mellitus	25%
Family history of coronary heart disease	43%
Clinical Presentation	
Silent ischemia	9%
Stable angina pectoris	64%
Unstable angina pectoris	25%
Acute myocardial infarction	2%
Multivessel coronary disease	50%
Previous myocardial infarction	52%
Previous coronary bypass	23%
Recurrent episodes of in-stent restenosis (>1)	25%

*Total cholesterol > 200mg/dl and/or on lipid lowering treatment

Definitions and Follow-up

Restenotic lesions were angiographically classified by two independent operators according to Mehran classification as: 1) focal (<10 mm), 2) diffuse, 3) proliferative, or 4) total occlusion.[2] A procedure was considered successful when residual stenosis was < 30% by quantitative coronary analysis (QCA) with TIMI flow 3. All patients were requested to undergo an elective repeat angiogram after 6 months following a successful procedure. Post-SES binary restenosis at follow-up was defined as >50% diameter stenosis occurring in the segment inside the SES or within 5-mm segment proximal or distal to the stent. Late luminal loss was calculated as the difference between the minimal luminal diameter (MLD) after the procedure and at six months.

Patients were prospectively followed-up to evaluate the incidence of major adverse cardiovascular events (MACE), defined as death, myocardial infarction or target lesion revascularisation (TLR). Target lesion revascularisation (TLR) was defined as any surgical or percutaneous re-intervention motivated by a significant luminal narrowing within the stent or in the 5-mm distal or proximal peristent segments.

Statistical analysis

Discrete variables are reported as counts and relative percentages and compared with Fisher's exact test. Continuous variables are expressed as mean ± standard deviation and compared with the Student *T* test. A p value < 0.05 was considered to be significant. All tests were two-tailed. Analyses were performed with SPSS version 8.0 statistical package (SPSS Inc. Chicago, IL, USA).

RESULTS

Baseline and procedural data

Baseline clinical characteristics of the 44 patients with ISR are shown in table 1. Diabetes was present in 25% of the patients. Clinical presentation was an acute coronary syndrome in 27% of cases. A quarter of the patients had previous recurrent episodes of ISR. According to the Mehran classification, 42% of the lesions were class I, 21% class II, 26% class III, and 11% class IV (table 2). Small vessel size (reference diameter < 2.5 mm) was present in 49%, long lesions (>20mm) in 30%, treatment of bypass grafts in 13%, and bifurcation stenting in 18%. The patients received on average 2.0±1.4 stents, with a mean stent length per lesion of 28±20mm (range 8-84 mm). Direct stenting was performed in 13 lesions (24.5%). Seven lesions (13.2%) were pre-dilated with a cutting balloon. Endovascular ultrasound was used in 25% of the procedures for stent sizing or to optimize the result. The procedure was successful in 43 patients (97.7%). One patient underwent emergency bypass surgery due to intimal dissection and acute vessel occlusion during the procedure.

Table 2. Angiographic and procedural characteristics

Lesions	53
Target coronary artery	
Left anterior descending	49%
Left circumflex artery	11%
Right coronary artery	26%
Left main	2%
Saphenous vein graft	9%
Left internal mammary artery	2%
Mehran class	
I (Focal)	42%
II (Diffuse)	21%
III (Proliferative)	26%
IV (Total occlusion)	11%
Small vessel size*	49%
Bifurcation stenting†	18%
Multivessel stenting†	25%
Glycoprotein IIb/IIIa inhibitors†	9%
Stent length per lesion, mm	28 ± 20
Stents per patient, n	2.0 ± 1.4

*pre-procedure reference diameter ≤ 2.5 mm
†percentages relative to the number of patients

Table 3. Quantitative angiographic analysis at baseline, post-procedure and follow-up*.

	Pre-procedure	Post-procedure	Follow-up
Reference diameter, mm	2.64±0.56	2.73±0.54	2.83±0.50
Minimum lumen diameter, mm	0.90±0.55	2.33±0.59	2.20±0.81
Diameter stenosis, %	66±19	16±15	23±25
Lesion length, mm	17.5±12.1	-	-
Acute gain, mm	-	1.42±0.70	-
Late loss, mm	-	-	0.17±0.76
Late loss excluding occlusions, mm	-	-	0.11±0.67
Post-SES restenosis†, %			14.6

SES=sirolimus-eluting stent
*related to 41 lesions with angiographic follow-up
†including one total re-occlusion

Angiographic results

The pre-procedure, post-procedure and follow-up quantitative angiographic data are shown in table 3. Representative sequences of angiograms from two patients are shown in figure 1. Mean reference diameter was 2.64±0.56 mm and mean lesion length was

17.5±12.1 mm. Angiographic follow-up was obtained in 33 patients (77% of patients with successful index procedure) with 41 lesions (79%). Late loss was 0.17±0.76 mm. Cumulative distribution curves of angiographic late loss (figure 2) show that the vast majority of the lesions (79%) had a late loss between –0.5 and +0.5 mm. Overall, post-SES binary restenosis was observed in 14.6% of the lesions. Table 4 shows the frequency of post-SES restenosis for some subgroups. No restenosis was observed in Mehran class I lesions; class II, III and IV lesions had post-SES restenosis in 22%, 25% and 20%, respectively (p=NS). In 5 out of 6 cases with post-SES restenosis the restenosis was focal or multifocal. For patients with post-SES restenosis, the average lesion length decreased from 31.7±15.3mm at baseline to 10.0±4.8mm at follow-up (p=0.01). One patient presented post-SES with silent total occlusion. Post-SES restenotic lesions were located within the SES in 5 lesions and at the proximal edge in the remaining 1. In two patients, post-SES restenosis occurred in an uncovered region injured during the procedure (gap between two SES implanted to treat two separate lesions in one patient and stent discontinuity by ultrasound examination due to possible stent fracture in another case).[15] Marked SES undersizing (stent diameter 2.7mm; vessel diameter 5.7mm) was found in another patient with post-SES restenosis.

The patients that developed post-SES restenosis had baseline clinical characteristics similar to the others. However, the lesions who developed binary restenosis were considerably longer (29.1±15.0 mm vs 16.1±11.0, p=0.01), were treated with more stents (2.2±0.7 vs 1.5±0.7, p=0.04), and the stented segment was longer (average stent length per lesion: 49.0±30.0 mm vs 25.5±16.3 mm, p<0.01) compared to lesions who presented less than 50% diameter stenosis at follow-up.

Table 4. Binary post-SES restenosis in subgroups*

	Post-SES restenosis
Total population (n=41)	14.6 %
Diabetics (n=8)	25.0 %
Small vessel size (n=20) †	10.0 %
Vein grafts (n=5)	20.0 %
Lesion length > 20mm (n=14)	28.6 %
Bifurcating stents‡ (n=7)	14.3 %
Mehran class[2]	
Type I (n=15)	0
Type II (n=9)	22.2 %
Type III (n=12)	25.0 %
Type IV (n=5)	20.0 %

Numbers in parenthesis are related to lesions with follow-up
* related to 41 lesions with angiographic follow-up
† pre-procedure reference diameter ≤ 2.5 mm
‡ related only to the in-stent restenosis lesions; in these series, there was no case of restenosis in the side-branches treated for de novo lesions.

Clinical Follow-up

Complete clinical follow-up was available for 43 patients (98%). After 1 year, the cumulative incidence of MACE was 20.9%. There were no deaths, 2 patients had non-Q-wave myocardial infarction (4.7%), of which 1 peri-procedural and 1 after 7 months, and 7 patients (16.3%) underwent TLR (including the patient who underwent emergency CABG). Target lesion revascularisation due to restenosis was performed in 5 patients (11.6%). One additional target lesion revascularisation was performed 5 days after the index procedure in a patient with recurrent angina and intravascular ultrasound evidence of incomplete right coronary artery ostium coverage. All repeat revascularisations were within 7 months follow-up. There were no documented episodes of early or late stent thromboses. It is worth noting that patients who refused to undergo angiographic re-evaluation had no adverse events during follow-up.

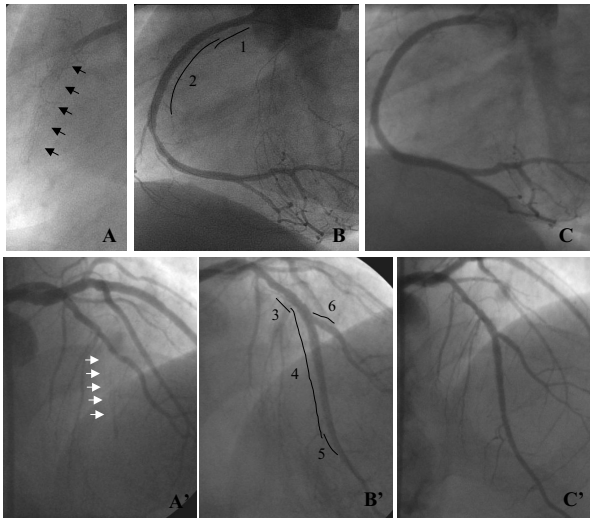

Figure 1. Sirolimus-eluting stent implantation for total occlusion due to in-stent restenosis: representative sequences of angiograms from two patients. Patient 1. **A.** Diagnostic angiogram showing total occlusion of the proximal right coronary artery due to ISR (arrows). **B.** Final result after implantation of two overlapping SES, 3x18 mm proximal (1), and 3x33 mm distal (2). Some minimal residual stenosis is visible at the distal stent edge. **C.** Six-month angiographic follow-up showing persistence of the good result obtained previously. Patient 2. **A'.** Diagnostic angiogram showing in-stent restenosis giving total occlusion of the mid part of the left anterior descending artery (LAD) (arrows), immediately after the origin of the second diagonal branch. **B'.** Final result after implantation of three overlapping SES in the LAD, 2.75x8 mm proximal (3), 2.5x33 mm in the middle (4), and 2.25x8 mm distal (5). Bifurcation stenting was necessary to preserve the second diagonal (6, SES 2.25x8 mm). **C'.** Six-month angiographic follow-up showing persistence of the good result in both vessels.

DISCUSSION

The major finding of the present study is that routine sirolimus-eluting stent implantation for in-stent restenosis is safe and associated with low recurrence rates in a broad range of clinical and anatomical settings.

The present series comprises patients and lesions commonly not included in previous reports,[12][13] [16] such as very long lesions, chronic total occlusions, small vessels, bypass grafts, and bifurcations. In fact, the majority of patients in our consecutive series, representative of the everyday practice, presented at least one of the aforementioned characteristics. Despite the

unselected nature of this population, clinical and angiographic outcomes appear superior to previous results for conventional approaches.[2] [18][19][20][21] Indeed, our findings compare favorably with those reported for vascular brachytherapy, which has been advocated as the treatment of choice for complex in-stent restenosis.[3][4][5][6][7] Moreover, SES implantation does not deviate from practice with conventional bare stents, and avoids most of the technical and logistical limitations that have hampered a more widespread use of brachytherapy.

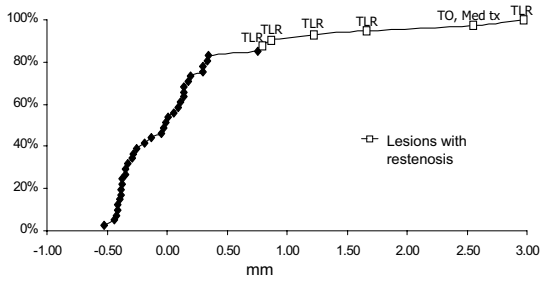

Figure 2. Cumulative distribution of late loss at angiographic follow-up. Lesions with binary restenosis are indicated by empty squares. Clinical outcome of each restenotic lesion is reported corresponding to the respective late loss value. This curve resembles a bimodal distribution and suggests that the failures cases might share unique features.

The outcomes of patients with in-stent restenosis after repeat treatment have been reported to be closely related to the baseline lesion morphology.[2] A progressive increase in risk profile occurs from lesions with a focal pattern to lesions with a more diffuse appearance and total occlusions.[2] Accordingly, in our series, SES was associated with a remarkably low incidence of recurrent restenosis in focal lesions. Indeed, all cases of repeat restenosis occurred in patients with more complex baseline characteristics. However, no clear differences in the rates of repeat restenosis were noted among higher risk categories (i.e Mehran classes II, III, and IV), in whom the rates of repeat restenosis have been reported to be 35, 50 and 85%, respectively, with conventional therapy. Thus, it is possible that SES implantation may reduce the prognostic value of the lesion pattern of in-stent restenoses for non-focal ISR, although the limited number of our observations does not allow a definitive conclusion. Conversely, our data suggest that lesion length may still have an impact on recurrent restenosis. Recently, sirolimus-eluting stents have been consistently shown to reduce neointimal proliferation in ISR as effectively as in *de novo* lesions.[21] Instead of reflecting an intrinsic drug resistance, repeat restenosis in complex lesions may actually be more closely related to local mechanical conditions that impair the therapeutic effect of the device (p.e. incomplete coverage of balloon-injured areas of neointimal hyperplasia, under-expanded stents). In fact, a possible technical reason for failure was documented in 3 of 6 cases (50%) of recurrent restenosis in our series, although the significance of these findings remains elusive. Two recent reports have confirmed these observations in a larger number of patients treated with sirolimus-eluting stents. [22][23]

This study evaluates a relatively limited number of patients and lesions. However, this is the largest series of patients described to date (table 5). Moreover, to the best of our knowlegde, this is the first study to assess the impact of sirolimus-eluting stent implantation in a broad range of different anatomical subsets of in-stent restenosis.

The rate of angiographic follow-up (79% of all lesions), although similar to other studies that enrolled patients with recurrent ISR, [3] [6][7] is not very high and could not represent the true binary restenosis for the entire cohort. This could be explained by the considerable number of recurrent restenosis and previous procedures suffered by some patients, therefore not willing to undergo 6-month angiography in the absence of symptoms. This was indirectly confirmed by the clinical follow-up of the patients who refused the angiographic control, who were all asymptomatic. Patients with failed brachytherapy were not included in the current report. We have recently shown that recurrent in-stent restenosis following vascular brachytherapy may exhibit a peculiar and different biological and clinical response to sirolimus-eluting stent implantation,[24] therefore representing a potentially confounding factor if analyzed conjointly with patients without prior local irradiation.

Table 5. Eluting-stents implantation for in-stent restenosis: angiographic results of the principal studies.

	TAXUS-III[16]	FIM – Rotterdam[12]	FIM - São Paulo[13]	ISR post-brachytherapy[24]		RESEARCH Registry
Drug	Paclitaxel	Sirolimus	Sirolimus	Sirolimus		Sirolimus
Patients	28	16	25	12		44
Inclusion criteria	- Single lesion - native coronary artery - Vessel size 3.0-3.5 mm	- Single lesion - native coronary artery - Vessel size 2.5-3.5 mm	- Single lesion - native coronary artery - Vessel size 2.5-3.5 mm	- Previous brachytherapy		- All clinical and anatomical conditions
Exclusion criteria	- Acute MI - Length > 30 mm - Total occlusion - LVEF<30% - renal dysfunction	- Saphenous vein graft	- Previous brachytherapy - Length > 36 mm in - Total occlusion			- Previous brachytherapy
Reference diameter	2.75±1.20	2.68±0.33	2.78±0.30	2.83±0.48		2.64±0.56
Lesion length	13.6 ± 6.4	18.4 ± 13.1	13.6 ± 7.65	-		17.5 ± 12.1
Stent length	22 ± 8	28 ± 18	22 ± 7	34 ± 30		28 ± 20
Time of follow-up	6 months	6 months	4 months	12 months	6 months	6 months
Late loss*	0.54 ± 0.51†	0.26 ± 0.67	- 0.05±0.30	0.16±0.42	0.68 ± 1.2	0.17 ± 0.76
Binary restenosis*	16.0%	20.0 %	0 %	4.0 %	40.0 %	14.6%

* in-stent plus 5-mm segment proximal and distal to the stent
†in-stent only

CONCLUSIONS

Routine utilization of sirolimus-eluting stent implantation to treat in-stent restenosis appeared safe and effective in an unselected series of cases, especially in patients with focal lesions. Sirolimus-eluting stent implantation also seems to be a promising strategy for complex in-stent restenosis. Further analysis with larger series and more prolonged follow-up, as well as a direct comparison with brachytherapy in a randomized fashion are needed to clarify the role of sirolimus-eluting stents in this context.

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Chapter 20 Clinical outcomes for sirolimus-eluting stent implantation and vascular brachytherapy for the treatment of in-stent restenosis

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Catheter Cardiovasc Interv. *In press*

Clinical outcomes for sirolimus-eluting stent implantation and vascular brachytherapy for the treatment of in-stent restenosis

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Purpose: To compare the mid-term clinical outcome of sirolimus-eluting stent (SES) implantation and vascular brachytherapy (VBT) for in-stent restenosis (ISR).
Methods: We assessed the 9-month occurrence of major adverse cardiac events (MACE) in 44 consecutive patients with ISR treated with SES implantation, and 43 consecutive patients treated with VBT in the period immediately prior.
***Results**:* Baseline clinical and angiographic characteristics of the two groups were similar. During follow-up, 3 patients (7%) died in the VBT group and 0 in the SES group. The incidence of myocardial infarction was 2.3% in both groups. Target lesion revascularization was performed in 11.6% of the VBT patients and 16.3% of the SES patients (p=NS). The 9-month MACE-free survival was similar in both groups (79.1% VBT vs 81.5% SES; p=0.8 by log rank).
Conclusions: The result of this non-randomized study suggests that sirolimus-eluting stent implantation is at least as effective as vascular brachytherapy in the treatment of in-stent restenosis.

Catheter Cardiovasc Interv. *In press*

INTRODUCTION

In-stent restenosis (ISR) represents the major limitation of coronary stenting (1). Treatment of ISR with conventional strategies is limited by the high rate of recurrence, which gradually increase from focal lesions to proliferative patterns and total occlusions (2).

The "mechanical" approach to treat ISR, with utilization of additional stents or debulking devices, has failed to show substantial benefits (3-6). Vascular brachytherapy (VBT), by targeting the "biological" component of neointimal proliferation, is the only strategy proven to be effective in randomized trials (7-11). However, its utilization is limited by complex logistic requirements and the necessity of highly trained operators. Moreover, recurrent restenosis still occurs in approximately one third of the patients treated with vascular brachytherapy (7-11).

Sirolimus- (12-13) and paclitaxel-eluting stents (14) have been shown in randomized trials to strongly suppress the development of neointimal hyperplasia in selected *de novo* lesions compared to bare stents. Also, promising results have been recently reported with drug-eluting stents for the treatment of in-stent restenosis, especially for patients with less complex forms of restenosis (15-17). A relatively low incidence of repeat restenosis has been shown after drug-eluting stent implantation in these preliminary series of cases. However, to date, the clinical efficacy of this new therapeutic approach has not been compared to conventional percutaneous techniches or to the "gold standard" vascular brachytherapy.

In this study we therefore aimed to comparatively evaluate the outcomes of patients with in-stent restenosis treated with sirolimus-eluting stent implantation or with catheter-based brachytherapy.

METHODS

Patient population

Since the 16th of April 2002, we have adopted a policy of sirolimus-eluting stent implantation for all patients undergoing percutaneous coronary interventions at our institution, as previously described elsewhere (18). In the first six months enrollment, 44 consecutive patients with in-stent restenosis and no previous brachytherapy at the same site were treated with SES implantation (SES group). A comparison group was composed by 43 patients treated with vascular brachytherapy (group VBT) in the months immediately prior, between 1st January 2001 and 15th of april 2002. This time period was selected to approximately match the number of patients with brachytherapy with the number of patients treated with sirolimus-eluting stent. All patients treated with both modalities were included in the present report. Informed, written consent was obtained from all patients.

Procedures

All patients were pre-treated with aspirin (at least 75 mg/d) and clopidogrel (75 mg/d or 300 mg bolus). During the procedure weight-adjusted heparin was administrated to achieve an activated clotting time of >300 sec. Vascular brachytherapy was performed in all patients with catheter-delivered beta-radiation. Two systems were used during the study period: Betacath™ (Novoste, Norcross, GA), and Galileo™ (Guidant corporation, Santa Clara, CA, USA), which have been described in detail elsewhere (11, 19). Operators were strongly advised to avoid implantation of new stents (20), and to avoid insufficient radiation dose delivery to injured areas (geographic miss) (21). Clopidogrel prescription was decided on an individual patient basis by the attending interventional cardiologist according to current practice guidelines. In the SES group, restenotic lesions were treated with implantation of the Cypher™ sirolimus-eluting stent (Cordis Europa NV, Roden, NL). Complete lesion coverage by this stent was recommended. In case additional stents were needed, care was taken to avoid gaps between adjacent stents. The final treatment strategy and device utilization other than SES were left to the operator's discretion. At least 3 months of clopidogrel treatment was prescribed thereafter. In both study periods, periprocedural adjunctive medications were left to the discretion of the operator.

Table 1. Baseline clinical characteristics and demographics of the two study cohorts.

	VBT (n. 43)	SES (n. 44)	p value
Age, y	61±10	63±13	ns
Males, n (%)	31 (73)	32 (73)	ns
Diabetes Mellitus, n (%)	11 (26)	11 (25)	ns
Hypertension, n (%)	13 (30)	21 (48)	ns
Hypercholesterolemia, n (%)	26 (60)	30 (68)	ns
Previous MI, n (%)	20 (47)	23 (52)	ns
Previous CABG, n (%)	9 (21)	10 (23)	ns
Multivessel disease, n (%)	20 (47)	22 (50)	ns
Clinical presentation, n (%)			ns
Stable Angina	34 (79)	32 (73)	
ACS	9 (21)	12 (27)	
Number of ISR lesions treated	44	53	-
ISR lesions treated per patient	1.0 ± 0.2	1.2 ± 0.5	0.02
Target Vessel, n (%)			ns
LAD	16 (36)	26 (49)	
LCX	9 (20)	6 (11)	
RCA	15 (34)	14 (26)	
LM	1 (2)	1 (2)	
Bypass grafts	3 (7)	6 (11)	
Mehran classification, n (%)			
Type I	10 (23)	22 (42)	0.05
Type II	19 (43)	11 (21)	0.02
Type III	10 (23)	14 (26)	ns
Type IV	5 (11)	6 (11)	ns
Multivessel procedure, n (%)	9 (21)	11 (25)	ns
Procedural success*, n (%)	42 (98)	43 (98)	ns
IIb/IIIa inhibitors, n (%)	14 (33)	4 (9)	0.007
Clopidogrel prescription, mo	7.5 ± 5.5	5.9 ± 2.6	0.005

ACS=Acute Coronary syndromes; CABG=Coronary Artery Bypass Graft; LAD=left anterior descending artery; LCX=left circumflex artery; MI=Myocardial Infarction; RCA=right coronary artery; LM=left main stem; TL=Target Lesion

*as judged by the operator, in the absence of in-hospital complications.

Definitions and follow-up

ISR was defined as a significant stenosis within a previous stented segment on visual assessment, together with objective evidence of ischemia. The lesions were angiographically classified according to Mehran et al. (2) by two independent operators. The primary composite endpoint was the incidence of major adverse cardiovascular events (MACE) during 9 months of follow-up, defined as death, myocardial infarction or target lesion revascularization (either percutaneous or surgical). The diagnosis of myocardial infarction was based on an increased level of creatine kinase to more than twice the upper limit of normal with an increased level of creatine kinase-MB isoform. Target lesion revascularization (TLR) was defined, for the patients in the brachytherapy group, as any surgical or percutaneous re-intervention due to restenosis within the irradiated segment or the 5mm proximal or distal segments, and for the patients in the SES group as any revascularization in the stent and in the 5 mm proximal and distal segments. Target vessel revascularization (TVR) was defined as any re-intervention driven by lesions located in the treated vessel beyond the target lesion limits. Survival status at follow-up was assessed by written inquires to the Municipal Civil Registries. Repeat revascularization procedures and episodes of acute myocardial infarction were prospectively collected in the hospital data base. For patients admitted to peripheral hospitals in the acute phase, the diagnosis of myocardial infarction was confirmed by the referring physician based on the same criteria. All re-interventions were prospectively collected in a dedicated electronic database.

Statistical methods

Discrete variables were presented as count and relative percentages and compared with Fisher exact tests or Chi-square. Continuous variables were presented as mean and standard deviations and compared with Student *t* test. Event-free survivals were calculated according to the Kaplan-Meier method and compared by the log-rank test. All tests were two-tailed, and a p value <0.05 was considered as significant.

RESULTS

Baseline characteristics

The baseline characteristics of the two groups were similar (table 1). Specifically, no difference was observed in the incidence of diabetes (26% VBT vs 25% SES; p=0.1), previous myocardial infarction (47% VBT vs 52% SES; p=0.6), previous coronary artery bypass graft (CABG) surgery (21% VBT vs 23% SES; p=0.8), or multivessel disease (47% VBT vs 50% SES; p=0.7). The majority of the patients in both groups had stable angina at hospital admission (79% VBT vs 73% SES; p=0.5). Almost all patients in the VBT group had single-lesion brachytherapy, except by one patient with 2 lesions treated. In the SES group, 53 ISR lesions were treated (1.2 ± 0.5 lesion per patient). In the SES group there were more lesions classified as Mehran type I (23% VBT vs 42% SES; p=0.05), whilst type II was more common in the VBT group (43% VBT vs 21% SES; p=0.02). However, both treatment groups had similar numbers of lesions with non-complex (Mehran Type I/II: 66% VBT vs 63% SES) or complex (Mehran Type III/IV: 34% VBT vs 37% SES; p=0.7 for all) morphologies. Quantitative coronary analysis did not show significant differences in baseline lesions' characteristics between the two groups (table 2). Average lesion length was 15.7±10.4 mm in the VBT group and 17.5±12.1 mm in the SES group (p=0.4). As expected, post-procedure minimal lumen diameter was bigger (1.84±0.41 mm VBT vs 2.33±0.59 mm SES; p=0.0008) and diameter stenosis smaller (28±12 % VBT vs 16±15 % SES; p=0.004) in the SES group.

In the VBT group average irradiated length was 48 ± 12mm, and average radiation dose administered was 23 ± 2 Gy. A new stent was implanted in 27% of the VBT patients. In the SES group each patient received on average 2.0 ± 1.4 stents, with a mean stent length of 28 ± 20 mm per lesion. In the VBT group periprocedural glycoprotein IIb/IIIa inhibitors utilization was more common (33% vs 9%; p=0.007), and clopidogrel prescription longer (7.5±5.5 months vs 5.9±2.6 months; p=0.005).

Clinical outcome

Complete information at follow-up was available in 100% of VBT patients and 97.7% of SES patients (1 patient moved abroad and was lost to follow-up). During nine months of follow-up, 3 patients (7%) died in the VBT group and 0 in the SES group (p=0.08 by log rank)(table 3). They were all thought to be cardiac deaths: one

patient with previous CABG operation developed severe hypotension after balloon angioplasty and irradiation of the right coronary artery and died 2 days after the procedure; two patients had a sudden death 3 months after treatment of a lesion in the proximal left anterior descending while still on combined antiplatelet treatment (one of them had a new stent implanted during the brachytherapy procedure). Subacute stent thrombosis could not be ruled out in these last 2 cases. A definite diagnosis of acute MI was made in 1 patient in each group. Target lesion revascularization was performed in 5 patients (11.6%) in the VBT group, and 7 patients (16.3%) in the SES group (p=NS). In the VBT group these recurrent restenosis were treated with 2 CABG operations, 1 balloon angioplasty, 1 stent implantation, and 1 sirolimus-eluting stent implantation. In the SES group 1 patient underwent emergency CABG surgery for vessel dissection and acute occlusion during treatment of a lesion in the proximal left circumflex artery, and the remaining 6 TLRs were accomplished percutaneously (3 with additional SES implantation, 3 with taxol-eluting stent implantation). Overall, the MACE-free survival at 9 months was similar in both groups (79.1% VBT vs 81.5% SES; p=0.8 by log rank) (figure 1).

Table 2. Quantitative coronary analysis at baseline

	VBT (n. 44)	SES (n. 53)	p value
Pre-procedure			
Reference diameter, mm	2.44 ± 0.45	2.64 ± 0.56	ns
MLD, mm	0.74 ± 0.52	0.90 ± 0.55	ns
Diameter stenosis, %	69 ± 20	66 ± 19	ns
Lesion length, mm	15.7 ± 10.4	17.5 ± 12.1	ns
Post-procedure			
Reference diameter, mm	2.61 ± 0.51	2.73 ± 0.54	ns
MLD, mm	1.84 ± 0.41	2.33 ± 0.59	0.0008
Diameter stenosis, %	28 ± 12	16 ± 15	0.004

MLD = Minimal Lumen Diameter

Table 3. Nine-month clinical outcome.

	VBT (n. 43)	SES (n. 44)
All MACE, %	20.9	18.6
Death, %	7.0	0
Myocardial infarction, %	2.3	2.3
Target Lesion Revascularization, %	11.6	16.3
Target Vessel Revascularization, %	4.7	4.7
Coronary bypass graft, %	7.0	2.3
Percutaneous coronary intervention, %	9.3	18.6

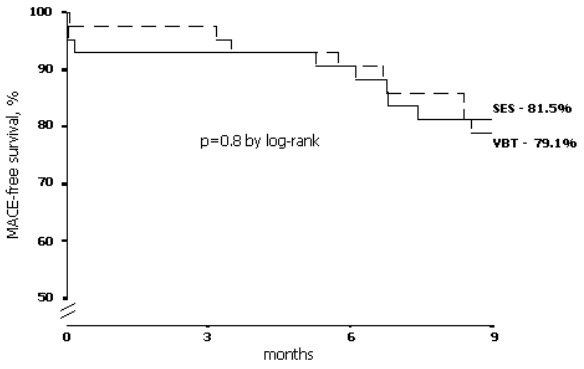
MACE=Major Adverse Cardiovascular Events

DISCUSSION

Vascular brachytherapy has been rigthly considered the gold-standard treatment for in-stent restenosis, at the least for more complex cases, after several randomized trials have shown its superiority over other conventional approaches (7-11). Despite these favorable results, brachytherapy has not been widely utilized, being still currently restricted, at least in Europe, to a limited number of centers. Complex logistic and technical requirements, as well as lack of reimbursement in some countries, have limited a more generalized utilization of brachytherapy. Furthermore, the identification of possible shortcomings such as geographical miss (21) and delayed re-endothelialization, which is associated with an increased risk of subacute thrombosis especially when a new stent is implanted (22), have made mandatory a specific training for the operators involved in brachytherapy procedures.

In the present study, treatment of in-stent restenosis with sirolimus-eluting stents was associated with similar clinical results at 9 months compared to vascular brachytherapy. These findings are of potential major interest. Routine utilization of sirolimus-eluting stent implantation does not deviate from the standard practice with conventional bare stents. Indeed, no additional requirements are needed to readily apply this new therapy at any catheterization laboratory.

Widespread utilization of drug-eluting stents is expected to change the current scenario, by reducing ISR to a minority of patients. (12,23) Moreover, recurrent restenosis after drug-eluting stent implantation presents peculiar characteristics, such as predominantly focal pattern, (24,25) which could improve its response to the various percutaneous treatments. However, despite the enthusiasm raised by the publication of the first clinical studies, drug-eluting stent penetration in common practice is still limited by cost restrains (26), and ISR remains the major limitation of PCI. In this early drug-eluting stents era, "provisional" SES utilization in case of bare stent failure is appealing and, based on the results of the present study and two prior reports (15,16), seems to be a feasible and effective strategy.



Kaplan-Meier curves of survival-free from major adverse cardiac events (MACE) in the brachytherapy (VBT) and in the sirolimus-eluting stent (SES) groups.

In the evaluation of our results, two additional pieces of information should be taken into account. Although not statistically significant, a slightly higher rate of TLR was observed in the SES group. However, in this group routine angiographic follow-up was scheduled by protocol, and performed in 77% of the patients, while only a minority of patients in the VBT group underwent elective angiography (30%). We have previously shown that angiographic follow-up have a negative impact on clinical outcome due to more repeat revascularization procedures ("oculo-stenotic reflex") (27). Furthermore, a late "catch-up" phenomenon (continuous increasing of angiographic late-loss after 6 months) has been reported for VBT (28,29), while data regarding SES for both de novo (30) and ISR (16) lesions suggest that the early results are predictive of

the long-term findings. On the other hand, although not statistically significant, we observed an increased mortality in the brachytherapy group (VBT: 7%; SES: 0%; p=0.08), suggesting once again the possibility of serious adverse events related to the prolonged endothelial damage after vessel irradiation.

Study limitations

Our study presents a number of limitations that suggest some caution when interpreting the results. First of all, the two groups were not randomized, and were treated in different time periods. Moreover, while the SES group was composed of a consecutive series of patients, the patients undergoing VBT group were selected by the operators based on clinical and morphological consideration. Accordingly, more patients in the SES group presented Mehran type I lesions (23% VBT vs 42% SES), because in the VBT phase most of these patients underwent percutaneous re-intervention with conventional techniques. However, we cannot ignore the fact that baseline clinical characteristics of the 2 cohorts of patients were remarkably similar. Additionally, if we consider together lesions of Mehran class I and II, the difference among the two groups disappears (66% VBT vs 63% SES; p=0.7). This was indirectly confirmed by the lack of difference in lesion length between the two groups. Other imbalances were observed in procedural characteristics and peri-procedural medications. The higher rate of glycoprotein IIb/IIIa inhibitors in the VBT-treated patients, and the longer clopidogrel prescription in the same group, could have generated a clinical advantage, especially in those with acute coronary syndromes (31,32). More lesions were treated per patient in the SES group; while on one side this strategy could favour recurrent restenosis and repeat revascularizations, especially in patients with angiographic follow-up, on the other side a possible positive impact of a more complete revascularization on clinical outcome cannot be ruled out.

Another limitation is represented by the low number of patients in both groups. It should be noticed, however, that the present study is, to the best of our knowledge, the first comparison between VBT and SES in the treatment of ISR, and in this setting the study which included the higher number of patients treated with SES reported so far (15,16). Moreover, the first randomized trial comparing vascular brachytherapy with conventional balloon dilatation included only 55 patients (8).

CONCLUSIONS

In this study, routine sirolimus-eluting stent implantation to treat in-stent restenosis appeared at least as effective as vascular brachytherapy in the treatment of in-stent restenosis, with the advantage of simpler logistic and technical requirements. Further prospective, randomized investigation with larger study population and longer follow-up are mandatory to confirm these findings.

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Chapter 21 Effectiveness of sirolimus-eluting stent implantation for recurrent in-stent restenosis after brachytherapy

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Effectiveness of sirolimus-eluting stent implantation for recurrent in-stent restenosis after brachytherapy

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Coronary vascular brachytherapy is, to date, the only effective treatment available for complex instent restenosis (ISR).[1] However, its efficacy is hampered by late restenosis,2 late thrombosis,[3,4] edge effect,[5] geographic miss,[6] and delayed healing.[3] Moreover, the fate of the patients after "failed" brachytherapy is uncertain, as well as the result of the various percutaneous treatments employed thereafter. Sirolimus is a macrolide antibiotic produced by Streptomyces hygroscopicus with immunosuppressive effects; it is approved for the prevention of renal transplant rejection.7 The main effect of sirolimus is the interruption of G1 to S cell cycle progression mediated by its binding to a cytosolic receptor (FK506 protein binding protein 12) and a cascade of subsequent actions. Importantly, sirolimus inhibits proliferation and migration of vascular smooth muscle cells, a key element in the development of restenosis after percutaneous coronary interventions (PCIs). Recently, stent-based local sirolimus delivery has been shown to strongly suppress neointimal hyperplasia and prevent restenosis in de novo lesions followed up for 2 years.[8,9] The revolutionary results obtained with drugeluting stents have encouraged the assessment of their efficacy in more complex clinical and morphologic subsets. The first human experience evaluating the sirolimus- eluting stent (SES) for the treatment of ISR has been recently reported; it showed this strategy to be highly effective.[10] We describe here the first series of SES implantation for recurrent ISR after brachytherapy.

• • •

The patients described in this report consist of 2 cohorts treated during separate time periods. The first cohort was treated between March 2001 and June 2001, as part of a pilot study on SESs for treatment of ISR. Since April 2002, shortly after European Community market approval, SES implantation has been adopted as the default strategy in all patients treated with PCI at our institution, irrespective of clinical presentation and coronary morphology. These latter patients have been included in the RESEARCH Registry (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospitals) and will be followed up for 1 year.[11] The only exclusion criteria were unavailability of an adequately sized SES at the time of the procedure and enrollment in another revascularization protocol (SESs were available in diameters from 2.25 to 3.0 mm and lengths of 8, 18, and 33 mm). All patients treated with SES after "failed" brachytherapy were scheduled for 6-month angiography.

ISR was defined as >50% diameter stenosis by quantitative coronary angiography within a previously stented vessel segment and classified as proposed by Mehran et al.[12] Treatment strategy and device utilization other than stenting was left to the physician's discretion. The procedure was considered successful when residual stenosis _30% by quantitative coronary angiography was achieved together with Thrombolysis In Myocardial Infarction (TIMI) flow grade 2 to 3. The study stent utilized was the sirolimus-eluting Cypher (Cordis Europa NV, Johnson & Johnson, Roden, The Netherlands), which contains a 140 µg sirolimus/ cm2 metal surface area in a slow release formulation (>28 days). Pretreatment with clopidogrel for 48 hours or a 300-mg loading dose was required. During the procedure, intravenous heparin was given to maintain an activated clotting time >300 seconds. After the procedure, all patients received aspirin indefinitely (>75 mg/day) and clopidogrel (75 mg/day) for at least 2 months. Clinical status information was collected at follow-up visits or by telephone contact with the patient or referring physician. Data are presented as number and relative percentage or mean ± SD. Median and range have been reported when nedded for a better description.

From the beginning of the study until August 15, 2002, 12 consecutive patients (both cohorts) underwent PCI with SES implantation for recurrent ISR after local radiation therapy. All of them presented with angina pectoris and/or myocardial ischemia as documented by stress test or thallium scan. Coronary brachytherapy had been previously performed in 11 patients with catheter-based local irradiation (10 beta, 1 gamma) and in 1 patient with phosphorus-32 radioactive stent implantation.

Baseline clinical and angiographic characteristics are listed in Tables 1 and 2, respectively. Nine patients (75%) had had more than 1 previous episode of restenosis. Average time from the preceding percutaneous reintervention was 24 months (range 111 to 1,678 days, median 719). Remarkably, 9 patients (75%) presented with a proliferative pattern of restenosis, 5 of whom (42%) had a totally occluded target vessel. The occlusion dated more than 3 months in 4 patients.

Overall, we implanted 18 SESs (average 1.5/patient). Mean stent length was 33.9 ± 30.1 mm (range 8 to 92; median 18), and mean stent diameter was 2.88 ± 0.33 mm. Multivessel PCI was performed in 3 patients (25%). Angiographic success was obtained in 11 of 12 patients (92%). The remaining patient showed a 34% residual stenosis during quantitative coronary angiography and stent underexpansion despite very highpressure inflation (24 atm). Individual clinical outcomes are listed in Table 3. With the obvious exception of the single patient presenting with acute myocardial infarction, no

postprocedural cardiac enzyme elevation was observed, and all the patients were discharged free from events.

Table 1. Patients' baseline characteristics and demographics

Patients	12
Age, years	62±11
Men	9 (75%)
Current smoker	4 (33%)
Hypercholesterolemia*	11 (92%)
Systemic hypertension	6 (50%)
Diabetes mellitus	3 (25%)
Family history of coronary heart disease	4 (33%)
Stable angina pectoris	7 (58%)
Unstable angina pectoris	4 (33%)
Acute myocardial infarction	1 (8%)
Multivessel coronary disease	10 (83%)
Previous myocardial infarction	9 (75%)
Previous coronary bypass	4 (33%)
Time from last target lesion revascularization, (d)	111-1678 (719)
Time from brachytherapy, (d)	111-1968 (792)
Episodes of in-stent restenosis	
> 1	9 (75%)
> 2	5 (42%)

*Total cholesterol > 200mg/dl and/or on lipid lowering treatment
Values are mean±SD, range (median), or number of patients (%)

Table 2. Angiographic and procedural characteristics

Variable	
Target coronary artery	
Left anterior descending	2 (17%)
Left circumflex artery	5 (42%)
Right	4 (33%)
Left main	1 (8%)
Pre-procedure	
Reference diameter (mm)	2.83±0.48
Minimum lumen diameter (mm)	0.67±0.76
Diameter stenosis (%)	77±25
Post-procedure	
Reference diameter (mm)	2.76±0.38
Minimum lumen diameter (mm)	2.38±0.45
Diameter stenosis (%)	13±11
Acute gain (mm)	1.71±0.58
Late loss (mm)	0.68±1.20
Multivessel coronary procedure	3 (25%)
Other devices utilization	
Cutting Balloon	3 (33%)
Cross Safe *	1 (8%)

* Intraluminal Therapeutics Inc. Carlsbad, California

Average follow-up was 8.5 ± 4.5 months. Ten patients (83%) underwent angiography between 4 and 7 months after the procedure. Two patients who refused angiographic follow-up were asymptomatic after 4 and 6 months. One patient died after 9.5 months because of congestive heart failure, shortly after hospital admission for acute pulmonary edema. He was 79 years old, with a history of 2 coronary artery bypass graft operations and 2 PCIs. Left ventricular dysfunction and end-stage congestive heart failure were diagnosed before the last coronary angioplasty. During the 4-month follow-up, no intravascular ultrasound evidence of neointimal hyperplasia was found.

Recurrent ISR after SES implantation was found in 4 out of 10 patients who underwent angiography during follow-up (40%). One of them, in whom complete stent expansion could not be achieved at index procedure, was found to have silent reocclusion after 4 months. No further treatment was performed, and at 19 months the patient remained asymptomatic. Two other patients, both diabetics, presented with stable angina (Canadian Cardiovascular Society class 3) and ISR that required target lesion revascularization. In 1 of them, intravascular ultrasound showed a clearly underexpanded stent with a very small minimal instent diameter (1.3 mm). In the fourth case, a very focal restenosis (>5 mm) was diagnosed by elective angiography 5 months after the procedure. Originally, the patient had been treated with 4 SESs (overall length 92 mm) for chronic total occlusion of the left anterior descending artery (ISR). Intravascular ultrasound examination confirmed the absence of neointimal hyperplasia in the remaining portion of the stents. The patient was asymptomatic, but percutaneous revascularization was performed based on intravascular ultrasound findings.

Another patient had recurrent angina 4 months after the procedure. Angiography showed minimal in-stent hyperplasia in the region of interest, whereas a severe lesion due to ISR requiring percutaneous treatment was found in a different vessel.

Table 3. Individual clinical and angiographic outcome

Patient	Vessel	BT	Mehran Class	No. of ISR	Clopidogrel (months)	Follow-up (months)	Clinical follow-up (months)	Clinical Status follow-up	Angiographic Control (time-%DS)
1	Right	Beta	II	3	6	9.5	Death (9.5)	Death	4 months - 7%
2	Right	Beta	IB	2	8	12	0	symptomatic	4 months - 15%
3	Right	Beta	II	2	2	14	0	symptomatic	6 months - 13 %
4	Right	Gamma	IV	4	L	7	0	symptomatic	7 months - 25 %
5	Circumflex	Beta	IV	1	6	19	0	symptomatic	4 months - 100%
6	Circumflex	Beta	IV	2	L	5	TLR (5)	Stable angina	5 months - 71%
7	Circumflex	Beta	III	3	2	6	0	symptomatic	-
8	Circumflex	Beta	IB	3	3	7	TVR * (7)	symptomatic	7 months - 17 %
9	Circumflex	Beta	III	1	6	8	TLR (6)	Stable angina	6 months - 98 %
10	Left main /circumflex	Beta	IC	2	L	5	Non-TVR (5)	Stable angina	5 months - 13 %
11	Left anterior descending	32P Rx Stent	IV	1	6	4	0	symptomatic	-
12	Left anterior descending	Beta	IV	3	L	5	TLR (5)	Stable angina	5 months - 62 %

*Distal to the index lesion due to disease progression
BT=Brachytherapy; ISR=in-stent restenosis; L=lifelong; Non-TVR=non-Target Vessel Revascularization; TLR=Target Lesion Revascularization; TVR=Target Vessel Revascularization; %DS=percentage diameter stenosis by quantitative coronary analysis.

One of the lesions treated with an SES during the index procedure was composed of echolucent tissue ("black hole").[13] Interestingly enough, the intravascular ultrasound examination at follow-up showed a reappearance of this tissue, although it did not significantly affect the lumen area.

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SESs have been recently shown to strongly prevent the development of neointimal hyperplasia after stenting. The first randomized clinical trial reported an exceptional 0% binary restenosis rate.8 Whether a similar result is obtainable in different clinical situations and for more complex coronary lesion subsets is the subject of extensive investigation. Preliminary results for their use in the treatment of ISR are positive, although less impressive than in de novo lesions.[10]

In the present investigation, we sought to assess the safety and outcome of SES implantation in patients with recurrent ISR after brachytherapy. The strategy evaluated is safe and is believed to be clinically effective, considering the complex population under investigation. The 0% incidence of in-hospital events as well as the absence of subacute stent thrombosis is noteworthy because the average stent length was remarkably high, and these patients are likely to have endothelial dysfunction. The only death that occurred is highly unlikely to be related to either the procedure or to the stent, but rather to the severely compromised left ventricular function. Nevertheless, our report raises a series of unresolved issues. The antiproliferative effect of sirolimus after brachytherapy seems to be strongly reduced compared with other situations. The 40% incidence of restenosis in our population is noteworthy. Diabetes mellitus, a well-known risk factor for restenosis, may also represent a predisposing factor for failure in this setting. However, in 2 cases, technical causes of failure (stent underexpansion) could be implicated, and in a third patient, a very focal neointimal growth was observed compared with the very long baseline lesion and total stent length. The optimal duration of combined antiplatelet therapy is unclear. In this series there was a striking variety in the duration of clopidogrel prescribed after the procedure due to decisions made on an individual patient basis. Currently, we prescribe combined antiplatelet therapy for at least 12 months after long stent implantation, but this deserves further evaluation.

Our investigation presents a few limitations. First, we do not have a control population. Whether a conventional approach would have provided comparable results cannot be inferred from our data. Second, the present series of patients is quite heterogenous; this is not surprising given the "real world" setting. The time elapsed from the last target vessel revascularization was considerably different among patients. The underlying physiopathologic process of late (around 2 years) recurrent restenosis after brachytherapy and subsequent response to treatment is not known (whether it is neointimal tissue or late atherosclerotic progression is unclear). Moreover, the incidence of black hole may be higher than suspected, and the biologic properties of this tissue may be responsible for a blunted response to antiproliferative drugs. Last, but not least, the number of patients in our investigation was low, and larger studies with extended follow-up are warranted to draw definitive conclusions.

In this investigation, 12 patients were treated with sirolimus-stent implantation for recurrent ISR after failed brachytherapy. The strategy evaluated was safe and is believed to be clinically effective, although our data suggest a different attenuated efficacy of sirolimus in preventing neointimal growth in this setting compared with the treatment of de novo lesions.

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Chapter 22 Incidence of Thrombotic Stent Occlusion During the First 3 Months After Sirolimus-Eluting Stent Implantation in 500 Consecutive Patients

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Am J Cardiol. *In press.*

Incidence of Thrombotic Stent Occlusion During the First 3 Months After Sirolimus-Eluting Stent Implantation in 500 Consecutive Patients

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Sirolimus-eluting stents (SES) have been used in our institution for all percutaneous interventions, without clinical or anatomical exclusion criteria as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. We analyzed the incidence of (sub)acute stent thrombosis (SAT) after sirolimus-eluting stent implantation in an unselected population of 510 consecutive patients. At 3-month follow-up, SAT was diagnosed in 2 patients (0.4%), 6 hours and 11 days after the procedure, respectively. Both cases occurred in diabetic females with complex coronary lesions. Intravascular ultrasound examination revealed inadequate stent expansion and uncovered distal dissection as possible mechanical explanations in both.

Am J Cardiol. *In press.*

We analyzed the incidence of (sub)acute stent thrombosis after sirolimus-eluting stent implantation in an unselected population. 510 consecutive patients received sirolimus eluting stents, without clinical or anatomical exclusion criteria. During 3 months follow-up sirolimus-eluting stents showed a low incidence of (sub)acute thrombosis of 0.4% that is comparable to data previously reported for bare metal stents.

Sirolimus-eluting stents (SES) have proven to significantly reduce restenosis in selected patients with relatively simple lesions[1]. Importantly, this late benefit was accomplished without compromising the well-established low incidence of short-term complications with currently available bare stents. Specifically, in these earlier studies SES have been associated with a low incidence of stent thrombosis, a condition largely reported to a carry high morbidity and mortality risk[2]. However, these results cannot be directly extrapolated to patients with more complex profiles, such as those commonly treated in the daily practice. After bare metal stent implantation, the incidence of sudden stent thrombosis has been previously shown to be increased in patients with acute coronary syndromes, long stents, small vessels, chronic total occlusion and multivessel intervention[3]. We therefore investigated the incidence of (sub)acute stent thrombosis (SAT) occurring in the first 3 months after the procedure in an unselected cohort of consecutive patients treated with sirolimus-eluting stent implantation at our institution.

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Since 16th April 2002, the sirolimus-eluting stent (Cypher™; Cordis Corp., Johnson & Johnson, Warren, NJ, USA) has been utilized as the device of choice for all percutaneous coronary interventions (PCI) performed at our institution, as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospitals (RESEARCH) registry. The study design has been described elsewhere[4]. In brief, the RESEARCH is a single-center registry conducted with the main purpose of evaluating the effectiveness of SES implantation in the patients treated in the "real world". Therefore, SES has been utilized for virtually all clinical situations and lesion morphologies, with no specific contraindication.

Table 1: Baseline and Procedural Characteristics (n=510)

	Men (n=359)	Women (n=151)
Age, years	61±12	63±11
Diabetes mellitus, %	16.0	23.7
Current smoker, %	39.3	32.6
Systemic hypertension , %	40.9	59.0
Previous myocardial infarction, %	34.8	22.8
Previous angioplasty, %	26.5	20.3
Previous coronary bypass, %	10.1	10.7
Double-vessel disease, %	31.7	25.7
Triple-vessel disease, %	22.5	28.4
Stable angina pectoris , %	52.1	51.7
Unstable angina pectoris, %	31.5	33.1
Acute myocardial infarction, %	16.7	13.9
GP IIB/IIIA inhibitors, %	27.9	21.3
Treated coronary artery*		
Left main stem, %	3.7	3.3
Left anterior descending, %	57.4	57.0
Left circumflex, %	36.5	29.8
Right , %	34.3	41.1
Multivessel SES implantation, %	25.3	23.2
Number of SES per procedure	2.1±1.3	2.1±1.2
Total stented length, mm/patient	38±27	38±27
Adjacent stented length > 36mm, %	17.5	17.2
Small stent diameter (≤2.5mm) , %	36.5	33.9
Postdilatation performed, %	56.6	51.0
Intravascular ultrasound use, %	20.6	20.5
Maximum pressure, atm	17.2±2.6	17.2±2.8
Reference diameter, mm	2.70±0.49	2.70±0.54
Minimal lumen diameter pre, mm	0.75±0.45	0.71±0.45
Diameter stenosis pre, mm	71±17	71±18
Minimal lumen diameter post, mm	2.31±0.49	2.35±0.46
Diameter stenosis post, mm	15±12	14±9

* not mutually exclusive - in patients with multivessel disease, several arteries have been treated.

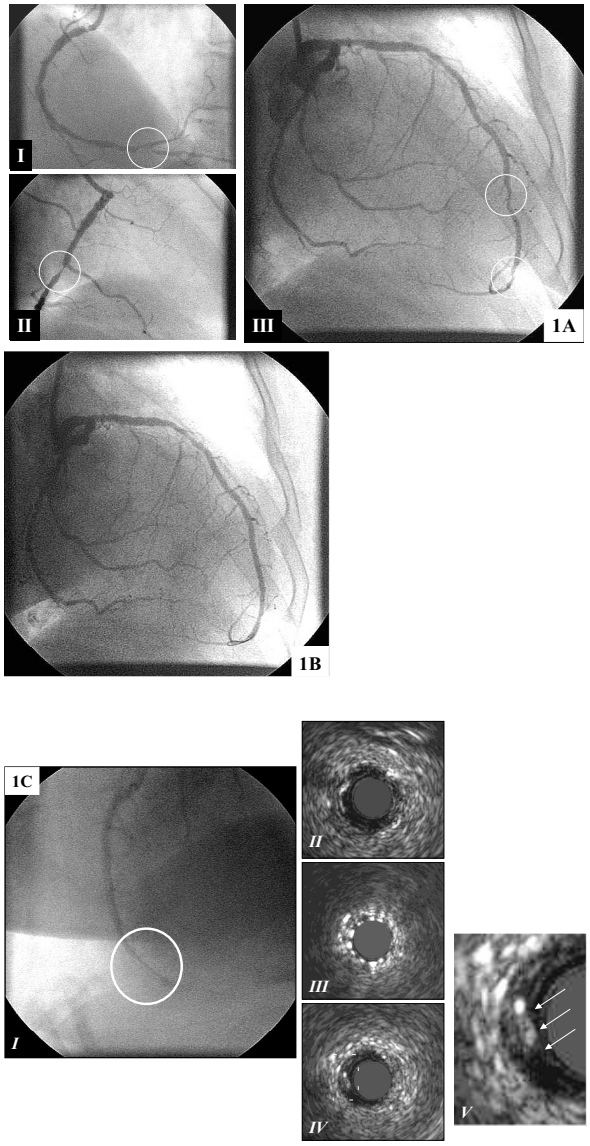

Figure 1.
1A) Pre-intervention angiogram. Multiple lesions in the distal (I) and mid (II) RCA. Lesions in the distal LAD (lesion length 6.91mm; RD pre 2.63mm, MLD pre 1.58mm; DS pre 40%) and apical LAD (lesion length 9.82mm; RD pre 1.71mm, MLD pre 0.89mm; DS pre 48%) (III).
1B) Final result after SES implantation in the distal LAD (SES 3.0/8mm, 2.25/18mm; both at 12 atm; RD post 2.51mm, MLD post 2.58mm; DS post 0%) and apical LAD (SES 2.25/8mm; 10 atm; RD post 1.95mm; MLD post 1.75mm; DS post 10%).
1C) Coronary angiography 6h after the index procedure showed total occlusion of the SES in the apical LAD (apart from the stents in the distal LAD) (I). IVUS showed an under-expansion of the apical stent (III; minimal stent area 2.00mm^2) in comparison to the proximal (II; lumen area 3.81mm^2) and distal (IV; lumen area 3.10mm^2) reference and a distal edge dissection (V, arrows) that was not visible on the angiogram at the time of the index procedure.

All procedures were performed according to standard techniques and the final interventional strategy was left to the discretion of the operators. At the time of the initiation of this study, SES were available in diameters from 2.25 mm to 3.00 mm and lengths of 8, 18, and 33 mm. GPIIb/IIIa inhibitors were given at the discretion of the operator including all situation associated with high risk for subacute stent thrombosis such as acute coronary syndromes, long stents, small vessels, chronic total occlusion and multivessel intervention. All patients were on life-long aspirin administration and received a loading dose of clopidogrel (300mg), which was maintained for at least 3 month (75mg/d).

Clinical follow-up at 3 month was performed by scheduled visits at the outpatient clinic or by direct contact (phone call or regular mail). Recordings of all repeat interventions (surgical and percutaneous) and re-hospitalizations were prospectively collected in a dedicated database. Survival status at 30 days was assessed by written inquiries to the Municipal Civil Registries. The local ethical committee approved the study and written informed consent was obtained in all patients.

Thrombotic stent occlusion was angiographically documented as a complete occlusion (TIMI flow 0 or 1) or a flow limiting thrombus (TIMI flow 1 or 2) of a previously successfully treated artery (TIMI flow 3 immediately after stent placement and percent in-lesion diameter stenosis <30%). Acute was defined as occurring <24 hours, subacute as occurring > 24 hours to <30 days following the study procedure. Late was defined as occurring > 30 days after the index procedure. Discrete variables were presented as count and percentages and continuous variables were expressed as mean ± 1 standard deviation.

Between 16th April and 17th September 2002, a total of 510 consecutive patients (842 lesions) were treated with 1093 SES (2.1 ± 1.3 SES per patient). The baseline characteristics are shown in Table 1. Overall, 15.7% of patients had acute myocardial infarction and 32.4% unstable angina at admission. Multivessel stent implantation was performed in 25%, stents with small nominal diameter (2.5 or 2.25mm) were implanted in 25.7%, and a long stented segment (> 36mm) was recorded in 17.5%. Glycoprotein IIbIIIa inhibitors were used in 24% of cases.

Clinical 3 month follow-up information was obtained in all patients. During the first 3 month after the procedure, 2 patients (0.4%) developed SAT. Both patients were on therapy with aspirin and clopidogrel at the time point of event.

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In the present study, SAT occurred in 2 among 510 consecutive unselected patients treated sirolimus-eluting stent. The 0.4% incidence of SAT at 3 month observed in our series is low and comparable to that previously reported for conventional bare metal stents[2,5]. Both patients with stent thrombosis were diabetic females with complex coronary lesions. In these two cases IVUS examination revealed mechanical factors that had possibly predisposed to the complication (inadequate stent expansion and uncovered distal dissection). This is in accordance with recent findings in a large series of bare metal stents[6]. SAT was found to be mainly related to inadequate postprocedure lumen dimensions or procedurally related abnormal lesion morphologies (dissection, thrombus, or tissue prolapse). Stents in the left anterior descending artery have been reported to be more often involved in stent thrombosis than other vessels, but in that series diameters of the left anterior

descending were smaller than in the right coronary artery[7].

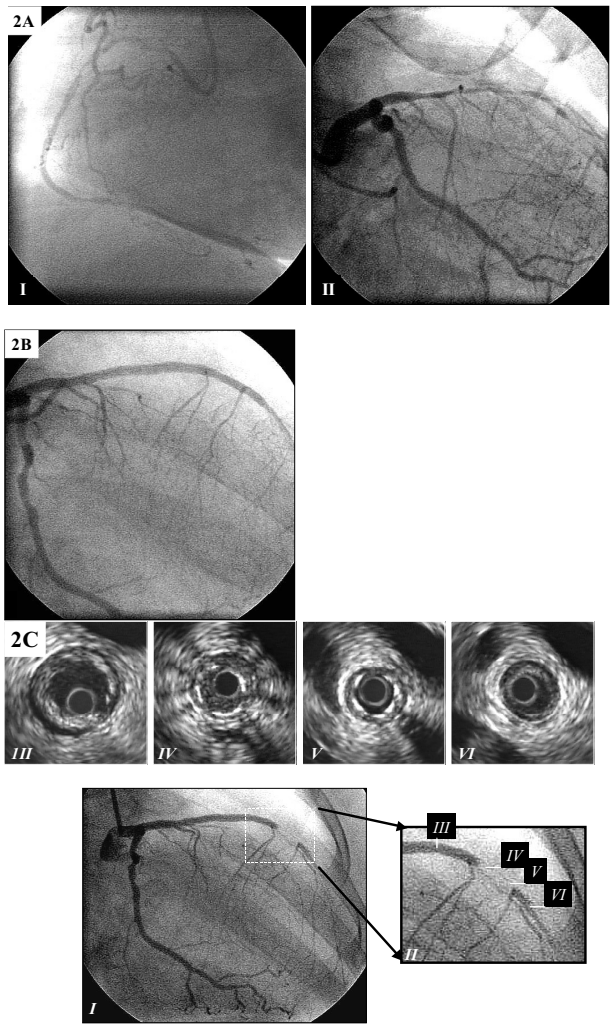

Figure 2:
2A) Pre-intervention angiogram showing spontaneous recanalization of the RCA (I) and a chronic total occlusion of the LAD (II). The LAD is visualized by simultaneous contrast injection in the left and right coronary arteries (LAD is filled by collateral flow from the RCA).
2B) Final result after recanalization of the LAD and implantation of two SES stents (3.0/33mm, 16 atm and 2.5/33mm, 14 atm; RD post 2.59mm; MLD post 1.79mm; DS post 33%).
2C) Coronary angiogram 11 days after the index procedure showing occlusion of the distal LAD (I, II). IVUS showed speckled echolucent material within the lumen (IV) and revealed an under-expansion of the stent (V; minimal stent area 2.27mm^2) in comparison to the proximal reference (III, gap between two stents; lumen area 8.55mm^2) and distal reference (VI, lumen area 2.54mm^2).

While diabetes is a well established predictor of adverse outcome[8], the impact of gender is controversial. In recent studies comparing the outcome for women and men after with bare metal stent implantation, a higher event rate[9], a lower event rate[10] or similar event rates[11] have been reported in women as compared to men.

Combined oral antiplatelet therapy[12] and systematic high-pressure stent implantation[13] have contributed to reduce the incidence of thrombotic occlusion after conventional coronary stenting[14]. Due to the fact that SES have virtually the same physical properties of bare metal stents, a similar approach was utilized to accomplish optimum SES deployment. In our series, the average implantation pressure was 17 atmospheres and balloon post-dilatation was performed in approximately half of the cases. All patients were maintained under dual antiplatelet treatment.

Previous studies suggested that sirolimus could significantly enhance agonist-induced platelet aggregation[15] and induce endothelial function impairment[16]. Animal models showed focal remnants of residual fibrin deposition adjacent to the struts that may reflect a delay in arterial repair or simply impaired fibrin degradation secondary to the local effects of the drug[17]. However, although these features could potentially increase the risk of thrombotic complications, our findings suggest a minimal risk of SAT after SES implantation, even in patients with well-known risk factors for short-term thrombotic complications. Importantly, though similar SAT rates have been reported in clinical trials with SES[1], the present report allowed a comprehensive evaluation of the risk of SAT in a large range of clinical settings, including patients commonly not enrolled in randomized studies.

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Chapter 23 Coronary Restenosis After Sirolimus-Eluting Stent Implantation. Morphological Description and Mechanistic Analysis From a Consecutive Series of Cases

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Coronary Restenosis After Sirolimus-Eluting Stent Implantation: Morphological Description and Mechanistic Analysis from a Consecutive Series of Cases

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Background: We described the clinical and morphological patterns of restenosis after sirolimus-eluting stent (SES).
Methods and Results: From 121 patients with coronary angiography obtained> 30 days after SES implantation, restenosis (diameter stenosis>50%) has been identified in 19 patients and 20 lesions (located at the proximal 5-mm segment in 30% or within the stent in 70%). Residual dissection after the procedure or balloon trauma outside the stent was identified in 83% of the proximal edge lesions. Lesions within the stent were focal and stent discontinuity was identified in some lesions evaluated by intravascular ultrasound.
Conclusions*: S*irolimus-eluting stent e*dge restenosis* is frequently associated with local trauma outside the stent. *In-stent* restenosis occurs as a localized lesion, commonly associated with a discontinuity in stent coverage. Local conditions, instead of intrinsic drug-resistance to sirolimus, are likely to play a major role in post-SES restenosis.

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Introduction

Sirolimus-eluting stents (SES) have been reported to reduce restenosis by inhibiting neointimal growth,[1] though post-SES restenosis may still occur in some cases.[2] Currently, the clinical and morphological features of restenosis after SES implantation are unknown. In this study we described a consecutive series of patients with angiographic restenosis after SES implantation.

Methods and Results

Since April 2002, SES (Cypher™; Cordis Europa NV, Roden, The Netherlands) have been utilized as the device of choice for percutaneous coronary intervention (PCI) in our institution, as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry,[3] a single-center registry designed to evaluate the impact of SES implantation in the "real world". During follow-up, coronary angiograms were obtained as clinically indicated by symptoms or positive ischemic tests. In addition, follow-up angiograms were obtained at 6±1 months for "complex" patients, typically with SES implantation to treat in-stent restenosis, bifurcations, left main, chronic total occlusions, very small vessels (SES diameter 2.25mm), long stented length (>36mm), and acute myocardial infarction. Intravascular ultrasound (IVUS) was performed at the discretion of the operator. The study protocol was approved by the institutional ethics committee and written informed consent was obtained from all patients.

Binary restenosis was defined by diameter stenosis >50% and classified as 1) *in-stent*, if inside the stent or 2) *edge restenosis*, if located within the 5-mm segments distal or proximal to the stent margins. Restenosis at an ostial location was classified as *in-stent*, unless clearly located outside the limits of the SES, in which case it was classified as *edge restenosis*. Discrete variables were presented as counts and percentages. Continuous variables were presented as mean±standard deviation and compared by Student's T test.

To date, 192 patients with at least one of the aforementioned "complex" characteristics have completed ≥ 7 months from the index procedure. A coronary angiogram performed >30 days after the angioplasty has been obtained in 121 patients (221 lesions). Among these, post-SES restenosis was identified in 19 patients and 20 lesions (Table). IVUS was available at follow-up for 11 patients with restenosis (58%). In total, 6 lesions (30%) were located at the proximal edge and 14 were *in-stent* (70%). Local injury outside the stent was observed in 5 edge restenosis (83%), as evidenced by the presence of angiographic or IVUS residual dissection after the procedure (patients #1, 3, and 4), by balloon dilatation at a non-stented area in a patient with extensive manipulation before and after implantation of 4 stents due to acute occlusion (patient #2), or by balloon post-dilatation outside the stent (patient #5).

Among the 14 *in-stent* lesions, 12 (86%) were focal (restenosis length < 10mm)[4] and presented a peculiar angiographic pattern manifested by a very localized stenotic site bordered by segments without evidence of lumen compromise (Figure 1). Stenosis length decreased from 19.1±19.1mm at baseline to 7.6±5.6mm at follow-up (p=0.046). The ratio restenosis length/stent length was 0.3±0.2. A gap between stents or stent fracture at the site of the restenosis was detected by IVUS in 4 patients at follow-up. A gap was diagnosed by the absence of stent struts in at least one IVUS cross-section in the examination of the region between two stents (patients #13, 18, and 19); a stent fracture was diagnosed by the non-visualization of struts within the stent (patients #15, and 18). One patient presented both stent gap and fracture in separate sites (patient #18). In this patient, no IVUS was performed at the index procedure (IVUS was done only at follow-up). In the other patient with stent fracture (patient #15), the stent

Patients with restenosis after sirolimus-eluting stent implantation: clinical, procedural, and morphological characteristics

Patient number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	Total
Age (years)	63	77	52	66	70	78	77	58	69	43	58	50	52	50	46	72	45	48	61	56± 11
Gender	M	M	M	M	M	F	M	M	F	M	M	M	M	M	M	M	M	M	M	89% (men)
Diabetes	0	+	0	0	0	0	0	+	+	+	0	+	+	0	0	0	+	0	0	37%
Symptoms/ischemia at follow-up	0	+	+	0	+	+	0	0	+	+	0	0	+	+	0	+	+	+	0	58%
Lesions treated	1	1	3	1	3	3	2	3	2	3	2	3	2	1	2	6	1	1	2	42
Lesions with restenosis	1	1	1	1	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	48%
Vessel	LAD	LAD	LAD	DG	SVG	LAD	LCx	RCA	RPL	LCx	DG	DG	LAD	RCA	LAD	RCA	SVG	LCx	RCA	DG	-
Procedural, angiographic and IVUS findings																				
Treatment previous in-stent restenosis	0	0	0	0	0	0	0	0	0	+*	0	0	0	0	+	0	+	+*	+	0	25%
Mod/sev calcification	0	+	0	+	0	+	+	0	0	0	0	+	0	0	0	0	0	0	0	0	25%
CTO	0	0	0	0	+	+	0	0	0	0	0	0	+	+	+	0	0	+	+	0	35%
Trauma outside the stent/residual dissection	+	+	+	+	+	0	...	...	...	...	...	...	...	...	...	...	...	...	...	...	83%†
Residual edge lesion‡	0	0	+	+	0	0	...	...	...	...	...	...	...	...	...	...	...	...	...	...	33%†
Post-dilatation with balloon≥ 0.5mm larger	+	0	+	0	+	0	0	0	0	+	0	0	0	0	+	+	+	0	+	+	45%
Bifurcation stenting	0	0	+ §	0	0	+ §	0	0	+ ||	0	+ ||	+ ||	0	+ §	0	0	0	0	0	+ ||	35%
Ostial	0	0	0	+	0	0	+	0	+	0	+	+	0	0	0	0	0	0	0	+	30%
Stented length>33mm	0	0	+	0	+	0	0	+	0	0	0	0	0	+	+	+	0	+	+	0	40%
2.25-mm diameter SES	0	0	0	+	0	0	0	0	0	0	+	0	0	0	0	0	0	+	0	0	15%
Stent fracture or gap between stents¶	0	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	0	+	0	+	0	0	+	+	50%#
Stent underexpansion at restenosis site¶	0	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	+	0	0	0	+	0	0	0	25%#
Number of any above (+diabetes)	2	3	5	5	4	3	2	1	3	3	4	2	3	5	4	3	3	5	5	4	range 1 - 5
Post-SES restenosis characteristics																					
Location	prox	prox	prox	prox	prox	prox	in-st	in-st	in-st	in-st	in-st	in-st	in-st	in-st	in-st	in-st	in-st	in-st	in-st	in-st	in-st	
Total occlusion	0	0	0	0	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10%
Focal lesion (length< 10mm)	+	+	+	0	0	0	+	+	+	+	0	0	+	+**	+	+	+	+	+**	+	86%††

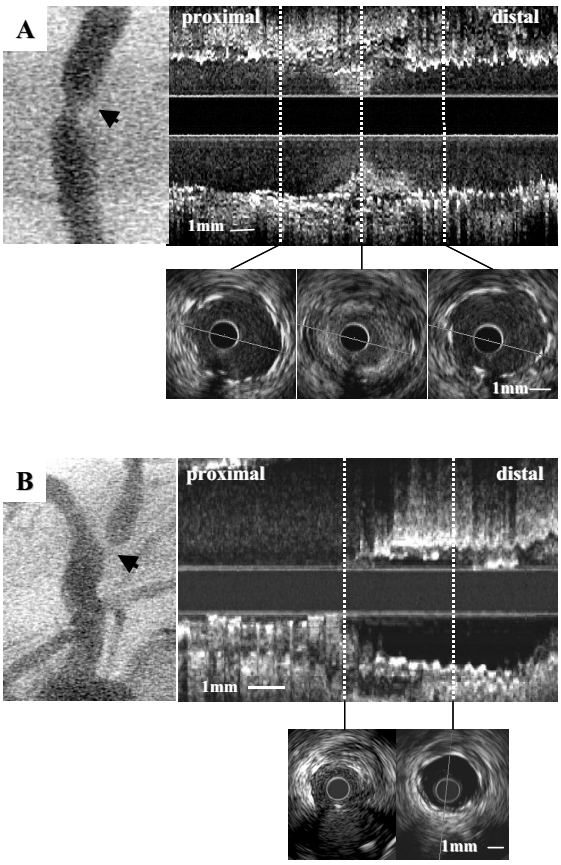
CTO=chronic total occlusion; DG=diagonal; IVUS=intravascular ultrasound; in-st=*in-stent* restenosis; LAD=left anterior descending; LCx=left circumflex artery; M=male; NA=IVUS not available; prox=proximal edge restenosis; RCA=right coronary artery; RPL=right postero-lateral branch; SES=sirolimus-eluting stent; SVG=saphenous vein graft
*ISR post-brachytherapy
†relative to proximal edge restenosis
‡angiographic diameter stenosis>30% or IVUS plaque burden>50%
§main vessel restenosis
||side branch restenosis
¶diagnosed by IVUS
#relative to the number of *in-stent* restenosis with available IVUS.
**more than 1 "focal" site
††relative to the number of *in-stent* restenosis

discontinuity was not evident after the procedure, being only detected at the follow-up. In all cases, the stent gap or fracture could not be noticed angiographically and measured <1 mm in length by IVUS (Figure 1).

Among the 6 ostial lesions (30%), the ostium was not covered by the stent at angiographic inspection in 1 case (classified as proximal edge restenosis). The remaining 5 lesions seemed to be fully covered by stent on angiography. IVUS was available for only one of these cases. In this patient, although angiographically unnoticed, a short area at the ostium was observed to be uncovered by SES (Figure 2). Among the 6 ostial lesions, 4 were located in the side branch of bifurcation stenting treatment, all treated with "T" stent technique (stent in the side branch implanted with its proximal border located at the ostium of the branch; stent in the main vessel implanted encompassing the side branch ostium, thereby creating a "T" configuration).[5]

Discussion

In approximately 90% of patients with *in-stent* restenosis post-SES, the lesion was very localized and



Focal restenosis at a gap between stents. In A, a short restenosis (angiogram, arrow head) was noted at a site were no stent struts were visualized on IVUS examination (IVUS cross-section, mid). Stent coverage was complete at the proximal and distal segments, with no neointimal tissue present (IVUS cross-sections left and right respectively). Longitudinal IVUS reconstruction showed the localized pattern of the restenosis. In B, an ostial restenosis (angiogram, arrow head) was associated with incomplete coverage by the sirolimus-eluting stent (IVUS cross-section left and longitudinal reconstruction). The distal segment presented no neointimal proliferation inside the stent (IVUS cross-section right and longitudinal reconstruction).

bordered by segments with no evidence of neointima. The effect of the drug in the non-restenotic portions indicates that an intrinsic resistance to sirolimus was unlikely in most of our patients. Among lesions evaluated by IVUS, stent discontinuity was identified in 36% of cases (and in 50% of restenosis located inside the stent), suggesting that a decrease in local drug availability may have contributed to the development of restenosis in these cases. Accordingly, our findings suggest that incomplete lesion coverage by the SES may also influence the occurrence of restenosis at the stent borders and at ostial sites. We may speculate that, although no clinical data is currently available, techniques that ensure complete vessel scaffold could constitute an alternative for SES implantation at bifurcations.[6] *Edge restenosis* occurred more frequently in the proximal than the distal stent border. Whether this finding is associated with a more effective drug effect in the outflow stent border remains to be clarified. In addition, 37% of our cases were diabetics. It may be hypothesized that the presence of diabetes mellitus may lead to a higher predisposition to post-SES restenosis.

The current study presents several limitations. Angiographic follow-up was available for complex patients or for those with recurrent symptoms, therefore precluding an evaluation of the total restenosis rate for the global treated population. Moreover, the lack of IVUS limits a more detailed description of the mechanisms involved in the occurrence of post-SES restenosis in some patients.

Conclusions

Restenosis after sirolimus-eluting stents occurs within or adjacent to the stent. *Edge restenosis* is frequently associated with local trauma outside the stented segment. *In-stent restenosis* occurs as a very localized lesion, associated with complex anatomy (especially ostial lesions), stent discontinuity, or diabetes. A systemic drug-resistance to sirolimus seemed to be unlikely in most patients.

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Chapter 24 Clinical, Angiographic, and Procedural Predictors of Angiographic Restenosis after Sirolimus-Eluting Stent Implantation in Complex Patients – An Evaluation from the RESEARCH study

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Background: The factors associated with the occurrence of restenosis after sirolimus-eluting stent (SES) implantation in complex cases are currently unknown.
Methods and Results: A cohort of consecutive complex patients treated with SES implantation was selected according to the following criteria: 1) treatment of acute myocardial infarction, 2) treatment of in-stent restenosis, 3) 2.25-mm diameter SES, 4) left main coronary stenting, 5) chronic total occlusion, 6) stented segment > 36 mm, and 7) bifurcation stenting. The present study population was composed of 238 patients (441 lesions) from whom 6-month angiographic follow-up was obtained (70% of eligible patients). Significant clinical, angiographic, and procedural predictors of post-SES restenosis were evaluated. Binary *in-segment* restenosis was diagnosed in 7.9% of lesions (6.3% *in-stent*, 0.9% at the proximal edge, 0.7% at the distal edge). The following characteristics were identified as independent multivariate predictors: treatment of in-stent restenosis (OR 4.16; 95% CI: 1.63 – 11.01; p<0.01), ostial location (OR 4.84; 95% CI: 1.81 – 12.07; p<0.01), diabetes (OR 2.63; 95% CI: 1.14 – 6.31; p=0.02), total stented length (per 10 mm increase) (OR 1.42; 95% CI: 1.21 – 1.68; p<0.01), reference diameter (per 1.0 mm increase) (OR 0.46; 95% CI: 0.24 – 0.87; p=0.03), and left anterior descending artery (OR 0.30; 95% CI: 0.10 – 0.69; p<0.01).
Conclusions: Angiographic restenosis after sirolimus-eluting stent implantation in complex patients is an infrequent event, occurring mainly in association with lesion-based characteristics and diabetes mellitus.

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Introduction

In-stent restenosis is the major limitation hampering the medium-term efficacy of coronary stenting. Several reports have previously evaluated the impact of baseline and procedural characteristics on the risk of subsequent restenosis after bare metal stent implantation, with a number of high-risk parameters, such as diabetes, lesion length, and vessel size, been consistently identified in most studies.[1-7] Unfortunately, these characteristics are commonly found in the daily practice, where treatment of complex patients frequently appears as a challenging therapeutic dilemma.

Sirolimus-eluting stents (SES) have been proven to strikingly decrease neointimal growth, leading to a marked reduction in restenosis rates.[8-10] In 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),[8] no cases of binary angiographic restenosis were seen after sirolimus-eluting stent implantation. Moreover, restenosis was significantly reduced from 36.3% with conventional stents to 8.9% with sirolimus-eluting stents in the randomized SIRolImUS-eluting Bx velocity balloon expandable stent trial (SIRIUS)[9] and from 42.3% to 5.9% in the E-SIRIUS trial,[10] with diabetes, small vessel size, and long lesions being identified as predictors of post-sirolimus-eluting stent restenosis in the SIRIUS trial.[9] Nevertheless, these randomized studies have been largely restricted to selected patients treated with single-lesion elective stenting. It is currently unknown what are the factors related to angiographic restenosis after sirolimus-eluting stent implantation in highly complex subsets.

Sirolimus-eluting stent implantation was recently shown to effectively improve the 1-year clinical outcomes in the "real world" practice in patients enrolled in the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) study.[11] In the RESEARCH, a parallel angiographic substudy was conducted to evaluate the late angiographic findings of complex patients treated with sirolimus-eluting stents. The present report aimed to evaluate the value of clinical, angiographic, and procedural factors in predicting the risk of binary restenosis in highly complex patients treated with sirolimus-eluting stent implantation in the RESEARCH study.

Methods

Study Design and Patient Population

The study design of the RESEARCH has been previously reported elsewhere.[11] In brief, sirolimus-eluting stent implantation (Cypher; Johnson & Johnson-Cordis unit, Cordis Europa NV, Roden, the Netherlands) has been introduced as the default strategy for all patients undergoing percutaneous coronary interventions in our institution since April 2002. All procedures were performed according to standard techniques and the final interventional strategy was left to the discretion of the

operator with the aim of achieving a final residual stenosis < 50% by *on-line* quantitative coronary angiography in the presence of TIMI 3 grade flow. Also, the utilization of periprocedural glycoprotein IIbIIIa inhibitors and antithrombotic medications was entirely left at the discretion of the attending team.

Patients receiving sirolimus-eluting stents were considered as candidates for angiographic re-evaluation if presenting at least one following: 1) treatment of acute myocardial infarction, 2) treatment of in-stent restenosis, 3) utilization of very small sirolimus-eluting stent (2.25-mm nominal diameter), 4) treatment of left main coronary, 5) treatment of chronic total occlusion (more than 3 months), 6) total adjacent stented segment longer than 36 mm, and 7) bifurcation stenting (sirolimus-eluting stent implanted in the both the main vessel and the side branch). Patients with the aforementioned characteristics who had not undergone repeat intervention in the first month and not presented any formal medical contraindication for angiographic re-study were considered eligible for angiographic follow-up at 6 to 8 months. Coronary angiograms performed prematurely due to clinical indications were used as the follow-up angiography if performed after 4 months or if restenosis was detected. In other cases, a second angiogram was obtained between 6 and 8 months. Importantly, although all patients were approached for angiographic follow-up, patient refusal was not considered as an exclusion criterion to be enrolled in the RESEARCH. Angiographic re-study was not requested for non-residents in The Netherlands.

During the first 6 months of enrollment, a total of 362 consecutive patients had at least one high-risk criterion above (57% of all patients treated with sirolimus-eluting stents in the period). From these, 2 patients moved to another country, 10 patients have died at 6-month follow-up, 6 patients had repeat intervention before 30 days (surgical or percutaneous), and 3 patients were considered to have a medical contra-indication to the angiographic follow-up (one patient with previous stroke and disabling dementia, one patient with severe allergic contrast reaction at the index procedure, and one patient with end-stage hepatic failure due to auto-immune hepatitis). From the remaining 341 patients, angiographic re-evaluation at 204 ± 34 days was obtained from 238 patients (70% of eligible patients), who compose the present study population.

Quantitative Coronary Angiography

Quantitative coronary angiographic analysis was performed as previously described, utilizing a validated computer-based edge-detection system (CASS II, Pie Medical, Maastricht, The Netherlands)[12]. Interpolated reference diameter, minimal luminal diameter, and diameter stenosis were obtained at baseline, post-stenting, and at follow-up. In-stent restenosis was defined by diameter stenosis >50% and was classified as in-stent if inside the stent, or in-segment if located within the stented segment plus the 5-mm segments distal or proximal to the stent margins.[9] Restenosis at an ostial location (within 3 mm of the vessel origin) was classified as *in-stent*, unless clearly located outside the limits of the SES.[13]

Statistical Analysis

Continuous variables were presented as mean ± standard deviation (SD) and were compared using Student's unpaired t-test. Categorical variables were presented as counts and percentages and compared with the Fisher's exact test. Demographic, clinical, procedural, and angiographic variables were tested in univariate and multivariate logistic analyses for their value in predicting binary restenosis. All variables shown in Table 1 and Table 2 were considered in multivariate logistic regression analyses regardless of their univariate findings. The final model was built iteratively and evaluated for lack of fit with the Hosmer-Lemeshow test. The global predictive accuracy was assessed by means of the C-index (the area under the receiver operating characteristic curve). Finally, an internal validation was performed utilizing a bootstrap technique.[14] The model was repeatedly applied to 1000 replicated bootstrapped samples and the C-index for each individual sample was calculated. The C-index obtained from each bootstrapped sample was then subtracted from the initial C-index value of the original population. The average of the differences were considered as a measure of the optimism in the model fit. Finally, a corrected C-index was calculated by subtracting the average of the optimism estimates from the original C-index. The bootstrap correction has been described as a nearly unbiased internal validation, penalizing for any model overfitting.[14] Presented 95% confidence intervals of all multivariate estimates were derived from the bootstrapping analysis.

Table 1. Clinical characteristics of 238 patients treated with SES implantation

Male sex, %	73
Age, years ± SD	60 ± 12
Height, cm ± SD	172 ± 9
Weight, kg ± SD	82 ± 14
Hypercholesterolemia, %*	58
Hypertension, %	56
Diabetes mellitus, %	22
Insulin-dependent diabetes	6
Non insulin-dependent diabetes	16
Previous myocardial infarction, %	32
Previous bypass surgery, %	11
Previous percutaneous intervention, %	28
Vessel disease	
1-vessel disease, %	40
2-vessel disease, %	35
3-vessel disease, %	25
Clinical presentation	
Stable angina, %	54
Unstable angina, %	21
Acute myocardial infarction, %	26
Periprocedural IIbIIIa inhibitor, %	27

*Total cholesterol>200mg/dl and/or receiving lipid-lowering treatment

Results

From the 238 patients (441 lesions) included in this analysis, 13 (6%) had left main coronary stenting, 35 (15%) had at least one chronic total occlusion, 45 (19%) received sirolimus stents to treat at least one restenotic lesion, 50 (21%) had bifurcation stenting, 62 (26%) were in the acute phase of a myocardial infarction, 68 (28%) had at least one 2.25-mm SES implanted, and 83 (35%) had very long stenting (>36 mm) in at least one vessel

(Tables 1 and 2). On average, 1.41 ± 0.81 stents were implanted per lesion and 39% of lesions had at least 2 stents overlapped. Most lesions were classified as type B2 or C (71%), 22% received bifurcation stenting (stent implanted in both the main vessel and the side branch), 8% were chronic total occlusions (duration >3 months), and 3% were located in the left main coronary. The mean vessel size was 2.50 ± 0.61 mm (range 1.00 – 4.59 mm), and the average stented length was 26.0 ± 20.3 mm (range 8 – 117 mm)

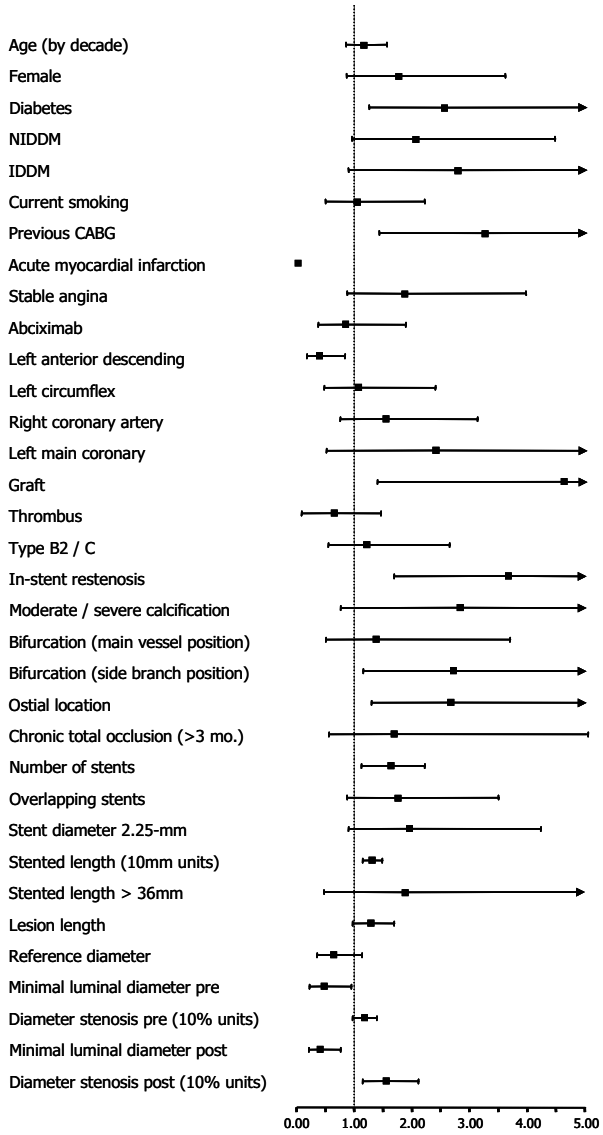
Table 2. Procedural and angiographic characteristics of 441 lesions treated with SES implantation

Treated Vessel	
Left main coronary, %	3
Left anterior descending, %	43
Left circumflex artery, %	22
Right coronary artery, %	30
Bypass graft, %	3
Lesion type	
Type A, %	6
Type B1, %	23
Type B2, %	43
Type C, %	28
Chronic total occlusion > 3 months, %	8
Moderate / severe angiographic calcification, %	7
Ostial location, %	22
Bifurcation treatment*	22
Treatment of in-stent restenosis, %	13
Number of stents implanted ± SD	1.41 ± 0.81
Overlapping, %	39
Total stented length, mm ± SD	26.0 ± 20.3
Stented length > 36 mm, %	17
Utilization of 2.25-mm SES, %	18
Reference diameter, mm ± SD	2.50 ± 0.61
Pre-procedure minimal luminal diameter, mm ± SD	0.69 ± 0.54
Pre-procedure diameter stenosis, % ± SD	72.2 ± 20.0
Lesion length, mm ± SD	16.1 ± 11.8
Post-procedure minimal luminal diameter, mm ± SD	2.13 ± 0.58
Post-procedure diameter stenosis, % ± SD	17.2 ± 11.1
Follow-up minimal luminal diameter, mm ± SD	2.10 ± 0.69
Follow-up diameter stenosis, % ± SD	22.8 ± 19.9
Late loss, mm ± SD	0.04 ± 0.49
Binary restenosis, %	7.9
In-stent, %	6.3
Proximal edge, %	0.9
Distal edge, %	0.7

SD=standard deviation; SES=sirolimus-eluting stent
*SES implantation in both the main vessel and the side branch

At the follow-up angiogram, 7.9% of lesions had binary *in-segment* restenosis. Among these, 6.3% were located inside the stent (*in-stent*), 0.9% were located in the proximal edge, and the remaining 0.7% occurred at the distal edge. Due to the limited number of lesions with edge restenosis (7 observations), further analyses were performed for all lesions grouped as *in-segment* restenosis.

Figure shows the univariate relationship between demographic, angiographic and procedural characteristics and the incidence of post-SES restenosis, and significant univariate parameters are shown in Table 3. In the multivariate analysis, the following variables were identified as independent predictors: treatment of in-stent restenosis, ostial location, diabetes mellitus, total stented length, reference diameter, and left anterior descending artery (Table 4). The final multivariate model fitted well the data (Hosmer-Lemeshow test p-value = 0.94; chi square value = 2.93; d.f.= 8) and had a good predictive accuracy (C-index = 0.83), which was virtually unchanged after the bootstrapping correction (corrected C-index = 0.82). The actual restenosis rates for patients with "high-risk characteristics" (as derived from the multivariate model) are shown in Table 5.



Univariate odds ratio of binary angiographic *in-segment* restenosis after sirolimus eluting stent restenosis according to demographic, clinical, procedural, and angiographic characteristics.

Discussion

The present study reported on the predictors of angiographic restenosis following sirolimus-eluting stent implantation in complex patients. Overall, our series included patients with smaller vessels and longer lesions, compared to all trials conducted to date.[8-10] Moreover, a considerable proportion of patients had previous in-stent restenosis, bifurcation stenting, chronic total occlusions, thrombus-containing lesions, and calcified vessels, conditions that were formally excluded from previous trials. Nevertheless, the binary restenosis rate after

sirolimus-eluting stents in such a complex patient population was detected in only a minority of cases (7.9% of lesions). It is worth noting that the expected restenosis rate for *de novo* lesions included the present report would range from 40.1% to 43.0% if treated with bare metal stents, as calculated from prediction equations derived from previous metanalysis with conventional stents.[3,6]

Table 3. Clinical, procedural, and angiographic univariate predictors of *in-segment* restenosis after SES restenosis.

	OR	95% CI	p-value
Bypass graft	4.61	1.39–15.33	0.01
Treatment of in-stent restenosis	3.66	1.68–7.96	<0.01
Previous bypass surgery	3.24	1.42–7.41	<0.01
Bifurcation stenting (side branch position)	2.77	1.15–6.33	0.02
Ostial location	2.66	1.30–5.46	<0.01
Diabetes mellitus	2.54	1.24–5.21	0.01
Number of stents implanted	1.62	1.19–2.22	<0.01
Post-procedure diameter stenosis (per 10% increase)	1.55	1.14–2.10	<0.01
Total stented length (per 10 mm increase)	1.30	1.14–1.48	<0.01
Pre-procedure minimal luminal diameter	0.46	0.22–0.95	0.04
Post-procedure minimal luminal diameter	0.39	0.20–0.76	<0.01
Left anterior descending artery	0.37	0.16–0.82	0.02
Acute myocardial infarction	0	-	<0.01

Table 4. Clinical, procedural, and angiographic multivariate predictors of *in-segment* restenosis after SES restenosis.

	OR	95% CI	p-value
Intercept coefficient = -2.34			
Treatment of in-stent restenosis	4.16	1.63 – 11.01	<0.01
Ostial location	4.84	1.81 – 12.07	<0.01
Diabetes mellitus	2.63	1.14 – 6.31	0.02
Total stented length (per 10 mm increase)	1.42	1.21 – 1.68	<0.01
Reference diameter (per 1.0 mm increase)	0.46	0.24 – 0.87	0.03
Left anterior descending artery	0.30	0.10 – 0.69	<0.01

CI=confidence interval; OR=odds ratio; SES=sirolimus-eluting stent

In the SIRIUS trial, small vessel size, long lesion length, and diabetes have been shown to significantly increase the incidence of restenosis after sirolimus-eluting stent.[9] These characteristics were confirmed as predictors of post-SES restenosis in our study, which additionally extended the list of independent parameters to also include ostial location and treatment of in-stent restenosis (as negative factors) and left anterior descending artery location (as a protective factor). Interestingly, most characteristics identified as predictors of post-sirolimus-eluting stent restenosis have long been recognized as major predictors of restenosis following balloon angioplasty or conventional bare stent implantation.[1-7,15-17] It seems intuitive to assume that the increased incidence of restenosis after SES in patients with these risk factors may reflect an extreme background tendency to tissue reaction and neointimal growth, which was not sufficiently inhibited by the antiproliferative action of the drug.

Table 5. Actual rates of post-SES *in-segment* restenosis according to the presence of high risk characteristics*

	In-segment restenosis rate
Treatment of in-stent restenosis	19.6%
Ostial location	14.7%
Diabetes mellitus	14.3%
Stented length > 26 mm †	13.9%
Reference diameter < 2.17 mm ‡	10.3%
Non-LAD location	10.8%

LAD=left anterior descending artery; SES=sirolimus-eluting stent
* presence of multivariate independent predictors
† higher tercile for stented length
‡ lower tercile for reference diameter

Restenosis after SES has been previously shown to be associated with incomplete lesion coverage in some cases, as detected by intravascular ultrasound.[13] In the present study, lesions involving ostial sites had a higher risk of restenosis, which may be, at least partially, related to technical difficulties in stent positioning and vessel scaffolding at the ostium. We may speculate that the presence of "traditional" risk factors for restenosis may potentially act as a predisposing factor, which will lead to restenosis in case a subtle device-related or procedure-related local failure is eventually superimposed. Unfortunately, small gaps between stents and minor ruptures in the metallic stent mesh or in the polymer integrity are not detectable by conventional coronary angiography[13] and could not be evaluated in this report.

The treatment of in-stent restenosis with SES was associated with a greater than 4-fold increase in the risk of restenosis after adjustment for other independent variables. Although SES implantation has been associated with low rates of repeat restenosis after treatment of non-complex in-stent restenosis,[18,19] the efficacy of this device for more complicated cases remains to be established.[20,21] Re-dilatation of restenotic lesions (i.e. exposure to "double injury") has been previously shown to trigger a peculiar local vascular response, distinct from that observed after the first dilatation.[22] Modifications in the reparative mechanisms, especially after endovascular brachytherapy,[20] may decrease the responsiveness of restenotic lesions to the antiproliferative drug.

Curiously, lesions located in the left anterior descending artery had a decreased restenosis rate in our series. Whether this factor represents a true protective characteristic has to be further investigated in future studies. Although post-SES restenosis was not detected in any patient admitted with acute myocardial infarction, this characteristic was not included in our final multivariate model, suggesting that perhaps acute myocardial infarction at admission *per se* was not an important factor affecting restenosis in our population. Post-sirolimus-eluting stent restenosis in our study was almost entirely restricted to the segment inside the stent (approximately 80% of the restenoses). This finding represent a major difference from previous trials with SES, where restenosis more frequently occurred at the stent edges.[9,10] In the RESEARCH, all operators were strongly advised to actively cover the entire injured vessel area and to avoid residual dissection at the stent borders and gaps between stents. In addition, the stent placement strategy aimed to cover the treated segment "from healthy tissue to healthy tissue", in order to avoid the free borders of the stents to terminate in grossly diseased segments. However, it

remains speculative whether these procedural strategies might have had any impact in reducing the incidence of restenosis at the stent edges.

Study Limitations

The present report may suffer from its relatively limited study population, which was restricted to complex patients fulfilling pre-defined criteria to be included in this angiographic substudy. Therefore our results cannot be directly extrapolated to the entire cohort of consecutive patients treated in the RESEARCH and further analyses are needed to fully assess the angiographic outcomes of subsets not included in the current study. Ten patients with early death could not be re-studied at 6 months, and a higher rate of angiographic follow-up (approximately 70% in this study) would be desirable for a comprehensive evaluation. However, it should be emphasized that the present study was designed to enroll all unselected patients treated in our institution, and that patient refusal for angiographic follow-up did not preclude enrollment in the RESEARCH study. Obviously, this "real life" scenario differs substantially from that of randomized trials and limits the compliance to angiographic re-study.

Conclusion

Angiographic restenosis after sirolimus-eluting stent implantation in complex patients is an infrequent event (7.9% of lesions), occurring mainly in association with local, lesion-based characteristics and diabetes mellitus.

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Chapter 25 Comparison of Late Luminal Loss Response Pattern Following Sirolimus-Eluting Stent Implantation or Conventional Stenting

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Submitted for publication

Comparison of Late Luminal Loss Response Pattern Following Sirolimus-Eluting Stent Implantation or Conventional Stenting

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Background: We investigated the pattern of late luminal loss following sirolimus-eluting or bare stent implantation.
Methods and Results: The study population comprised 238 patients treated with sirolimus-eluting stents and 526 patients treated with conventional stents. The distribution of late loss of sirolimus stents was largely skewed to the right and differed from the distribution for bare stents. When divided according to the presence of binary restenosis (diameter stenosis > 50%), restenotic lesions in the bare stent group (26.0%) had a late loss of 1.40±0.64 mm and in the sirolimus group (7.9%) of 1.16±0.76 mm. Non-restenotic lesions in the bare stent group had a late loss of 0.58±0.44 mm, whilst the late loss of non-restenotic lesions in the sirolimus group remained close to zero (-0.05±0.33 mm). Differences between post-stenting and follow-up measurements in the sirolimus group ("late loss") resembled variations observed in repeated angiographic measurements, as assessed from a random sample of 30 segments measured repeatedly. After multivariate adjustment, stent type did not influence the degree of late loss in restenotic lesions. However, non-restenotic bare stents had a significantly larger estimated luminal loss (0.58 mm; 95% CI: 0.52 – 0.65 mm) than sirolimus-eluting stents, for which the predicted late loss was almost zero (-0.04 mm; 95% CI: -0.10 – 0.02).
Conclusions: The pattern of late loss after sirolimus-eluting stent implantation follows a peculiar behavior, different from lesions treated with conventional stents. Whether this is explained by an unusual statistical distribution or a biological all-or-none response of restenosis following sirolimus-eluting stenting remains to be investigated.

Submitted for publication

Introduction

The pathophysiological processes involved in lumen renarrowing after percutaneous coronary intervention have been largely studied over the last decades. However, it remains a matter of debate whether restenosis simply represents an extreme form of the "normal" vessel healing response after mechanical dilatation, or if it is related to specific mechanisms that ultimately lead to vessel renarrowing.[1-7] Although several cutoff criteria have been proposed to dichotomize patients with restenosis from those without restenosis, it has been widely recognized that, to some extent, late luminal reduction is an ubiquitous phenomenon, occurring even for those categorized as not having binary restenosis.[1,7]

Recently, drug-eluting stents with the antiproliferative agent sirolimus have proven to markedly reduce neointimal growth in clinical trials. In the First-In-Man study[8] and in 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),[9,10] no cases of binary angiographic restenosis were seen after sirolimus-eluting stent (SES) implantation. Restenosis (diameter stenosis > 50% at follow-up) after SES implantation occurred in 9% of cases (compared to 36% with bare stents; $p<0.001$) in the recent randomized SIRolImUS-eluting Bx velocity balloon expandable stent trial (SIRIUS).[11] However, SIRIUS included more complex patients than RAVEL and FIM, which could at least partially account for the occurrence of restenosis in some cases. Moreover, we have recently shown that post-SES restenosis frequently occurs in association with particular local conditions in complex cases.[12] Nonetheless, the late luminal renarrowing response after sirolimus-eluting stent implantation is currently poorly understood. In the present study, we examine the pattern of late luminal loss following sirolimus-eluting stents in comparison with conventional bare metal stent implantation.

Methods

Study Design and Patient Population

Since April 2002, sirolimus-eluting stents (Cypher; Johnson & Johnson-Cordis unit, Cordis Europa NV, Roden, the Netherlands) have been utilized as the device of choice for every percutaneous procedure in our institution, as detailed elsewhere.[13] The final interventional strategy was left to the discretion of the operator, as was the utilization of periprocedural glycoprotein IIbIIIa inhibitors and antithrombotic medications.

Patients treated with SES were considered as candidates for angiographic re-evaluation if presenting at least one following: 1) treatment of acute myocardial infarction, 2) treatment of in-stent restenosis, 3) utilization of very small SES (2.25-mm nominal diameter), 4) treatment of the left main coronary, 5) treatment of chronic total occlusion (more than 3 months), 6) adjacent stented segment longer than 36 mm, and 7) bifurcation stenting (SES implanted in the both the main vessel and the side branch). Patients not undergoing a repeat intervention in the first month, and without a formal medical contraindication were considered eligible for angiographic follow-up between 6 and 8 months. Importantly, although all such patients were approached for angiographic follow-up, patient refusal was not considered as an exclusion criterion to be treated with sirolimus stents. Angiographic re-study was not requested for non-residents of The Netherlands.

During the first 6 months of enrollment, a total of 362 consecutive patients had at least one criterion above (57% of all patients treated with SES in the period). From these, 2 patients moved to another country, 10 patients had died at 6-month follow-up, 6 patients had repeat intervention before 30 days, and 3 patients were considered to have a medical contra-indication to the angiographic follow-up. From the remaining 341 patients, angiographic follow-up (204±34 days) was obtained from 238 patients (70% of eligible patients), who compose the present study population. A total of 441 lesions were treated and included in the present report.[14] Apart from being older (63±12 years vs. 60±12 years; p=0.02), non-included patients had similar baseline characteristics compared to patients with angiographic follow-up. This protocol was approved by the hospital ethics committee and written informed consent was obtained from every patient.

Table 1. Clinical and angiographic characteristics

	Bare stents (526 pts; 734 les)	SES (238 pts; 441 les)	p-value
Age, y	60±10	60±12	0.6
Male	84	73	<0.01
Diabetes	17	22	0.1
Acute coronary syndrome*	58	46	<0.01
Left main coronary	1	3	0.02
Left anterior descending	41	43	0.5
Left circumflex artery	23	22	0.7
Right coronary artery	35	29	0.02
Bypass graft	0	3	<0.01
Reference diameter, mm	2.80±0.59	2.50±0.61	<0.01
Pre-procedure minimal luminal diameter, mm	0.91±0.39	0.69±0.54	<0.01
Pre-procedure diameter stenosis, %	67.0±12.6	72.2±20.0	<0.01
Lesion length, mm	10.0±7.5	16.1±11.8	<0.01
Post-procedure minimal luminal diameter, mm	2.43±0.54	2.13±0.58	<0.01
Post-procedure diameter stenosis, %	19.9±9.1	17.2±11.1	<0.01
Follow-up minimal luminal diameter, mm	1.63±0.64	2.10±0.69	<0.01
Follow-up diameter stenosis, %	40.6±18.8	22.8±19.9	<0.01
Late loss, mm	0.80±0.61	0.04±0.49	<0.01
Binary restenosis	26.0	7.9	<0.01

Values are mean±SD or percentages
* unstable angina or acute myocardial infarction

In order to better evaluate the angiographic outcomes of patients treated with SES, a control group for comparison was composed of patients treated with bare metal stents included in the Evaluation of Oral Xemilofiban in Controlling Thrombotic Events (EXCITE) trial, which study design and main results have been reported elsewhere.[15] Briefly, the EXCITE randomized a total of 7232 patients to the oral glycoprotein IIbIIIa inhibitor xemilofiban or placebo, administered before percutaneous coronary revascularization and maintained for up to 6 months. The trial included a substudy with 526 patients (734 lesions) treated with coronary stenting, for whom baseline, post-procedure and 6-month angiographic re-evaluation was obtained and comprised the control population of the present study. Due to the negative results of the trial in preventing restenosis, all patients were included in the present report regardless of the allocated treatment.

Quantitative Coronary Angiography

Coronary angiograms were obtained before intervention, after stenting, and at follow-up. The projection showing the maximal degree of stenosis ("worst view") was selected at baseline and used for the subsequent analysis. Quantitative coronary angiographic analysis was performed as previously described, utilizing a validated computer-based edge-detection system (CASS II, Pie Medical, Maastricht, The Netherlands)[16]. Interpolated reference diameter, minimal luminal diameter, and diameter stenosis were measured at all time-points. Late loss was calculated as the difference between the minimal luminal diameter after stenting and at follow-up. The target lesion was defined as the entire segment involving the implanted stent and the 5-mm distal and proximal borders adjacent to the stent.

Statistical Analysis

Categorical variables were expressed as percentages and compared by Fisher's Exact Test. Continuous variables were presented by their mean and standard deviation and compared by Student's T test. The frequency distribution of late loss was graphically represented using histograms and tested for normality utilizing the Kolmogorov-Smirnov goodness-of-fit test. The method proposed by Bland and Altman[13] was utilized to evaluate the variation in the measurements of luminal diameters at post-procedure and at follow-up as well as for the variations between repeated measurements in a random sample of segments in the index angiogram. In Bland and Altman's method, the average of the two measurements for an individual lesion is plotted against the difference between them, with 95% limits of agreement being calculated to evaluate the measurement concordance. Also, the regression line of difference on average was depicted in the graphs as well as the correspondent R square value. Multivariate estimates of late loss were calculated by general linear models adjusted for stent type (bare or sirolimus stents) and for the following baseline and procedural variables (that differed between the study groups): gender, diabetes, clinical syndrome at presentation, treated vessel, lesion length, reference diameter, and post-procedure minimal luminal diameter.

Results

Patients treated with SES had a higher risk profile for restenosis than the control group with bare stents, according to previously proposed risk factors (Table 1). Specifically, in the sirolimus group lesion length was longer (16.1±11.8 mm vs. 10.0±7.5 mm; p<0.01), reference vessel diameter was smaller (2.50±0.61 mm vs. 2.80±0.59 mm; p<0.01), post-procedural minimal luminal diameter was smaller (2.13±0.58 mm vs. 2.43±0.54 mm; p<0.01). Diabetes tended to be more prevalent among patients treated with sirolimus stents, although not reaching statistical significance (22% vs. 17%; p=0.1).

Nevertheless, the total binary restenosis rate was significantly lower (7.9% vs. 26.0%; p<0.01) and the overall late lumen loss significantly smaller (0.04±0.49 mm vs. 0.80±0.61; p<0.01) in the sirolimus group than in the bare group.

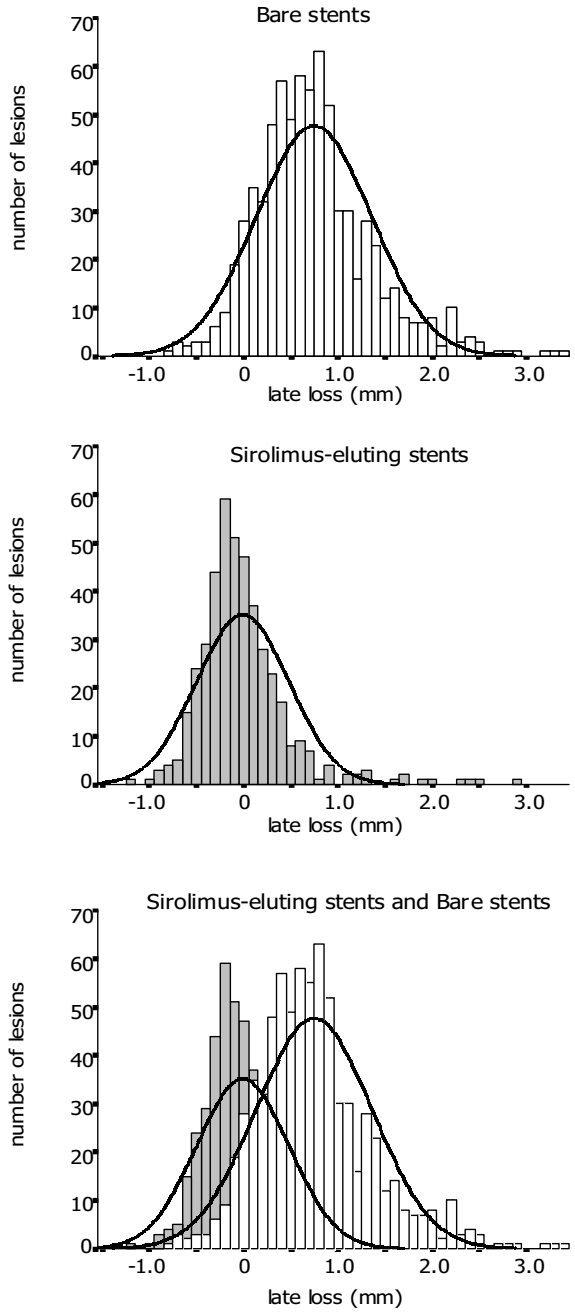

Figure 1. Frequency distribution of late loss values for all lesions treated with bare metal stents (upper panel) and with sirolimus-eluting stents (mid panel). The lower panel shows both stent types together. The superimposed curves represents the normal probability function based on the mean and variance of the data. P<0.001 by Kolmogorov-Smirnov test for both stent types.

Frequency Distribution of Late Loss

Overall, patients treated with bare stents had an average late loss of 0.80 mm (range: -0.75 to 3.48 mm) and patients treated with SES had an average late loss of 0.04 mm (range: -1.12 to 2.97 mm; p<0.01 vs. bare stents). Although presenting an apparent bell-shaped pattern (Figure 1), the frequency distribution of late loss values strongly deviated from normality for both stent groups (p<0.001 by Kolmogorov-Smirnov test for normality for both). The frequency distribution of late loss was then analyzed after separating the lesions into 2 categories according to several proposed definitions for binary restenosis.[4,17,18] Also, lesions were separated according to the previously described intersection point between lesions with and without excessive late loss after conventional stenting (i.e. minimal luminal diameter at follow-up of 1.09 mm).[7] All analyses gave similar findings and further results in this study are presented for the most commonly utilized criterion of binary restenosis, which defines restenosis as a luminal diameter stenosis > 50% at follow-up.

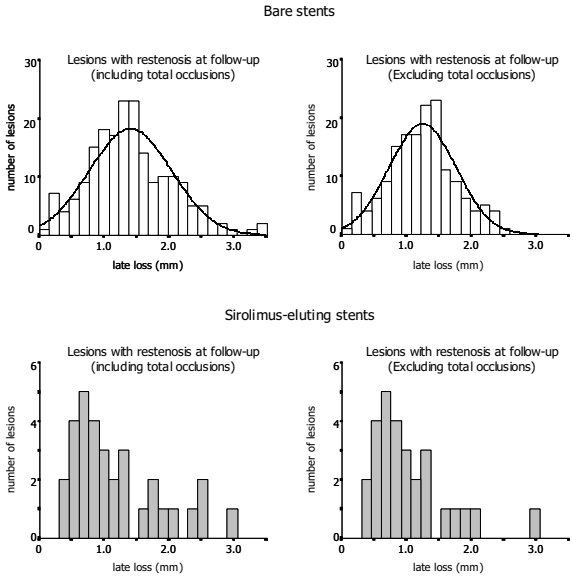

Figure 2. Frequency distribution of late loss for all lesions with restenosis at follow-up (right) and for lesions with restenosis excluding total occlusions (left). Graphs for the bare stent group are shown in the upper panels and and for the sirolimus group in the lower panel. The superimposed curves represents the normal probability function based on the mean and variance of the data. P=0.1 by Kolmogorov-Smirnov test for all restenotic bare stents and P=0.5 for restenotic bare stents excluding total occlusions.

The frequency of late loss values of restenotic lesions among controls (26.0% of lesions; mean late loss: 1.40±0.64 mm) followed a bell-shaped format with a tendency to deviate from normality, although not reaching statistical significance (p=0.1 by Kolmogorov-Smirnov test for normality) (Figure 2), while the late loss of lesions with binary angiographic restenosis after SES implantation (7.9% of lesions) had a mean late loss of 1.16±0.76 mm (p=0.02 vs. bare stents) and presented an uncharacteristic distribution pattern (Figure 2). Due to the fact that lesions presenting with total occlusions at follow-up (TIMI flow 0 or I) may be associated with distinct physiopathological processes of lumen renarrowing (e.g. thrombosis instead of progressive neointimal proliferation),[7] and due to the low incidence of late total

occlusions in both groups (sirolimus: 0.9% vs. bare stent: 4.1%; p<0.01), restenotic lesions were also analysed after exclusion of occlusions. Amongst controls, the frequency of late loss for non-occluded restenotic lesions presented a bell-shaped format resembling a normal distribution (p=0.5 by Kolmogorov-Smirnov test for normality) with an average lumen loss of 1.24±0.52 mm (Figure 2). In the sirolimus group, non-occluded restenosis presented an uncharacteristic distribution pattern (mean late loss: 0.96±0.64 mm; p<0.01 vs. bare stents) (Figure 2).

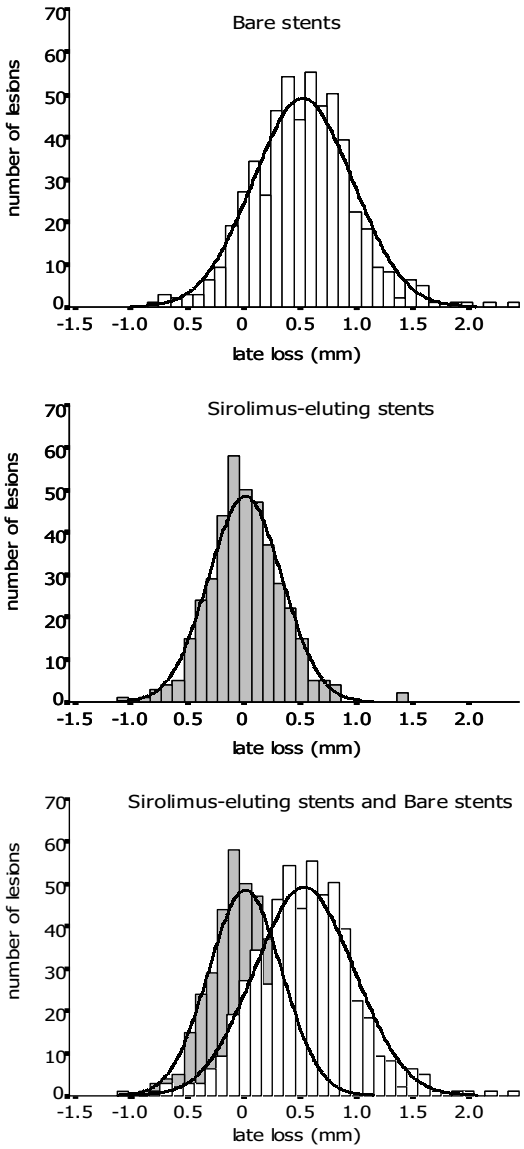

Figure 3. Frequency distribution of late loss for non-restenotic lesions in the bare stent group (upper panel) and in the sirolimus group (mid panel). The lower panel shows both stent types together. The superimposed curves represents the normal probability function based on the mean and variance of the data. P=0.3 by Kolmogorov-Smirnov test for bare stents and P=0.5 for sirolimus-eluting stents.

Non-restenotic lesions in the bare stent group presented a frequency distribution of late loss close to normality (p=0.3 by Kolmogorov-Smirnov test for normality), with an average late loss of 0.58±0.44 mm (Figure 3). However, non-restenotic lesions in SES presented a mean late loss close to zero (-0.05 mm with a standard deviation of 0.33 mm) and a frequency distribution also close to normality (p=0.5 by Kolmogorov-Smirnov test for normality) (Figure 3).

Repeatability of Measurements

Previous studies from our institution have evaluated the repeatability of quantitative angiographic measurements from acquisitions performed at the beginning and at the end of the catheterization (i.e. images were acquired within an interval of some minutes, but the X-ray system had to be repositioned to the same projection after being moved to acquire other views).[16,19] The average difference between both measurements was reported to be 0.03 mm (medium-term repeatability accuracy) with a standard deviation of 0.18 mm (medium-term repeatability precision).[16,19] The calculations performed to assess accuracy and precision in this context are the same as those used for late loss and its standard deviation respectively. Interestingly, the late loss and standard deviation of lesions without binary restenosis in the sirolimus group (and not in the bare stent group) were similar to the accuracy and precision of repeated measurements of the same vessel segment. These findings suggest that the values of late loss for lesions with no restenosis after SES implantation may potentially reflect solely the variability of repeated measurements, with a minimal (or absent) component due to actual neointimal accumulation (or vessel enlargement). Conversely, even when not classified as restenotic according to binary criteria, lesions treated with bare stents did present some extent of luminal loss, implying that mild neointimal proliferation may be present also in non-restenotic lesions after conventional stenting.

In order to further evaluate this concept, we analyzed in our patients the intra-procedural measurement repeatability of a random sample of 30 vessel segments not related to the target lesion. In this analysis, the selected segments were measured in the same projection at the beginning and at the end of the index procedure; all paired measurements were done blindly, without knowledge of the matched values. The vessel diameters differed between baseline and the end of the procedure by -0.02 mm (95% CI: -0,59 – 0,56 mm) (repeatability accuracy) with a standard deviation of 0.29 mm (repeatability precision). The corresponding Bland and Altman plot is depicted in Figure 4. For comparison, the Bland and Altman plot is also shown for late loss (difference in diameters after stenting and at follow-up) of lesions without restenosis in the sirolimus group (late loss -0.05 mm; 95% CI: -0.69 – 0.59 mm) and in the bare stent group (late loss 0.58 mm; 95% CI: -0.28 – 1.45 mm) (Figure 4). The resemblance between the analyses for repeated measurements and late loss in the sirolimus stents was evident and clearly differed from the graph for bare stents. In addition, the regression lines of difference on average (and respective R square values) are shown, and demonstrate a strikingly similar behavior of the values through the range for the repeated measurements and the sirolimus group.

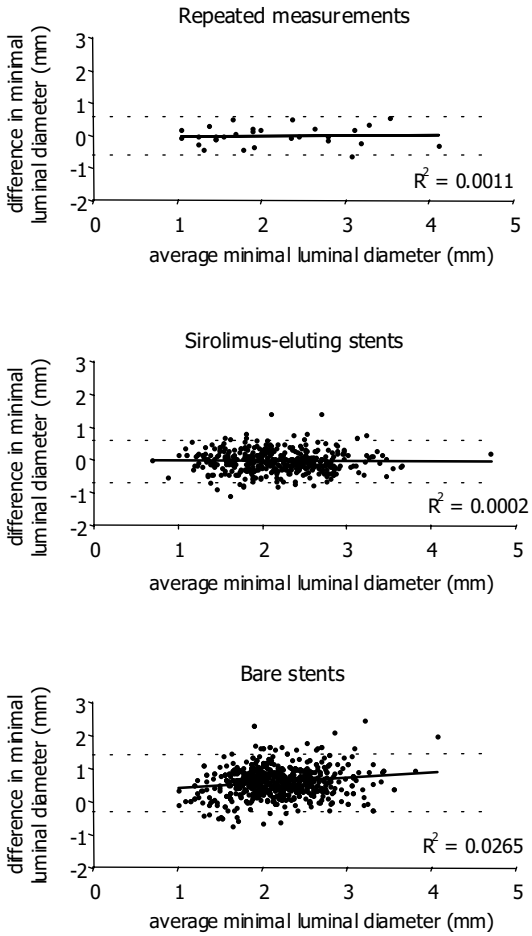

Figure 4. Bland and Altman plots. Measurement repeatability of luminal diameters at the beginning and at the end of the index procedure (same projection) of a random sample of 30 vessel segments (upper panel); difference in minimal luminal diameters after stenting and at follow-up ("late loss") for lesions without restenosis in the sirolimus group (mid panel) and in the bare stent group (lower panel).

Multivariate Estimates of Late Loss

In order to correct for baseline and procedural differences between the sirolimus and bare stent groups, we performed a multivariate analysis to estimate the value of late loss after adjustment for potential confounders. Estimates of late lumen loss for patients treated with bare stents or SES are shown in Table 2. Restenotic lesions had a comparable estimated late lumen loss whether occurring in bare stents (1.26 mm; 95% CI: 1.15 – 1.36 mm) or in SES (1.32 mm; 95% CI: 1.14 – 1.51 mm) (p-value for the effect of stent type=0.7), even after exclusion of late total occlusions. Adjusted estimates for non-restenotic lesions, however, have shown a different behavior for bare stents and SES. While non-restenotic bare stents had a predicted late loss of 0.58 mm (95% CI: 0.52 – 0.65 mm), the predicted late luminal loss of SES without restenosis was around zero (-0.04 mm; 95% CI: -0.10 – 0.02) (p-value for the effect of stent type<0.01).

Discussion

The present study shows that the pattern of angiographic late lumen loss after sirolimus-eluting stent implantation follows a peculiar behavior, which differed from lesions treated with conventional stents. The distribution of late loss of sirolimus stents appeared largely skewed to the right (i.e. most late loss tended towards smaller values), which could merely represent a distinct feature explained by an unusual statistical distribution. Nevertheless, the possibility of a biological all-or-none response of restenosis following sirolimus-eluting stent implantation remains to be investigated. Substantial luminal renarrowing occurred in a minority of lesions diagnosed as restenotic, according to binary definitions. In most patients, however, luminal dimensions were maintained, with zero late loss at follow-up. In the latter group, eventual differences in luminal measurements between post-stenting and follow-up resembled variations expected to occur in repeated angiographic measurements. This pattern of late angiographic outcome differed from that observed after bare stent implantation. After conventional stenting, the late loss of non-restenotic lesions in bare stents (adjusted estimate 0.58 mm) was significantly higher than in non-restenotic sirolimus stents, which predicted late loss was maintaned close to zero.

It has been reported that some degree of late loss occurs even for non-restenotic lesions after percutaneous interventions with bare stents.[1,7] In a previous study with conventional stenting, Schomig et al. have shown that lesions in the lower range of lumen renarrowing still presented a late lumen loss of approximately 0.5 mm,[7] a figure similar to that observed in our control group. Sirolimus-eluting stent implantation, however, has been shown in our series to virtually abolish neointimal formation in non-restenotic lesions. The elimination of neointima creates a peculiar scenario, in which the angiograms of non-restenotic lesions obtained immediately post-procedure and at follow-up are usually indistinguishable. In this context, the measurements performed to calculate the late loss (i.e. the difference in luminal diameters between both angiograms) actually mimic repeated measurements of the "same" angiogram, a fact that is readily appreciated by the average "late loss" of almost zero. Moreover, the standard deviation of late loss measurements (0.3 mm) represent the normal fluctuations of repeated measurements performed in the same segment. Interestingly, similar findings were observed in the FIM and RAVEL studies, where all cases were free of restenosis. In the FIM study,[8] "late loss" was 0.16±0.3 mm (slow release formulation), while in the RAVEL trial "late loss" was reported to be -0.01±0.33 mm.[9,10]

Table 2. Multivariable estimates of late loss for bare stents or sirolimus-eluting stents.*

	Estimated late loss (mm)	95% CI	p-value for the effect of stent type	model R^2
Overal population			<0.01	0.44
Bare stents	0.76	0.68 – 0.84		
SES	0.11	0.02 – 0.19		
Lesions with restenosis at follow-up (including total occlusions)			0.7	0.64
Bare stents	1.26	1.15 – 1.36		
SES	1.32	1.14 – 1.51		
Lesions with restenosis at follow-up (excluding total occlusions)			0.4	0.81
Bare stents	1.17	1.09 – 1.24		
SES	1.20	1.06 – 1.34		
Lesions without restenosis at follow-up			<0.01	0.55
Bare stents	0.58	0.52 – 0.65		
SES	-0.04	-0.10 – 0.02		

*adjusted for the following variables: gender, diabetes, acute coronary syndromes, vessel treated, reference diameter, lesion length, and post-procedural minimal luminal diameter

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Our results may underscore the importance of locally occurring mechanisms in the pathophysiology of post-SES restenosis. Indeed, preliminary reports have shown that restenosis after SES implantation is associated with a variety of lesion- and stent-related conditions.[12,20] Identification of the role of specific local conditions on restenosis after SES is likely to lead to technical modifications or device improvements in an attempt to further reduce the restenosis rate.

It is noteworthy that due to the relatively limited number of patients treated with sirolimus stents in the present study, it is not possible to rule out that systemic or patient-based factors may induce, in rare cases, some extent of mild neointimal proliferation even in the absence of restenosis. Obviously, apart from factors influencing the mechanisms involved in the vascular healing process, the presence of an intrinsic resistance to sirolimus may reduce the efficacy of the drug in inhibiting neointimal growth. However, the clinical relevance of this is still to be clarified.

In addition, due to the low incidence of lesions presenting actual luminal renarrowing after SES implantation, it was not possible to identify the distribution pattern of late loss in this group of lesions. Because of this, lesions were separated into two groups according to the usual cutoff definition of binary restenosis and further analyses with increased number of lesions are warranted to validate the present results. A higher rate of angiographic follow-up would be desirable to fully evaluate the angiographic outcomes.[4] However, the present study enrolled a unique cohort of unselected patients with complex procedures, which differs from patients usually included in randomized trials and may limit the compliance for angiographic re-study. Moreover, the non-randomized nature of our study with SES precluded the inclusion of an unbiased control group. However, this limitation was partially overcome by the comparison of patients treated with sirolimus stents with patients treated with conventional stents enrolled in a recent multicenter trial.

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Chapter 26 Post-Sirolimus-Eluting Stent Restenosis Treated With Repeat Percutaneous Intervention: Late Angiographic and Clinical Outcomes

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Background: We evaluated the clinical and angiographic outcomes of patients with restenosis after sirolimus-eluting stent (SES) implantation undergoing treatment with repeat percutaneous intervention.
Methods and Results: A total of 24 consecutive patients (3.8% of patients receiving SES in the period) have undergone repeat percutaneous intervention to treat post-SES restenosis (27 lesions). Diabetes was present in 46% and SES was implanted at the index procedure to treat a *de novo* lesion in 70%. On average 1.9 ± 1.2 SES were implanted at the initial intervention with a mean stented length of 41.2 ± 27.0 mm. Post-SES restenosis was located within the stent in 93% of lesions. An apparent mechanical cause could be identified in 44%. From the 27 lesions, 1 (4%) was re-treated with a bare stent, 3 (11%) with balloon dilatation, and the remaining 23 lesions (85%) with repeat drug-eluting stent implantation (SES in 12 lesions [44%] and paclitaxel-eluting stents in 11 lesions [41%]). The event-free survival rate was 75.0% after 487 ± 42 days from the index procedure (269 ± 68 days from the post-SES treatment). The overall recurrent restenosis rate was 40%. The recurrent restenosis rate of lesions re-treated with drug-eluting stents was 29.4%.
Conclusions: Our findings show that the treatment of post-SES restenosis is currently suboptimal and warrants further investigation.

Submitted for publication

Introduction

Sirolimus-eluting stents (SES) have recently proven effective in reducing restenosis and the need for repeat revascularization compared to conventional stenting.[1-4] Nonetheless, post-SES restenosis still occurs in a small proportion of patients, with repeat revascularization procedures being required in up to 5% of patients.[1-4] However, the best therapeutic approach for patients presenting with restenosis after SES implantation is currently unknown. The present study aimed, therefore, to evaluate the clinical and angiographic outcomes of patients undergoing repeat percutaneous intervention to treat post-SES restenosis.

Methods

Since April 2002, our institution has adopted a policy of utilizing drug-eluting stents as the device of choice for all patients treated with percutaneous intervention, as described elsewhere.[1] Until October 2003, 631 consecutive patients have received at least one sirolimus-eluting stent (79% of all patients treated in the period). From these, a total of 24 consecutive patients (3.8%) have undergone repeat percutaneous intervention for post-SES eluting stent restenosis (27 lesions) and comprise the present study population. Post-sirolimus eluting stent restenosis was defined as a significant luminal stenosis (> 50% diameter stenosis by quantitative coronary angiography) located within the stent or in its 5-mm proximal or distal segments, identified at an angiogram performed > 3 months after the index procedure.

Patients were treated preferably with repeat implantation of drug-eluting stents, according to our policy, as explained above. Sirolimus-eluting stents were available up until March 2003, since then paclitaxel-eluting stents have been utilized as the default drug-eluting stent at our hospital. Nevertheless, the final interventional strategy was entirely left at the discretion of the operator. All patients receiving repeat drug-eluting stent implantation were maintained on lifelong aspirin and clopidogrel for at least 3 months.

Patients were followed-up to assess the incidence of major cardiac adverse events, defined as all-cause death, non-fatal myocardial infarction (> 2X creatine kinase increase with an increased creatine kinase-MB), or repeat target lesion revascularization (re-intervention to treat a significant lesion within the stented segment or in its 5-mm borders). Angiographic follow-up was obtained 6 months after the treatment of post-SES restenosis to evaluate the incidence of recurrent restenosis (> 50% diameter stenosis).

Results

Overall, patients frequently had diabetes (46%) and none had received SES during the acute phase of a myocardial infarction Table 1. The right coronary artery was treated in approximately half the lesions (44%) and SES were implanted at the index procedure to treat a *de novo* lesion in 70%. In-stent restenosis or failed brachytherapy lesions treated with SES at the index

procedure (26%) had complex morphologies in the majority of cases (Mehran Class III or IV 86%). The remaining lesion (4%) was a balloon restenosis. On average 1.9 ± 1.2 sirolimus-eluting stents were implanted at the initial intervention, with a mean stented length of 41.2 ± 27.0 mm.

Table 1. Patient and lesion characteristics at index procedure (n=24 patients, 27 lesions)

Age, years ± SD	61 ± 12
Male, %	71
Diabetes, %	46
Multivessel disease, %	67
Clinical presentation at index procedure	
Stable angina, %	88
Unstable angina, %	12
Treated vessel	
Right coronary artery, %	44
Left anterior descending, %	26
Left circumflex, %	15
Left main coronary, %	4
Saphenous vein graft, %	11
Ostial location, %	30
Chronic total occlusion (>1 month), %	26
Lesion type at the index procedure	
De novo lesion, %	70
Balloon restenosis, %	4
In-stent restenosis, %	15
Post-brachytherapy restenosis, %	11
Mehran Classification at the index procedure*	
Type I or II, %	14
Type III, %	43
Type IV, %	43
Number of SES implanted at the index procedure, ± SD	1.9 ± 1.2
Total length of SES implanted at the index procedure, mm ± SD	41.2 ± 27.0

SES=sirolimus-eluting stents
* Related to in-stent restenosis or post-brachytherapy restenosis at the index procedure (N=7)

Table 2. Post-SES restenosis angiographic characteristics (n=27)

Post-SES restenosis location	
In-stent, %	93
Proximal edge, %	4
Distal edge, %	4
Possible cause of post-SES *	
Ostial location, %	30
Gap or fracture between SES, %	11
Trauma outside the stent / residual dissection, %	7
Stent underexpansion, %	7
No apparent cause, %	56
Lesion length of post-SES restenosis, mm ± SD	12.8 ± 9.9
Treatment of the post-SES restenosis	
Balloon dilatation, %	11
Bare stent implantation, %	4
Repeat SES implantation, %	44
Paclitaxel-eluting stent implantation, %	41
Total length of repeat stent implantation, mm ± SD †	21.5 ± 15.8

SES=sirolimus-eluting stents
* Categories not mutually exclusive (intravascular ultrasound examination available for 18 lesions [67%])
† Related only to lesions treated with repeat stent implantation (n=24 lesions)

Lesion characteristics of post-SES restenosis are summarized in Table 2. In most cases, the restenosis was located within the stented portion (93%). In the majority of cases, post-SES restenosis occurred without an apparent mechanical cause (56%), as evaluated by angiography and intravascular ultrasound (the latter available for 67%). The mean length of post-SES restenotic lesions was 12.8 ± 9.9 mm; 14 lesions (52%) were short (<10 mm long), 5 lesions (19%) were multi-focal, 7 lesions (26%) were > 10-mm long, and 1 lesion (4%) presented as total vessel occlusion.

Of the 27 post-SES restenotic lesions, 3 (11%) were treated with balloon dilatation in small segments not considered suitable for repeat stenting, and 1 lesion (4%) in a large saphenous graft was treated with a PTFE-covered stent. For the remaining 23 post-SES restenoses (85%), repeat drug-eluting stent implantation was chosen as the therapeutic strategy. Sirolimus-eluting stents were implanted in 12 lesions (44%) (patients treated up to March 2003) and paclitaxel-eluting stents were used for 11 lesions (41%) (patients treated since March 2003). For lesions treated with repeat stent implantation, the stented length was significantly shorter in the repeat procedure than in the index procedure (21.5 ± 15.8 mm vs. 42.6 ± 26.9 mm respectively; $p<0.01$).

Complete clinical follow-up was available for all patients at an average of 487 ± 42 days from the index procedure (269 ± 68 days from the post-SES treatment). A 78-year old patient died 412 days after the index procedure (209 days after post-SES restenosis treatment) due to pneumonia and progressive heart failure. There were no myocardial infarctions during the follow-up period. Target lesion revascularization was required in 5 patients (20.8%) after the treatment of post-SES restenosis due to recurrent restenosis. Overall, the event-free survival rate was 75.0%.

Angiographic follow-up was obtained for 17 patients with 20 lesions (71% of patients, 74% of lesions) at 271 ± 49 days. Overall, there were 8 lesions (40%) with recurrent restenosis after percutaneous treatment of post-SES restenosis (Table 3). In 2 of these cases (10%), the target vessel was totally occluded in its proximal portion at the follow-up angiogram, precluding direct assessment of the treated site (mid/distal vessel in both cases). There was no clinical evidence of sudden thrombotic occlusion during the follow-up and both lesions were classified as recurrent restenosis. The recurrent restenosis rate of 17 lesions re-treated with drug-eluting stents was 29.4%, with no major differences between sirolimus- or paclitaxel-eluting stents (33.3% vs. 25.0% respectively) (Table 4).

Discussion

The main finding of the present study was that, although post-sirolimus-eluting stent restenosis occurred as an infrequent event, its treatment with repeat percutaneous intervention was associated with relatively high rates of recurrent restenosis. Repeat drug- (sirolimus or paclitaxel) eluting stent implantation, the most frequent treatment used in our series, appeared to be safe, with no documented complications related to re-exposure to local antiproliferative agents. However, the overall recurrence of restenosis after repeat drug-eluting stent implantation was 29.4%.

Table 3. Quantitative Coronary Analysis of Post-SES restenosis lesions treated with percutaneous intervention*

	Reference diameter, mm	Minimal luminal diameter, mm	Diameter stenosis, %	Lesion length, mm	Late loss, mm	Restenosis rate, %
Baseline at index procedure	2.57 ± 0.57	0.49 ± 0.40	79.3 ± 16.6	18.0 ± 12.9	…	…
After index SES implantation	…	2.11 ± 0.46	16.6 ± 10.1	…	…	…
Post-SES restenosis	…	0.76 ± 0.45	72.8 ± 14.0	12.8 ± 9.9	…	…
After treatment of post-SES restenosis	…	2.26 ± 0.60	17.6 ± 16.2	…	…	…
Late angiographic follow-up	…	1.49 ± 1.07	49.1 ± 32.7	10.8 ± 17.8	0.77 ± 0.96	40.0

Number are mean ± SD; SES=sirolimus-eluting stents
* Related to 20 lesions with angiographic follow-up (74% of eligible)

Our results may underscore the complex nature of lesions presenting with restenosis after initial SES implantation. The underlying processes associated with post-SES restenosis are currently unknown, which limits the development of more effective therapeutic approaches. Previous observations have shown that local features may play an important role in post-SES restenosis.[5,6] Interestingly, the identification of a presumed contributing factor (based on procedural and intravascular ultrasound findings) did not influence the outcomes after re-treatment in our series; the recurrence restenosis rate in this subset was still 37.5%. One may speculate whether forms of constitutional or acquired cellular mechanisms leading to drug resistance may influence the recurrence of post-SES restenosis.[7] It is worth noting that the recurrent rates were at least 25% across several subsets, including some lesion types that have been traditionally considered to have a benign prognosis for in-stent restenosis (e.g. short restenotic lesions).

Table 4. Subset analysis - restenosis recurrence after repeat percutaneous intervention for post-SES restenosis *

Subgroup	Recurrent restenosis rate (%)
De novo lesion at index procedure (n=13)	30.8
Restenotic lesion at index procedure (n=7)	57.1
Ostial location (n=6 lesions)	33.3
Non-ostial location (n=14 lesions)	42.9
Short (<10mm) post-SES restenosis (n=11)	36.4
Multifocal or long (>10mm) post-SES restenosis (n=9)	44.4
Post-SES with possible known cause (n=8)	37.5
Post-SES with no apparent cause (n=12)	41.7
Post-SES treated with drug-eluting stent implantation (n=17)	29.4
Post-SES treated with sirolimus-eluting stent implantation (n=9)	33.3
Post-SES treated with paclitaxel-eluting stent implantation (n=8)	25.0
Post-SES treated with balloon dilatation or bare metal stent implantation (n=3)	100.0

SES = sirolimus-eluting stent
* Related to 20 lesions with angiographic follow-up (74% of eligible)

The present study has several limitations related to its small sample size, its non-randomized, observational design, and the heterogeneity of the study population. Nevertheless, our findings have shown that the treatment of this new medical condition, namely post-SES restenosis, is currently suboptimal and warrants further investigation.

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Chapter 27 One-Year Cost-Effectiveness Of Sirolimus-Eluting Stents as Compared To Bare Metal Stents In The Treatment Of Single Native *De Novo* Coronary Lesions

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Submitted for publication

One-Year Cost-Effectiveness Of Sirolimus-Eluting Stents as Compared To Bare Metal Stents In The Treatment Of Single Native *De Novo* Coronary Lesions

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Aims - To assess the balance between costs and effects of the sirolimus-eluting stent in the treatment of single native *de novo* coronary lesions in the RAVEL study.
Methods and results – In total, 238 patients with single, de novo lesions were randomised to percutaneous coronary intervention with sirolimus-eluting stents or conventional bare stents. Patients were followed-up to 1 year and the treatment effects were expressed as 1 year survival free of major cardiac events (MACE). Costs were estimated as the product of resource utilization and Dutch unit costs. At 1 year, the absolute difference in MACE free survival was 23% in favour of the sirolimus-eluting stent group. At the index procedure, sirolimus-eluting stent implantation had an estimated additional procedural cost of € 1,286. At 1 year, however, the estimated additional cost difference has decreased to € 54 due to the reduction in the need for repeat revascularisations in the sirolimus group (0.8% vs. 23.6%; $p<0.01$). After adjustment of actual results for the consequences of angiographic follow-up (correction based on data from the BENESTENT II study), the difference in MACE-free survival was estimated at 11.1% and the additional 1-year costs at € 166.
Conclusion – The 1-year data from RAVEL suggest an attractive balance between costs and effects for the sirolimus-eluting stents in the treatment of single native *de novo* coronary lesions. The cost effectiveness of drug-eluting stents in more complex lesion subsets remains to be determined.

Submitted for publication

Introduction

Sirolimus-eluting stents have been recently proven to markedly reduce coronary restenosis and the need for subsequent revascularisation compared to conventional stenting.[1-3] Sirolimus-eluting stents have been available for routine use since April 2002 in Europe and since April 2003 in the USA. Due to the clear clinical superiority of these devices, it would be expected that clinicians would want to use the new stent as extensively as possible. However, sirolimus stents have been commercialised with a high price relative to conventional bare stents, which may increase up-front procedural costs and has been perceived as an important limitation for a more widespread utilization of these devices in the clinical practice. On the other hand, the reduction of repeat intervention procedures during follow-up may be cost saving, which may eventually lower total costs. Therefore, in the current era of cost containment policies, the question arises as to how the additional effects compare to the additional costs.

The present study addresses this question for patients included in the RAVEL study. It is important to note that the RAVEL study included a protocol-mandated angiogram scheduled at 5-7 months of follow-up.[1] It is known from the BElgium NEtherlands STENT II (BENESTENT II) study that this policy may bias both cost and effectiveness estimates of the treatments, when compared to patients without routine angiographic follow-up.[4] Since routine angiographic follow-up is not standard practice in the "daily life" of most centers, the question needs to be raised of whether the results would differ if angiographic follow-up had not been performed. This issue was addressed in this manuscript by an analysis that combines estimates of costs and effects from the RAVEL study (comparing drug-eluting with bare stents) with estimates of the effect of angiographic follow-up from the BENESTENT II study (comparing results with and without scheduled angiographic follow-up).

Material and methods

The study protocol and main findings of the RAVEL study have been detailed elsewhere.[1] In brief, the RAVEL was a randomised, double-blind study of 238 patients with diagnosis of stable or unstable angina scheduled to treat a single *de novo* target lesion in a native coronary vessel. Patients were treated with either a bare metal Bx VELOCITY stent (Cordis Corp, Johnson & Johnson) or a similar sirolimus-eluting Bx VELOCITY stent. Both stents were indistinguishable, except under microscopy. At 30 days, 6 and 12 months, patients returned for evaluation- and were specifically questioned to identify the possible interim development of angina, as well as to monitor major adverse cardiac events including additional revascularisation of the index target lesion. Diagnostic angiography was performed at 180±30 days or preceding a re-intervention. The decision to perform a re-intervention was left to the investigator's discretion, but he was asked to register whether it was based on clinical symptoms or guided by angiographic results.

Cost-effectiveness

Effectiveness was assessed by using the composite of 12-month major adverse cardiac events (MACE), which

included all-cause death, non-fatal myocardial infarction, and target lesion revascularisation (either surgical or percutaneous). With respect to costs, the analysis was limited to the direct medical costs. The balance between costs and effects after 12 months was assessed by computing the incremental cost-effectiveness ratio (the average 1-year costs per patient treated with drug-eluting stents minus the average 1-year costs with bare stent implantation divided by the percentage change in MACE-free survivors after 1 year).

For cost-effectiveness, two scenarios were investigated. The first scenario reflects the actual protocol-driven resource use and effectiveness observed in the RAVEL study (which included a 6-month angiogram). For the estimation of the costs and effects of this scenario, similar methods were used as in the assessments of costs and effects in the BENESTENT II study,[4] the DEBATE II study,[5] and the ARTS trial.[6] Resource use data were collected from the case record form for the initial procedure (number of balloons, type and number of stents, type and number of catheters, etc.), hospital admissions (coronary care unit, intensive care unit, conventional ward), and major therapeutic and diagnostic procedures after the initial procedure. Unit costs were estimated, before the analysis of the data, on the basis of detailed information from the Erasmus Medical Center, Rotterdam, The Netherlands, following a similar approach as reported previously.[7] Costs per patient were calculated as the product of each patient's resource utilization and the corresponding unit cost. Information about the price of the sirolimus-eluting stent as well as the bare stent was obtained from the manufacturing company. In both arms, the medication costs include those of eight weeks of anti-platelet therapy.

The second scenario excludes follow-up angiography as a standard procedure. The rationale for this approach is to exclude the effect of the so-called "oculo-stenotic reflex", which may increase the incidence of repeat intervention in patients undergoing protocol-mandated angiographic re-evaluation.[4,8] It is noteworthy that the information collected at the time of the repeat revascularisations on whether the new intervention was driven by angina was indicative of the effect of angiographic follow-up. However, these records were not informative of the impact of follow-up angiograms on the number of angiographies and repeat procedures that would have taken place before and after 5-7 months. It is expected that some of the procedures performed during the follow-up visit would normally have been carried out either in the months before or after the protocol-driven angiogram. With respect to the angiograms and interventions that would have been performed *before* the pre-specified time-point, it is expected that these were postponed knowing that angiograms were already scheduled at the 5-7 month follow-up. One would therefore expect a *lower* revascularisation rate before a pre-specified angiographic follow-up than would have been the case without such a specification. Conversely, if there is a pre-specified angiogram, there may be less need for later angiography and for late repeat procedures than without angiographic follow-up.

In the BENESTENT II study,[4] which compared balloon angioplasty with stenting, a one-to-one sub-randomisation was carried out assigning the patients either to clinical follow-up alone (409 patients) or to angiographic and clinical follow-up (418 patients). So, half of the BENESTENT II study had the same design as the RAVEL study, with pre-specified angiographic follow-up, and the other half had the design without such follow-up, as it is preferred for the purpose of a cost-effectiveness analysis. In the BENESTENT II, with angiographic follow-up, the percentage of patients with repeat revascularisations were 18.27% (stenting) versus 22,28% (balloon). Without angiographic follow-up, the percentages of repeat revascularisations were 7,77% versus 16,26% respectively. With angiographic follow-up, the percentage of patients with unscheduled angiograms was 8,17% versus 12,86% (with and without stenting). Without angiographic follow-up the percentages of unscheduled angiograms were 14,08% versus 20,20%. So, on average, the inclusion of angiographic follow-up increased the number of repeat revascularisations with a factor 1.6 and decreased the number of unscheduled angiograms with a factor 0.6. As such the data from the BENESTENT II offer a source for estimating the effect of angiographic follow-up on both the occurrence of angiograms and repeat interventions. Moreover, it also offers information about the timing of these procedures.

To estimate the effects of angiographic follow-up on treatment, the time after the initial procedure was divided into three periods: 1) from the index procedure to month 5; 2) from month 5 to month 7; and 3) from month 7 to month 12. For each period, estimates were made of the rate of non-scheduled angiographies and repeat-revascularisation. Differences were estimated in terms of relative risk ratios and those significantly different from 1.0 were included in the analysis. Subsequently, estimates of patients free of repeat revascularisations were obtained by multiplying the number of repeat revascularisations observed in RAVEL with the relative risk ratios derived from BENESTENT for all three periods. Finally, estimates of average MACE-free survival were obtained by multiplying the revascularisation rate times the relative risk scores in those patients who only had repeat revascularisations. Patients who died or had a myocardial infarction were counted as having had an event.

A similar procedure was followed with respect to costs. For this analysis, estimates were needed of the costs associated with a repeat procedure and the costs of an angiogram, not only of the procedure itself but also of the additional costs associated with these procedures. Estimates of these costs were obtained by using the data from the RAVEL study and applying a linear regression analysis with costs as the dependent variable and the various events as independent variables. It was noted that the resulting cost estimates were not just the cost of the procedure but that they had to be interpreted as the additional costs associated with the treatment of a patient who undergoes such procedures. Total costs were corrected on the basis of the increase in the expected numbers of non-scheduled angiograms and the expected decrease in the number of repeat revascularisations.

Statistical analysis

All analyses were based on the intention-to-treat principle. In estimating the risk ratios from BENESTENT II,

an assessment was made on whether these relative risks differed between the randomised treatments (stent or balloon) by testing for differences in the log transformed risk ratios. In case that the hypothesis of a similar effect could not be rejected (95% significance), data from both procedures were pooled to estimate the relative risks. A correction for the number of angiograms and repeat procedures was made when the risk ratios differed (95% significance) from one.

With respect to the scenario assuming angiographic follow-up, cost effectiveness was expressed in terms of probability ellipses using Fieller's approach, which was used to estimate the upper 95% limit of the cost-effectiveness ratio.[9]

With respect to the scenario assuming no angiographic follow-up, the uncertainties surrounding the estimate were addressed by a combination of bootstrapping and multivariate sensitivity analysis. Bootstrapping means that one simulates a number of new trials, say 1,000, of exactly the same size of the original trial. One does so by drawing patients at random (with replacement) from the original trial. Each bootstrap leads to a new estimate of average costs and average effects. The resulting 1,000 estimates can be summarized in terms of a distribution and by truncating the upper and lower 2,5% one obtains estimates of the 95% confidence intervals. This is very convenient method when the distribution cannot be obtained in a classical way.[10]

Table 1. Costs Associated with Observed Resource Use

	Sirolimus stent (N=120)	Bare stent (N=118)	Unit Cost (€)	Sirolimus stent (N=120)	Bare stent (N=118)	Differen.
	resource use per patient			cost (€)		cost (€)
Index procedure						
Procedure time (in minutes)	70.8	70.6	18	1,288	1,285	3
Study stent	1.03	1.02	2,000/672	2,050	683	1,367
Other stent type	0.02	0.03	712	12	24	-12
Guiding Catheter	1.10	1.07	98	107	104	3
Guidewire	1.08	1.04	115	124	120	4
Balloon	1.32	1.37	491	646	674	-28
Doppler	0.03	0.06	523	13	31	-18
IVUS Catheter	0.23	0.29	614	143	177	-34
Contrast medium	192.08	200.18	1	98	102	-4
Procedure related medication				67	63	-4
CCU days	0.30	0.26	963	289	252	37
ICU days	0.29	0.29	1058	307	305	2
Non-CCU/ICU days	2.12	2.24	343	727	768	-41
Total procedure costs				5,872	4,588	1,284
Follow-up						
Re-PTCA (target and non target)	0.03	0.31		107	908	-800
CABG (target and non target)	0.01	0.01	7,448	62	126	-64
Transfusion	0.01	0.01	60	1	1	0
Vascular surgery	0.01	0.02	4,341	36	74	-37
Non-scheduled angiographies	0.08	0.10	2,160	180	220	-40
Protocol angiographies	0.90	0.74	2,160	1,944	1,592	351
Emergency room visit	0.15	0.12	44	7	5	1
Observation unit <24 hrs adm.	0.02	0.20	193	3	39	-36
Outpatient rehabilitation	0.08	0.18	23	2	4	-2
CCU days	0.17	0.64	963	161	612	-452
ICU days	0.14	0.11	1,058	151	117	35
Non-CCU/ICU days	2.15	2.50	343	737	858	-121
Rehabilitation	0.24	0.37	343	83	128	-45
Total follow up costs				3,473	4,683	-1,210
Total direct medical cost (excluding medication)				9,345	9,271	74
Medication				624	644	-20
Total direct medical cost (including medication)				9,969	9,915	54

Results

In total, 120 patients were randomised to sirolimus-eluting-stent implantation, and 118 patients to bare metal stents. With the exception of a higher percentage of men in the control arm, the two groups had similar baseline and procedural characteristics. At 1 year, the sirolimus and bare stent group had similar mortality (1.7% vs. 1.7% respectively) and myocardial infarction rates (3.3% vs. 4.2% respectively). The 1-year incidence of MACE was significantly reduced in the active group compared to the controls (5.8% vs. 28.8%; p<0.01 by log-rank test), mainly due to a marked decrease in the need for repeat revascularisation in the sirolimus group (0% vs. 22.9%; p<0.01). Table 1 presents the estimates of costs after one year. It appears that the additional costs of the initial procedure are almost completely recouped by the decrease in the costs of follow-up. Using the observed event rates and overall costs in RAVEL, without correcting for the impact of protocol-mandated follow-up angiograms, at the end of the first year the total costs are estimated to be only €54 per patient higher in the sirolimus-eluting stent group, compared to the bare stent group. Costs per MACE-free survivor are estimated at €234 with an upper 95% limit of €5,679.

When considering the results in Table 1 it may be noted that the costs of the scheduled angiograms are higher in the sirolimus-group than in the bare stent group (which is related to the higher number of patients with repeat procedures in the bare stent group). This might suggest that without such follow-up, the costs of the initial procedure would have been completely recouped. However, that would neglect the effect of the "oculo-stenotic reflex" since the difference in repeat percutaneous revascularisation procedures between the 2 groups suggest that such a reflex may have had an effect on the costs and the outcomes.

Table 2 summarizes the frequency of non-scheduled angiograms and repeat revascularisation procedures in patients with and without protocol-mandated follow-up angiography in BENESTENT II trial.[4] The need for non-scheduled angiography in each group is depicted according to the time of its occurrence, either before, during, or after the period in which follow-up angiograms were scheduled. There were no significant differences in the relative risk ratios for non-scheduled angiography in the stent and balloon arms in BENESTENT II. As shown in Table 2 (pooled data of the balloon and stent groups), protocol-mandated angiographic follow-up had no significant effect on the risk of unscheduled angiography during the first five months, and no correction factor was applied for this period. However, between 5 and 7 months (period of the scheduled angiography), patients with no protocol-mandated angiography had significantly more non-scheduled angiograms (increased by a factor of 3.577) and less repeat procedures (reduced by a factor of 0.387). Also, after 7 months, the group with protocol-mandated angiography had more non-scheduled angiograms, which were accordingly corrected by a factor of 2.146. After correction of the RAVEL data according to the expected effects of angiographic follow-up, the difference in the number of repeat procedures was then estimated at 11.8% instead of 23.6%. Moreover, the difference in the number of unscheduled angiograms was estimated at 3.8% instead of 1.9%.

Table 2. Non-scheduled angiograms and repeat revascularisation in the BENESTENT II trial.[4]

	Without angiographic follow-up (Angioplasty with and without stents)	***With*** angiographic follow-up (Angioplasty with and without stents)	Relative Risk (95% C.I)
Months 1-5			
Angiograms	8.6%	7.2%	1.192 (0.747-1.904)
Repeat revascularisations	6.1%	8.9%	0.691 (0.424-1.126)
Months 6-7			
Angiograms	3.4%	1.0%	3.577 (1.187-10.776)*
Repeat revascularisations	3.4%	4.5%	0.387 (0.212-0.704)*
Month 8-12			
Angiograms	5.1%	2.4%	2.146 (1.023-4.501)*
Repeat revascularisations	2.4%	2.6%	0.929 (0.399-2.164)

Differences of log transformed risk-ratios where not statistically significant based on 95% confidence interval surrounding these differences
CI=confidence interval
* Significant risk-ratio used in RAVEL C/E model

Table 3 shows the results from the regression analyses relating the costs per patient to the costs of the initial procedure and the occurrence of all major cardiac events, other serious adverse events, as well as angiograms (r^2=0.35; F-value = 10.76; P-value (F-test)<0,0000). Applying the derived relative risks to the patient-specific data leads to the estimates of both costs and effects as presented in Table 4. Without routine angiographic follow-up the difference in costs between the sirolimus-eluting stent and the bare metal stent at 1 year was estimated to be €166. The costs per additional MACE-free survivor are now estimated to be €1,495 with an upper 95% limit of €61,243. Figure 1 presents the estimates of both cost and effects after a combination of bootstrapping and multivariate sensitivity analysis using the normal distributions surrounding the estimates of the relative risks.

Table 3. Cost Estimates Based on Multi-variate Analysis

	Cost estimate	Standard error
Initial costs	5.097	253
Additional costs of drug-eluting stent	1.360	311
Death*	1.194	1.197
Myocardial infarction	3.693	788
Coronary bypass surgery	12.147	1.316
First repeat percutaneous intervention	4.374	455
Additional repeat PCI	6.665	705
Non-scheduled angiography	3.561	538
Other serious adverse events	4.411	246

PCI=percutaneous coronary intervention
* Death was not a significant predictor

Table 4. Costs and Effects Based on Different Scenarios

	With angiographic follow-up			Without angiographic follow-up		
	Sirolimus Stent (N=120)	Bare Stent (N=118)	Difference	Sirolimus Stent (N=120)	Bare Stent (N=118)	Difference
Clinical events, %						
Death, %	1.7	1.7	0	1.7	1.7	0
Myocardial Infarction, %	3.3	5.1	-1.8	3.3	5.1	-1.8
Target lesion revascularisations, %	0.8	23.6	-22.8	0.8	11.8	-11
surgical, %	0.8	0.8	0	0.8	0.3	0.5
percutaneous, %	0.0	22.9	-22.9	0.0	11.5	-11.5
MACE Free, %	94.2 (89.9-98.4)	71.2 (62.9-79.4)	23.0 (13.7-32.2)	94.2 (88.9-97.5)	83.1 (64.2-90.9)	11.1 (1.7-28.0)
Angiography, %	8.3	10.2	-1.9	10.3	14.1	-3.8
Total direct medical cost (€)	9,969 (8,910-10,504)	9,915 (8,722-10,449)	54 (-1,054-1,296)	8,065 (7,052-9,463)	7,899 (6,821-9,591	166 (-1,376-1,487)

MACE=major adverse cardiac events

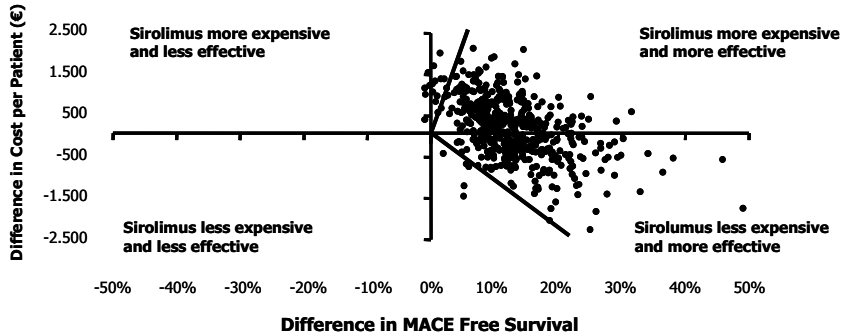
Discussion

In this report, we analysed the balance between costs and effects in the RAVEL trial, while recognising the potential increase in interventions due to the "oculo-stenotic reflex" associated with protocol-driven angiographic follow-up. Two scenarios were presented: one with scheduled angiographic follow-up, based on actual data from the RAVEL study, and the second scenario that corrected for the effect of protocol-driven angiograms. The first scenario leads to an estimated cost difference at the end of 1 year of €54 per patient, and a cost per MACE-free survivor of €234. The second scenario leads to an estimated cost difference of €166 at the end of 1 year, and a cost per MACE-free survivor of €1,495. Both point estimates seem to be well within a range of what may be considered acceptable from a societal standpoint.

These results need to be assessed in light of the study limitations. A first limitation is that the analysis is primarily based on data from the RAVEL study, which included only 238 patients with a primary endpoint of angiographic late loss at 6 months; MACE and resource utilisation were only secondary endpoints. Cost-effectiveness was not a formal endpoint, mainly because of protocol-mandated angiographic follow-up, the effect of which on outcomes was adjusted based on the BENESTENT II study. Our analysis has therefore of the costs and effects without angiographic follow-up has at least three sources of uncertainty. First, there is the limited number of observations in the RAVEL study. Second, there is the estimate of effects of the "oculo-stenotic reflex" from the BENESTENT II study; and third, there is the estimate of the costs that need to be subtracted as a result of this reflex. All these are considered in our estimate leading to an upper 95% limit of €61,243. These numbers might be even higher when considering that the patients in the BENESTENT II study differ from those in RAVEL. The fact that the difference in MACE-free survival, when one considers only the revascularisations that were labelled as being "clinically driven", was so close to that of the combined analysis suggests that this last potential source of error may have been relatively small.

An alternative approach would have been to recalculate costs and effects by excluding the events which were not "clinically driven". We decided against this approach, since it would not account for the effects of the protocol-driven angiograms on the rate of clinically-driven angiograms and on the reintervention rate before month 5 and after month 7.

The RAVEL included a relatively non-complex group of patients, admitted for single-lesion stenting (single-vessel disease in 71%) of short coronary stenosis (average lesion length 9.58 mm). How the sirolimus-eluting stent will perform in other patient populations with different risks of reintervention needs to be studied, not only in terms of efficacy but also in terms of cost-effectiveness. Moreover, the RAVEL was an international study and that no account was taken of differences in treatment patterns. Unit cost estimates were obtained from one hospital and treated as if they were not surrounded by uncertainty. It was noted that the estimated differences in costs were highly dependent on the price difference between the sirolimus stents (€ 2,000) and the bare stents (€ 672). As an example, when the price of the bare



Estimates of cost and effects after a combination of bootstrapping and multivariate sensitivity analysis using the normal distributions surrounding the estimates of the relative risks.

metal stent was set around €500, as it is in the UK, the total 1-year cost difference between both treatments was estimated at €341 instead of €166.

A final important limitation concerns the outcome of the study. Sirolimus-eluting stent implantation increased MACE-free survival, which is a combined endpoint of death, myocardial infarction, and repeat-revascularisations. In practice it may only reduce the need for revacularisations.[1-3,11] Furthermore, it may be hypothesized that the anti-restenotic effect of sirolimus stents may improve the rate of recurrent ischaemic symptoms and quality of life parameters. However, direct quality-of-life data have not been collected to demonstrate the extent of the potential benefit of sirolimus stents in this regard. As such, cost per additional MACE-free survivor may not be the optimal way of expressing the balance between costs and effects in this scenario. In addition, by calculating costs per MACE-free survivor, or costs per repeat procedure prevented, one cannot compare the results obtained to those of other health care interventions such as hip-replacements. Given the lack of comparable outcomes, one might well ask the question how much society is prepared to pay to prevent repeat intervention during the first year after the initial intervention. However, when doing so, it may be important to recognize that the burden associated with the need for a repeat intervention may not be limited to a short period of anginal pain, but also should consider increased anxiety and disability, and most notably an increased incidence of even more hospitalizations, some of which may result in repeat interventions.

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Chapter 28 Drug-Eluting Stents: Cost Versus Clinical Benefit

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Drug-Eluting Stents: Cost Versus Clinical Benefit

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INTRODUCTION

The publication in January 2001 of the First In Man results showing zero restenosis after sirolimus-eluting stent implantation produced enormous excitement in the cardiological community [1]. The long awaited tool, a safe restenosis-proof easy-to-use stent, had been found. It was not too long thereafter that paclitaxel-eluting stents also demonstrated their capability to decrease restenosis. Today both sirolimus- and paclitaxel-eluting stents have been shown in randomized trials to reduce restenosis as compared to conventional metallic stents (Figure 1) [2-6]. Most of these studies have been recently released in form of abstracts during medical meetings and are still unpublished [3-6]. In addition to sirolimus and paclitaxel, other agents have shown promising early results in recent studies, enlarging the body of evidence demonstrating the potential benefits of what are known as "drug-eluting stents".[7] Regulatory agencies have been very active evaluating some of these devices in the US, Europe, South America, and Asia. The sirolimus eluting-stent has been available for routine use in Europe, South America, and Asia since the first half of 2002, and is expected to be marketed in the US in early 2003. Paclitaxel eluting-stents have also received CE (Conformité Européenne) marking for commercialization in Europe and are now beginning to be commercialized.

The case seemed to be closed. Restenosis, the Achilles' heel of percutaneous revascularization, appeared defeated. However, since the availability of sirolimus-eluting stents, very little has changed in the everyday life of almost all interventional laboratories in Europe. Why? Has the new treatment presented any undesirable effect? Was the desire to defeat restenosis not as great as supposed? The answer is none of the above. The limitation currently impeding more widespread use of the new technology is non-technical, non-medical, and non-biological. The list price of the sirolimus-eluting stent in Europe is €2,300 (US$ 2,500). This high price relative to bare stents, as well as the absence of incremental reimbursement in most countries, has been an obstacle to more widespread utilization of drug-eluting stents.

Restenosis: The Problem

Coronary restenosis has long been considered the main limitation hampering the efficacy of percutaneous revascularization. Although stent implantation has been shown to reduce restenosis in vessels with reference diameter ≥ 3.0mm, as compared to balloon angioplasty, in-stent restenosis still occurs in 10-40% of the patients. In the last 3 decades, a great deal of money and effort has been expended evaluating an endless list of failed "concepts", "strategies", devices, and drugs to decrease restenosis. But is in-stent restenosis really so bad?

The occurrence of restenosis remains largely unpredictable for a particular patient, although powerful "predictors of restenosis" have been described that are helpful to characterize a population of patients. Furthermore, in-stent restenosis has a high recurrence rate. In its most complex forms, repeat restenosis may occur in up to 50-80% after re-dilatation with balloon, rotablator, or laser. Brachytherapy has been demonstrated to reduce the incidence of repeat restenosis. However, the use of brachytherapy has been restricted to a relatively small number of centers. The need for a multidisciplinary approach, with addition of radiation oncologists and physicists to the interventional team, poses logistic limitations to the implementation of the technology as a standard therapy in most hospitals. Nevertheless, although effective for most patients, treatment failure still occurs in approximately 30% of cases after brachytherapy.

Patients with restenosis frequently express the recurrence of symptoms as a "déjà vu" phenomenon occurring unexpectedly in their daily life, with rapidly progressive or "new onset" angina, so-called "unstable angina pectoris". However, unlike patients with *de novo* lesions, where plaque rupture and thrombus formation are the underlying substrate, "unstable angina" due

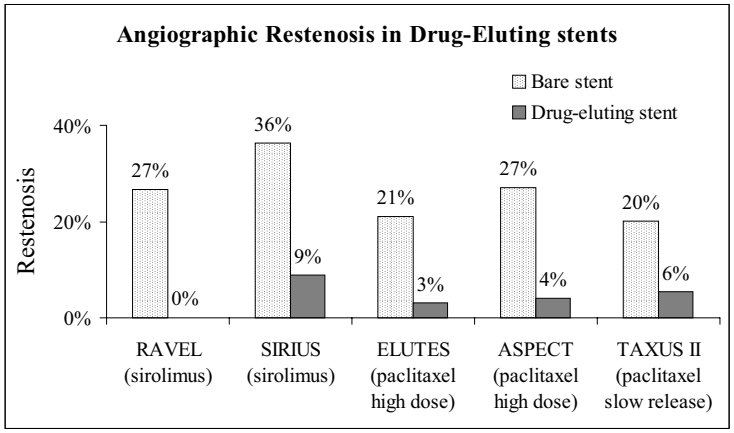

Figure 1. Incidence of angiographic restenosis in randomized trials with drug-eluting stents [2-6]

to restenosis is related to rapidly progressive lumen renarrowing due to exaggerated neointimal growth. As a consequence, restenosis is rarely complicated by myocardial infarction or death [8], as in the natural history of unstable patients with *de novo* lesions. Instead, refractory angina pectoris is the main complication of untreated restenosis. The lack of any effect of restenosis on mortality is readily appreciated by the comparison of angioplasty versus surgery [9]. In most randomized trials, death and myocardial infarction rates were virtually identical between the two treatment modalities in spite of a much higher rate of repeat-intervention due to restenosis after angioplasty. It is therefore unlikely that reduction of restenosis would have a direct impact on myocardial infarction or mortality rates. Nevertheless, it is worth noting that sirolimus-treated patients in the SIRolImUS-Eluting Bx Velocity™ Balloon-Expandable Stent trial (SIRIUS) showed a significantly smaller incidence of non Q-wave myocardial infarction between hospital discharge and 9 months follow-up (0.2% vs. 1.3%; p=0.037) [5].

An anticipated high risk of in-stent restenosis is one of the major reasons for patients refusing angioplasty and opting for other treatment modalities (e.g. surgery or medical). Similarly, the potential occurrence of restenosis currently limits the use of percutaneous treatment for conditions such as intermediate lesions and vulnerable plaques. The introduction of drug-eluting stents will hopefully broaden the selection of appropriate candidates for angioplasty, with a shift of patients from medical and surgical treatments towards percutaneous intervention.

Drug-Eluting Stents: What are the benefits?

In the First In Man [10] study and in 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) [2], which included patients with single non-complex de *novo* lesions, the rate of binary angiographic restenosis (diameter stenosis > 50%) after sirolimus-eluting stent implantation was zero at 2 years and at 6 months, respectively. The efficacy of sirolimus-eluting stents was confirmed in the subsequent SIRIUS trial. In this study, in-stent binary restenosis (within the margins of the stent) was reduced by 91% (3.2% vs. 35.4%; p<0.01) and in-segment restenosis (including the stented portion and the 5mm segments proximal and distal to the stent) was reduced by 75% (8.9% vs. 36.3%; p<0.01)[5]. In the SIRIUS trial, long lesion length, small reference vessel size, and diabetes were shown to be independent predictors of increased risk of restenosis (in-stent and in-segment), either in patients treated with sirolimus-eluting stents or with bare stents. However, sirolimus-eluting stents markedly reduced restenosis for patients at both extremes of the risk spectrum. Non-diabetics with short lesions (< 12mm) and large vessels (≥ 3.0mm) had an 81.7% risk reduction of in-segment restenosis, while patients at the highest risk (diabetics with longer lesions [≥ 15mm] and small vessels [<2.5mm]) had a significant 64.5% decrease in the risk of restenosis. Similarly, in the RAVEL trial [11], patients with vessel size <2.36 mm (one third of the population) presented with the same rate of binary restenosis (i.e. no restenosis) as patients in the upper tercile (reference diameter > 2.84). Recently, sirolimus-eluting stents have shown promising results for the treatment of in-stent restenosis in a series of 25 patients with relatively simple lesions (4% binary restenosis rate at 1 year) [12]. Sirolimus-eluting stents have also been evaluated for highly complex patients with in-stent restenosis. In an initial experience with 16 patients (including 50% with multiple previous interventions, 44% needing implantation of ≥ 36mm sirolimus-eluting stents, 25% with failed brachytherapy, 19% with total occlusions, and 6% with transplant vasculopathy), binary restenosis rate at 4 months was 20% and death rate was 12.5% at 9 months [13].

Non-polymer coated paclitaxel-eluting stents have been shown to reduce binary angiographic restenosis in the European Evaluation of Paclitaxel Eluting Stent trial (ELUTES) [3] and the ASian Paclitaxel-Eluting stent Clinical Trial (ASPECT) [4]. In these studies, non-polymer paclitaxel stents (high-dose formulation) were associated with 3% and 4% restenosis rates, respectively, versus 21% and 27% in bare stent controls [3,4]. Polymer-covered paclitaxel-eluting stents have been evaluated in the multicenter, randomized Treatment of De Novo Coronary Disease Using a Single Paclitaxel-Eluting Stent trial-II (TAXUS-II) [6]. In this study, the incidence of in-segment restenosis at 6 months was reduced from 20-24% in the bare stent group to 6% and 9% in the slow- and moderate-release paclitaxel stent formulations respectively. However, when analyzing patients treated only with the study stent, restenosis was observed in only 2% in the slow-release and 1% in the moderate-release paclitaxel stents. These results confirmed the previous findings of the smaller TAXUS-I trial [14], in which patients treated with the slow-release polymer-covered paclitaxel stents showed no restenosis, as compared to 10% in the control group.

Drug-Eluting Stents: Where are the side effects?

In 2 recent reports from the same series of patients, Liistro et al. and Virmani et al. have described a late "catch up" phenomenon after implantation of a high dose (800 µg) paclitaxel derivative QP2-eluting stent [15,16]. The restenosis rate was 13% at 6 months and 62% at 12 months. Histological analysis showed signs of delayed healing with active inflammation still present at 1 year. However, the authors emphasized that "potential problems such as the non-erodable thick polymer sleeve, very high concentration of the active drug, extended release kinetics, open stent architecture, and inhomogeneous drug delivery (possibly affected by the interspace polymer sleeve) may have compromised the performance of the QuaDS-QP2 stent" and concluded that "…the overall clinical success of any drug-eluting stent may be dependent on multiple design factors and not the drug alone".

Short-term as well as long-term efficacy should be evaluated separately for each drug-eluting stent, since a "class-effect" is unlikely to occur due to the myriad of possible variations in the complex metallic platform/polymer (or not)/pharmacologic agent. Indeed, a number of drug-eluting stents have already been proven ineffective in reducing restenosis, with even worse results being reported, as compared to conventional bare stent[17].

To date, the sirolimus-eluting stent has the largest body of data and longest period of follow-up. The First In Man study has shown persistent positive results up to 2 and 3 years, without any evidence of late catch-up restenosis[10,18]. In the RAVEL trial [2], no further events due to restenosis were observed between 6 months and 1 year. With paclitaxel, no rebound effect was seen from 6 to 12 months in TAXUS-I, ELUTES, and ASPECT trials [3,4,14].

Obviously, a very delayed loss of the initial benefit, for instance after 3-4 years, cannot yet be ruled out. However, in this hypothetical setting, should a repeat intervention after 3 years be viewed as a therapeutic failure? In a recent analysis of surgically treated patients with multivessel disease included in the Bypass Angioplasty Revascularization Investigation (BARI) trial [19], significant stenoses were detected after 4 years in 10-15% of internal mammary grafts and 25-30% of saphenous vein bypass grafts. It seems clear that a meaningful comparison between the results of treating multivessel disease with drug-eluting stents versus surgical revascularization will need an extended period of follow-up to fully assess the differences (or similarities) in outcomes with the two strategies.

In the First In Man and RAVEL trials, no binary angiographic restenosis was observed [1,2]. However, in the subsequent SIRIUS trial restenosis (in-segment) did occur in approximately 9% of the cases. Indeed, in diabetics with small vessels and long lesions, in-segment restenosis was observed in 23.7% of cases. Does this mean that sirolimus-eluting stents are not restenosis-proof? The populations treated in the "zero-restenosis" First In Man and RAVEL trials and in the "some-restenosis" SIRIUS trials were significantly different in terms of their intrinsic risk of restenosis. SIRIUS included patients with a higher risk profile and more complex lesion anatomy. It seems logical to assume that these differences in baseline characteristics could justify, at least in part, the differences in outcomes between the two studies. However, if so, what would be the performance of the new device in the "real world", where complex cases are the rule? In everyday practice, will the effects still be worth the cost of the new treatment? To evaluate this question, the sirolimus-eluting stent has been used as the device of choice for every percutaneous intervention in Rotterdam since April 2002, as part of the RESEARCH (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital) registry [20]. Patients were treated without clinical or anatomical restriction and the incidence of major adverse cardiac events (MACE) is to be evaluated (defined as death, non-fatal myocardial infarction or repeat-revascularization). In this study, sirolimus-eluting stent implantation was observed to be safe in patients with acute coronary syndromes, with a 30-day MACE rate similar to a control group treated with bare stents (6.1% vs. 6.6% respectively; p=0.8) [20]. In a preliminary analysis of the 6-month outcomes of first 280 patients enrolled, including patients with multivessel stenting, acute myocardial infarctions, total occlusions, bifurcation lesions, and in-stent restenosis, the incidence of target vessel revascularization and major adverse cardiac events were 2.9% and 6.7% respectively. Although promising, these preliminary long-term results must be interpreted with caution until final results are available.

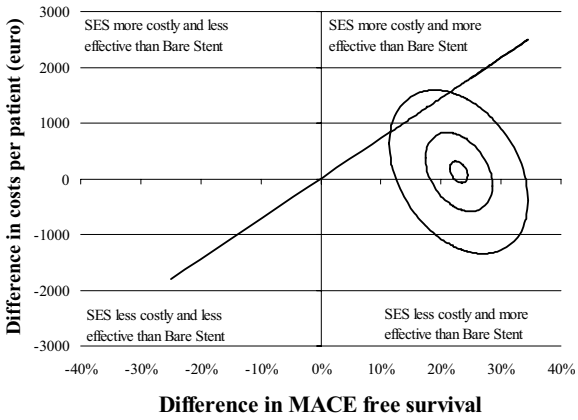

Figure 2 – Probability ellipses concerning both costs and effects at 1 year of sirolimus-eluting stent versus bare stent in the RAVEL trial. The outer ellipse defines the smallest area containing both costs and effects with 95% probability; the middle ellipse with 50%, and the inner ellipse with 5%.

In the RAVEL trial, stent malapposition (as observed by intravascular ultrasound) was more frequent at 6 months in sirolimus-eluting stent patients than in the control arm [21]. Moreover, in SIRIUS [5] late acquired stent malapposition was more commonly observed in the sirolimus group. However, in TAXUS-II [6] patients treated with bare stents or paclitaxel-eluting stents there were similar rates of late-acquired malapposition. Nevertheless, these observations of late malapposition by ultrasound have not been associated with any adverse events throughout the follow-up period in any of these studies.

Drug-Eluting Stents: The costs

Developmental and research costs, acquisition of exclusive and expensive licenses from pharmaceutical companies, building of new manufacturing facilities, low production yield in the early stages of the new product are all cited as reasons to explain the high cost of drug-eluting stents. However, at the present stage, the real economic value of drug-eluting stents is still unclear as well as the profit made by the leading industries manufacturing these devices. In an analysis from the RAVEL trial (B.A. van Hout, PhD. Personal Communication, October 2002) the utilization of the sirolimus-eluting stent resulted in a mean additional procedural cost of €1,286, as compared to the control group based on costs in the Netherlands. However, due to the decrease in re-interventions attributable to the sirolimus-eluting stent at the end of the first year of follow-up the estimated cost difference had decreased to 54 €. In other words, in the RAVEL trial the reduction of major event risk from 28.8% to 5.8% after sirolimus-eluting was accomplished at an extra cost of €54 per patient. To account for the so-called "oculo-stenotic reflex" that could have artificially increased the rate of re-interventions due to the protocol-mandated angiographic follow-up, both costs and effects were corrected based on the data from the BENESTENT II

study. In this analysis, after 1 year the adjusted event rate was 16.9% and 5.8% in the bare and sirolimus groups respectively, and the sirolimus-eluting stent was associated with an additional cost of €166 per patient. The balance between costs and effects seemed highly attractive (Figure 2), with a minimal increase in costs for an approximately 60% risk reduction in the worst case. For comparison, previous studies evaluating the "anti-restenotic" effect of conventional stents have shown "only" a 30% risk reduction of adverse event as compared to balloon dilatation, at an additional cost after 1 year of approximately US$ 1,000 per case[22].

The cost and effect estimations derived from the RAVEL trial cannot be directly extrapolated to other situations. In this study, only simple lesions were treated with implantation of a single stent and the late target lesion revascularization was zero. The balance between costs and effects in more complex situations, where restenosis may occur in a small but sizeable number of patients, have to be specifically analyzed. Furthermore, the number of stents used per procedure may markedly increase procedural costs, potentially limiting the use of this new technology for the treatment of multivessel disease. It is estimated that approximately 1,000,000 percutaneous interventions are performed each year in the US and approximately 80% of them receive stents. Assuming a 100% usage of drug-eluting stent, at a rate of 1.5 stent per patient and a potential US$ 2,000 difference between drug-eluting and bare stents, an extra 2.4 billion dollars would be added in procedural costs per year. With a 15% reduction in reinterventions (at a cost of US$10,000 –12,000 per procedure for repeat percutaneous coronary procedure and US$20-30,000 per procedure for coronary bypass surgery), the cost-offset with unrestricted usage of drug-eluting stents in the patients at present receiving bare metal stents would be about 1.5 billion dollars each year. However, if there is any substantial movement from coronary bypass surgery to drug-eluting stents, additional savings from avoiding the high cost of bypass surgery could potentially result in an attenuation of net costs for payors. Nevertheless, although potentially "cost-effective" in reducing repeat-revascularization, it is clear that utilization of drug-eluting stents will require a re-distribution of budgets and priorities in the health system as a whole, with a shift of an enormous amount of money to manufacturers. This phenomenon is likely to be repeated with the introduction of other new technologies that can replace open surgical procedures with less invasive technologically-driven procedures and will continue to present a challenge for the foreseeable future.

Historically, all relevant technological innovation in interventional cardiology has been incorporated into clinical practice. Today, an arsenal of multiple types of guiding catheters, new generation contrast agents, steerable guidewires, adjunctive medications, intracoronary diagnostic tools, dilatation devices, distal protection devices, and access closure devices encompass the armamentarium of what has been named "percutaneous intervention", only vaguely resembling the first days of coronary angioplasty. The speed with which new technologies are integrated over time seems to be dependent on their efficacy, safety and economic factors and vary from country to country. Curiously, as performed in the late 80's in Europe, balloon angioplasty was associated with a procedural cost of approximately 4,300 US$ [23], while in the mid 90's, coronary stenting was performed at a cost of approximately 4,400 US$ [22]. History has shown that an "outsider" (not belonging to the leading corporations) may unexpectedly introduce a competitive and successful product with a lower price so that the major companies are compelled to reduce the price of their own product, triggering an overall lowering of the costs. We foresee that some of the manufacturers of new eluting-stent designs may purposely target the non-US market with lower regulatory barriers as a "profitable" field of expansion, so that the non-US patient in Europe, South America, Far East, and Africa may soon benefit from a low-priced non-FDA approved drug-eluting stent.

Conclusions

By dramatically decreasing the rate of restenosis, drug-eluting stents constitute one of the most important advances in interventional cardiology. However, at present cost constraints and lack of incremental reimbursement have limited their utilization in daily practice in many countries, although initial analyses of the sirolimus-eluting stent have shown a highly favorable cost-effectiveness profile in reducing repeat-revascularization and combined major cardiac events. A more comprehensive understanding of the impact of the new treatment in a wide variety of patients, as well as market competition with changes in the cost of these device costs, are likely to redefine the relationship between costs and benefits.

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Summary and Conclusions

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Unrestricted Utilization of Sirolimus-Eluting Stents in the "Real World". The Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry

Unrestrictive sirolimus-eluting stent implantation was shown to be overall safe and beneficial for patients with *de novo* lesions treated in the "real world". A total of 508 consecutive patients with *de novo* lesions treated with sirolimus-eluting stents had a cumulative rate of 1-year major adverse cardiac events (death, myocardial infarction, or target vessel revascularization) of 9.7%, which was significantly better than the 1-year event rate of 14.8% in 450 consecutive patients treated with conventional strategies (HR 0.62 [95% CI 0.44–0.89]; p=0.008), a difference that was mainly driven by a marked reduction in the need for clinically driven target vessel revascularization in the sirolimus group (3.7% vs. 10.9%; p<0.001) (*Chapter 3*). Importantly, the reduction of restenosis and the need for further revascularization with sirolimus-eluting stents was accomplished while maintaining the excellent short-term results already achieved with current percutaneous techniques (*Chapter 3*). Even in patients with an increased risk for thrombotic complications (i.e. patients with acute coronary syndromes), sirolimus-eluting stent implantation was shown to be at least as safe as conventional stenting (*Chapters 4, 5, and 6*). During the first month after the procedure in patients with unstable angina or acute myocardial infarction, the rate of major adverse events was similar between patients treated with sirolimus-eluting stents (6.1%) and controls (6.6%; p=0.8), and stent thrombosis occurred in 0.5% and 1.7% respectively (p=0.4) (*Chapter 4*). In addition to being safe, sirolimus-eluting stent implantation was shown to substantially improve the mid-term outcomes of patients with ST elevation acute myocardial infarction (*Chapters 5 and 6*). At 6 months the angiographic restenosis was zero (*Chapter 5*) and the need for subsequent repeat revascularization was 1.1% at 10 months (compared to 8.2% for controls; HR 0.21 [95% CI 0.06–0.74]; p=0.01). Importantly, no patient treated with sirolimus-eluting stents required additional revascularization between 1 and 10 months (*Chapter 6*). However, the benefit of sirolimus-eluting stent implantation on outcomes of patients with high risk for clinical complications were shown to be almost exclusively related to its anti-restenotic effect, with virtually no effect on the risk of death during the follow-up. The presence of renal impairment at baseline was identified as an important independent predictor of 1-year death among patients treated with percutaneous revascularization (HR 2.15 [95% CI 1.10 – 4.28]; p=0.03), a hazardous effect that was not modified by sirolimus-eluting stent implantation (*Chapter 7*).

The risk of in-stent restenosis after conventional stenting is an important parameter to be considered when evaluating the best revascularization modality for an individual patient. Indeed, certain subsets of patients have been tradionally referred for surgical or medical therapy in face of a presumed high risk of restenosis (or when the clinical consequences of restenosis, once it occurs, are assumed to be disastrous). The introduction of drug-eluting stents has the potential to modify this scenario and was evaluated *Chapters 8 to 21*. Sirolimus-eluting stents were safe and effective for the treatment of left main coronary artery disease, with no post-discharge fatal events and percutaneous re-intervention (*Chapter 9*), with a zero angiographic restenosis rate for elective patients (*Chapter 10*). Similarly, in 99 patients with multivessel coronary disease involving the left anterior descending artery treated with sirolimus stents, the 1-year incidence of death, myocardial infarction, or any repeat revascularization (including lesions in segments not treated in the index procedure) was 85.6 %, which is comparable to previous series with surgical revascularization (*Chapter 11*).

Sirolimus-eluting stents were utilized for the treatment of 56 patients with *de novo* chronic total occlusions and compared with a similar group of 28 patients treated in the period immediately before the introduction of sirolimus stents. The results were described in *Chapter 12*. At 1 year, the cumulative survival-free of major adverse cardiac events was 96.4% in the SES group versus 82.8% in the BMS group (p<0.05). The clinical and angiographic outcomes of 91 patients (112 lesions) with very small vessels treated with 2.25-mm diameter sirolimus-eluting stents were detailed in *Chapter 13*. The reference diameter was 1.88±0.34, which was substantially smaller than all previous randomized studies of conventional stents for small vessels (vessel size in these series ranged from 2.23 mm to 2.55 mm). At follow-up, the binary restenosis rate was 10.7% and the late loss was 0.07±0.48 mm, which favorably contrasts with the late loss of bare stents for small vessel in previous randomized trials (range 1.12 mm to 0.54 mm). The 12-month target lesion revascularization rate was 5.5%. *Chapter 14* examined the impact of sirolimus stents on another subset at extremely high risk for restenosis. A total 96 patients with very long stented segments (at least 41 mm long) had a binary restenosis rate of 11.9%, with an in-stent late loss of 0.13± 0.47mm. At long-term follow-up (mean 320 days), the overall incidence of major cardiac events was 8.3%. The dramatic reduction of restenosis with sirolimus-eluting stents opened new therapeutic possibilities for bifurcation lesions.

Chapter 15 illustrates a case of multiple bifurcation lesions treated with different stenting techniques that ensure complete vessel scaffolding at the treated site. At 6-month angiographic follow-up, no restenosis was present. The outcomes of patients undergoing bifurcation stenting is further explored in *Chapter 16*: restenosis rates in the main vessel and in the stented side branch were 6.8% and 13.6% respectively, and at 6 months the incidence of major adverse cardiac events was 10.3%. In *Chapter 17*, a group of patients with angiographically

mildly stenotic (<50% stenosis) lesions treated with sirolimus stents were evaluated. After a mean follow-up period of 399 ± 120 days, there were no further major cardiac events. Although not explored in this thesis, these findings may indicate a future role of percutaneous intervention for the treatment of special groups of patients with mildly stenotic lesions identified to be at high risk for further events (e.g. plaque vulnerability). *Chapter 18* (as well as *Chapter 3*) demonstrated that over-dilatation of undersized sirolimus-eluting stents, a technical adjustment that is commonly needed in the clinical practice, had no adverse impact on the late outcomes.

Chapters 19 to 21 analyzed the impact of sirolimus-eluting stent implantation for patients with previous failed percutaneous treatment. A total of 44 consecutive patients with 53 in-stent restenotic lesions (without previous brachytherapy) treated with sirolimus stents were described in *Chapter 19*. At baseline, 37% had complex restenosis morphologies (proliferative pattern or total occlusions). At follow-up, post-SES restenosis was observed in 14.6%. No restenosis was observed in focal lesions. For more complex lesions, restenosis rates ranged 20-25%. At 1-year follow-up, the overall incidence of target lesion revascularization due to restenosis was 11.6%. These findings were compared with those of brachytherapy, the current gold standard treatment for complex in-stent restenosis in *Chapter 20*. No differences in outcomes were found between patients with in-stent restenosis treated with sirolimus-stents or brachytherapy. Finally, *Chapter 21* examined the effect of sirolimus-eluting stent implantation on the outcomes of patients with recrudescent restenosis after brachytherapy. The data have demonstrated that this population was at a high risk for further repeat restenosis, which was found in 40% of patients even after sirolimus-eluting stent implantation.
Although sirolimus-eluting stents were shown to be safe and effective, short-and mid-term complications were still identified in a number of patients and are described in *Chapters 22 to 26*. The incidence of stent thrombosis was shown to be low (0.4%) (*Chapter 22*), a figure comparable to that previously reported for bare stents. *Chapter 23* described some morphological and mechanistic characteristics of patients with post-sirolimus restenosis. Restenotic lesions located within the stent were focal and stent scaffolding discontinuity was identified as a relatively common finding. Moreover, residual dissection after the procedure or balloon trauma outside the stent was identified in 83% of edge restenosis. Among patients with complex characteristics, the 6-month *in-segment* restenosis rate was 7.9% (6.3% *in-stent*, 0.9% at the proximal edge, 0.7% at the distal edge), with the following characteristics identified as independent multivariate predictors (Chapter 24): treatment of in-stent restenosis (OR 4.16; 95% CI: 1.63 – 11.01; p<0.01), ostial location (OR 4.84; 95% CI: 1.81 – 12.07; p<0.01), diabetes (OR 2.63; 95% CI: 1.14 – 6.31; p=0.02), total stented length (per 10 mm increase) (OR 1.42; 95% CI: 1.21 – 1.68; p<0.01), reference diameter (per 1.0 mm increase) (OR 0.46; 95% CI: 0.24 – 0.87; p=0.03), and left anterior descending artery (OR 0.30; 95% CI: 0.10 – 0.69; p<0.01). Interestingly, post-sirolimus restenosis appeared to occur as an "all-or-none" phenomenon (*Chapter 25*), with lesion-based characteristics (instead of patient-based) playing an important role in the incidence of post-sirolimus restenosis. Although occurring in a small proportion of patients, post-sirolimus restenosis has been shown to be relatively resistant to repeat percutaneous treatment (*Chapter 26*). A total of 24 consecutive patients (27 lesions) with restenosis after sirolimus-eluting stent implantation have undergone repeat angioplasty. From the 27 lesions, 1 (4%) was re-treated with a bare stent, 3 (11%) with balloon dilatation, and the remaining 23 lesions (85%) with repeat drug-eluting stent implantation (SES in 12 lesions [44%] and paclitaxel-eluting stents in 11 lesions [41%]). The event-free survival rate was 75.0% after 487 ± 42 days from the index procedure (269 ± 68 days from the post-SES treatment). The overall recurrent restenosis rate was 40%. The recurrent restenosis rate of lesions re-treated with drug-eluting stents was 29.4%.

Finally, although restenosis, the Achilles' heel of percutaneous revascularization, appeared under control after the introduction of drug-eluting stents, the penetration of these devices in the everyday life was smaller than what would be expected from their proven clinical benefit. The limitation currently impeding a more widespread use of the new technology is non-technical, non-medical, and non-biological. The high price relative to bare stents has been an obstacle to more widespread utilization of drug-eluting stents. The balance between costs and effects of sirolimus-eluting stents was studied in *Chapter 27* utilizing the data from the randomized RAVEL trial. The utilization of the sirolimus-eluting stent resulted in a mean additional procedural cost of €1,286, as compared to the control group based on costs in the Netherlands. However, due to the decrease in re-interventions attributable to the sirolimus-eluting stent at the end of the first year of follow-up the estimated cost difference had decreased to 54 €. In other words, in the RAVEL trial the reduction of major event risk from 28.8% to 5.8% after sirolimus-eluting was accomplished at an extra cost of €54 per patient. The benefits and limitations of drug-eluting stents as an anti-restenotic strategy and their relationship with potential costs is frequently complex and multifactorial. *Chapter 28* provides a discussion on the main issues involved in the balance between costs and effects of the new technology.

In conclusion, sirolimus-eluting stent implantation for unselected patients in the "real world' is safe and effective in reducing major adverse cardiac events across several high-risk subsets. The reduction in the risk for restenosis with drug-eluting stents will potentially extent the indications of percutaneous treatment to subgroups currently considered for surgical or medical treatment. Although infrequent, post-sirolimus eluting stent restenosis still occurs in a minority of patients. The risk factors for restenosis after sirolimus-eluting stent implantation resemble those described for bare metal stents. Moreover, features that potentially impair complete lesion coverage may have an important role in post-sirolimus restenosis, which appears to occur as an all-or-none phenomenon.

Samenvatting en Conclusies

Samenvatting en conclusies

Onbeperkt gebruik van de met sirolimus gecoate stents in de klinische praktijk: De Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) Registratie

Implantatie van de met sirolimus gecoate stents is veilig met een gunstig effect bij patiënten met de novo (nieuwe) lesies in de klinische praktijk. In totaal 508 opeenvolgende patiënten met de novo lesies werden behandeld met deze nieuwe stent. Het cumulatieve event percentage (sterfte, hartinfarct of revascularisatie van dezelfde kransslagader) was 9.7% in het eerste jaar, hetgeen significant beter was als de event-percentages van een controlegroep van 450 opeenvolgende patiënten (14.8%) (HR 0.62 [95%CI 0.44-0.89]; p=0.008). Dit verschil was vooral te danken aan de significante reductie van revascularisatie als gevolg van restenose in dezelfde kransslagader (3.7% vs 10.9%; p<0.001) (Hoofdstuk 3). Het is belangrijk te weten dat de restenose reductie en de noodzaak tot een nieuwe revascularisatie met gecoate stents bereikt werd terwijl de uitstekende korte-termijn resultaten die reeds bereikt werden met behulp van de huidige percutane technieken gehandhaafd bleef (Hoofdstuk 3). Zelfs bij patiënten met een verhoogd risico op trombotische complicaties (dwz patiënten met acuut coronair syndromen) bleek de gecoate stent tenminste even veilig als bij de conventionele stent (Hoofdstukken 4,5 en 6). In de eerste maand na de procedure waren de event percentages bij patiënten met onstabiele angina pectoris of hartinfarct gelijk tussen patiënten behandeld met de gecoate stent (6.1%) en de conventionele stent (6.6%; p=0.8), en stent trombose kwam voor bij respectievelijk 0.5% en 1.7% (p=0.4) (Hoofdstuk 4). Behalve de veiligheid, bleek de gecoate stent de middenlange-termijn prognose van patiënten met een ST elevatie acuut hartinfarct substantieel te verbeteren (Hoofdstukken 5 en 6). Na 6 maanden was er geen angiografische restenose (Hoofdstuk 5) en de noodzaak tot een hernieuwde revascularisatie was slechts 1.1% na 10 maanden (in vergelijking tot 8.2% in de controlegroep; HR 0.21 [95%CI 0.06-0.74]; p=0.01). Daarbij was het belangrijk te weten dat er geen noodzaak was tot een nieuwe revascularisatie tussen 1 en 10 maanden bij patiënten die werden behandeld met de gecoate stent (Hoofdstuk 6). Het gunstige effect van de gecoate stent was echter vooral te danken aan het anti-restenose effect waarbij er geen verschil in sterfte was gedurende de follow-up. Nierfalen bleek een belangrijke voorspeller te zijn voor 1-jaars sterfte (HR 2.15 [95%CI 1.10-4.28]; p=0.03), een bevinding die echter niet werd beïnvloed door de gecoate stent (Hoofdstuk 7).

Het risico van in-stent restenose na conventionele stentimplantatie is een belangrijke parameter bij de evaluatie van het beste beleid van de individuele patiënt. Bepaalde subgroepen patiënten werden inderdaad traditioneel doorverwezen naar chirurgie of voor medicamenteuze behandeling in geval een hoog risico op restenose wordt verwacht (of als wordt aangenomen dat de eventuele klinische restenose consequenties rampzalig zouden zijn). De introductie van de gecoate stent zou dit scenario eventueel kunnen veranderen en dit werd geëvalueerd in de Hoofdstukken 8 tot 21. Gecoate stents bleken veilig en effectief te zijn voor de behandeling van hoofdstamstenose bij electieve patiënten na ontslag uit het ziekenhuis zonder fatale events en percutane reinterventies zonder angiografische restenose bij electieve patiënten (Hoofdstuk 10). Eveneens waren bij 99 patiënten met meervatslijden, met inbegrip van de LAD, de 1-jaars event-percentages (sterfte, hartinfarct en hernieuwde revascularisaties, inclusief lesies die tijdens de indexprocedure onbehandeld waren) van de gecoate stent slechts 14.4%, (and not 85.6%??), hetgeen vergelijkbaar is met eerdere studies na chirurgische revascularisatie (Hoofdstuk 11).

De met sirolimus gecoate stents werden gebruikt voor de behandeling van 56 patiënten met de novo chronische totale occlusies en vergeleken met een vergelijkbare groep van 28 patiënten die werden behandeld in de periode direct voorafgaand aan de introductie van de gecoate stent. De resultaten zijn beschreven in Hoofdstuk 12. Na 1 jaar waren de cumulatieve event percentages in de gecoate stent groep 3.6% en 17.2% in de conventionele stent groep (p<0.05). De klinische en angiografische resultaten van 91 patiënten (112 lesies) met erg kleine vaten die werden behandeld met een 2.25-mm sirolimus gecoate stent werden beschreven in Hoofdstuk 13. De referentie diameter was 1.88±0.34, hetgeen substantieel kleiner was dan alle eerdere gerandomiseerde studies van conventionele stents in kleine vaten (diameter varieerde in deze studies van 2.23 mm tot 2.55 mm). Gedurende de follow-up was de binaire restenose percentage 10.7% en de 'late loss' was 0.07±0.48 mm, hetgeen gunstig afsteekt tegen de 'late loss' van de conventionele stents in kleine vaten in eerdere gerandomiseerde studies (van 1.12 mm tot 0.54 mm). De 12-maanden klinische restenose percentage was 5.5%. Hoofdstuk 14 onderzocht het effect van de gecoate stent op een subgroep van patiënten met een zeer hoog risico op restenose. In een groep van 96 patiënten met erg lange gestente segmenten (tenminste 41 mm lang) was de binaire restenose percentage 11.9% met een in-stent 'late loss' van 0.13 mm±0.47 mm. Op de lange-termijn (gemiddeld 320 dagen) was het totale event percentage 8.3%. De dramatische reductie van restenose van de gecoate stent zorgde voor nieuwe behandelings mogelijkheden voor bifurcatie lesies.

Hoofdstuk 15 illustreert een voorbeeld van meervoudige bifurcatie lesies behandeld met verschillende stent technieken om verzekerd te zijn van een volledige coating van het behandelde segment. Na 6 maanden angiografische follow-up werd er geen restenose gevonden. De prognose na bifurcatie stenting is verder onderzocht in Hoofdstuk 16: restenose percentages in de hoofdstam en in de gestente zijtak waren respectievelijk 6.8% en 13.6%, en na 6 maanden was het cardiale event percentage 10.3%. In Hoofdstuk 17 wordt de gecoate stent geëvalueerd in een groep patiënten met een matige stenose (angiografisch <50%). Na een gemiddelde follow-up van 399±120 dagen waren er geen additionele cardiale

events. Hoewel niet onderzocht in dit proefschrift, kunnen deze bevindingen een toekomstige rol spelen bij de percutane behandeling van deze speciale groep patiënten maar met een matige stenose met een hoog risico op toekomstige events (bijvoorbeeld plaque vulnerability). Hoofdstuk 18 (en in Hoofdstuk 3) toonde aan dat overdilatatie van kleinere gecoate stents, een technische aanpassing dat gewoonlijk nodig is in de klinische praktijk, geen nadelig effect had op de lange-termijn uitkomsten.

In de Hoofdstukken 19 tot 21 wordt de invloed van de gecoate stent onderzocht bij patiënten waarbij een eerdere percutane behandeling was mislukt. In totaal 44 opeenvolgende patiënten met 53 in-stent restenotische lesies (zonder eerdere brachytherapie) worden beschreven in Hoofdstuk 19. Tijdens baseline had 37% een complexe restenose morfologie (snelgroeiend patroon of totale occlusie). Bij follow-up werd restenose bij de gecoate stent geconstateerd bij 14.6%. Geen restenose werd waargenomen bij focale lesies. Voor de meer complexe lesies varieerden de restenose percentages van 20% tot 25%. Na 1 jaar was de totale in-stent restenose incidentie 11.6%. Deze bevindingen werden vergeleken met brachytherapie, de huidige gouden standaard behandeling voor complexe in-stent restenose (Hoofdstuk 20). Geen verschillen in uitkomsten werd gevonden tussen patiënten met in-stent restenose, behandeld met de gecoate stent of brachytherapie. Tenslotte werd in Hoofdstuk 21 het effect van de gecoate stent onderzocht bij patiënten met hernieuwde restenose na brachytherapie. De resultaten laten zien dat deze patiëntpopulatie een hoog risico heeft op voortdurende restenose, hetgeen werd gevonden in 40% van alle patiënten, zelfs na implementatie van de gecoate stent.

Hoewel de gecoate stents veilig en effectief bleken te zijn, werden er toch complicaties gevonden op de korte- en middenlangetermijn bij sommige patiënten. Dit is beschreven in de Hoofdstukken 22-26. Stent trombose bleek weinig voor te komen (0.4%) (Hoofdstuk 22), hetgeen vergelijkbaar is met eerdere studies van de conventionele stent. Hoofdstuk 23 beschrijft enige morfologische en mechanische karakteristieken van patiënten met restenose in de gecoate stent. Restenotische lesies binnen de stent waren focaal en discontinuïteit in de stent structuur werd geïdentificeerd als een relatief normale bevinding. Bij 83% van de patiënten met edge restenose werd er na de procedure residuele dissectie of letsel ten gevolge van de ballon gevonden. Na 6-maanden was het in-segment restenose percentage onder de patiënten met complexe karakteristieken 7.9% (6.3% in-stent, 0.9% bij de proximale edge, 0.7% bij de distale edge), waarbij de volgende parameters werden geïdentificeerd als onafhankelijke multivariabele voorspellers (Hoofdstuk 24): behandeling van in-stent restenose (OR 4.16; 95%CI 1.63-11.01; p<0.001), ostial locatie (OR 4.84; 95%CI 1.81-12.07; p<0.01), diabetes mellitus (OR 2.63; 95%CI 1.14-6.31;p=0.02), totale stent lengte (per 10 mm toename) (OR 1.42; 95%CI 1.21-1.68; p<0.01), referentie diameter (per 1.0 mm toename) (OR 0.46; 95%CI 0.24-0.87; p=0.03) en LAD (OR 0.30; 95%CI 0.10-0.69; p<0.01). Een interessante bevinding was dat in-stent restenose van de gecoate stent lijkt voor te komen als een "alles of niets" fenomeen (Hoofdstuk 25) waarbij lesie-gerelateerde karakteristieken (in plaats van patiënt-relateerd) een belangrijke rol spelen bij het voorkomen van restenose van de gecoate stent. Hoewel restenose van de gecoate stent slechts voorkomt in een klein deel van de patiënten, is het relatief resistent met betrekking tot een hernieuwde percutane behandeling (Hoofdstuk 26). In totaal 24 opeenvolgende patiënten (27 lesies) met restenose in de gecoate stent ondergingen een nieuwe dotterprocedure. Van de 27 lesies, werd er 1 (4%) behandeld met een conventionele stent, 3 (11%) met een ballondilatatie, en de overige 23 lesies (85%) opnieuw met een gecoate stent (sirolimus in 12 lesies [44%], en paclitaxel in 11 lesies (41%). Het event-vrije overlevings percentage was 75.0% na 487±42 dagen na de index procedure (269±68 dagen na de post-SES behandeling). In totaal was het hernieuwde restenose percentage 40%. Het hernieuwde restenose percentage na opnieuw te zijn behandeld door gecoate stents was 29.4%.

Tenslotte, hoewel restenose, de Achilleshiel van percutane revascularisatie, onder controle lijkt te zijn na de introductie van de gecoate stent, is het gebruik van deze stents, ondanks het gunstige effect, in de klinische praktijk minder dan we zouden verwachten. De belangrijkste beperking om deze nieuw gecoate stent meer te gebruiken is niet-technisch, niet-medisch, en niet-biologisch. Het grootste obstakel is de hoge prijs, in vergelijking tot de conventionele stent. De balans tussen kosten en baten van de gecoate stent is bestudeerd in Hoofdstuk 27 gebruikmakend van de gegevens van de RAVEL studie. Toepassing van de gecoate stent leidde tot een gemiddelde toename van de procedurele kosten van €1,286 in vergelijking tot de controle groep, gebaseerd op de kosten in Nederland. Aan het eind van het eerste jaar bleek echter dat door het gebruik van de gecoate stent dit verschil, dankzij een verminderde noodzaak tot reinterventies, te zijn verminderd tot slechts €54. Met andere woorden, de extra kosten om tot een event-reductie in de RAVEL studie van 28.8% tot 5.8% te komen, bedroegen dankzij de gecoate stent, slechts €54 per patiënt. De gunstige effecten en de beperkingen van gecoate stents als een anti-restenotisch strategie en hun relatie met potentiële kosten is veelal complex en multifactoriëel. Hoofdstuk 28 gaat in op de belangrijkste redenen die betrekking hebben op de balans tussen kosten en baten van deze nieuwe techniek.

We kunnen concluderen dat de met sirolimus gecoate stent bij ongeslecteerde patiënten in de klinische praktijk veilig en effectief is in het terugdringen van cardiale events, ook bij verschillend subgroepen met een hoog risico. Door de restenose reductie met de gecoate stent zal de indicatie voor percutane behandeling zeer zeker worden uitgebreid, vooral bij die patiënten waarbij op dit moment chirurgische of medicameteuze behandeling wordt overwogen. Hoewel weinig voorkomend, zal restenose na implantatie van gecoate stents toch plaatsvinden bij een kleine minderheid. De risicofactoren voor restenose zijn dezelfde als die bij de conventionele stent. Tenslotte, kenmerken die mogelijk de volledige coating van het behandelde segment aantasten, kunnen een belangrijke rol spelen bij de in-stent restenose van de gecoate stent waarbij het lijkt op een "alles of niets" fenomeen.

Acknowledgements

Coming to the Thorax has always been the golden dream. It is the gold standard.

Rotterdam, 26th January 2002. Wintertime. A temperature something like 30°C less than what I got just 12 hours before. Six suitcases (not exactly small). And me alone (Francine was still in Brazil awaiting her visa). Saturday. My new address written on a piece of paper. Took a cab: "Please, can we go to Claverstrati?". Silence. "What?". "Claverstrati avenue", I said and handed the piece of paper to the driver. "Ah, Klaverstraat". The temperature inside the taxi was something like 30°C more than what I got just 5 minutes before. The radio blaring in Dutch. I arrived, I thought. Not too fast, my friend… I did not have the keys of the apartment. I had the phone number of the owner of the apartment, who lived in Ireland. But no keys. "Somebody will be waiting for me, they know I'm coming today", I thought. But there was no somebody. And no keys. And that was Saturday afternoon, wintertime, 6 suitcases (not exactly small), me in the street in front of the apartment. Fortunately, the neighbor (thanks, Miki) saved me. She saw me through the window of her apartment and understood that I could be me (that is, that the guy in the street with 6 suitcases [not exactly small] could be the new neighbor she knew was coming soon. She had a spare key and phoned my landlady. I arrived, I thought. Not too fast, my friend… Saturday, late afternoon, my first day in Rotterdam. Where do I eat? Do I have a phone? That was the turn of my landlady and her son in law to save me. Thanks a lot Lijnie and Aad, you have absolutely made everything much smoother for me. I bought some food and declared myself arrived.

But the story begun much earlier. Last week of March 2001. Dr. Expedito Ribeiro had just arrived from the ACC meeting: "Pedrinho, I have talked to Patrick there. He said you can come". Expedito, I have no words to thank you. Not only for your support in many many instances, but for the friendship that developed along the road between us and your family, Cida, Maira, and Henrique. You have been pivotal to this thesis since the very beginning.

I went immediately to Dr. Eulógio Martinez, whom I will never be able to thank enough. Prof. Eulógio Martinez, I can say, was a turning point in my personal and professional life. Not only because of the many specific things that I have learned from him, but mainly and especially because of the diffuseness of his influence on my way of viewing things. For the uncountable times I found myself embarrassed and slightly out of key in a conversation with him by not being able to follow his thinking and broad generosity. For his subtle way of letting me know that life is always bigger than what I thought. For showing me how to exercise the tough practice of searching, recognizing, and sincerely admiring somebody else's virtues. During these last 2.5 years, I have sent to him or received from him a total of 307 emails. That kept my "continued education" on medical and life issues going.

Dr. Paulo Soares. My friend. Bia, Gustavo. You came here to Rotterdam at our very beginning just to check if we were ok and were not missing everybody too much. That touched us deeply. That is friendship. Making us feel at home in Rotterdam as you used to do in São Paulo. That is priceless.

I have also to thank all my colleagues from the Cath Lab at the Heart Institute. Drs. Kajita, Gama, Horta, Esteves, Perin, Beck, and Zalc, to whom I am happily coming back. I worked closely with Kajita and Esteves at Sirio Libanes, shared the same "afternoons" with Marcus Gama, Pedro Horta, and Marco Perin, and Leonardo Beck was my classmate during the graduation course. You have worked in my place while I was in Rotterdam, providing me support. And above all, you kept my position unquestioned while I was apart. That was priceless and I fully acknowledge it. Thank you very much. I also thank all nurses, secretaries, and technicians. Paula, thanks for taking care of my things so devotedly.

I thank Prof. José A.F. Ramires for endorsing my stay in Rotterdam for these almost 2 and a half years and also for kindly accepting in participating in my defense committee. That honors me and pushes my responsibilities even further.

I am indebted to Prof. Eduardo M. Krieger who helped me with the sponsorship application.

But then here I am at the Thoraxcenter. Monday. What to do? Before coming I was prepared by Marco Costa who gave me lots of tips and tricks. "Take your time in the beginning. It takes a while until things start to appear. In the meantime, try to know the place and don't forget that it's important to hold on the chances as they come out. It is also important to write quickly, so you can move on to the next stuff with no delay". Marco, since before coming (and actually even before knowing you personally) you have been essential to my stay here and I foresee that our friendship will strengthen more and more as time goes by.

But there I was. Thorax, first Monday morning. Anja soon assigned me a seat and a computer at the Cath Lab (thanks, Anja for all your help with everything!). Great. Faster than I thought! Two days latter, around 18:00, Prof. Serruys enters the room: "Come and take two plastic glasses with you". And disappeared to his room. "Have I understood ok?", I thought. With some hesitation, I went to his room with the plastic glasses that I took from the coffee machine. Prof. Serruys: "Here is a bottle of champagne. Why don't you open it so we can drink something while I explain to you the projects we are currently involved in?". "Fantastic! I am in!", I thrilled. He started to talk and write on the board. But then I realized: "This champagne is too warm…". I tried to duck it, and did not open the bottle, in the hope that Prof. would forget the champagne thing. At that time I did not know Prof.'s memory… And after 5 minutes: "Where is our champagne?", he asked again. Well, no chance to escape it now. I opened it. I have kept until now my impression of that 0.2 second, when the warm bottle exploded and spread champagne everywhere. I did not know what to do. With one hand I tried to cover the top of the bottle (which was not exactly efficient), while with the other hand I tried to reach some paper to dry it up. Prof. Serruys just glanced calmly at me: "Try to avoid the laptop. I once have seen a laptop dying because of a soup. Anyway, what I was saying is that the vulnerable plaque is a hot topic…". I finally (though still stressed) managed to pour some champagne in our glasses (only half of the bottle was left) and we kept our conversation. After some minutes, he continued: "And here there is something we could try to do. You know

that the people in the 23rd floor are outstanding. Pick up some paper and take notes. Why don't you set up a meeting – take note – with Nicudeiungui and Tonfanderstin?" I still have this paper with my spelling of the names of Profs. Nico de Jong and Anton van der Steen. I thank Prof. Tom van der Steen, one of the first persons that I then met in Rotterdam, who honors me with his participation in my thesis committee.

I was wondering where I should put my acknowledgment to Prof. Serruys. I soon understood that my recognition for what he has done for me could be placed anywhere. Indeed, everywhere. Through Prof. Serruys' hands I was exposed to a new world (I am sorry for the jargon, but this is absolutely true). I was presented to a universe where details are essential. Where actually they are no longer "details". Yet, I was taught that dissecting intricacies is what matters in the end. And he masters as nobody can the know-how to unravel the niceties of life. Prof. Serruys showed me that full understanding of the ground one is stepping in is an obligatory pre-requisite to be "au fait" with the edge of knowledge. And that the constant pursuit of pushing these borders forward is what distinguishes the professional researcher. But on the other hand, and here is the mystery, keeping a dose of improvisation is fundamental. I heard from him: "At all moments you must always be trying and thinking about something new. So, for a period, in that particular issue, you will be a beginner and that is good because it keeps the thing alive." I must also thank Mme. Danielle Serruys, who always received me with a smile at their home, gave us tips for our trips (to Barcelona, Venice, skiing, etc.), and invited us for a wonderful New Year's Eve.

Soon I realized that I was the only fellow with a seat in the cath lab. I was placed at the room with the assistants. All others (fellows) were in "Z" building. At that time, Evelyn Regar (I owe you the arrangements for our first apartment and several dinners at her place with Frank her husband), Kengo Tanabe, Ronald Lee, Muzaffer Degertekin. With Tanabe-san, Ronald, and Muza we did the very first start for the data collection and organization of the RESEARCH. I remember vividly our group discussions about what to do and the day Ronald created the name: Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (the RESEARCH). Kengo was an example of precision and accuracy and together with Muza (thanks a lot for the honor of choosing me as the paraninph of your thesis) were the first to show me the paths in the Thorax.

Shortly after that, Francesco Saia and Akis Arampatzis came. My two paraninphs. Aki, mag ik gara gara classics? I still have to go to Greece to visit you and to be introduced to real Greek food, though the things you have showed us in Delft were unforgettable. Akis, have you counted how many QCA's and other things were have worked out together? Akis is a conqueror. He came to Rotterdam alone, leaving his Vicky in Greece who was already waiting for the little (not so little) Alexandros. Even apart from his family and missing them as I know he missed, Akis managed to conquer his clinical and research training, and above all, the esteem of all his friends.

Francesco Saia. Or better, France, Chico, Chicão, Chiquinho. We have worked for 1 and a half year close by about 2 meters from each other (the "assistants room" had become progressively busy). With Chico and Barbara his wife, I learned more about respect and patience, food and ski (Francine's and mine last passion), Roma and San Valentino. Francine and I went to Italy twice with Chico and Barbara. There, we met their families (his father Toto knew Garrincha personally!!) and friends (thanks to Anna and Armando for the oil) and were introduced to Italy in a "non-touristic" way, which was wonderful. Francesco explained to me that espagueti a bolonhesa does not exist. And that macarrão does not exist (or that it does exist, but is just a type of pasta [which he is not very much fond of]). And that pasta can (must?) be eaten everyday. Fine. But now I am confused, especially after being explained by Angela that spaghetti bolognese (or spagbo, in the UK) is actually one of the most important and traditional dishes of the English cuisine. Chico, I have to express my heartfelt gratitude. Working together was a pleasure that I hope we will keep doing for the rest of our professional lives.

To Angela Hoye I owe a lot. We also used to sit about 2 meters from each other (the "assistants room" really got increasingly busy). I could see Angela helping everyone with the English language, working intensively in the lab, mastering the CTO stuff, and building up her own thesis. But above this, I have understood (though I am not even close to be able to do it) how to properly say "ectatic", "glycosilated hemoglobin", and "highly learned opponent" (something I will have to use during the thesis defense and which will pose no mercy on me – everyone will see that I still don't now how to pronounce it properly).

Then Andrew Ong appeared. And May, his wife, and little Natasha. Andrew is amazing. I had never seen anyone so multifocal. Knows about everything (and I mean everything). But above all, he has an extremely acute (and polite) sixth sense to "see" things. Andrew, I really regret that we could not work together for a longer period. Only less than 1 year. That was not enough. But at least I had time to introduce Natasha to good music (brazilian, of couse). The T-SEARCH is with you. Take care of the child. And Gaston Rodriguez, who went to Natal, Brazil for his honeymoon and got all camarões he wanted to. Gaston, I will go to Las Leñas and I hope I will get all snow I want to. Maniyal Vijayakumar, Vijay, Marco Valgimigli, and Jiro Aoki-san - fireworker, snow-boarder, traveler - that was a pleasure to work with you. Carlos van Mieghem, Carlão, with whom I worked closely in one of the last chapters of the thesis, which reminded me of the very first beginning of the works, when we forgot the world and digged into the case report forms, dossiers, films, and etc to get the data we needed. I thank Johannes Schaar, who is unravelling the vulnerable plaque puzzle with his palpography, for the nice dinners when we could get together and exchange our medical and non-medical ideas.

The assistants in the cath lab that shared the room with me in the last years and who many many times helped me with the Dutch language in "decoding" reports from referring hospitals, getting important clinical details from patients at 3:00 am, and calling patients. When I first arrived Timo Lerderink and Martin van der Ent were there. Then Marcel

Geleijnse, Ben Gho, Eric Duckers, Robert-Jan van Geun, Michelle Michels (thanks a lot for the "orthopedic" help for Francine), and Kadir Caliskan. I also thank all personnel, secretaries, nurses, and technicians from the Cath Lab. Titia, Mieke, Elles, Edith, Marjo, Janine, Anne Marie, Gio, Emile, Ben, Jurgen, John. And Jan Tuin and Paula Delfos. Everybody.

I am extremely indebted to all the seniors in the cath lab. During the entire period of data collection, clinical and angiographic follow-up of the study, they were all supportive. Frequently coming with details of a patient just seen 5 minutes ago, calling to my attention a complication that occurred on the weekend, helping in organizing the myriad of parallel analyses we intended to do, or giving their scientific feedback for a manuscript. Many thanks to Dr. Pieter Smits (I wish I could ski as you do. But, Pieter, why did you have to choose slalom as your specialty. That's too humiliating). To Dr. Georgios Sianos one of the largest contributors for the work in this thesis. Thanks a lot George. To Dr. Sjoerd Hofma, who kindly involved me in his exciting endothelial studies. Dr. Eugene McFadden is one of the most active, well-prepared, and generous people that I ever met. I deeply thank to Dr. Willem van der Giessen, my co-promotor, who on several times showed me hidden subtleties in a manuscript and who helped me to formulate the final propositions of this thesis.

Prof. Pim de Feyter is a gentleman, who I thank for agreeing to be part of the inner committee of this thesis. You were one of the first to come to me with a proposal to write a paper, only 5 weeks after my arrival at the Thorax. But above all, I am extremely grateful to you for allowing me to work with the multislice CT. That was a gift from you. It not only gave me the opportunity to learn something new, but also gave me the chance to work with the MSCT team, a unique experience. Koen Nieman, who knows parts of my Brazil that few people know (including me). Koen defended his *Cum Laude* thesis on the day of my birthday and gave me during his own thesis party a birthday gift (a "barbecuer") that helped making our weekends sunnier. That touched me extremely. I was the one who should be giving a gift. That gesture shows how large Koen's kindness is.

Filippo Cademartiri and Nico Mollet, two friends who I had never seen in bad mood and who had the patience to listen (and answer!) my questions of beginner. You shared with me your vast (and unique) experience with MSCT and helped me in developing conjoint projects. And we also drank some beers together. I have no words to thank you. Grazie. Bedankt.

Ron van Domburg is a separate chapter. He has been doing RESEARCH's for the last 20 years and I have no means to thank Ron for teaching me how to do, for letting me know how to know how, for opening to me without restrictions his database of a lifetime so I could learn the best way to organize our study. Ron, it goes without saying that this thesis is also yours. At Ron's, we had one of the headquarters of the RESEARCH, where a total of 6 medical students worked hard (Marco van Duuren, Leo Noordzÿ, Daan ten Keurs, Tommy Liu, Mahican Emeni, Karel Sonnenschein, and Joost Daemen). I need to thank Joost in special. His work capacity, accuracy, and sharpness are remarkable and were decisive for many manuscripts included in this thesis (which is clearly seen by the number of chapters he appears as author). At Ron's too, our subanalyses on psychological parameters and quality of life were worked out with Dr. Susanne Pedersen, also Professor at the University of Tilburg, and with Priya van Vooren, whom I thank sincerely.

In the "5th floor" there is the Clinical Epidemiology Group, headed by Dr. Eric Boersma, and their Friday sessions, which has given me important methodological lessons. There I found Nestor Mercado, my dearest friend, who was the very first person to invite me for a scientific work in the Thorax, a collaboration that we kept alive throughout may stay in Rotterdam that we will certainly maintain.

Arno Ruiter and Paul Cummins also stay in the "5th floor". Or better, they are everywhere. Arno is a marathoner. Only by thinking I get breathless. Paul is Paul. He is unique. Full stop. Or Non-Stop Paul. Thanks a lot for the two of them for everything we did together. Paul, I am wating for your visit. I had the pleasure in the same "5th floor" to see Nico Bruining and Sebastiaan working with their brilliant Intelligate IVUS. I also found in the "5th floor" Wil Barthelemy and Sarah Frasen, and Ad Van Druner, and Annet Louw, and all the others who also helped immensely.

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Family -

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My parents in law, Romildo and Lêda. Cristiane and Pedro with their Isabela, Natália, Júlia. Gisela and Osmar, with our Biazinha. Marcão and Letícia. Whom a missed as my other half. Porque vocês estiveram aqui conosco, presente sempre, é assim que sentimos.

And Francine, minha vida.

Curriculum Vitae

Pedro A. Lemos was born in Brasilia, Brazil on June 4th 1970. He obtained his medical degree in 1993 at the University of Brasilia, Brasilia, Brazil. He completed his training in the University of São Paulo Medical School from 1994 to 1999, which included internal medicine, clinical cardiology, and interventional cardiology. He worked as a senior cardiologist at the Emergency Department of the Heart Institute of the University of São Paulo Medical School, and in 2000 assumed his current position as a senior interventional cardiologist at the same institution. During a sabbatical leave from January 2002 to April 2004, he worked as a research fellow at the Interventional Cardiology Department of the Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands, under the supervision of Professor Patrick W. Serruys.

Pedro A. Lemos is a member of the São Paulo State Society of Cardiology, of the Brazilian Society of Cardiology, of the Brazilian Society of Interventional Cardiology, and of the Latin American Society of Interventional Cardiology.

List of Publications

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