A NEW ERA IN INTERVENTIONAL CARDIOLOGY: DRUG ELUTING STENTS; FIRST CLINICAL EXPERIENCE

Een nieuw tijdperk binnen interventie cardiologie: met medicijnen voorziene stents; de eerste klinische ervaringen

Cover illustrations:

Front Cover : ***"Pacific Yew Tree"*** (source of ***"taxus brevifolia"***):
The garden of the drug store and head physician`s pavilion.
Topkapı Palace-İstanbul

Back Cover : On the left; Erasmusbrug (-bridge), Rotterdam
On the right; Bosphorus Bridge (Boğaziçi Köprüsü), İstanbul

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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 defence shall be held on

Wednesday, December 17, 2003 at 9.45 hours

by
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born at Diyarbakır, TURKEY

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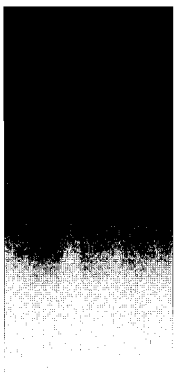
Financial contribution for the production of the thesis from the 'Nederlandse Hart Stichting' is gratefully acknowledged.

Babam, Annem, Levent ve Ayşe`ye
Ve beni sabırla destekleyenlere....
Ve Hacı Recep Efendi`ye
Ve Kaya Bey`e



INTRODUCTION AND OVERVIEW OF THE THESIS

Percutaneous treatment for atherosclerotic coronary artery disease has developed rapidly in the last 20 years. At the beginning, balloon angioplasty was used. However, restenosis mainly due to negative vascular remodeling and neointimal hyperplasia and acute closure of the vessel remained major limitations of the balloon angioplasty.

In-stent restenosis (Part-I)

Coronary stents have resolved many of the problems of balloon angioplasty by preventing negative remodeling, residual dissection and elastic recoil. Now, coronary stenting has become the most frequently performed percutaneous coronary intervention. However, although stents significantly reduce restenosis when compared with balloon angioplasty, restenosis rates are still high at follow-up. Furthermore, the treatment of in-stent restenosis (ISR) is technically challenging, costly and the recurrent restenosis rate is extremely high. Alternative treatment modalities were clearly required for prevention of ISR.

Drug eluting stents (Part-II)

The systemic drug therapies to prevent restenosis have been disappointing. Intracoronary radiation is an important therapy to prevent restenosis after percutaneous transluminal intervention. However, the widespread use of intracoronary radiation therapy is limited by considerable logistic requirements and potential side effects. Advances in the understanding of the cellular mechanisms responsible for neointimal proliferation and improvement in local drug delivery technology have provided to develop drug eluting stent (DES) for preventing ISR.

The development of DES has generated tremendous enthusiasm in prevention of restenosis. Local administration of drug offers advantages. The active drug can reach the vessel at the time of vessel injury. The DES is simple to use and provide higher tissue concentration of the drug. Systemic release of drug is minimal and may reduce the risk of systemic toxicity.

A precise understanding of the molecular events responsible for the neointimal hyperplasia has also allowed a rational selection of potential therapeutic candidates for stent based delivery to prevent restenosis. The leading first generation antiproliferative agents for drug-eluting stents have been selected from a large list of candidate drugs. Currently, lead investigational agents include sirolimus, paclitaxel, actinomycin-D, everolimus and dexamethasone.

First clinical experiences with sirolimus eluting stents (Part-III)

Sirolimus (rapamycin), an inhibitor of in-stent restenosis in the coronary arteries, is having a substantial effect on the care of patients with coronary artery disease, was discovered in a soil sample from Easter Island (known locally as Rapa Nui). A naturally occurring product that is isolated from Streptomyces hygroscopicus, sirolimus is an extremely lipophilic (hydrophobic) macrolide that was initially developed as an antifungal agent on the basis of its ability to inhibit the growth of yeast. Although it was discovered in the 1970s while screening fermentation products, more than 20 years after it was demonstrated that sirolimus is a potent immunosuppressive agent with anti-inflammatory and anti-proliferative effects. Subsequently, it was reported that sirolimus significantly reduces the proliferative response after coronary angioplasty. Preclinical efficacy studies showed 35%-%50 reduction in in-stent neointimal hyperplasia with sirolimus-eluting stents (SES) compared to bare metal stent in animal models.

In this part of the thesis, we evaluated recent clinical applications and intravascular ultrasound findings of SES for the treatment of both de novo and in-stent restenosis. In addition, we addressed the question regarding fate of site branches after SES implantation for de novo coronary lesions. In order to evaluate the long-term efficacy of SES, the persistence of neointimal hyperplasia inhibition were investigated by intravascular ultrasound at 2 years follow-up.

Evaluation of vessel wall response to drug eluting stents (Part-IV)

Although the inhibition of neoitimal hyperplasia is remarkable, the effects of SES on the vessel wall have not been fully investigated in man using serial volumetric intravascular ultrasound (IVUS) follow-up. Animal studies have demonstrated that the histological characteristics of DES are similar to those after intracoronary brachytherapy which raises the concern of potentially increased stent malapposition, aneurysm formation, edge effect and late thrombosis.

A sub-analysis of the first 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 that included all patients with IVUS investigation at 6 month follow-up revealed a 21% incidence of incomplete stent apposition (ISA) in the SES group compared to 4% in the the bare stent group ($p<0.001$). The interpretation of the data is limited by the lack of baseline IVUS immediately after stent implantation. However, these findings raised the question whether, and to what extent, SES affect the plaque burden behind the stent struts as well as vascular remodeling. In part IV, we evaluated the effect of DESs (sirolimus and paclitaxel) on the coronary vessel wall and remodeling as well as the incidence of incomplete stent apposition and aneurysm formation by serial three-dimensional IVUS.

Paclitaxel, is a Taxol derivates and microtubule inhibitors that prevent cell migration and proliferation by inducing the mictotubules to form long, stable chains. Paclitaxel's mechanism of action consists of polymerization of tubulin, which results in the formation of abnormally stable and nonfunctional microtubules. Previous in-vitro studies demonstrated inhibition of migration and proliferation of vascular smooth muscle cells by paclitaxel. In the TAXUS trials, were a large randomized trial designed to test the safety, feasibility, and effectiveness of paclitaxel eluting stents for the treatment of de novo coronary lesions.

In Taxus-II, compared with a bare metal stent, paclitaxel-eluting stents reduced in-stent neointimal formation and restenosis and improved 12-month clinical outcome of patients with single de novo coronary lesions. Similar to SESs, in paclitaxel eluting stents there were some concerns regarding edge effect and vessel wall response to the eluted paclitaxel. In this part of the thesis, we also reported more detailed IVUS analysis of distal and proximal edge of the stent and the changes at peristent area after paclitaxel eluting stent implantation.

The performance of drug eluting stent in the " real world" (Part V)

The FIM and RAVEL trials, in simple lesions subset, have demonstrated no restenosis with dramatic clinical improvements. However, with the broader application of the technique in the (SIRolImUS-coated Bx Velocity stent in the treatment of patients with de novo coronary artery lesions) SIRIUS, it was shown that restenosis was markedly reduced but was not eliminated. Therefore, in part V, for the first time, we investigated the efficacy of SES in the everyday practice. We addressed the question that, is SES implantation is safe and effective in unselected patients including, unstable angina, acute myocardial infarction, and complex coronary lesions?

The failure: Actinomycin-D eluting stents (Part-VI)

The impressive results in the prevention of in-stent restenosis obtained by drug-eluting stents releasing sirolimus or paclitaxel have led to the evaluation of several antiproliferative drugs and delivery platforms in order to reduce ISR.

Actinomycin-D is an anticancer drug that selectively inhibits RNA synthesis. Following preclinical studies, the ACTION (Actinomycin-D Eluting Stents Improve Outcomes by Reducing Neointimal Hyperplasia) study was a large randomized trial designed to test the safety, feasibility, and effectiveness of 2 different\ doses of actinomycin-D eluting stents for the treatment of de novo coronary lesions. In this part of the thesis, the findings of ACTION trial were evaluated.

Stenting in percutaneous coronary revascularisation: From balloon angioplasty to Drug eluting stents

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Background

Atherosclerotic coronary artery disease (CAD) has a major impact on health and on medical economics. Much of the clinical presentation of CAD is the result of disease progression, which may occur slowly over time or as a more dynamic modification in the coronary atherosclerotic plaques. The aims of invasive treatment of patients with coronary artery disease are stabilization of the plaque and alleviation (or resteration) of coronary flow limitation. Mechanical means to eliminate the effects of plaque obstruction, either by coronary surgery or by percutaneous intervention, may play an important part in improving the outcome and quality of life in patients with CAD.

Over the last 20 years, percutaneous coronary intervention (PCI) has become an increasingly used and successful treatment option. Over 1.5 million percutaneous coronary revascularisation procedures are performed annually world wide, most being intracoronary stenting.

The percutaneous transluminal coronary angioplasty:

Until the 1990s percutaneous balloon coronary angioplasty (PTCA) alone was the main method of undertaking PCI. A number of studies had demonstrated its superiority in decreasing angina and improving outcomes in selected patients compared to medical treatment alone, but results varied when it was compared to coronary artery bypass surgery (CABG). The ACME trial[1] compared angioplasty with medical treatment for patients with single vessel disease and exercise induced myocardial ischaemia. At six months 64% of the medically treated group still had angina compared to 46% ($p < 0.01$) of the angioplasty group who were largely not taking anti-anginal medication. The value of intervention in improving symptoms was further supported

by the RITA-2 trial,[2] with a significant improvement in exercise tolerance in those treated with angioplasty. The longer term results versus surgery were, however, less convincing. Additionally, RITA -1[3] trial showed that early mortality was similar, but at 6 months those patients randomised to coronary angioplasty (PTCA) had a higher incidence of angina (32% versus 11%), and a higher need for revascularisation (38% versus 11%) compared to those patients who underwent surgery. This recurrence rate did not fall despite multiple drug trials designed to test whether the response of the vessel wall to balloon damage could be attenuated.

Published meta-analyses[4] indicated that while there is no notable difference in mortality between PTCA and surgery at one and 3 years, further intervention is required more frequently in the angioplasty patients; in the first year 33.7% of patients initially treated with angioplasty required a further procedure compared to 3.3% of those treated with surgery **(Figure1).** Balloon angioplasty alone improves symptoms compared to medical treatment, but because of early failure the procedure is worse than surgery in the short and medium term follow up.

Problems with balloon angioplasty

Balloon intervention suffers from two major (acute and chronic) problems.

Acute: High pressure balloon inflation induces less controlled disruption of the atherosclerotic plaque, which may cause extensive intimal dissections with vessel thrombosis and (sub)acute closure, the leading cause of short-term failures of angioplasty in earlier series. Mortality rates of up to 16% had been reported under these circumstances, depending on the patient's clinical condition at the time of urgent surgical referral.[5,6]

These complications have partially been overcome by improving the recognition of high-risk coronary lesions[7] and by technological improvements such as the introduction of coronary stents. Stent use has being advocated to improve outcome following acute coronary closure, the concept being that scaffolding of the loose and potentially obstructive intima would restore flow and reduce the need for emergency coronary surgery. The outcome following stent placement for bailout appeared good, with mortality rates of less than 5%.[8] Roubin et al[9] have obtained optimal angiographic result can be in 93% of cases after bailout stenting, with a mortality rate of 1.7%. Clinical evidence suggests that the earlier the stent is deployed after a poor angiographic result, the better the outcome. Indeed, one reason for the increase in stent use was the desire not to wait until the artery closed, at which time stenting is more difficult and potentially unsuccessful.

Chronic: Initial concepts on recurrence or restenosis after balloon angioplasty centred on the neointimal (smooth muscle cell) response. However, clinical drug trials to limit the impact of smooth muscle cell hyperplasia were generally not successful.

Concepts evolved to include the importance of the acute luminal diameter gain, recoil, and the impact of negative remodelling. It was generally felt that such mechanical issues were more important than the impact of tissue in-growth.

Negative remodelling is a major cause of human angioplasty restenosis, where > 40% of specimens retrieved at necropsy show no evidence of neointimal formation.[10] Intravascular ultrasound studies also show that remodelling causes between two thirds and three quarters of the lumen loss in restenosis lesions.[11] The mechanisms that contribute to remodelling after balloon angioplasty, as well as whether remodelling represents primarily a medial or adventitial response to injury, are still currently unknown. Nevertheless important, vessel remodelling is virtually abolished by stent implantation.

The larger the lumen that can be achieved and maintained after PCI, the less impact any restenotic tissue might have.[12] Additionally 60% or so of the loss of lumen is caused by elastic recoil and negative remodelling. Quantitative angiographic data from a number of trials clearly showed that stents produced a significantly greater acute luminal gain,[13] and prevented recoil. Although tissue response to stenting is exacerbated it has less impact since the arterial lumen is larger. Serruys et al[13] presented that the difference in final acute minimal luminal diameter can be increased from about 1.7mm with angioplasty to about 2.7 mm with stents.

Coronary stenting for the treatment of coronary artery disease:

Stents represent a major advance in the treatment of obstructive coronary artery disease since the advent of balloon angioplasty. The mechanical properties of stents permit scaffolding the vessel from its endoluminal side, allowing the repair of dissected and occluded coronary arteries and alleviating the need for urgent bypass surgery.

In 1991, stent use was still facing skepticism because of an unacceptably high (20% to 25%) incidence of thrombotic complications.[14] Systemic anticoagulation proved disappointing in reducing the catastrophic consequences of stent thrombosis, such as myocardial infarction and sudden death. However, after documentation of their effective anti-restenotic effect[13 15] and the obviation of the need for anticoagulation after the development of high-pressure implantation techniques and potent dual antiplatelet schemes,[16-18] coronary stent utilization has been increasingly applied since and is currently the main method of percutaneous revascularization. Angioplasty procedures doubled in Europe between 1992 and 1996,[19]while an estimated 601 000 percutaneous coronary revascularizations were performed in the United States in 1997.[20] The popularity of coronary stents is due not only to the fact that they reduce restenosis, but also that they are relatively easy to use and result in a reliable, superior angiographic aspect.

Stenting versus balloon angioplasty:

Two major trials (BElgian NEtherlands STENT [BENESTENT-I][13] and STent REStenosis Study [STRESS][15]) have clearly shown that stenting in native vessels reduces the incidence of recurrence. In terms of reduction in restenosis rates, the results were remarkably similar in both trials. In the BENESTENT study, the primary clinical end points of myocardial infarction, need for CABG or re-PTCA, and stroke had a relative risk of 0.68 (95% confidence interval 0.5 to 0.92) in those patients randomised to stenting compared to those undergoing PTCA alone ($p = 0.02$). The angiographic restenosis rate, measured quantitatively on follow-up angiogram, was 22% for stenting and 32% for PTCA. For the STRESS trial the restenosis rate was 29.1% for stenting versus 42% in the PTCA arm ($p = 0.011$). A number of equivalence studies have now been published comparing newer stents with the stents used in these trials. Any stent which produces a good acute result leads to recurrence rates of between 15–20% compared to historical results of 35% for PTCA. The MUSIC,[21] and FINESS[22] trials have confirmed even lower restenosis rates. Use of intravascular ultrasound to optimize the best possible result leads to restenosis rates of <10%, but this cannot be justified in terms of time and costs.

Stenting versus surgery:

Coronary stents, used as an adjunct to PTCA, reduce restenosis and the need for repeat revascularisation. Stents should have made an impact, reducing the difference between PCI and coronary surgery when compared with those previous studies of angioplasty versus surgery. There are a number of randomised studies comparing stenting with surgery for multivessel disease. In the ARTS trial,[23] treatment according to randomisation was successful in 97% of patients treated with stents and 96% of those treated with surgery. Only 0.5% of stented patients needed urgent bypass grafting and a further 1.7% needed elective surgery. At one year the rates of death, acute myocardial infarction or stroke were low and did not differ between the groups (9.5% PCI versus 8.8% surgery). However, the event-free survival was higher in the surgical patients (87.3% versus 73.3%) due to the need for reintervention in the stented patients. While eliminating in-stent restenosis is the current research aim for many groups worldwide, even when as in this study it results in a 14% difference in need for reintervention, stenting remains cost effective compared to surgery.

The Stent or Surgery (SoS)[24] trial was also conducted to assess the effect of stent-assisted percutaneous coronary intervention (PCI) versus CABG in the management of patients with multivessel disease. The primary outcome measure was a comparison of the rates of repeat revascularisation. Secondary outcomes included death or Q-wave myocardial infarction and all-cause mortality. All patients were followed-up for a minimum of 1 year and the results are expressed for the median follow-up of 2 years. 21%

of patients in the PCI group required additional revascularisation procedures compared with 6% in the CABG group (p<0.0001). The incidence of death or Q-wave myocardial infarction was similar in both groups (PCI 9%, CABG 10% p=0.80). There were fewer deaths in the CABG group than in the PCI group (PCI 5%, CABG 2%; p=0.01). SOS trial indicated that the use of coronary stents has reduced the need for repeat revascularisation when compared with previous studies that used balloon angioplasty, though the rate remains significantly higher than in patients managed with CABG. Therefore, in-stent restenosis caused by intimal hyperplasia remains a problem.

The problem: In-stent restenosis

Restenosis is the most important limitation of stent implantation for coronary artery disease. The absolute number of in-stent restenotic lesions is increasing in parallel with the increasing number of stenting procedures and with complexity of culprit lesions. While this may be < 10% for intravascular ultrasound (IVUS)-guided selected cases and 15% for BENESTENT-like lesions, these figures may be significantly higher for more complex patients trated in the so-called "real life". For the 1.5 million angioplasties carried out worldwide each year at a stent rate of 85%, repeat procedures would be required in ~ 200000 patients.[25] The situation, however, is worse than this. Certain patient subsets have a higher incidence of in-stent restenosis. Data suggest that the rates are higher for both small vessels stented (up to 45%) and for multiple stents (32%).[26,27] Diabetics are a particular at risk group, and pre-stenting surgery was advocated based on the BARI trial data. In-stent restenosis rates of up to 55% have been reported.[28]

Mechanisms of in-stent restenosis

The mechanisms involved in the restenosis after balloon dilatations are elastic recoil of the artery, local thrombus formation, vascular remodelling with shrinkage of the vessel and an exuberant healing process with neointimal cellular proliferation and matrix synthesis.[11] Stent implantation minimizes elastic recoil and remodelling of the treated vessels; however, stents exacerbate the normal proliferative reaction in response to the traumatizing intervention.[29] Therefore, the response to vascular injury resulting from a stent implantation differs from that caused by PTCA alone.

After PTCA, neointimal proliferation occurs at the site of disruption of the internal elastic lamina.[30]Histological data from trials on porcine coronary arteries have demonstrated that appropriately sized stents, once implanted, compress the media, but do not fracture the internal elastic lamina; thus, leading to very little neointima formation. Neointimal proliferation is stimulated proportionally to the depth of strut penetration into the elastic lamina or a lipid core and the importance of medial fracture.[31]

Pattern of cell response: Stent struts provide a scaffold for the formation of platelet-rich thrombi into which inflammatory cells from the circulation migrate. Metallic stent struts activate platelets and macrophages. Cytokines and growth factors also contribute to smooth muscle cell proliferation. In addition, upregulation of genes and metalloproteinases leads to cell growth, remodeling of extracellular matrix, and smooth muscle cell migration. [32]A combination of these factors may result in significant luminal narrowing several months after stent placement. Each of these processes is a potential target for antirestenosis therapy.

Risk factors associated with in-stent restenosis:

Several risk factors have been determined by multivariate analysis of different stented populations. A greater likelihood of stent restenosis has been associated with certain situations.

Stent implantation at the site of a restenotic lesion: Repeat PTCA or stenting for restenotic lesions is associated with a high rate of restenosis.[33] The different histological substrate of restenotic lesions may predispose to a higher incidence of restenosis, although this association has not always been found after correction for confounding variables.[33]

Multiple stent implantation: This association has been reported in several studies.[27]One proposed mechanism is related to the overlapping of stents; however, more recent reports have failed to confirm this association.[34,35]

Extent of the residual stenosis: Early quantitative angiographic studies have demonstrated that final lumen diameter is the best inverse predictor of restenosis.[36] This has been confirmed by more recent IVUS assessment of the minimal stent lumen cross-sectional area **(Figure 2).**[37] An increased residual plaque burden has also been associated with a higher rate of restenosis.[38]

Diabetes mellitus: The involved mechanisms are not clearly understood, but increased level of growth factors, including insulin itself, may promote smooth muscle cell proliferation and matrix protein secretion. Diabetic patients have an increased risk of restenosis and also a higher risk of death and myocardial infarction.[28,39]

Other risk factors: Certain factors, such as total occlusions,[40] venous bypass grafts,[41] small vessels[26,42] or long lesions,[43]are well recognised to increase the risk of restenosis. Other factors such as a residual dissection flap, high inflation pressure stent implantation or a left anterior descending localisation, remain controversial, as does the role of a full metal jacket in difficult long lesions. **Figure 3** summarises the univariate analysis of the clinical and quantitative coronary angiographic (QCA) predictors of coronary restenosis investigated in a total of 9,120 treated lesions in 8,156 patients (36% with stent). All the QCA were analysed in the same corelab.[44]In the multivariate analysis, only the use of stent (OR 0.83, 95% CI 0.72–0.97); the lesion length (OR

1.05, CI 1.04–1.06); the post-intervention minimal lumen diameter (OR 0.53, CI 0.46–0.61); a previous CABG (OR 0.69, CI 0.53–0.9); and diabetes mellitus (OR 1.33, CI 1.16–1.54) were found to be predictors of restenosis.

Prevention of in-stent restenosis

A countless number of studies have evaluated the anti-restenotic properties of many mechanical devices and drugs has been done to prevent restenosis, none of them proving to be effective in reducing the incidence of in-stent restenosis. Experience with systemically administered drugs, such as antiplatelet agents, anticoagulants, calcium-channel blockers, angiotensin converting- enzyme inhibitors, cholesterol-lowering agents, and antioxidants, has proven negative. These agents were previously tested in animal models and found to be beneficial. The lack of efficacy in human studies may be in part due to insufficient concentration of drug at the injury site or lack of chronic dosing. In general, although animal models provide new insight into the mechanism of restenosis, biological and mechanical differences meant that therapeutic success of anti-restenotic therapies was not achieved in human beings.

Intracoronary radiation has emerged as a promising modality to attenuate the intimal hyperplastic reaction.[45,46] Despite the lack of benefit for preventing restenosis in de-novo lesions, brachytherapy was effective in reducing recurrent restenosis. However, edge restenosis and late thrombosis are providing some concerns about the potential lifelong effects of this approach.

Based on the review of the mechanisms of restenosis, it appears clearly that stents offer major advantages with the prevention of the negative recoil and the prevention of abrupt vessel closure. However their use could only be generalized with an optimal, local, control of the intimal hyperplasia process. This concept led to the development of drug-eluting stents (DES).

Drug eluting stents

***The clinical benefits*:** Several antiproliferative agents with different stent design are under investigation for their safety and efficacy in the treatment of coronary lesions. Sirolimus is a natural macrocyclic lactone with potent immunosuppressive and anitimitotic action, which was approved in 1999 as an antirejection drug in renal transplant recipients. Sirolimus blocks cell-cycle progression and expression of inflammatory cytokines, thus inhibiting cellular proliferation. With the hypothesis that the immunosuppressive properties of sirolimus might inhibit neointimal proliferation, a drug eluting stent was made by coating the stent with sirolimus[47].

Since the first report of human experience with drug eluting stent made in Sao Paulo[48] and Rotterdam[49] demonstrating the striking impact of drug eluting stents on neointimal proliferation with remarkable improvement of patient outcome, many clin-

ical controlled studies have been performed or still ongoing. In the first RAndomized study with the sirolimus-eluting Bx VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions (RAVEL),[50] which included patients with single, noncomplex de novo lesions, the rate of binary angiographic restenosis after sirolimus-eluting stent implantation was zero at 6 months. The efficacy of sirolimus-eluting stents was confirmed in the subsequent multicenter randomized double-blind study of the sirolimus-coated Bx Velocity stent in the treatment of patients with de novo coronary artery lesions (SIRolImUS-eluting Bx velocity balloon expandable stent trial; SIRIUS)[51]. In this study, in-stent binary restenosis (within the margins of the stent) was reduced by 91% (3.2% versus 35.4%; $P<0.01$) and in-segment restenosis were reduced by 75% (8.9% versus 36.3%; $P<0.01$).5 In the SIRIUS trial[51], 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), in patients treated either with sirolimus-eluting stents or with bare stents. However, sirolimus-eluting stents markedly reduced restenosis for patients at both extremes of the risk spectrum **(Figure 4).** Nondiabetics with short lesions (12 mm) and large vessels (>3.0 mm) had an 81.7% risk reduction of in-segment restenosis, whereas patients at the highest risk (diabetics with longer lesions [>15 mm] and small vessels [<2.5 mm]) 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 (ie, no restenosis) as patients in the upper tertile (reference diameter >2.84)[52].

Paclitaxel is a potent antineoplastic drug that polymerises tubulin, leading to the formation of abnormally stable and nonfunctional microtubules. Cell replication is blocked in the G0/G1 and G1/M phases and a reduction of vascular cell proliferation and migration has been demonstrated.[53]

Non-polymer–coated paclitaxel-eluting stents have been shown to reduce binary angiographic restenosis in the European evaLUation of a Taxol-Eluting Stent trial (ELUTES)[54] and the ASian Paclitaxel-Eluting stent Clinical Trial (ASPECT).[55]In these studies, non-polymer paclitaxel stents (high-dose formulation) were associated with 3% and 4% binary angiographic 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).[56] In this study, the incidence of in-segment restenosis at 6 months was reduced from 20% and 24% in the bare stent group to 6% and 9% in the slow- and moderate-release paclitaxel stent formulations, respectively. However, when patients treated only with the study stent were analyzed, 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,[57] in which patients treated with the slow-release polymer-covered paclitaxel stents showed no restenosis, as compared with 10% in the control group. **(Figure 5)**

Concerns regarding drug eluting stents: The randomized multicenter SCORE trial[58] (Quanam stent, paclitaxel-derivative coated) was intended to evaluate efficacy of the QuaDS-QP2 stent, which is covered by external polymer sleeves as drug delivery system versus the bare stent. At follow-up, the interim SCORE analysis revealed significant reduction in in restenosis in the drug eluting stent group (6.4% vs 36.9%). In contrast to this beneficial findings, due to both frequent stent thrombosis and side branch occlusion caused by sleeve covered stent design the 30 day MACE was 10.2 % and incidence of procedural MI was 7.1%. Due to these negative results the trial was stopped.

In the registry of 15 patients implanted with QuaDS-QP2 stents for the treatment of in stent restenosis, 6-and 12 months angiographic restenosis rates were dismal 13% and 62%, respectively[59]. The reports from the same series of patients, 16 have described a late catch-up phenomenon after implantation of a high-dose paclitaxel-derivative QP2-eluting stent.. Histological analysis showed signs of delayed healing with active inflammation still present at 1 year. However it was speculated that that delayed restenosis at 12 months might be related to toxic tissue tissue levels of the drug and/or inflammatory reaction to the polymer[59].

These findings raised some concerns regarding the thrombosis and late cath-up phenomenon. 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 years, without any evidence of sub acute or late thrombosis and late catch-up restenosis.[60] and in the RAVEL trial, 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 the TAXUS I-II, ELUTES, and ASPECT trials[54-57]. However, a very delayed loss of the initial benefit, at 3–4 years follow-up, cannot yet be ruled out.. We can conclude that the overall clinical success of any drug-eluting stent may be dependent on multiple stent structure design factors and not the drug alone. Therefore, short-term as well as long-term efficacy should be evaluated separately for each drug-eluting stent.

Aneurysm formation and malapposition has been reported in normal swine coronary arteries following high dose paclitaxel drug eluting stent. In the RAVEL trial, stent malapposition was more frequent at 6 months in sirolimus-eluting stent patients than in the control arm. Moreover, in SIRIUS, late acquired stent malapposition was more commonly observed in the sirolimus group. However, in TAXUS II[32] patients treated with bare stents or with paclitaxel-eluting stents, there were similar rates of late acquired malapposition. Nevertheless, these ultrasound observations of late malappo-

sition have not been associated with any adverse events throughout the follow-up period in any of these studies. Coronary aneurysm formation was identified <2% of patients and was similar in both bare metal stents and drug eluting stent arms of both paclitaxel and sirolimus eluting stent trials.

Clinical studies with drug eluting stents thus far constitute single vessel disease, short, and long lesions (lesions up to 30mm) and vessel diameter ranging from 2.5 mm to 3.5mm; many other lesion types remained unstudied. Despite dramatic clinical improvements in the early studies mostly in simple lesions subsets, today it appears that they do not offer a zero-percent restenosis rate. In SIRIUS trial, restenosis did occur in 9% of the cases. Indeed, in diabetics with small vessels and long lesions, in-segment restenosis was observed in 23.7% of cases. Therefore, these new technologies have to prove their efficacy in the "real world" of interventional cardiology. In order to evaluate this concern, 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 anatomic restriction, and the incidence of major adverse cardiac events is to be evaluated (defined as death, nonfatal myocardial infarction, or repeat revascularization).

***The costs of drug eluting stents*:** In the mid 1990s, when use of the Palmaz-Schatz stent reduced angiographic restenosis from 32% after balloon angioplasty to 22% in the stent group, interventional cardiology moved into the "stent era", stents being implanted in 70–90% of PCI procedures. The impact of a device which promises to reduce restenosis (relative to a conventional stent) more than the Palmaz-Schatz stent did in the past (relative to a balloon) was, therefore, be easily visualised. Therefore, it is natural that interventionists want drug eluting stents, and patients demand them. This enthusiasm, however, comes with a cost. The SES is being marketed in the Europe almost fivefold that of a bare stent. This creates an important evaluation of the financial implications of its use, at a time of expansion in PCI, in an increasingly cost conscious health service.

The cost and effects analysis of RAVEL trial, after 1 year the adjusted event rates were 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 6),** with a minimal increase in costs for an ~60% risk reduction in the worst-case scenario[61]. Since in this study, only simple lesions were treated with implantation of a single stent, and the late target lesion revascularization was zero, the cost estimations derived from the RAVEL trial cannot be directly extrapolated to other situations. Therefore, the balance between costs and effects in more complex situations, in which restenosis may occur in a small but sizable number of patients, has to be specifically analyzed.

Conclusion

Stent-based drug delivery applied directly at the site of vessel injury represents a very attractive and emerging technique which provides both the mechanical advantages of stenting (prevention of elastic recoil and negative remodeling) along with a biological solution (pharmacological antiproliferative action) for the prevention of restenosis. Given the results available so far, local administration of anti-proliferative and immunosuppressive drugs delivered by coronary stents is the most promising technique in the treatment of coronary artery lesions ever tested. The results of recently reported randomized clinical trials on drug eluting stents have demonstrated a remarkable reduction of in-stent restenosis as compared to bare stents. These results are not achieved by any other technique or drug therapy. However, further investigations and additional data are required for subsets still under investigation, such as chronic total occlusions, bifurcations, small vessels, left main stem and very long lesions. Moreover, some additional questions are still to be addressed. For example, how long will the inhibitor effects of DESs persist? And will there be subgroups of patients such as those with diabetes who are more resistant than others to the therapeutic actions of DESs? Hopefully, after the completion of planned and ongoing trials many of these issues will be answered.

Based on these initial impressive results of drug eluting stent, we could expect a dramatic change in the clinical practice which will open a new "era" of interventional cardiology. The clinical impact of the elimination of restenosis will influence the approach to coronary artery disease, the future of cardiac surgery and health-economics in cardiology.

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Figure Legends

Figure 1 : Percutaneous transluminal angioplasty (PTCA) versus coronary arter bypass graft (CABG) surgery.

Figure 2 : Restenosis rate in function of the stent length and the minimal cross sectional area after stent implantation, as asses by IVUS (adapted from de Feyter et al.)

Figure 3 : Univariate predictors of restenosis (adapted from Mercado et al)

Figure 4 : Detailed beneficial effect of sirolimus eluting stent (Moses et al)

Figure 5 : Binary restenosis rates of both drug eluting stent (DES) and bare metal stent (BMS) group.

Figure 6 : Probability ellipses concerning both costs and effects at 1 year of sirolimus-eluting stent (SES) vs bare stent in the RAVEL trial. (Adapted from Lemos et al)

Figure 1

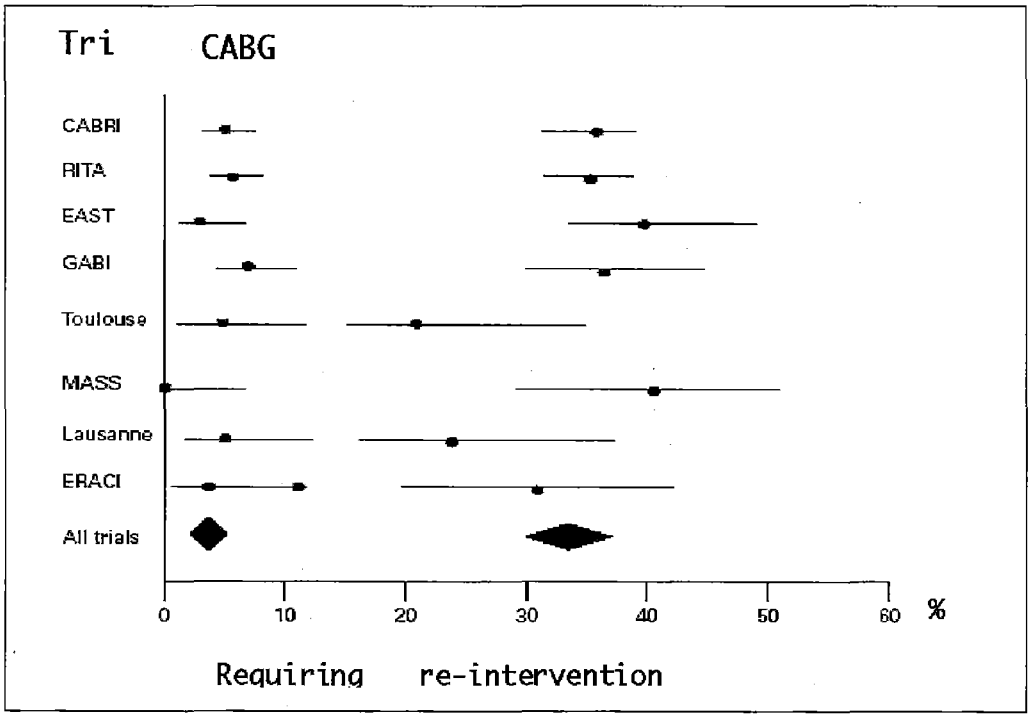


Figure 2

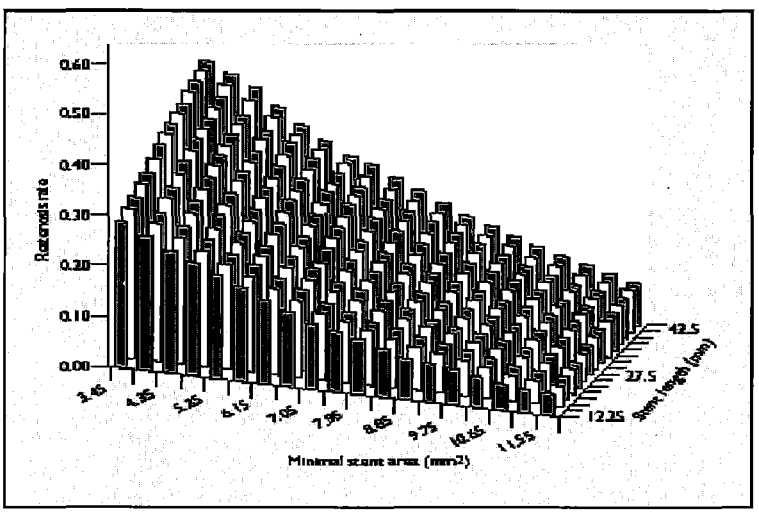


Figure 3

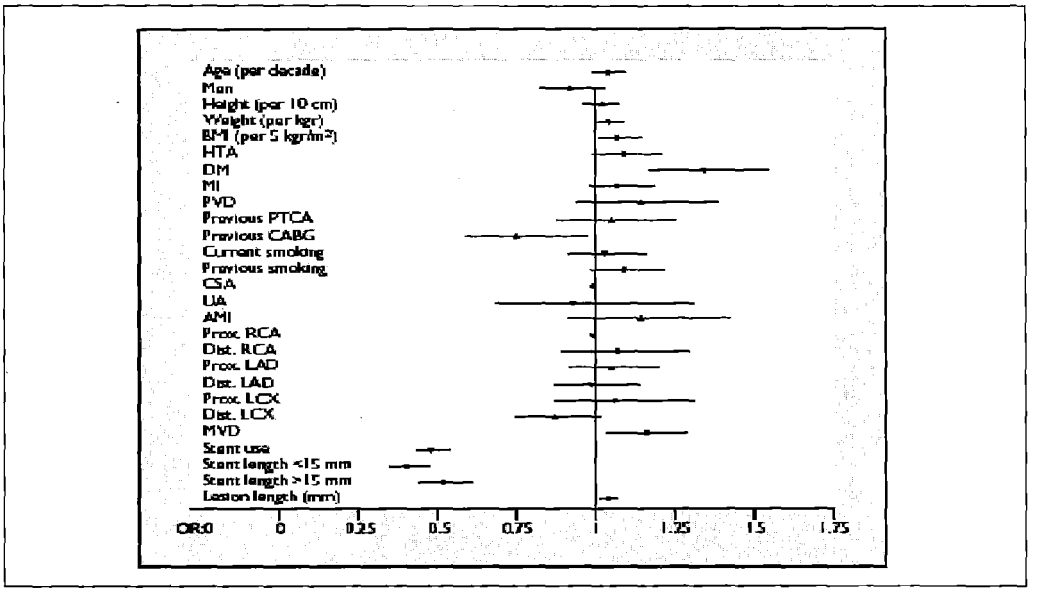


Figure 4

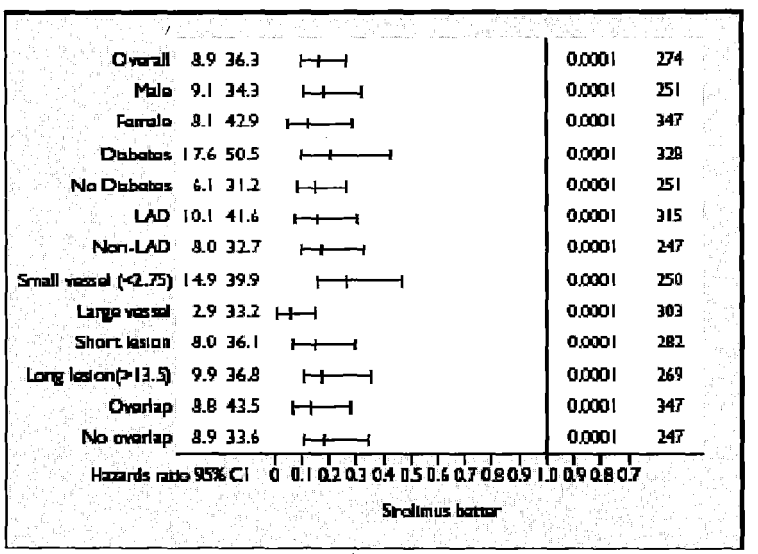


Figure 5

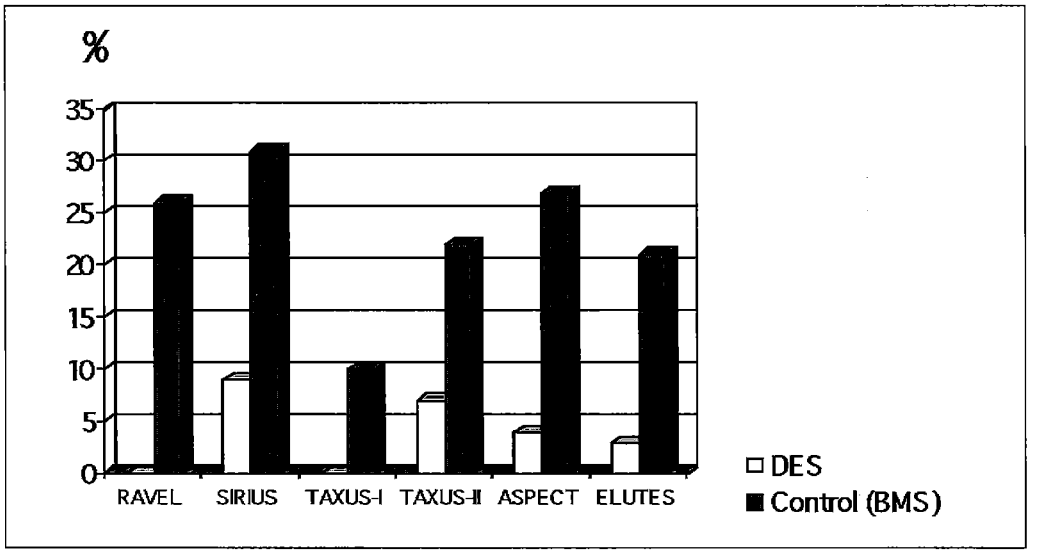
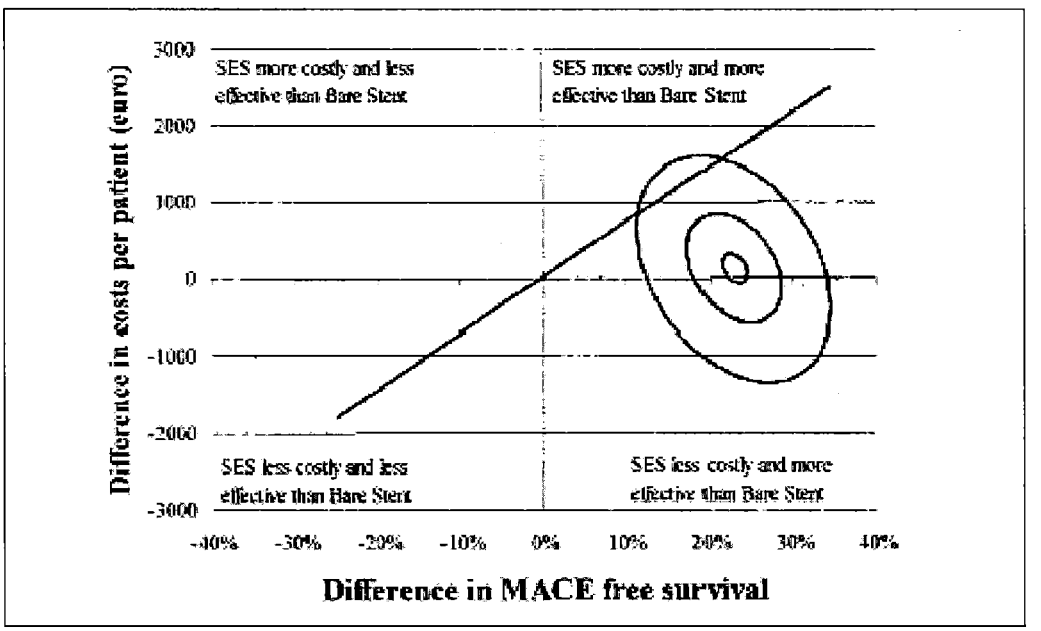
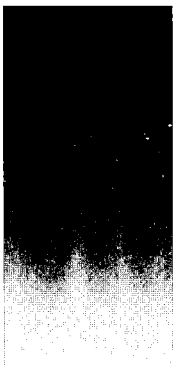


Figure 6





CHAPTER 2

OTHER STAINLESS STEEL STENTS AVAILABLE OUTSIDE THE UNITED STATES AND IN DEVELOPMENT

Muzaffer Degertekin, Michael J.B. Kutryk, Patrick W. Serruys

Textbook of Coronary Stenting [Section-II Chapter14]
Editors: Gregg W. Stone and Martin B. Leon
In press

Other Stainless Steel Stents Available Outside The United States And İn Development

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INTRODUCTION

The first human implantation using the self-expanding Wallstent was carried out in 1986[1]. However, initial development of coronary stents was hampered by several problems. Firstly, the risk of subacute thrombotic coronary artery occlusion several days after the procedure emerged as a novel, stent-specific hazard, prompting complex anticoagulation regimens associated with increased bleeding and prolonged hospital stays[2] [3-6]. Secondly, although, the Wall stent, Palmaz-Schatz, the Gianturco-Roubin and Wiktor stents developed concurrently, they were only available to selected centers under strict research regulations and stent usage could not expand. Thirdly, the limitation of stenting to acute and threatening occlusions of coronary lesions after angioplasty yielded early success and complication rates that were not always competitive with those of routine angioplasty[7-9].

Coronary stent implantation was widely accepted based on the results of the BENESTENT[10] (BElgian NEtherlands STENT) and STRESS[11] (STent REStenosis Study) trials and was facilitated by the elimination of anticoagulant therapy after stent implantation[12-14]. Subsequently, the use of coronary stents has extended beyond the limited indications. The popularity of coronary stents is due not only to the fact that they reduce restenosis, but also that they are relatively easy to use and result in a reliable, superior angiographic images.

When deployed, the self expandable mesh stents shorten considerably due to the nature of the design and often expanded unpredictably in the treatment segment, making precise placement difficult even when used by expert operators. The early generation were less resistant to external radial forces which may lead to recoil after place-

ment[15-17]. Coverage of the lesion site and resistance to recoil is better with a slotted tube design. Nowadays, the average recoil and shortening is < 5% with the new generation tube design. The stent cut from a continuous metal tube was less flexibile, making advancement of the device through the tortuous vessel difficult. However, this problem has been solved by a connecting ring design which provides maximum flexibility for enhanced trackability and conformability as well as radial strength and almost elimination of elastic recoil[18].

In 1995, coronary stents were used in most coronary angioplasty procedures at leading centers and in 30-60% of all cases at other centers[19]. In current practice, more than 80% of all coronary interventions involve stenting in current practice and each year, over 1 million percutaneous interventions are performed[20].

The increased popularity of coronary stenting as a primary treatment modality and application of stenting techniques to a broader and more complex range of lesion types have motivated industry to respond to those demands with development of competitive stent designs. No single stent configuration design incorporates all of the characteristics of the ideal stainless steel stent (Table 1), and each has its own particular advantages and disadvantages. The enthusiasm for coronary stenting and intent to improve clinical outcomes have motivated the design and development of a wide assortment of stents.

At present, there are over 70 standard and customized stainless steel stent types manufactured by more than 30 companies available for the use in the coronary system and even more under clinical investigation. Despite the clinical and economic interests in stent development, only two stents (Gianturco-Roubin I, Cook, Bloomington, IN, and Palmaz-Schatz, Johnson and Johnson, Warren, NJ) were approved for use in the United States before 1997. However, within the past 5 years, more than 30 new stent designs have been approved by the United States Food and Drug Administration (FDA). In this chapter, we focus on stainless stents available outside the United States and in development.

CORDYNAMIC APOLLO STENT ™

The Cordynamic ***Apollo*** stent™ (***Iberhospitex SA, Barcelona, Spain***) is a stainless steel tubular stent with segmented multicellular slotted tube with alternating connections (Figure 1). Two radiopaque markers were utilized on the delivery system to obtain the best final results. The stent is suitable for direct stenting due to its low (< 1mm) profile. The nominal pressure is 10 atmospheres; at 14 atmosphere the stent expands 0.25 mm more than nominal pressure. Rated burst pressure 16 atmosphere. Minimal recommended guiding catheter is 0.056 inch, 5 Fr. The stent is currently undergoing clinical assessment.

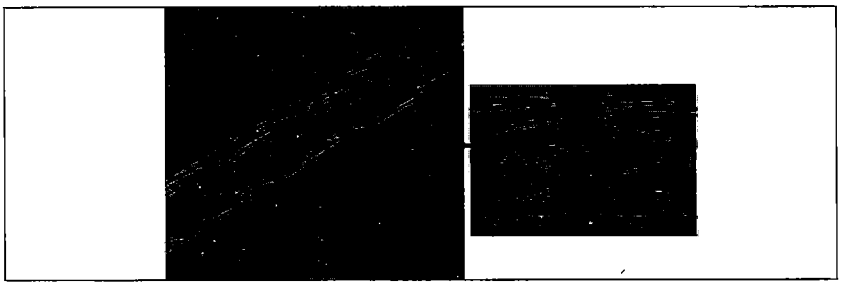

Figure 1

COROFLEX AND COROFLEX DELTA CORONARY STENT SYSTEMS

The ***Coroflex*** stent (***B Braun Melsungen AG, Berlin, Germany***) is a lasercut balloon expandable tubuler stent which has rounded edges and is electropolished. The stent is configured with multiple sinusoidal ring elements with connecting bridges at their midpoints (Figure 2) which allows superior flexibility. The ***Coroflex Delta*** has a design similar to the ***Coroflex*** stent, with increased strut thickness to provide greater radial strength. It is suitable for direct stenting of appropriate lesions and particularly useful in tortuous anatomy where flexibility is important. Minimum guiding catheter is 6 Fr. There are no currently published trials of the ***Coroflex*** stent.

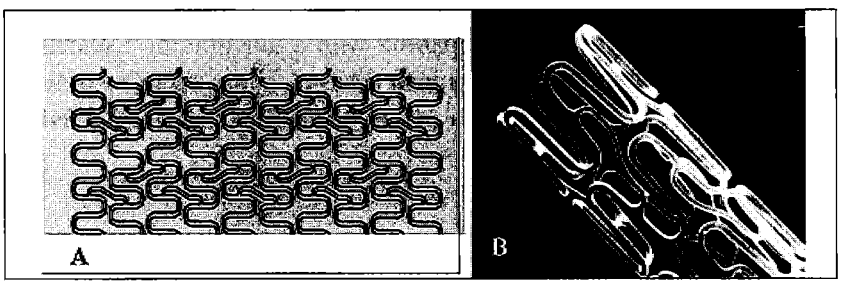

Figure 2

THE DURAFLEX CORONARY STENT SYSTEM

The ***Duraflex*** coronary stents (***Avantec Vascular Corporation, San Jose, USA***) is a balloon expandable, stainless steel tubular stent. The stent consists of circumferential rings linked by flexible cross bridges. The ***Duraflex*** stent is pre-mounted on a high performance, high pressure, rapid exchange balloon delivery system. The unique config-

uration yields a device with superior trackability, high radial strength and longitudinal flexibility (Figure 3). The low profile allows easy compatibility with contemporary 5 Fr guiding catheters.

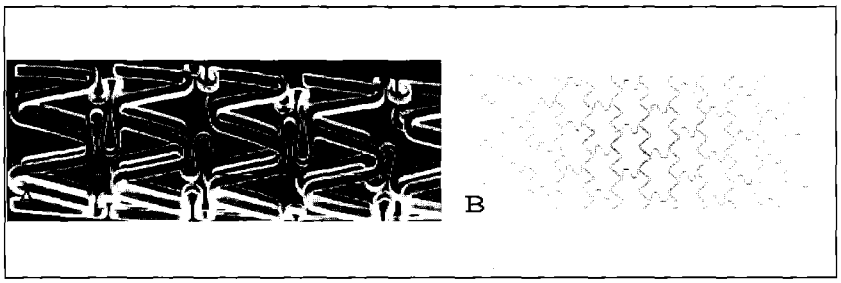

Figure 3

GENIC™, GENIC™SV and GENIC™ LV STENT SYSTEMS

The ***Genic*** coronary stent (***Blue medical Devices BV, Helmond, The Netherlands***) is a stainless steel tubular stent with helical sinusoidal waveform geometry conforms to the natural dynamic tortuous coronary anatomy and prevents strenching of the vessel. The ***Genic*** coronary stent is premounted on a semi-compliant, high pressure rapid exchange stent delivery catheter, with optimized trackibility and distal flexibility. The delivery system is compatible with a 5Fr guiding catheter. The open cell design of ***Genic*** stents enable side branch access without decrease of robustness in the design (Figure 4). The ***Genic*** stents are also available for small (***Genic*** SV) and long (***Genic*** LV) vessels.

Figure 4

GENIUS^{TM} STENT

The ***Genius*** coronary stent (***EuroCor Interventional Bonn, Germany***) is a tubular, balloon expandable stent with multicellular-modular ring design. Each ring is connected to its neighbor by alternating short and S-shape links (Figure 5). Its low crossing profile, ideal for tight lesions and narrow and distal arteries. ***Genius*** stents opens at relatively low pressures which minimize trauma to the vessel wall. The balloon ends of the stent are soft and comply very well with the often healthy segment of the vessel at the ends of the stent to avoid unnecessary injury. In the animal experiment IVUS guided stainless steel ***Genius*** stent implantation resulted in significant lower neointimal hyperplasia compared to Tenax, polymer-coated Genius or phosphorylcholine-coated Biodivysio stents[21]. In multicenter registry study 250 patients were enrolled and 5months follow-up results are pending. In another multicenter study of ***Genius*** stent 100 patients were included and restenosis rate was 11%. Randomized studies using the Genius stent are currently underway.

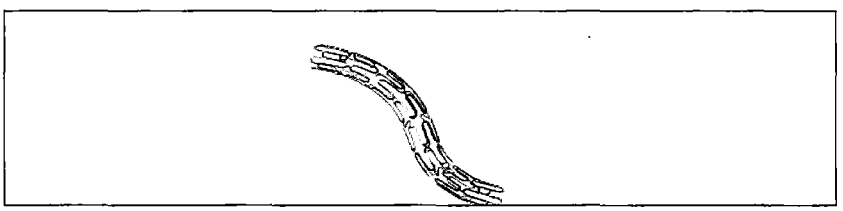

Figure 5

GRYPHUS CORONARY STENT

The ***Gryphus*** stent (***Endo Vascular Devices, Santa Clara, USA***) is a stainless steel tubular stent with a closed design. The basic cell incorporates two single multi-angled bridged by a serpentine-shaped link. The multi-angled loops with rounded ends allow excellent side branches access. The "S" shaped bridges are arranged in alternating succession to provide high flexibility. The diamond shape structure of the cells provides high radial support, minimal foreshortening and continuous support without gaps to prevent plaque prolapse. The strut thickness varies through the length of the stent from 0.075 to 0.088 mm according to the localization. The struts are thinner on the S-shaped junction where flexibility is desired and thicker where greater radial strength is required. The structural integrity has been evaluated in-vitro. After pulsatile stresss test that simulate the radial strain of an artery, all 16 stent were intact without any sign of fracture.. The first human implantation was performed in 1998 and there is considerable clinical experience with this stent. The ***Gryphus*** stent registry involved 5 international centers and more than 150 patients received the stent in de novo and in-stent

restenosis lesions. The multicenter randomized trial will recruit 1000 patients is in progress.

The JOSTENT ™ CORONARY STENTS

The ***JOSTENT Flex (JOMED AB, Helsingborg, Sweden)*** is a stainless steel tubular stent designed with cells connected with spiral bridges which gives both flexibility and high radial strength to the stent. It was specially designed for use in lesion with complex morphology and difficult to reach coronary lesions. This new design provides increased individual cell area and further options that allow implantation in vessels up to 5 mm in diameter[22-24]. The stent is mounted directly onto the markers. The profile of the stent is less than 1.1mm and balloon overhang on each side is 1 mm. The ***JOSTENT Flex*** is available in lengths of 9 to 32 mm and from 2.0 to 5.0 mm in diameter.

JOSTENT Flex stent is available as bare stent and premounted versions. There are two different delivery systems, which are based on different shaft constructions. The JOSTENT ***Flex Supreme*** system has a stiffening wire construction whereas the JOSTENT ***Flex Master*** is based on a stainless steel shaft construction. Both systems have low crimped profiles and stent security and expansion is supported a special balloon design, K-folding: a combination of a distal four fold and a proximal un-uniform fold.

JOSTENT side branch was specifically designed for side branches applications and incorporates larger cells that minimize the risk of the side branch occlusion and can be expanded up to 6.0mm in diameter to allow access for further PTCA and stenting of side branches. The ***JOSTENT side branch*** is a combination of ***JOSTENT Flex*** and ***JOSTENT Plus.*** The proximal and distal portions of the stent are based on the Plus design, ensuring high radial strength and flexibility, whereas the mid portion utilizes the spiral links of the ***JOSTENT Flex*** to maximize access to side branches. The stent is available in lengths of 18-26mm.

JOSTENT Bifurcation has been designed for treating lesions in or at bifurcations (Figure 6). The design is based on a combination of the ***JOSTENT Flex*** and ***JOSTENT plus***. The proximal and distal part of the stent have different design. The distal portion of the stent is based on the ***JOSTENT Plus*** design, ensuring high radial strength, whereas the proximal portion of the stent utilizes the spiral Links of the ***JOSTENT Flex*** to maximize access to bifurcation. At the distal part of the stent the cells are larger and can be expanded up to 6.0 mm in diameter to allow further stent placement in the bifurcated vessels, allowing the placement of a second stent through struts of the first stent. The ***JOSTENT bifurcation*** is available in two lengths, 16 and 28 mm.

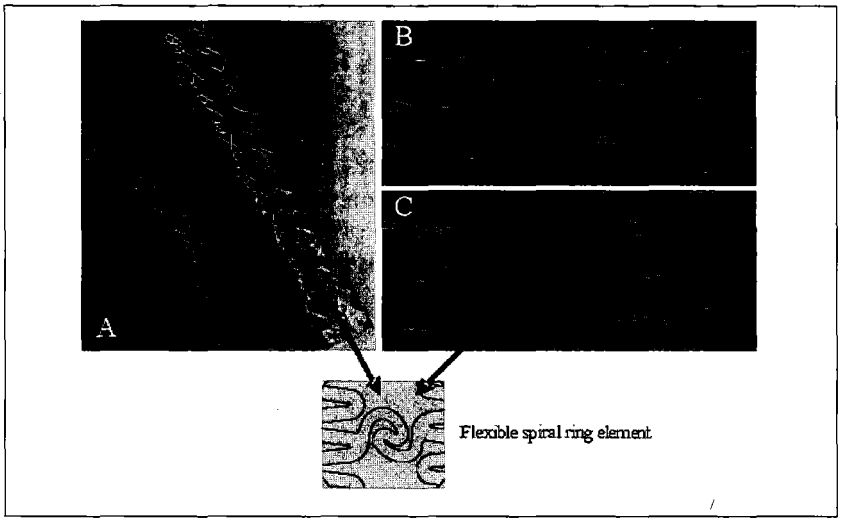

Figure 6

MAC TM and MAC plus INERT STENTS

The ***MAC plus*** and ***MAC plus Inert*** (***AMG GMbH, Raesfeld-Erle, Germany***) stents are stainless steel tubular stent that are designed with a series of sinusoidal rings linked with radially arranged connecting bridges which provides high radial strength and superior longitudinal flexibility. ***MAC plus*** and ***MAC plus Inert*** stents mounted on a low profile, semi-compliant balloon. There is some clinical experience with the earlier generation MAC stent. An initial evaluation of the MAC stent was performed in a single center and 70 patients received 74 MAC stents[25]. All stents were successfully implanted. At 6 months, the angiographic restenosis rate was 17%. In another multicenter trial performed in Korea, 143 patients were treated with MAC stent. At 6-month follow-up angiographic restenosis rate was 18 %. ***MAC plus*** and ***MAC plus Inert*** stents are available in diameters of 2.5 to 4.0 and in lengths of 10,14,18,24 mm.

MED-X FLEXY TM STENT

The ***Med-X Flexy*** stents (***Med-Xcor, Trevoux, France***) are laser-cut tubular stents. After a first generation with closed cell design and multiple sinusoidal hinge points, the new design of the ***Med-X Flexy*** stents was developed with multiple sinusoidal rings each of which is connected to its neighbor with single short, articulating bridge that provides flexibility and low profile (Figure 7). It can be used in more distal and tortuous lesions. The ***Med-X Flexy*** stents are constructed with a low quantity of metal and thin rectangular struts, in order to reduce platelet activation and thrombus formation. In addition, thermic treatment of the ***Med-X Flexy*** stent allows for a device

that does not require high-pressure inflation. Two golden markers at both ends of the stents are allowing precise and safe positioning in case of ostial or lesion in bifurcations.

An initial evaluation of the ***Med-X Flexy*** stent, 60 patients with single de novo lesions were treated by with ***Med-X Flexy*** stent. At 6 month follow-up angiographic restenosis rate and target lesion revascularization were16 and 15% respectively.

Figure 7

MEGAflex TM CORONARY STENT

MEGAflex coronary stents (***EuroCor, Trevoux, France***) are stainless steel balloon- expandable tubular stent. ***MEGAflex*** stents are constructed with a modular ring design. Each corrugated ring is connected to its neighbor with two bridges. It is very good for bifurcation stenting because of the particular stent window design. The stent can be easily advanced through stents due to its smooth and rounded strut features. In angulated lesions, it provides a 1:1 conformity to complex vessel morphologies. The ***MEGAflex*** stent is available in lengths of 9 to 27 mm for use in vessels of 2.5 to 4.0 mm. Clinical assessment of the ***MEGAflex*** stent in several registry trials is currently undergoing.

THE MATRIX TM CORONARY STENT

The ***Matrix*** coronary stent ***(Sahajanand Medical Tech. SURAT, INDIA)*** is a tubular balloon expandable stent with new design and improvements which enable to treat standard lesions, distal lesions, lesions in tortuous anatomy and calcified lesions. The stent has been designed using Finite Element Analysis in order to ensure ideal expansion, structural integrity, minimum foreshorthening and optimum durability. The unique design of ***Matrix*** stent with " S" shaped struts and the longitudinal struts allows the stent to flex at a controlled segment thus assuring minimal foreshortening (Figure 8). Its unique deformation upon expansion assures zero shortening as well as orthogonal concentration of forces in the radial direction assuring maximum strength. Unique connecting ring design provides maximum flexibility for enhanced trackability and conformability. The stent pre-mounted on a high pressure balloon and 6F guiding

catheter can be used. The optimum cell size and the structure of the ***Matrix*** stent provide better vessel wall coverage and side branch access without causing 'Stent Jail' with no plaque protrusion into the stent.

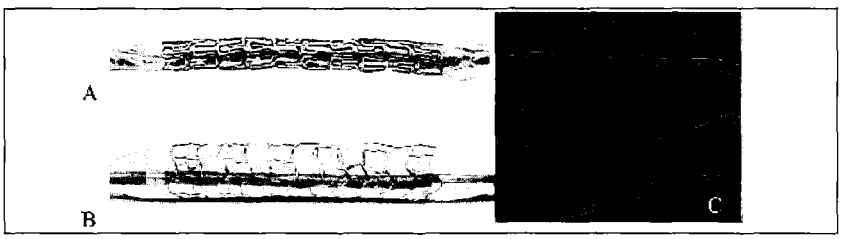

Figure 8

NEXUS ™ AND NEXUS II ™ CORONARY STENT

Nexus and Nexus II Coronary stents ***(Occam International BV, Eindoven, The Netherlands***) are balloon expandible, stainless steel stents. It has a tubular design. With multiple cells and multiple "V" connections for high radial strength combined with longitudinal flexibility (Figure 9). The ***Nexus*** stents are suitable for wide range of applications and have easy side branch access. It is available un-mounted and pre-mounted on a rapid exchange balloon. The ***Nexus II*** stent is designed with proportionately more metal that provides increased radial force compared to the first-generation devices.

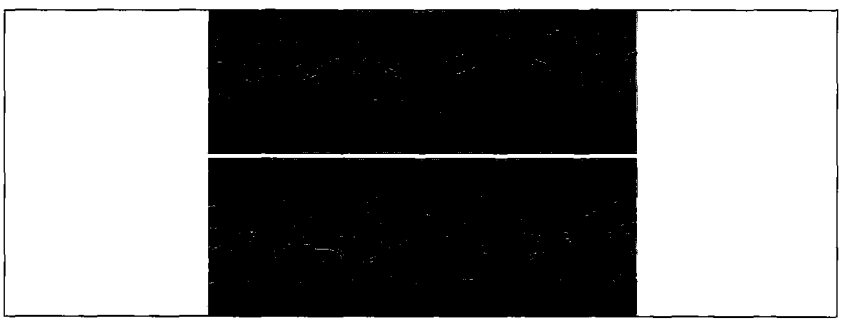

Figure 9

THE PROLINK ™ STENT

The ***Prolink*** stent (Vascular concepts limited, Crawley, UK) is balloon expandable stainless steel stent with thin corrugated rings connected by three articulating bridges. The modular design of the ***Prolink*** stent allows for flexibility and side branch access

and provides adequate radial support, while the fully closed cell design prevents plaque prolapse (Figure 10). The ***Prolink*** stents are available in lengths of 10 to 30 mm for use in vessels of 2.5 to 4.0 mm in diameter.

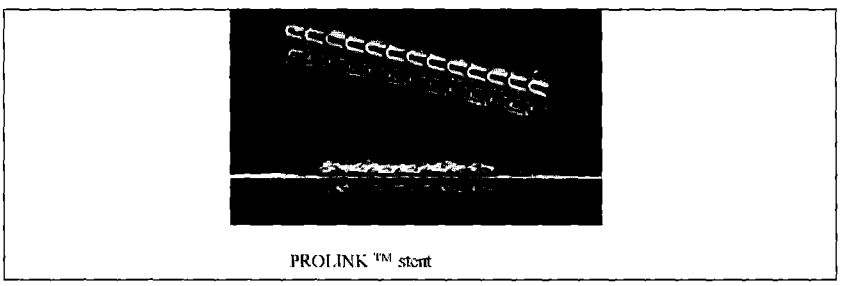

Figure 10

PURA ™ STENT FAMILY and MONEO ™ STENT

PURA stents (***Devon Medical, Hamburg, Germany***) are slotted tube, balloon expandable stents with "Y" shaped geometry of the longitudinal connecting branch points (Figure 11). The first generation ***PURA-A*** stents were developed in 1995. The design provides the stent to be loaded on low-profile balloon catheters. In the multicenter randomized trial[26], restenosis rate of ***PURA-A*** stent at 6 month follow-up was 17.8% and survival free of myocardial infarction was 78.9 % that was highly comparable with other contemporary stents. The ***PURA-A*** stent is available as a single segment 7 mm long for the treatment of short lesions and in both articulated and non articulated versions for use in longer lesions. The original design of the ***PURA-A*** stent was modified, resulting in the ***PURA-VARIO*** family of devices. ***PURA-VARIO*** stents are configurated with 4 mm segments connected with specially designed articulating curve bridges. Each segment is composed of six radially arranged cells. The 2 mm long curved articulations give the device high flexibility. The new generation ***PURA-VARIO -AS*** and ***AL*** stents have six cells arranged circumferentially around each segment with six connecting articulations between each segments. In these stents the strut width has been decreased and the result is a lower profile device compared with the previous- generation. ***PURA-VARIO-AS*** stent is designed for use in vessels less than 3.5 mm. For use in vessels over 3.5 mm, the ***PURA-VARIO-AL*** ("L" large) with eight circumferentially arranged cells and eight articulations has been introduced. Side branch access id not possible due to result of intricate design. There is considerable experiences with the use of ***PURA*** family of stents in Europe[27,28].

The ***Moneo*** stent is the newest generation of ***PURA*** family stents. The stent is designed with variable strut dimensions to improve radiopacity and flexibility of the

device. The ***Moneo*** stents are available in diameters from 2.5 to 4.0 mm and in lengths of 10 to 24 mm.

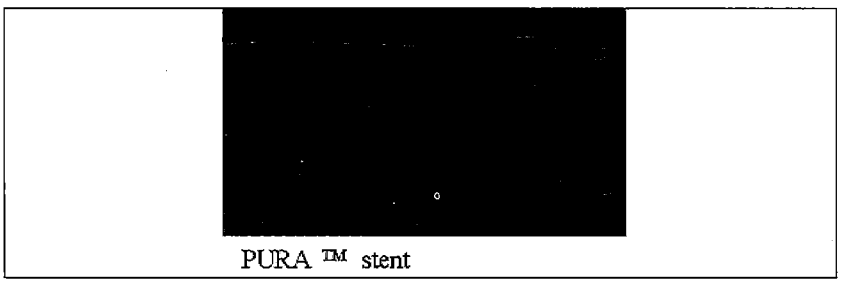

Figure 11

R STENT ™, R STENT SVS ™, and R STENT RESCUER ™

The ***R stent*** (***Orbus Medical Technologies, Inc, Fort Lauderlade, FL, USA***) is made from medical stainless steel. The ***R stent*** is a tubular stent consists of continuous a dual-helical spiral. This configuration provides the ***R stent*** with omni directional flexibility, high radial strength, and optimal side branch access (Figure 12). The flexibility of the ***R stent*** in conjunction with its low profile provide physicians with the ability to track and navigate through tortuous and highly calcified lesions. The ***R stent*** `s radial hoop strength, which exceeds 30 psi, provides the required scaffolding and support to restore normal flow rheology. The strut thickness of the ***R stent*** allows for reasonable radiopacity without obscuring the lesion area. The stent is mounted to the balloon between two radiopaque marker bands that delimit the working length of the balloon.

The ***R stent SVS*** (Small Vessel System) was designed for specific treatment of lesions 2.25mm or less. The crossing profile of ***R stent SVS*** is 0.97mm and balloon overhang is less than 0.5mm to reduce edge dissection.

Two multicenter European registries, ***DIRECTOR (direct stenting study with ORBUS R stent) and RESTOR (R stent Efficacy and safety trial by ORBUS)*** have completed. The safety and efficacy of the ***R stent*** was established by ***RESTOR*** trial in addition to clinical reports on the use of the ***R stent*** [29-32]. In ***RESTOR*** trial the procedural success was 97.5%. The 6-month MACE rate was 11.6% (3.3% non-Q MI, 0.8% CABG and 7.4% TLR). The binary restenosis rate was 20%. In ***DIRECTOR*** trial direct coronary stenting (without dilatation) has been used for treatment of coronary stenosis. A group of 129 patients with de novo lesions were included by 17 centers in 8 countries. Target lesion revascularization rate was 6.3% at 6-months. The binary restenosis rate of 20% was found [33].

Figure 12

THE SEAQUEST ™ STENT

The ***Seaquest*** stent (***CathNet-Science SA, Paris, France***) is a third generation balloon expandible, stainless steel tubular stent. The ***Seaquest***™ stent is designed as a series of rings, each with repeating S shape. Each ring is connected to its neighbor by a single oblique and asymmetrically placed bridge. As a result, the expansion of this stent design shows zigzag corrugation in parallel. These zigzag corrugations and links between segments introduced in an asymmetric rotating configuration provide an optimal longitudinal flexibility (Figure 13). This permits easy access to very distal lesions even tortuous anatomy. The smaller stent are designed with five cells and larger diameters are designed with six cells. This differentiated design ensures comparable cell distribution and metal surface area in vessels of different sizes. The large cell size allows side branch patency. The ***Seaquest*** ™ stents are available in diameters from 2.5 to 4.0 mm and in lengths of 10.5 to 24 mm. The multi-center European clinical observation of ***Seaquest*** ™ stent conducted in France. Total 245 stents were successfully implanted to 215 patients. During hospital stay, MACE were seen in 6 patients. Repeat PTCA in 1 patient (0.05%) for a subacute stent thrombosis. In 3 other multicenter trials, more than 700 patients were enrolled to receive ***Seaquest*** ™ stents. Six month angiographic and clinical outcome are pending.

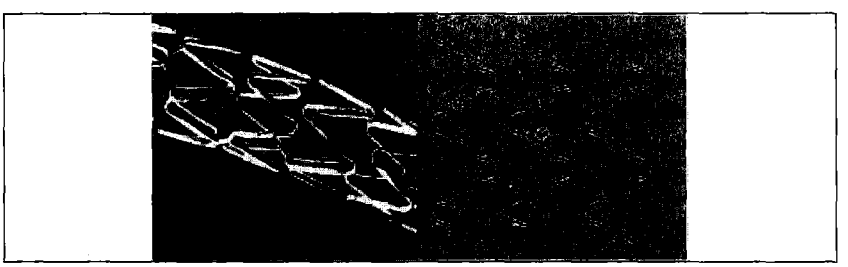

Figure 13

TSUNAMI ™ CORONARY STENT

Tsunami ™ stent (***Terumo Corporation, Japan***) is a balloon-expandable slotted tube stent. The stent has double-linked diamond cell structure that are joined by two connecting bridges (Figure 14). This configuration yields a device with excellent flexibility that conforms to the natural tortuosity of coronary vessels once deployed. The tip and distal shaft of the delivery balloon has hydrophilic M coat™ decreasing friction when moistened. In addition to the M coat™ the benefits of ultra low profile (0.038 inch for 3.0 mm system), the unique double-link connection, the smooth stent surface, and the Tri-fold balloon combine to ensure superb stent delivery, trackability and crossability. Tsunami™ stent`s minimal balloon overhanging (<1 mm) lessens injury during dilatation. In addition, the stent edge design reduces flaring risk providing more secure procedure. The ***TESTER***™ ***(TErumo STEnt Registry)*** trial was designed to establish safety and efficacy of Tsunami coronary stents. From 4 centers, in a group 100 patients with single de novo coronary lesions were treated with ***Tsunami***™ stents. Procedural success was 98%. At 6-month follow-up angiographic restenosis rate was 14.7 % and 83% of the patient were MACE free at 210 days follow-up.

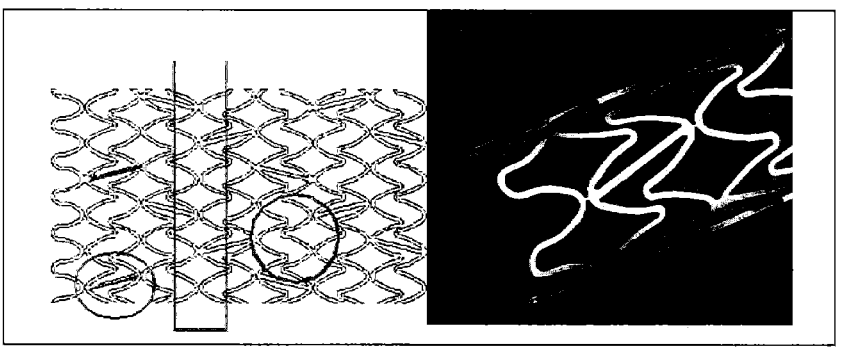

Figure 14

SPIRAL FORCE™ AND ZEBRA ™ STENTS

Spiral Force™ stent (***Bolton Medical Inc., Fair Lawn, NJ***) is balloon expandable, third- generation, stainless steel slotted tube stent. The ***spiral force*** stent features a unique spiral strut design in which all struts are connected with inverted C flex joints, that allow for a great deal of flexibility. The flex joints also allow the stent to conform to bends in the coronary artery by closing the segment in the tight portion while opening the joint in the wider portion of the curve. Because all the struts are connected in the spiral force design, the stent has superior radial force and minimum recoil.

a coronary stent.[20] Compared with balloon angioplasty, coronary stents have had a dramatic impact on restenosis rates. However, despite technical advancements, in-stent restenosis remains the major challenge of interventional cardiology and is reported to be 15-20% in BENESTENT like lesions and may occur in over 30-60 % of patients with complex coronary lesions [10,11,24,34,35]. Furthermore, the treatment of in-stent restenosis is a greater challenge than restenosis following balloon angioplasty as recurrence is more common after percutaneous treatment of in stent restenosis.

In-stent restenosis is due mostly to neointimal hyperplasia with many processes potentiating this. Over distension of the diseased vessel causes endothelial disruption, internal elastic lamina fracture, and medial dissection. Lumen enlargement is caused by a combination of plaque reduction, axial plaque redistribution towards the proximal and distal segments outside the stent, plaque extrusion, and vessel expansion. However, vessel injury by an angioplasty balloon or stent struts leads to the activation of platelets and mural thrombus formation [36,37]. The presence of vascular injury, mural thrombus and metallic foreign body activates circulating neutrophils and tissue macrophages [37-39] which initiates a cascade of events. The end result of this cascade is uncontrolled proliferation of smooth muscle cells and deposition of extracellular matrix leading to luminal narrowing 3 to 6 months after the stent implantation.

IMPACT OF STENT DESIGN ON STAINLESS STEEL STENTS RESTENOSIS

Attempts have been made to better clinical outcomes after stainless steel stent implantation by improving stent design. In animal models, it has been suggested that stent surface material and geometric configuration could be important in determining the amount of neointimal tissue and stent thrombosis. Design characteristics such as hoop strength and metallic surface area have been shown to influence neointimal hyperplasia in animal experiments [40,41]. It has also been proposed that the amount of vessel wall injury may depend on stent design. One study revealed that, compared to coil stents, tube stents induce less negative remodeling including stent recoil, resulting in a wider luminal area[42]. Equivalency trials which compare different designed stents mostly looked at Palmaz-Schatz stents [ASCENT (Palmaz-Schatz vs MULTI-LINK)[43], SMART (Palmaz-Schatz vs AVE Micro stent-II)[44], NIRVANA (Palmaz-Schatz vs NIR)[45], Jostent vs Multilink Duet stents[24]]. All showed no major difference between each other (Table 3). Despite the large randomized trials demonstrating no difference between different stent design in terms of late clinical outcome, there may be a substantial difference in device performance between different stents when they are used in more challenging coronary lesions. However, recently, the impact of stent strut thickness on restenosis and clinical events have been evaluated in humans.[46] Kastarti et al. demonstrated that angiographic and clinical restenosis rate were signifi-

cantly less (15.0% versus 25.8 %) among patients who received a stent with thin struts. Consistently, another trial performed by Briguri et al[47] also revealed that struts thickness was an independent predictor of restenosis in coronary arteries with a reference diameter of 2.75 to 2.99mm and the incidence of angiographic restenosis rate was 23.5% in the thin group and 37% in the thick group.

Metal composition and characteristics of the stent surface have also been thought to promote stent thrombosis and to be important for the performance of stainless steel stents[48,49]. In this regard, electromechanical polishing of stainless steel stents has been shown to result in a less thrombogenic surface[50]. Initial animal experiments with nitinol slotted tube stents, have shown less thrombogenity and vascular injury in comparison with stainless steel stents.[51] However, despite similar lumen loss and binary angiographic restenosis rate, the stainless steel stents showed significantly less target lesion revascularization [52].

Besides attempts to decrease restenosis by changing the design and mechanical properties of stents to prevent in-stent restenosis, an enormous amount of research into many mechanical devices[34,35,53] and systemically administered drugs has been done but none have been proven to be effective. Many different biological mechanisms contribute to restenosis and drugs that target only one pathway often for a restricted period of time, may be of limited value in such a complex multifactorial process. Experience with systemically administered drugs, has proven almost universally negative [34,36,54-58]. These agents were previously tested in animal models and found to be beneficial. The lack of efficacy in human studies may be in part due to insufficient concentration of drug at the injury site or lack of chronic dosing. In general, although animal models provide new insight into the mechanism of restenosis, biological and mechanical differences mean that the therapeutic success of anti-restenotic therapies has been achieved in human beings.

THE FATE OF STAINLESS STEEL STENTS IN THE *"DRUG ELUTING STENT ERA"*

Recent advances in the understanding of the cellular mechanisms responsible for smooth muscle cell proliferation together with improvement in stent coating and eluting technology have provided the scientific background to develop drug eluting stent. In order to solve the problem of restenosis the concept of using stents coated with agents that could potentially inhibit neointimal hyperplasia has emerged.

Nowadays, attention is focusing on drug eluting stents. Preclinical studies demonstrated a 35% -50% reduction in in-stent neointimal hyperplasia or late loss with sirolimus and paclitaxel eluting stents [59-62]. The first clinical application of these eluting stents in single de novo lesions, showed remarkable results in inhibition of neointimal hyperplasia at 4 month and up to 2 years follow-up[63-66]. These promising data

have recently been confirmed by the randomized trials such as RAVEL[67], SIRIUS (SIRolImUS-eluting stent in de novo native coronary lesions)[68] and TAXUS-II[69].

Considering the encouraging results of early clinical trials of drug eluting stents with antiproliferative agents [63-65,67] there is the potential to broaden the utilization of stents, and possibly eventually stainless steel stents will be substituted by drug eluting stents[70]. However, the performance of drug eluting stents in the "real world" of percutaneous coronary intervention which includes many lesion types such as, long lesions, chronic total occlusion, acute myocardial infarction, sapheneous vein grafts, left main lesions, etc. is yet to be determined. The results of earlier studies of single de novo lesion may not be applicable in this more complex group. Moreover, questions needs to be answered to maintain safety, to determine the optimal duration of antiplatelet therapy and to dense treatment strategies for the group who develop in-stent restenosis after drug eluting stent implantation.

Besides these unresolved issues, the costs of treatment of coronary lesions solely with drug eluting stents is another problem considering that the market price is currently almost 5 times more than that available stainless steel stents. In this regard, the rationale of treatment with drug eluting stents will be important[71]. In practice, by assessing the risk factors for in-stent restenosis with conventional stents, drug eluting stents implantation may be reserved for only those at most risk. Hybrid stenting (drug eluting stent plus stainless steel bare stent implantation) maybe another approach in the treatment of multi-vessel coronary artery disease. Therefore, despite the heightened enthusiasm of clinicians to substitute stainless steel stents with these new devices, in the economical reality of the **" real world",** stainless steel stents may still find a place in the cath-labs for a while.

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TABLE 1:
Desirable Stent Characteristics in Stainless Stell Stents

- Flexibility
- Trackability
- Low Profile
- Radioopacity
- Thromboresistancy
- Biocompatible
- Reliable expandibility
- High radial strength
- Circumferential coverage
- Low surface area
- Hydrodynamic compatibility

TABLE 2:
(I)-Technical specifications of the stents

Product	Degree of Radiopacity	Metallic Surface area	Stent design/strut configuration	Strut Thickness	Shortening	Profile (mm)	Expansion range	MRI safety	Recoil	Available diameters (mm)	Available lengths (mm)
Cordynamic Apollo stent	Moderate	11-20%	Tubular	0.11mm	<1%	<1mm	2.0-5.0mm	Safe	3-5%	2.5,3.0,4.0,4.5	9,14,18,23,28,36
Caroflex	Low	12%	Tubular	0.09mm	<1-3%	<1mm	2.5-4.5mm	Safe	4-5%	2.5,3.0,4.0	8,13,16,25
Caroflex-Delta	Low	14%	Tubular	0.12 mm	<1-3%	1.05mm	2.5-4.5mm	Safe	3-5%	2.5,3.0, 4.0	8,13,16,25
Duraflex	Moderate	14%	Tubular	0.12 mm	2%	1.1mm	2.5-4.5mm	Safe	2.2%	2.5,3.0,3.5, 4.0	8,14,18,25
Genic SV	Moderate	14.4 %	Tubular /	0.09 mm	2-3%	0.9mm	1.8-2.8mm	Safe	2.5-4.5%	2.0,2.5	10,14,18
Genic LV	Moderate	14.4 %	sinusoidal ring	0.11mm	4-5%	1.1mm	3.7-5.5mm	Safe	3.5-5.5%	4.0,4,5,5.0	18,22,28
Genic	Moderate	14 %		0.10 mm	4-3%	1.0mm	2.3-4.5mm	Safe	3-5%	2.5,3.0,3.5, 4.0	10,14,18,22,28
Genius	Moderate	17%	Tubular	0.11mm	<3%	<1mm	2.5-4.0mm	Safe	<2%	2.5,2.75,3.0,3.5,4.0	9,11,15,19,23,27
Gryphus	Moderate	15%	Tubular	0.09mm	5%	<1.0mm	3.0-4.5mm	Safe	2-4%	2.75,3.0,3.5,4.0	13,17,23
JoStent Flex	Moderate	16%	Tubular	0.09mm	5%	1.0mm	2.5-4.mm	Safe	4%	2.5.3.0,3.5,4.0	9,16,26,32
JoStent Plus	Moderate	16%	Tubular	0.09mm	5%	1.0mm	2.5-4.5mm	Safe	4%	2.5.3.0,3.5,4.0	9,17,27,33
MAC	Moderate	11-23%	Tubular/	0.125mm	1%	1.06mm	2.5-5.0mm	Safe	<2%	2.5.3.0,3.5,4.0	10,14,18,24,28
MAC plus inert	Moderate	11-23%	Sinusoidal ring	0.125mm	1%	1.06mm	2.5-5.0mm	Safe	<2%	2.5.3.0,3.5,4.0	10,14,18,24,28
Matrix	Moderate	11-19%	Tubular /	0.09 mm	0 %	1 mm	2.5-4.0mm	Safe	<5%	2.5.3.0,3.5,4.0	11,14,16,19,23.29
Med-x Flex	Moderate	13%	Tubular / Zig zag ring	0.07 mm	<5%	<1.0mm	2.5-4.0mm	Safe	2-4%	2.5.3.0,3.5,4.0	8,13,17,26

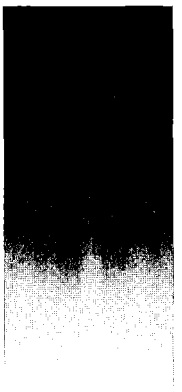
TABLE 2:
(II)-Technical specifications of the stents

Product	Degree of Radiopacity	Metallic Surface area	Stent design/strut configuration	Strut Thickness	Shortening	Profile (mm)	Expansion range	MRI safety	Recoil	Available diameters (mm)	Available lengths (mm)
Mega Stent	High	18-20%	Tubular	0.11mm	<2%	0. 9mm	2.5-4.0mm	Safe	1%	2.5, 2.75 30,3.5,4.0	9,11,13,15,17,19, 23,25,27
Nexus	Moderate	14%	Tubular	0.10	2.6%	<1. 0mm	2.5-5.0mm	Safe	2%	2.5,3.0,3.5,4.0	8,12,15,18,23
Prolink	Moderate	<5%	Tubular	0.07mm	<2%	<1.0 mm	2.5-4.0mm	Safe	4%	2.5-4.0	10,15,20,25,30
PURA–A	Low	10-15%	Tubular	0.12mm	1-5%	1.6 mm	3-5mm	Safe	2%	3.0,3.5,4.0	7,11,15,19
PURA Vario -AL	Low	10-18%	Tubular	0.07mm	5%	0.45 mm	3.5-4.5mm	Safe	3%	3.0,3.5,4.0	6,10,16,24,28
PURA Vario -AS	Low	10-18%	Tubular	0.07mm	7%	0.45 mm	2.5-3.5mm	Safe	3%	2.5,3.0	6,10,16,24,28
Maneo	Low	18%	Tubular	0.08mm	5%	1.1 mm	2.5-4.5mm	Safe	2%	2.5,3.0,3.5,4.0	10,16,24
R -stent	Moderate	12-18%	Tubular	0.13mm	<3%	1.0 mm	2.5-4.5mm	Safe	<3%	2.5,275,3.0,3.5,4.0	9,13,18,23,28,33
R-stent SVS	Moderate	12-17%	Tubular	0.12mm	<6%	0.097	2.0-2.25mm	Safe	<6%	2.0,2.25	7,10,13,15,18
Seaquest	Moderate	12-17%	Tubular	0.13mm	4%	1.0-1.27mm	2.5-4.0mm	Safe	<4%	2.5,3.0,3.5,4.0	10.5,17,24
Tsunami	Low	18%	Tubular	0.08mm	5%	0.08mm	2.5-4.0mm	Safe	5%	2.5,3.0,3.5,4.0	10,15,20,30
Spiral Force	Moderate	12%	Tubular	0.075mm	3.8-8.2%	1 mm	2.5-4.0mm	Safe	1.2%	2.5,3.0,3.5,4.0	9,13,17,21,27
Zebra	Moderate	13%	Tubular	0.075	2.5-10.8%	1 mm	2.5-4.0mm	Safe	1.2%	2.5,3.0,3.5,4.0	14,19

TABLE 3:
Some Stent Versus Stent Equivalence Trials

	Baim et al[42], ASCENT trial		Heuser et al[43], SMART trial		Baim et al[44], NIRVANA trial		Mehilli et al[23].	
	Palmaz-Schatz	**Multi-link**	**Palmaz-Schatz**	**Microstent-II**	**Palmaz-Schatz**	**NIR**	**Jostent**	**Multi-link Duet**
Patients ,n	520	520	331	330	430	418	252	253
Baseline								
RD, mm	3.0	3.0	2.9	2.9	3.0	3.0	3.2	3.2
Lesion length, mm	11	11	11	12	13	13	14	14
DS ,%	64	64	64	64	64	65	78	80
Post-procedure								
MLD, mm	2.7	2.8	2.8	2.8	2.8	2.8	3.1	3.1
DS ,%	10	8	8	5	8	8	7	6
Follow-up								
MLD, mm	1.9	2.0	2.0	1.9	1.9	2.0	2.0	2.0
Late Lumen Loss, mm	0.9	0.9	1.0	0.8	0.9	0.8	1.1	1.2
Restenosis rate, (>50%), %	21	17	23	25	19	22	24	25
TVR,%	11	11	11	12	13	12	14	15

RD, reference diameter; DS, diameter stenosis; MLD, minimum luminal diameter; TVR, target vessel revascularization



CHAPTER 3

DRUG ELUTING STENTS

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The Paris Course on Revascularization
Paris: Europa edition. 2002. ISBN 2-913628-07-9

Drug eluting stent

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Introduction

Over the last decade, coronary stents have revolutionized the field of interventional cardiology. Stent implantation has become the new standard angioplasty procedure[1-3]. However, the long-term success of coronary stenting is hampered by in-stent restenosis. This represents a major problem as the absolute number of in-stent restenotic lesions is constantly increasing in parallel with the steadily increasing number of stenting procedures and as the treatment of in-stent restenosis is, despite progresses in radiation therapy, technically challenging and costly.

In-stent restenosis is caused by exaggerated neointimal formation. Neointimal proliferation is considered as a component of the general vascular response to injury[4,5]. Catheter-induced injury consists in denuding of the intima and stretching of the media and adventitia (Fig 1a, 1b). The wound-healing reaction starts with the inflammatory phase, characterized by platelets, growth factor and smooth muscle cell activation (Fig 1c). The granulation phase is characterized by smooth muscle cell and fibroblast migration (Fig 1d) and proliferation into the injured area (Fig 1e). The remodeling phase is characterized by maturation of the neointima, proteoglycan and collagen synthesis, which replaces early fibronectin as major component of extracellular matrix (Fig 1f)[6].

The risk of in-stent restenosis is associated with patient specific factors such as genetic predisposition or diabetes mellitus[7], lesion specific factors such as vessel caliber[8], lesion length or plaque burden[9] and procedure specific factors such as extent of vessel damage, residual dissections[10], number of stents, minimal stent diameter or minimal stent area[11].

Over the last 2 decades, efforts for the prevention of restenosis were focused on optimizing stent characteristics and implantation technique. All attempts of systemic pharmacological therapy have not been not successful so far[12,13,14].

Rationale

A proposed explanation for the repeated failure of clinical drug studies has been that agents given systemic cannot reach sufficient levels in injured arteries. Local drug administration offers advantages. The active drug is applied to the vessel at the precise site and at the time of vessel injury. Local drug delivery

Figure 1.

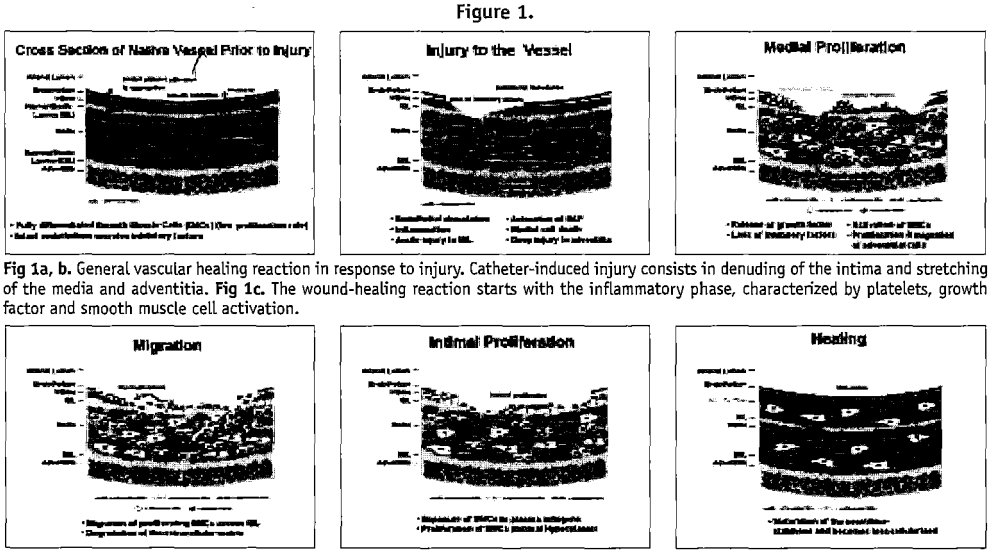


Fig 1a, b. General vascular healing reaction in response to injury. Catheter-induced injury consists in denuding of the intima and stretching of the media and adventitia. **Fig 1c.** The wound-healing reaction starts with the inflammatory phase, characterized by platelets, growth factor and smooth muscle cell activation.

Fig 1d, e. The granulation phase is characterized by smooth muscle cell and fibroblast migration and proliferation into the injured area. **Fig 1f.** The remodeling phase is characterized by maturation of the neointima, proteoglycan and collagen synthesis, which replaces early fibronectin as major component of extracellular matrix.

is able to achieve higher tissue concentration of the drug. No additional material or procedure is required. Systemic release is minimal and may reduce the risk of remote systemic toxicity.

The principle

The idea to combine the principle of mechanical scaffolding with that of local pharmacological action emerged early in the stent era. Stent-based antirestenotic therapies were hampered by complex multifactorial cellular and extracellular matrix responses to stent-induced injury, adverse and exaggerated tissue responses to materials bound to stents and the brevity of contact between delivered agents and target vascular tissue.

Polymers have shown conflicting results in the experimental setting[15-17] with some provoking a severe tissue response[18]. A number of other coatings like inert polymer[19], heparin[20-22], or phosphorylcholine[23,24] demonstrated improved biocompatibility and/or a reduction in (sub-) acute stent thrombosis rate. In the clinical practice, however, the acute beneficial effect on stent thrombosis is of minor relevancy as already modern generation uncoated stents show a very low (sub-) acute thrombosis rate. Furthermore, the acute beneficial effect did not translate in a substantial decrease in in-stent restenosis[25]. In response to this, the interest in coatings has shifted towards considering coatings as vehicles for local drug delivery. The goal is the controlled release of an efficient drug from a stable coating.

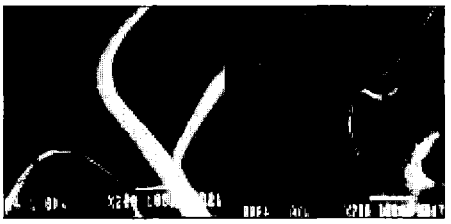
The delivery vehicles

The delivery vehicle must fulfill pharmacological, pharmacokinetic and mechanical requirements. The release of the drug into the vessel must take place in a manner that is consistent with the drug's mode of action. Drug release must be predictable and in controllable concentration and time spent. The delivery vehicle must be suitable for sterilization, it must follow the geometric change of configuration during stent expansion and resist mechanical injury caused by the inflation of the balloon (Fig 2). Today these problems are controlled, guaranteeing intact coating during clinical application. An overview of delivery vehicles for drug eluting systems is given in Table 1.

Table 1. Overview of drug delivery vehicles

- Poly vinyl pyrolidone/cellulose esters
- Poly vinyl pyrolidone/poly urethane
- Poly methylidene maloleate
- Poly lactide/glycoloide copolymers
- Poly ethylene glycol copolymers
- Poly ethylene vinyl alcohol
- Poly dimethyl siloxane (silicone rubber)

Figure 2.



Coated stent after sterilization and balloon expansion. The coating follows the symmetric changes of the stent struts without mechanic damage.

The drugs

The drug should be one that inhibits the multiple components of the complex restenosis process. Uncontrolled neointima tissue accumulation shows some parallels to tumor growths, thus the usage of anti-tumor strategies seems to be a logical consequence. Numerous pharmacological agents with antiproliferative properties have been tested for their potential to inhibit restenosis with mostly disappointing results[26]. Antimitotic compounds like methotrexate and colchicine have failed to inhibit smooth muscle cell proliferation and intimal thickening[27,28]. In these early studies, the drug effect was only limited to the elevation of the polymer vehicle's pro-proliferative action. In contrast, other agents such as angiopeptin[29], GP IIb/IIIa inhibitors[30,31] or steroids[32-34] have shown a promising inhibitory effect on neointimal proliferation. Potential candidates for local drug delivery are given in Table 2. There is a enormous variety of potential drugs, however, not all of them show convincing preclinical results, a prerequisite for clinical testing. The following drugs are now being tested in randomized clinical trials.

ACTINOMYCIN D (COSMEGEN®)

Actinomycin D (Fig 3) has been marketed worldwide since the 1960s. Actinomycin D is an antibiotic used for its antiproliferative properties in the treatment of various malignant neoplasmas (e.g. Wilms tumor, sarcomas, carcinoma of testis and uterus). It inhibits the proliferation of cells. Actinimycin D (C62H86N12016) forms via deoxyguanosins residues a stable complex with double-stranded DNA and inhibits DNA-primed RNA synthesis.

RAPAMYCIN (SIROLIMUS; RAPAMUNE®)

Rapamycin (Fig 4) is a FDA approved drug for the prophylaxis of renal transplant rejection (Rapamune®) since 1999. It is a naturally occurring macrocyclic lactone which is highly effective in preventing the onset and severity of disease in

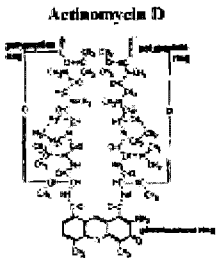
Table 2. Overview of potential candidates for drug elution

• **Anti-neoplastic**	• **Anti-thrombins**
- Paclitaxel (Taxol™)	- Hirudin and Iloprost
- Taxol derivative (QP-2)	- Heparin
- Actinomycin D	- Abciximab
- Vincristine	• Immunosupressants
- Methotrexate	- Sirolimus (Rapamycin™)
- Angiopeptin	- Tacrolimus (FK506)
- Mitomycin	- Tranilast
- BCP 678	- Dexamethason
- Antisnese c-muy	- Methylprednisolon
- Abbott ABT 578	- Interferon gamma 1b
	- Leflunomide
	- Cyclosporin

Migration inhibitor/ ECM modulators
- Halofuginone
- Propyl hydroxylase inhibitor
- C-proteinase inhibitor
- Metalloproteinase inhibitors
- Batimastat

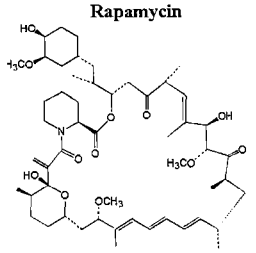
Enhance healing/Promote endothelial function
- VEGF
- 17-ß-estradiol
- Tkase inhibition
- BCP 671
- HMG CoA reductase inhibitors

Figure 3.



Chemical structure of actinomycin D.

Figure 4.



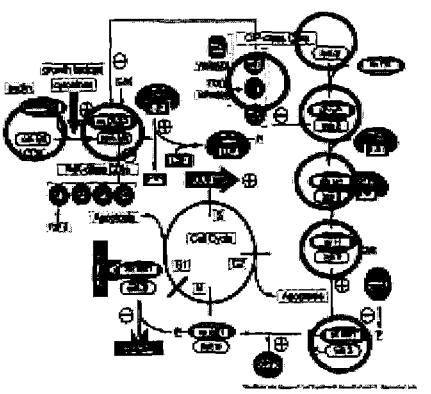
Chemical structure of rapamycin (sirolimus).

several animal models of autoimmune disease, such as insulin-dependent diabetes mellitus, systemic lupus erythematosus and arthritis.

Rapamycin blocks G1 to S cell cycle progression by interacting with a specific target protein (mTOR - mammalian Target Of Rapamycin) and inhibits its activation. The inhibition of mTOR suppresses cytokine-driven (IL-2, IL-4, IL-7 and IL-15) T-cell proliferation.

MTOR is a key regulatory kinase. 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 IL-2 induced transcription of proliferating cell nuclear antigen (PCNA) that is essential for DNA replication; the blocking of CD28-mediated sustained upregulation of IL-2 transcription in T cells and the inhibition of the kinase activity of the cdk4/cyclinD and cdk2/cyclin E complexes, essential for cell cycle progression. On overview over rapamycin effects within the cell cycle is given in Fig 5. The mechanism of action is distinct from other immunosuppressive drugs that act solely by inhibiting DNA synthesis, such as mycophenolate mofetil (CellCept) and azathioprine (Imuran). Rapamycin is synergistic with cyclosporin A and has much lower toxicity than other immunosupressive agents.

Figure 5.



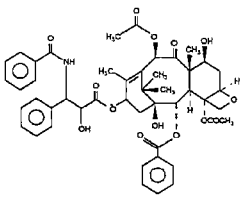
Overview of cellular mechanisms of action of rapamycin (sirolimus).

Paclitaxel (Taxol®)

Paclitaxel (Fig 6) 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.

Figure 6.

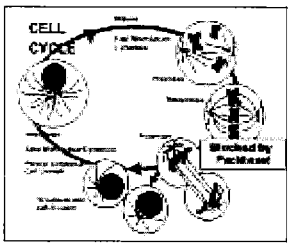
Paclitaxel



Chemical structure of paclitaxel.

It is a diterpenoid with a characteristic taxane-skeleton of 20 carbon atoms and has a molecular weight of 853.9 Daltons. Paclitaxel exerts its pharmacological effects through formation of numerous decentralized and unorganized microtubules (Fig 7). This enhances the assembly of extraordinarily stable microtubules, interrupting proliferation, migration and signal transduction[35,36]. Unlike other anti-proliferative agents

Figure 7.



Cellular mechanisms of action of paclitaxel.

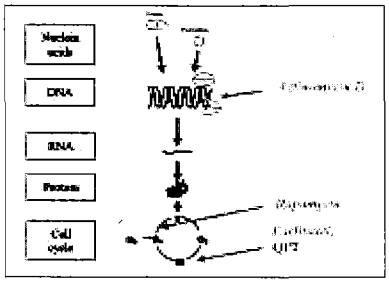
of the colchicine type, which inhibit microtubuli assembly, paclitaxel shifts the microtubule equilibrium towards microtubule assembly. It is highly lipophylic, which promotes a rapid cellular uptake, and has a long-lasting effect in the cell due to the structural alteration of the cytoskeleton.
A summary of the drug action on cellular level is given in Fig 8.

Experimental and clinical data

Experimental data

There are a variety of preclinical studies on different pharmacological principles and drugs available. The studies vary in the applied drug, its concentration, the stent preparation, coating, pharmacokinetic and the animal species. We restrict our summary of preclinical results to drugs, which are actually under clinical investigation.

Figure 8.



Overview of cellular mechanisms of action of drugs, that are now beeing clinically tested with drug eluting stents.

Despite major differences in study set-up and design, animal experiments for both, sirolimus and paclitaxel, showed
1. consistently a significant reduction of neointima formation for the drug eluting stent as compared to the bare stent with a clear dose response curve.
2. no increased inflammatory response in drug eluting stents as compared to bare stents.
3. less smooth muscle cell colonization and more residual fibrin deposition for the drug eluting stents as compared with the bare stents.

RAPAMYCIN (SIROLIMUS; RAPAMUNE®)

Rapamycin prevents proliferation of T cells but also proliferation[37,38] and migration[39] of smooth muscle cells. Furthermore, rapamycin has been shown to diminish smooth muscle cell hyperproliferation in several animal models of arteriopathy[40-42]. Pre-clinical efficacy studies demonstrated a 35 to 50% reduction in in-stent neointimal hyperplasia for the rapamycin coated stents as compared with bare metal stents at 28 days in the porcine and rabbit model[43]. The stents were coated with a thin layer of a poly-n-butyl methacrylate and polyethylene-vinyl acetate copolymer containing 185 µg sirolimus. Histological assessment revealed that the neointima of the sirolimus coated stents consisted of smooth muscle cells, matrix proteoglycans, and focal regions of residual fibrin adjacent to the stent struts. Focal medial necrosis or intimal hemorrhage was not observed within any of the bare metal or drug-coated stents. The morphology of non-stented reference arterial wall sections was similar for the metal and the drug-coated stents. A semi-quantitative histological grading system demonstrated less smooth muscle cell colonization and more residual fibrin deposition for the rapamycin eluting stents as compared with the bare metal stents. The focal remnants of residual fibrin deposition that

was observed in the vessel with rapamycin coated stents may reflect a delay in arterial repair or impaired fibrin degradation secondary to the local effects of the drug. Endothelialization scores were identical for the metal (2.9±0.4)-and the sirolimus eluting stents (2.9±0.4, P=0.66).

PACLITAXEL (TAXOL®)

In vitro and in vivo studies have shown that paclitaxel. may prevent or attenuate restenosis. Paclitaxel inhibits proliferation and migration of cultured smooth muscle cells in a dose-dependent manner[44]. In a rat balloon injury model, intraperitoneal administration of paclitaxel reduced neointimal area. The local, vascular administration of paclitaxel showed conflicting results. It reduced neointimal thickness in an atherosclerotic rabbit model[45-47] but did not reduce neointima formation in native pig coronary arteries following stent implantation[48].

Stent-based paclitaxel has been investigated by several groups, using different stent types and preparation (copolymer coatings for paclitaxel elution[49,50] or direct dip-coating of paclitaxel on a stainless steel stent[51] or self-expanding stents[52]) and animal models (pig[51,52], rabbit[49,50]). These studies consistently revealed a significant, dose-dependent inhibition of neointimal hyperplasia. Furthermore, they could show that the tissue responses in paclitaxel-treated vessels included incomplete healing, few smooth muscle cells, late persistence of macrophages and dense fibrin with little collagen as well as signs of positive remodeling of the stented segment.

There is, however, discrepancy regarding the long-term outcome. Farb and colleagues used polymer coated stents containing 42.0 or 20.2 µg of paclitaxel in a rabbit model. At 90 days after stenting neointimal growth was no longer suppressed[50]. In the Drachman series a much higher dose of paclitaxel was used (polylactide-co-sigma- caprolactone copolymer containing 200 µg paclitaxel), also in a rabbit model. Intimal and medial cell proliferation was reduced three-fold at seven days after stenting as compared to control stents. Six months after stenting, long after drug release and polymer degradation were likely complete, neointimal area was two- fold lower in paclitaxel-releasing stents[49].

The relevance of these findings for the application of either drug, drug concentration, and formulation in humans is unclear, as the response to injury and endovascular prosthesis is dependent of the species under study[53,54]. This is illustrated by the fact, that an inflammatory response to bare metal and polymer-coated stents has been seen in the porcine, but not the canine model[43].

Clinical data

ACTINOMYCIN D

There is no published research to date documenting the use of actinomycin D for treatment of coronary artery disease and/or restenosis. A phase 1, randomized clinical trial "ACTinomycin eluting stent Improves Outcomes by reducing Neointimal Hyperplasia" (ACTION) started in June 2001 to evaluate the safety and performance of the Multi-link tetra™ -D stent system. 360 patients were randomized to receive a actinomycin D coated stent (high dose 10 µg/cm^2; low dose 2.5 µg/cm^2) or a non-coated stent for treatment of de-novo lesions in native coronary arteries with a vessel caliber of 3.0 mm - 4.0 mm. Six month angiographic follow-up is expected to be completed in June 2002, 12 month clinical follow-up up is expected to be completed in the end of 2002.

RAPAMYCIN (SIROLIMUS)

The Sao-Paulo registry: Thirty patients with angina pectoris were electively treated with 2 different formulations of rapamycin-coated BX Velocity® stents (Cordis) (slow release [SR], n=15, and fast release [FR], n=15). All stents (18mm) were successfully delivered, (3.0-3.5 vessel caliber) and patients were discharged without clinical complications. At 4-months angiographic and IVUS follow-up, there was minimal neointimal hyperplasia in both groups (11.0±3.0% in the SR group and 10.4±3.0% in the FR group by ultrasound; in-stent late loss 0.09±0.3 mm [SR] and -0.02±0.3 mm [FR] by QCA). No in-stent or edge restenosis was observed. No major clinical events (stent thrombosis, repeat revascularization, myocardial infarction, and death) had occurred by 8 months[55]. At 1 year follow-up, IVUS volumetric analysis and angiography indicated minimal amounts of neointimal hyperplasia that were scarcely different from the 4 month data in both groups, with some patients showing no evidence of hyperplasia whatsoever. One late acute MI occurred in the fast-release group at 14 months. There were no other MACE and no restenosis in either group[56].

The Rotterdam registry: In Rotterdam, 15 patients were treated. All stent implantations were successful, one patient died on day 2 of cerebral hemorrhage and one patient suffered subacute stent occlusion due to edge dissection. At 6-months follow-up, QCA revealed essentially no change in minimal lumen diameter and percent diameter stenosis by angiographic criteria and hence no in lesion or in-stent angiographic restenosis was observed. Quantitative ultrasound showed that intimal hyperplasia volume and percent obstruction volume at follow-up were neglectable with 5.3mm^3 and 1.8% respectively. No edge effect was observed

in the segment proximal and distal to the stent[57]. At 9 months follow-up no further adverse events had occurred and all patients were angina free.

*The RAVEL trial (**RA**ndomized study with the sirolimus coated BX **VE**locity™ ballooon-expandable stent in the treatment of patients with de novo native coronary artery **L**esions):* The multicenter, prospective, double blind clinical trial compared bare metal and the drug coated stent. Two hundred thirty-eight patients were randomized to a single rapamycin coated (140µg/cm²) versus a bare metal BX velocity stent. At six months follow-up, the restenosis rate of the treated group was zero, the loss in minimal lumen diameter was zero, there was no target lesion reintervention and the event-free survival was 96.5%[58].

The SIRIUS study is a multicenter, prospective, randomized double blind trial that is conducted in 55 centers in the USA. Eleven-hundred patients with focal de novo native coronary arterial lesions (2.5mm to 3.5mm diameter, 15mm to 30 mm long) were randomized to treatment with rapamycin coated or bare metal BX velocity balloon expandable stents. The primary endpoint of the SIRIUS trial is target vessel failure (death, myocardial infarction, target lesion revascularization) at 9 months. In addition, secondary endpoints are core laboratory analysis of angiographic and intravascular ultrasound data to determine treatment effects on neointimal hyperplasia and in-stent restenosis. The six months follow-up will be completed in March 2002. Clinical follow-up will extend to 3 years in order to assess for late events.

In addition to the pivotal RAVEL and SIRIUS trials, feasibility studies are ongoing to assess efficacy of rapamycin coated stents in more complex lesion subset such as in-stent restenosis.

PACLITAXEL

Taxus trial family: There are several clinical trials on paclitaxel coated stents ongoing. The Taxus 1 trial is a safety study[61]. Patients with de novo lesions were randomized to receive a paclitaxel coated, slow release formulation (1.0µg/mm²) NIR conformer or a bare NIR stent. At 6 month follow-up, no restenosis was seen in the paclitaxel coated stent group while the restenosis rate in the bare stent group was 11%. The late lumen loss of 0.35±0.47mm was significantly lower in the paclitaxel coated stent group as in the bare stent group (0.71±0.88mm)[59]. Taxus -II is an efficacy study. 532 Patients are being enrolled to receive a paclitaxel coated, sequential slow and moderate release formulation stent. The TAXUS-III trial is a feasibility trail. 30 Patients were enrolled to receive a paclitaxel coated, slow release formulation stent for in-stent restenosis. Primary endpoint is the rate of major adverse cardiac events at 30 days follow-up. The Taxus IV pivotal study is enrolling 1600 patients with in-stent restenotic or de-novo lesions in the U.S. to receive a paclitaxel coated, moderate release formulation EXPRESS stent. Primary endpoint will be the target vessel revascularization rate at 8 months follow-up.

The Asian ASPECT trial showed a clear dose response. 177 patients were randomized to receive a high dose (3.1µg/mm²) paclitaxel coated, a low dose (1.3 µg/mm²) paclitaxel coated or a bare stent. The restenosis rate at 6 months was 4%, 12% and 27%, respectively[60].

The ELUTES trial (**Eva**l**LU**ation of pacli**T**axel-**E**l**u**ting **S**tent) assessed the safety and efficacy of four doses of paclitaxel versus an uncoated Cook V-Flex(tm) Plus stent. 192 patients were randomised to receive dosages of 0.2 µg/mm²; 0.7 µg/mm²; 1.4 µg/mm² and 2.7 µg/mm² or control stent. At 6-month follow-up, quantitive coronary angiography showed a clear dose relationship, with percent diameter stenosis ranging from 34% for the bare stent, to 33, 26, 23, and 14% for ascending dose densities of the paclitaxel-coated stents. Late loss reflected the same pattern with 0.73 mm for controls and 0.10 mm for the highest dose stent (p<0.005). The binary in-stent restenosis rate for controls was 21%, with 20, 12, 14, and 3% rates for ascending doses[61].

Quanam stent trials: In other clinical trials, the taxol derivate QP2 was used.

The *European QP2 pilot study* included 32 patients with de-novo or restenotic lesions who underwent QuaDS-QP2 stent implantation (Quanam Medical Corporation, Santa Clara, CA). The stainless steel, slotted tube stent was 13 or 17mm in length and coated with multiple polymer sleeves that slowly release QP2 (up to 4000 µg) (Fig 9). At 8-month follow-up, IVUS revealed only moderate neointima formation with a neointima burden of 13.6±14.9%[62].

In the South-American *QuaDS-QP-2 registry (BARDDS)*, thirty-two patients were treated with the QuaDS-QP-2 stent (containing up to 4000 µg QP2). 13 patients underwent

Figure 9.

The Quanam drug eluting stent. Quanam polymere sleeves loaded with a microtubular inhibitor. Polymere sleeves are tightly stretched over dedicated Quanam metal stents that are mounted on custom made rapid exchange balloon catheters.

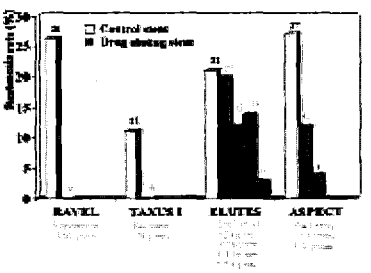
angiographic and IVUS follow-up (at 6-15 months). Although all 13 QuaDS- QP-2 stents were patent, two reinterventions have been required, both relate to either new disease or to distal, small-vessel disease beyond the stent. Twenty-five patients were asymptomatic at 2-year follow-up[63].

The multicenter, SCORE trial randomized 266 patients to receive a QuaDS-QP2 stent (4000 µg with an elution over 180d) or a bare stent. However, this trial has been stopped by the safety committee because of an excessive adverse event rate in the QuaDS-QP2 stent group of 10.2%[64], consisting in periprocedural myocardial infarction (MI 7.1%) and subacute stent thrombosis65 (SAT and death 6.3%), most probably caused by the polymer sleeves.

An overview of the angiographic restenosis rate and late lumen loss at 6 months follow-up angiography in randomized clinical trials of drug eluting stents is given in Fig 10 and Fig 11.

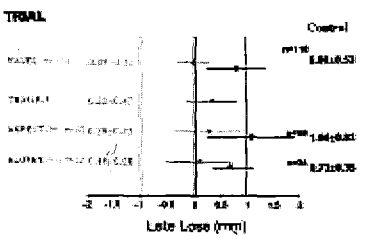
Besides these trials, a variety of other drugs are planned or just started enrolling patients in first clinical studies. Paclitaxel will be used in the upcoming PATENCY and DELIVER trials. Upcoming trials will include antisense c-myc, deaxamethosin (STRIDE), batimastat (BRILLIANT, BATMAN) and 17-ß-estradiol (EASTER, St. THOMAS) (Fig 12).

Figure 10.



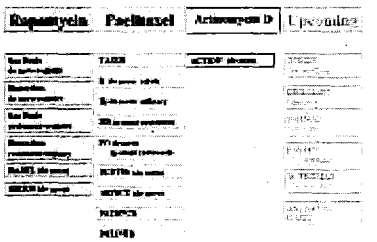
Aniographic restenosis rates (>50% diameter stenosis) at 6 month follow-up in randomized clinical trials of drug eluting stent.

Figure 11.



Aniographic late lumen loss at 6 month follow-up in randomized clinical trials of drug eluting stent.

Figure 12.



Overview of clinical trials with drug eluting coronary stents.

Contemporary application modalities and devices

Actinomycin D: Multi-Link Tetra™-D stent (Guidant, Santa Clara, CA, USA)

Stent: The stent is fabricated from medical 316L stainless steel tubing and is composed of a series of cylindrically oriented rings aligned along a common longitudinal axis. Each ring consists of 3 connecting bars and 6 expanding elements (Fig 13). The stent is pre-mounted on a delivery catheter.

Figure 13.

Actinomycin D: Multi-Link Tetra™-D stent (Guidant, Santa Clara, CA, USA).

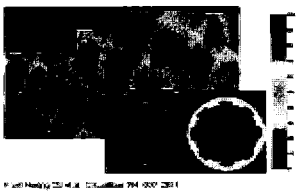
Coating: Actinomycin-D is the antiproliferative drug. The finished Multi-Link Tetra stent is coated with a polymer matrix (semi-crystalline ethylene-vinyl alcohol co-polymer: EVAL) which contains a maximal dose of 150 µg actinomycin-D (Fig 14-15). This is between 20 and 200 times less than the recommended total human adult dose of 500 (g /day given intravenously for 5 days.

Delivery system: The delivery catheter has a rapid exchange design (0.014 inch guide wire). It is equipped with two radiopaque markers located underneath the balloon to mark

Figure 14.

Multi-Link Tetra ™-D stent: Coating formulation (Guidant, Santa Clara, CA, USA).

Figure 15.



Drug concentration along the stent struts (Fram Hawang *et al.*, Circulation 2001).

the ends of the stent and has a "stepped" balloon design to optimize balloon shoulder configuration.

NIRx™-Paclitaxel eluting conformer coronary stent (Boston Scientific USA)

Stent: The stent is fabricated from medical 316LS stainless steel. The geometry is a continuos, uniform, multicellular design with adaptive cells capable to differential lengthening. This enables the stent to be flexible in the unexpanded configuration. Stent length is 15mm. The stent is pre-mounted on a delivery catheter (Fig 16).

Coating: The antiproliferative drug is paclitaxel. Paclitaxel is incorporated into a fast-release triblock coplymer carrier system on the stent. There are two drug concentration. The "low dose" concentration is 1.0 µg/mm² (loaded drug/stent surface area; total dose 85 µg per stent) and gives sustained release over approx. 28 days. The "moderate dose" is 2.0 µg/mm² (loaded drug/stent surface area) and provides a rapid release in the first 24h, followed by a slower release over the following 28 days.

Figure 16.

NIRx ™-Paclitaxel eluting conformer coronary stent (Boston Scientific USA).

Delivery system: The delivery catheter is a monorail design (0.014 inch guide wire/6F guiding catheter). It is equipped with two radiopaque markers located underneath the balloon to mark the ends of the stent.

Paclitaxel eluting stent (Cook Inc. USA)

Stent: The stent is a stainless steel, slotted tube design with high radial strength and low recoil.

The stent length is 15 mm, the diameter is 2.5, 3.0 or 3.5 mm (Fig 17).

Figure 17.

Paclitaxel eluting stent (Cook Inc. USA).

Coating: The antiproliferative drug is paclitaxel. Paclitaxel adhered to the abluminal surface with no polymer using a proprietary process. Paclitaxel is applied in two concentrations. The high dose is 3.1 µg/mm², the low dose is 1.3 µg/mm².

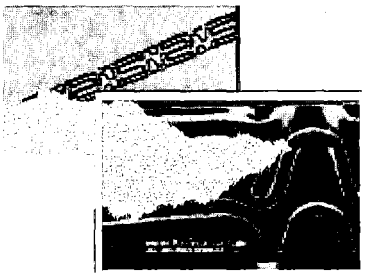
Delivery system: The delivery catheter is a monorail design (0.014 inch guide wire/6F guiding catheter). It is equipped with two radiopaque markers located underneath the balloon to mark the ends of the stent.

Cypher™: The sirolimus eluting BX™ velocity stent (Cordis, Warren, USA)

Stent: The stent is fabricated from medical 316LS stainless steel. It is available in 2 cell configurations (6 cell configuration: expanded diameter 2.5-3.25mm) and 7 cell design (expanded diameter 3.5-3.75mm). Stent length is 18mm (Fig 18). The stent is pre-mounted on a delivery balloon.

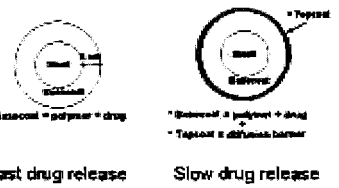
Coating: The antiproliferative drug is sirolimus. The stent contains 140µg/cm² which gives a total sirolimus content of 153 µg on the 6-cell stent and 180 µg on the 7-cell stent. The slow release coating formulation consists of 30% sirolimus by weight in a 50:50 mixture of the polymer polyethylenevinylacetate (PEVA) and polybutylmethacrylate (PBMA) (Fig 19).

Figure 18.



Cypher™: The sirolimus eluting BX™ velocity stent (Cordis, Warren, USA).

Figure 19.



The sirolimus eluting BX™ velocity stent: Coating formulation, (Cordis, Warren, USA).

Delivery system: The delivery catheter utilizes a rapid exchange design (0.014 inch guide wire/6F guiding catheter). It is equipped with two radiopaque markers located underneath the balloon to mark the ends of the stent. The delivery balloon is 2.5mm, 3.0mm and 3.5mm in diameter.

Procedure performance

Patient selection

INDICATIONS

The indications for drug eluting stent implantation are not yet established. Clinical data are up to now only available in patients with simple, short de novo lesions. An clinical example of sirolimus eluting stent implantation is given in Fig 20.

CONTRAINDICATIONS

There are up to now, no absolute contraindications for drug eluting stent implantation defined. Caution should be taken in patients after failed brachytherapy. There is no data available on the combined effect of radiation and cytostatic therapy in coronary arteries. In oncology, however, this combination is known to produce highly complex and poorly understood interactions[66-69].

Figure 20.

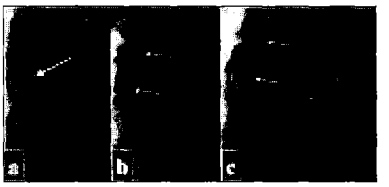


Figure 20. Clinical example of sirolimus eluting BX™ velocity stent implantation. **Fig 20a.** preprocedural angiogram of the right coronary artery with a short, de novo lesion (arrow) **Fig 20b.** Postprocedural angiogram after implantation of a 3.0/18mm sirolimus coated BX™ velocity stent **Fig 20c.** 6-month follow-up angiography. The angiogram shows a patent artery with no evidence for neointimal hyperplasia.

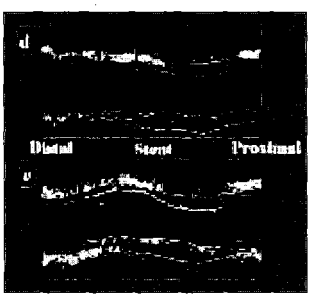


Fig 20d. Longitudinal IVUS view after sirolimus eluting BX velocity stent implantation. The lumen boundary (red) and the vessel boundary (green) is traced. **Fig 20e.** Longitudinal IVUS view at 6-month follow up. The yellow lines indicate the proximal and the distal end of the stent. Lumen (red) volume remained unchanged over time, no neointima formation within the stent is detected. Thus, the stent (light blue) boundary is superimposed to the lumen boundary. Vessel volume (green) remained stable over time.

Patient preparation - medication

Pre-procedural treatment requires no particular medication for drug eluting stent implantation other than antiplatelet regimen for routine angioplasty procedures: Aspirin (75mg-300mg) and ticlopidine or clopidogrel must be started at least 24h before the procedure, whereby we prescribe a loading dose of 750mg, followed by 250mg twice a day for ticlopidine and a loading dose of 300mg, followed by 75mg daily for clopidogrel. Beta-blockers, calcium antagonist and oral nitrates should be administered as usually prescribed.

In begin of the procedure, we routinely administer neuroleptics and analgesics. Repeat bolus is given during the procedure, if needed. Furthermore, we administer 325mg aspirin intravenously and 10 000 IU heparin immediately after arterial sheath placement. Activated clotting time (ACT)

is checked every 30 minutes after the first bolus injection in order to maintain ACT > 300 sec. Additional heparin is given if necessary.

During the procedure, GP IIbIIIa receptor blockers are given deliberately in patients with unstable angina, periprocedural intracoronary thrombus formation or dissection.

Angioplasty

For the angioplasty procedure, a standard angioplasty set is needed. We prefer the standard femoral approach for optimal guide support using 6F sheath and guiding catheter. Stent implantation is performed in conventional technique. It is important, that angioplasty is not stopped before reaching a satisfactory result.

Handling of the stent

Care should be taken while handling the drug eluting stent. The polymer coating is considered to be mechanically and chemically stable. Thus, there should be no drug release while preparing and handling the stent system during the procedure. However, we recommend not to stress the stent mechanically during unpacking and preparation to avoid cracking and flaking of the coating layer caused by distortion of the stent. In dependency of the drug and coating, losses up to 17% of the drug doses can occur during ex vivo manipulation. Furthermore, the stent should be placed rapidly into the coronary system. Losses to the blood lipids may occur during the brief (30-second) exposure to the coronary circulation before deployment. This was demonstrated in washout experiments with paclitaxel in which a 30-second exposure to pig blood at 37°C resulted in loss of <5% of the applied dose[51].

Stent implantation technique

The question of *direct stenting* has not been addressed yet. Possible concerns are, again, increased mechanical stress to the stent and prolonged blood exposure in lesions, were it is difficult to advance the stent into the lesion. Therefore, all clinical trial protocols recommend predilatation of the lesions.

Multiple stents

Another important question is the drug distribution in the vessel wall when multiple stents are used. Experimental studies with Actinomycin D eluting stents in pigs indicated 70 mg of Actinomycin D as the toxic dose. If an 40 mg coated stent is overlapped with another 40 mg coated stent, the toxic dose in that vessel is exceeded[70]. Vice versa, the drug concentration might drop to inefficient levels, when stents are placed with a "gap"in-between.

Complications

Procedural complications

Procedural complications include all complications typically linked to the angioplasty/debulking procedure.

Long-term complications

Up to now, no longterm complications are known. The animal experimental data, which are showing delayed or incomplete healing point to the potential danger of delayed thrombosis. This risk seems to be rather small for the sirolimus eluting stent. The Sao Paulo and the Thoraxcenter registry as well as the multicenter RAVEL trial prescribed clopidogrel for only two month after stenting and no (sub) acute or delayed thrombotic event was seen.

Theoretically, all potential complications related to the specific drugs used may apply. The systemic concentration of these drugs, however is extremely low or not even measurable. Under these circumstances, severe systemic complications seem very unlikely.

Postprocedural care

The arterial sheath is withdrawn immediately after the procedure and the access site sealed with a closure device (Perclose or Angioseal). In case of a difficult arterial puncture with substantial fibrosis, the sheath is removed 6 hours after the procedure and the artery manually compressed. All patients must receive effective antiplatelet therapy for at least 2 months. In our institution, we prescribe aspirin indefinitely in combination with ticlopidine (250mg twice a day) or clopidogrel (75mg daily).

Limitations

Although the principle of stent implantation is well established and although (most of) the applied drugs and polymers were used in clinical practice since years, there is little experimental and only preliminary clinical knowledge of the acute and long-term effects of drug-eluting stents in coronary arteries. Thus, a number of concerns and open questions have to be investigated in the future.

The concerns include drug toxicity as well as acute and late vascular effects. A number of toxic effects are known for all drugs applied in cancer therapy such hematological toxicity (neutropenia), neurotoxicity (peripheral neuropathy), hypersensitivity reactions, or cardiac disturbances. However, these side effects are described in patients undergoing high-dose chemotherapy for a malignant disease with plasma levels 100

to 1000 times higher (and over longer time periods) than plasma levels that result from a local delivery. Another concern is possible delayed wound healing and re-endothelialization. This would increase thrombogenicity and the danger of (late) stent thrombosis. Further potential side effects could be late positive remodeling and aneurysma formation. Thus the most suitable antithrombitic regimen following drug-eluting and/or biodegradable stent implantation still has to be evaluated.

A series of open questions exists on the mechanism of action and consecutively the design of local drug delivery systems and drug-eluting stents. Little is known of specific pharmakokinetic issues. There is a paucity of data on the most appropriate tissue concentration and the rate and duration and of drug-release over time. The tissue concentration is dependent on close mechanical contact of the stent to the vascular tissue and on physiological transport forces into the tissue. Hydrophobic drugs, like paclitaxel have greater variability in terms of drug delivery, while hydrophilic drugs, like heparin, have less variability and achieve higher local concentrations. Local concentrations and concentration gradients however, are crucial parameters for biological effects. The relationship between vascular effects and physicochemical properties of the drug-loaded stent is poorly understood. Drug distribution within the vessel wall seems to be significantly affect by the stent expansion pattern (uniform versus non-uniform)[71].

Conclusion and future perspectives

Drug-eluting stents represent one of the most promising fields in interventional cardiology today. However, a lot of unanswered questions still have to be resolved before determining their potential. Hopefully, after the completion of planned and ongoing trials many of these issues will be answered. Furthermore, these new technologies will have to proof effective in daily routine patients presenting with long lesions, small vessels, chronic occlusion, bifurcation, multivessel and/or left main stem disease or acute myocardial infarction.

Stent development will investigate a variety of possibilities to resolve the restenosis problem. Possibilities range from the further exploitation of different classes of drugs which are potential candidates for the inhibition of restenosis to the combination of biodegradability with drug delivery, or local gene therapy (e.g. local expression of proliferation regulatory genes; transfer of cytotoxic genes, VEGF).

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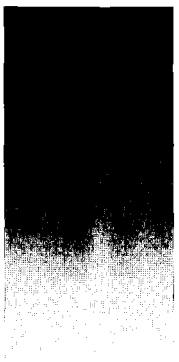

CHAPTER 4

SIROLIMUS ELUTING STENTS: IN THE TREATMENT ATHEROSCLEROTIC CORONARY ARTERY DISEASE

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Minerva Cardioangiol 2002;50:405-18

CARDIOLOGIA INTERVENTISTICA

MINERVA CARDIOANGIOL 2002;50:405-18

Sirolimus eluting stent in the treatment of atherosclerosis coronary artery disease

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Stent implantation represents the most commonly performed percutaneous coronary intervention nowadays. However, instent restenosis due to exaggerated neointimal hyperplasia remains a problem to overcome. Neointimal hyperplasia is a vascular response to stent injury; it mainly consists of smooth muscle cells proliferation . The underlying molecular mechanisms of restenosis were explained in this review article. Recently, drug-eluting stent has been proposed as a potential method to prevent instent restenosis. Animal studies have confirmed safety and efficacy of sirolimus-eluting stent implantation *in vivo*. The FIM trial, which was the first clinical study on sirolimus-eluting stent in *de novo* lesions, has shown an astonishing 0% restenosis rate. The RAVEL trial was the first prospective, double-blind, multi-center trial that randomized 238 patients at 19 institutions with *de novo* lesions into sirolimus-eluting *versus* bare Bx velocity stent. Six-month binary restenosis rate in the sirolimus-group was again 0% compared to 26.6% in the control group. Angiographic late loss and major cardiac event were also significantly lower in the sirolimus-group. The SIRIUS trial is an ongoing study conducted in 53 US centers that randomized 1100 patients with *de novo* lesion into sirolimus-eluting and bare stents. Preliminary results also showed a significant reduction in binary restenosis, late loss and repeat revascularization rates. Apart from *de novo* lesions, early experience of sirolimus-eluting stent implantation for instent restenosis in non-randomized study was also promising, achieving a single-digit repeat restenosis rate. As compare with standard coronary stent, a sirolimus-eluting stent shows considerable promise for the prevention of neointimal proliferation, restenosis and associated clinical events.

Key words: **Stents - Coronary disease - Atherosclerosis.**

In the percutaneous treatment of atherosclerotic coronary artery disease balloon angioplasty and coronary stent implantation are the "standard" of care. Compared to balloon angioplasty alone, coronary stents have a more favorable acute and late outcome by eliminating elastic recoil and negative remodeling [1,2] and reduce the incidence of restenosis by approximately 35-50%. Over the last decade, coronary stents have become the most commonly applied technique in the field of interventional cardiology and are being used in more than 80% of all procedures performed in the world. However, stents actually increase neointimal hyperplasia [3] and in-stent restenosis rates vary between 10-40% related to patient specific factors such as genetic predisposition,

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diabetes mellitus,[4] to lesion specific factors such as vessel size,[5] length, plaque burden,[6] total occlusion, bifurcation and to procedure specific factors such as extent of vessel damage, residual dissections,[7] number of stents, stent size and stent area.[8] Treating in-stent restenosis has become another challenging problem, regardless of which percutaneous approach is chosen such as repeat balloon angioplasty, atherectomy,[9] laser angioplasty, cutting balloon or repeat stenting,[10] 30-80% of the patients develop repeat in-stent restenosis.[11] Intracoronary radiation is the only therapy for in-stent restenosis proven effective in randomized clinical trials.[12, 13] However, restenosis is not eliminated, but still in the range of 20-30%. Furthermore, the widespread use of intracoronary radiation therapy is limited by considerable logistic requirements, and potential side effects such as edge effect,[14] geographic miss,[15] delayed healing [16] and late thrombosis.[17]

Numerous systemic pharmacologic agents have failed to inhibit in-stent restenosis possibly due to inadequate kinetics, insufficient local drug concentration, systemic side effects and other factors.[18-20] Local drug release at the site of vascular injury using polymer-coated stent is an elegant approach to achieve effective local concentration in a controlled duration. Recently, in the stent technology, the 3 major technical challenges have been mastered after many failed attemps:[21] the controlled release of an efficient drug from a stable coating. Consequently, attention has focused on usage of these stents as a local delivery vehicle of the anti-restenotic therapy and many antiproliferative agents are currently being investigated to assess their efficiency and safety in the prevention of in-stent restenosis. Among these agents studied in different stent models, Sirolimus is the one for which clinical efficiency has been shown in a randomized trial.[22]

Restenosis mechanism and the importance of cell-cycle

Neointimal hyperplasia is considered as a component of the general vascular response to injury and mainly consists of smooth muscle cells and extracellular proteoglycan matrix.[23, 24] Stent induced injury and foreign body response to the prosthesis provoke inflammation in the vessel wall, with release of cytokines and growth factors that induce signaling pathways to activate smooth muscle cell migration and proliferation.[7, 25] Clinical and experimental pathological studies have revealed 3 phases of vessel wall response to stent implantation. In early phase platelet activation, thrombus formation and fibrin deposition take place. Afterwards, the granulation phase is characterized by smooth muscle cell and fibroblast migration to the injured area. Finally, the vascular remodeling phase is characterized by maturation of the neointima, proteoglycan and collagen synthesis which replaces early fibronectin as a major component of extracellular matrix.[26]

Cytokines and growth factors are the messengers for vascular proliferative response. Injured endothelial cells, activated platelets, smooth muscle cells (SMCs), and macrophages secrete chemoattractants, regulators of growth and gene expression in vascular cells. Smooth muscle cells progress through DNA replication and mitosis in a regulated series of cell-cycle events that comprise the final common pathway downstream of vascular injury during the vasculoproliferative response. Resting SMCs are maintained in a non proliferative phase (Go). After arterial injury SMCs enter a gap period (G1) and prepare the factors necessary for DNA replication in the following(s) phase. After completion of DNA replication, the cells again enter a gap period (G2), when the proteins are synthesized in preparation for mitosis (M). Restriction points occurring at the G1-S and G2-M interphases ensure orderly cell-cycle progression [27] (Figure 1).

The cell cycle is regulated by the synthesis, activation, and degradation of molecules that modulate the proliferative phenotype.[28] The cyclins and their cognate regulatory enzymes, the cyclin dependent kinases (CDKs) exist in stable complexes and are positive regulators of cell division.[27] The CDK inhibitors

(CDKIs) are also critical negative regulators of the cell cyle. The activities of cyclin-CDK complex depend on the phosphorylation status of CDKs and steady state of levels of cyclins.

The major molecular events of the cell cycle are common among all cell types and regulation of the cell-cycle machinery is a final pathway for proliferative responses of vascular smooth muscle cells. The current data suggest that blocking the central cellular processes that would inhibit the downstream effects of injury driven growth factors and cytokines can be effective to prevent restenosis. This cytostatic approach of modulating the expression of cell-cycle regulatory proteins (CDK, $p27^{kip1}$) is different from antiproliferative strategies with a cytotoxic mechanism of action that involves killing proliferating cells. The advantages of a pure cytostatic therapy are that it does not induce cell necrosis and arterial wall thinning.[29] Therefore, nowadays, anti-restenosis therapy has focused on the cell-cycle targeting agents (Figure 2).

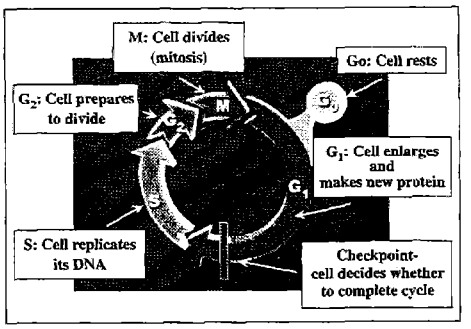

Fig. 1.—Schematic illustration of mechanism of cell cycle.

Sirolimus: the drug and mechanisms of action

Sirolimus, a macrolide antibiotic, is a natural fermentation product produced by the fungus *Streptomyces hygroscopicus*, which was originally found on Easter Island (the island of Rapa Nui). Sirolimus is a potent immunosuppressive agent with anti-proliferative and anti-inflammatory effects, approved by the FDA in 1999 for the prophylaxis of renal transplant rejection (Figure 3).

Sirolimus inhibits the proliferation of smooth muscle cell by blocking cell cycle progression at the G1/S transition. Sirolimus binds to its specific intracellular receptors, the FK506 binding protein (FKBP12), a member of immunophilin family proteins.[30] This complex (Sirolimus-FKBP12) inhibits a kinase called the mammalian target of sirolimus (mTOR), which is regulating cell cycle progression and prevents downregulation of $p27^{kip1}$ as well as retinoblastoma protein (pRb) phosphorylation. The inhibition of mTOR suppresses cytokine-driven (IL-2, IL-4, IL-7 and IL-15) T-cell proliferation. Mammalian TOR is a key regulatory kinase and 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 IL-2 induced transcription of proliferating cell nuclear antigen (PCNA) that is essential for DNA replication; the blocking of CD28-mediated sustained upregulation of IL-2 transcription in T cells and the inhibition of the kinase activity of the cdk4/cyclin D and cdk2/cyclin E complexes, essential for cell cycle progression.[31] The mechanism of action is distinct from other immunosuppressive drugs that act solely by inhibiting DNA synthesis, such as mycophenolate mofetil (CellCept) and azathioprine (Imuran). Sirolimus is synergistic with cyclosporin A and has much lower toxicity than other immunosupressive agents [32] (Figure 4).

Sirolimus prevents proliferation of T cells but also proliferation and migration of smooth muscle cells. Gregory *et al.*, demonstrated that intraperitoneal administration of sirolimus, resulted a dose-dependent inhibition of arterial intimal thickening caused by either chronic alloimmune or mechanical injury in a rat model.[33] Subsequent studies, by Gallo *et al.*, demonstrated that systemic SRL therapy significantly reduces the proliferative response after coronary angioplasty in the porcine

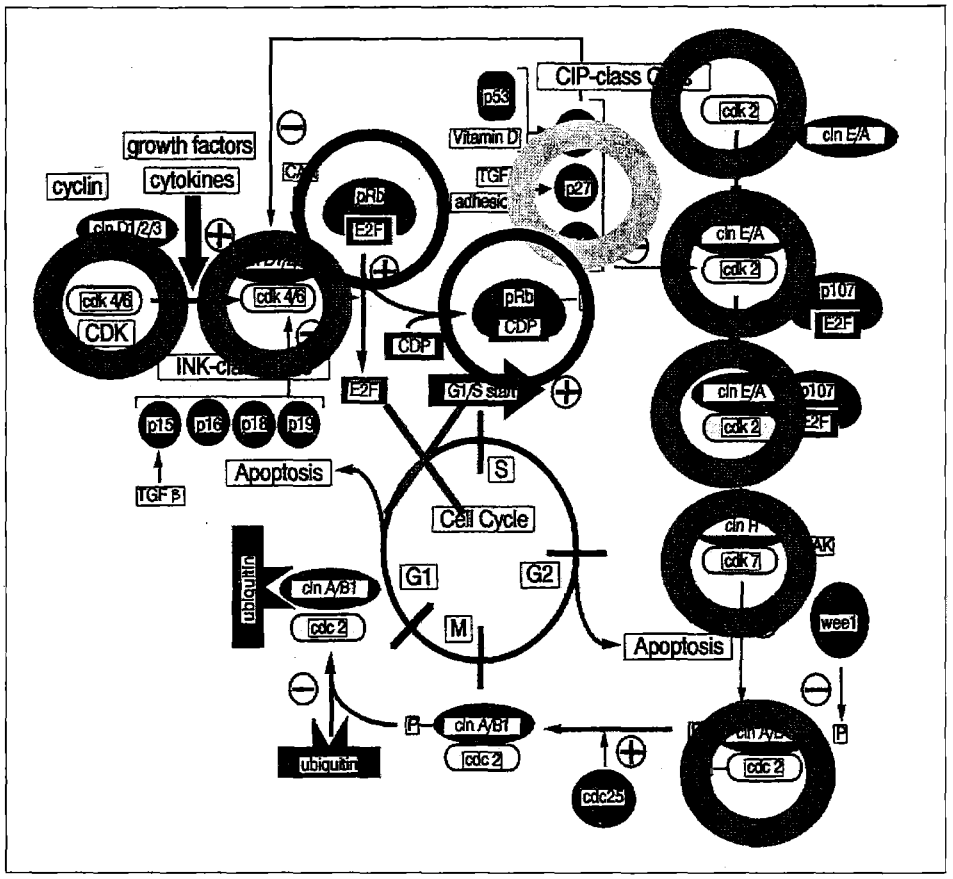

Fig. 2.—Sirolimus effects within the cell cycle. The cell cycle: a functionally integrated cascade of positive and negative regulatory factors. Sirolimus up and down regulation of proteins and enzymes (P27, P retinoblastome inhibition of CDK/cyclin.

model.[30] Additionally, human neointimal tissue extracted during atherectomy showed a robust upregulation of FKBP at the mRNA levels.[34]

Sirolimus is a lipophilic drug that has low solubility in aqueous solutions. Due to its lipophilicity, the drug passes easily through the cell membrane membranes, enabling intamural distribution and prolonged arterial tissue retention.[35] Further, cellular uptake is enhanced by binding to the cytosolic receptor, FKBP12, which also may enhance chronic tissue retention of SRL. Therefore, these pharmacologic properties of SRL in addition to proven antiproliferative activity, suggesting that the agent could be an effective agent for a stent-based delivery to prevent restenosis.

The sirolimus eluting stent

The sirolimus eluting BX velocity stent (Cypher™) is laser cut from 316 L stainless steel tubing is provided in 2 cell (6 and 7 cell) configurations. It is available in a length

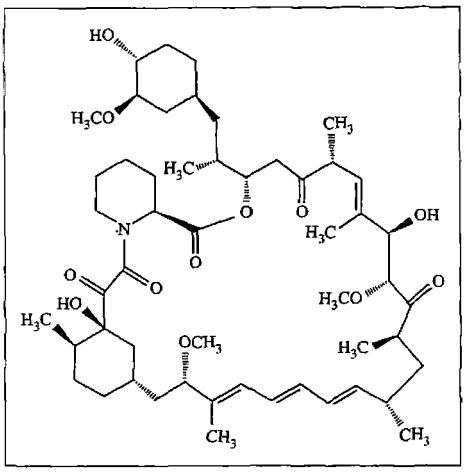

Fig. 3.—Chemical structure of sirolimus. Sirolimus (rapamycin), mw=914. *) Rapamune is a registered trademark of Wyeth Ayerst.

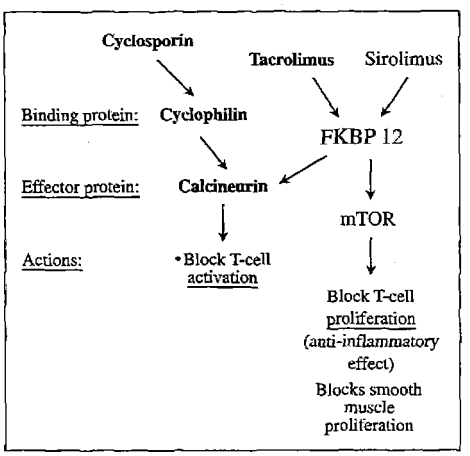

Fig. 4.—The mechanism of action of Sirolimus and other antiproliferative agents.

of 8, 18, 33 mm and 6 cell configuration: expanded diameter 2.25, 2.5, 2.75 and 3.0 mm). The 7 cell design (expanded diameter 3.5-3.75 mm) will be available in year 2003. The stent contains 140 g/cm² sirolimus which gives a total sirolimus content of 153 g on the 6-cell stent and 180 g on the 7-cell stent. The coating formulation consists of 30% sirolimus by weight in a 50:50 mixture of the polymers polyethylenevinylacetate (PEVA) and polybutylmethacrylate (PBMA). The thickness of two layers of polymers on the surface of the stent is 5-10 μ. To prolong the drug release drug free polymer is applied on to the top of the drug-polymer matrix, introducing a diffusion barrier.

In vivo *pharmacokinetics and preclinical efficacy experiments*

In vivo pharmacokinetics studies in the porcine coronary model demonstrated that the whole blood concentration of sirolimus peaks at 1 hour (2.63±0.74 ng/mL) after stent deployment and then declines below the lower limit of detection (0.4 ng/mL) by 3 days. Taking into account that renal transplant patients maintain chronic blood levels of sirolimus 8 and 17 ng/ml, the peak blood level after implantation of sirolimus eluting stent is actually negligible. The amount of residual sirolimus on the stent at 3 days is 43% of the initial quantity loaded on the stent. The drug is almost completely eluted by 15 days after implantation in fast release formulation and a modification of the coating (slow release formulation) provides to deliver at least 80% of drug within similar arterial tissue levels at 28 days. These data document the ability to deliver and achieve a potentially therapeutic arterial tissue concentration of sirolimus in the porcine model and insignificant levels in the systemic circulation using the non-erodable methacrylate and ethylens-based-co-polymer matrix (Figure 5).

The efficacy studies have demonstrated a profound reduction in strut-associated inflammation, with a 50% reduction in in-stent neointimal hyperplasia for the sirolimus eluting stents as compared with bare metal stents at 28 days in animal models.[36] Histological assessment revealed the presence of typical cellular components of the neointima and a similar degree of re-endothelialization for the sirolimus as compared with the bare metal stents. The morphology of non-stented reference arterial wall sections, including the vessel area, neointimal area and % area sten-

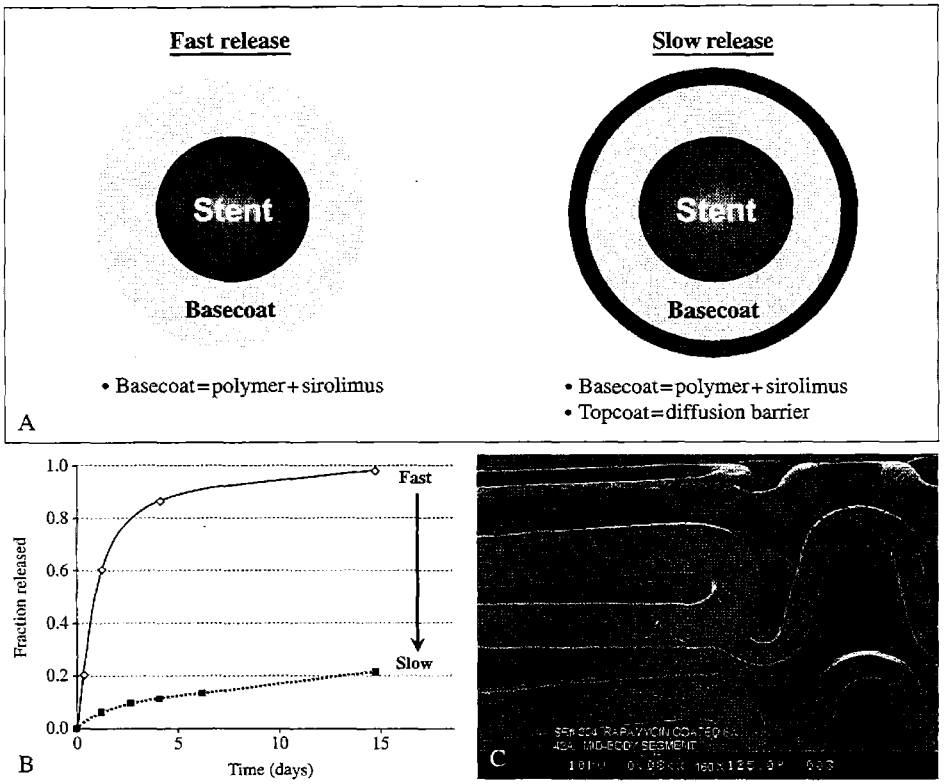

Fig. 5.—Drug release kinetics and coating formulation of sirolimus eluting stent.

osis was similar for the metal and the drug coated stents. A semi-quantitative histological grading system demonstrated less smooth muscle cell colonization and more residual fibrin deposition for the sirolimus eluting stents as compared with the bare metal stents. Therefore, critical reparative events, such as endothelialization and smooth muscle cell colonization of the neointima, with sirolimus eluting stents occur in a similar temporal sequence as observed with bare metal stents (Figure 6). The focal remnants of residual fibrin deposition observed in the vessel with sirolimus eluting stents may reflect a delay in arterial repair or impaired fibrin degradation secondary to the local effects of the drug.[36]

In addition , the evaluation of arterial wall protein documented a 70% reduction in the inflammatory cytokine MCP-1 for the SRL eluting compared with a bare metal stent. Sirolimus is not as potent as cyclosporine and tacrolimus to inhibit cytokine products and the potent immunosuppressive effect of sirolimus is directed toward inhibiting the proliferation of T cells by blocking IL-2 activation of $p70^{s6}$ kinase.[36]

Clinical trials

De novo *lesions*

The first clinical application of the sirolimus eluting stent FIM (First In Man) Trial was performed in Sao Paulo and Rotterdam. Forty-five patients were recruited to receive siroli-

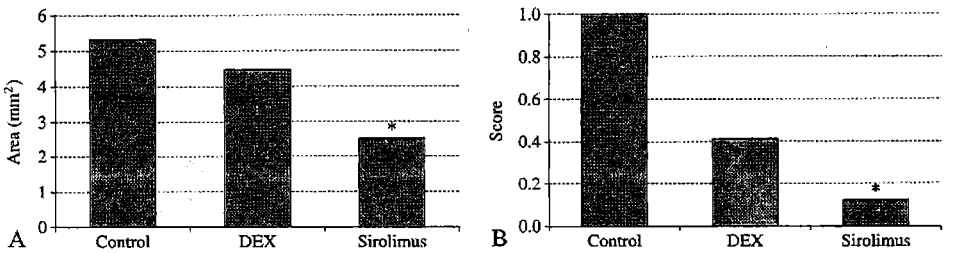

Fig. 6.—Sirolimus eluting stent revealed less inflammation and neointimal hyperplasia in comparison with uncoated (control) and Dexamethasone (DEX) coated stents in animal models. A) Neointimal area. B) Inflammation score.

mus eluting Bx Velocity stent for single *de novo* coronary lesions.

The Sao Paulo Registry

Thirty patients were electively treated with 2 different formulations of 18 mm sirolimus eluting Bx velocity stents [slow release (SR), n=15, and fast release (FR), n=15].

All stents were successfully implanted, and patients were discharged without clinical complications. At 4-months angiographic and intravascular ultrasound (IVUS) follow-up, there was minimal neointimal hyperplasia in both groups by ultrasound and quantitative coronary angiography [in-stent late loss, 0.09±0.03 mm (SR) and 0.02±0.3 mm (FR)]. No in-stent or edge restenosis was observed. No major clinical events (stent thrombosis, repeat revascularization, myocardial infarction, death) had occurred by 9 months.[37] At 1 year follow-up, IVUS volumetric analysis and angiography indicated minimal amounts of neointimal hyperplasia that were scarcely different from the 4 month data in both groups, with some patients showing no evidence of hyperplasia whatsoever. No patient showed more than 50% DS restenosis at 1 year follow-up angiography. One late acute MI occurred in the fast-release group at 14 months.[38]

Rotterdam registry

In Rotterdam, 15 patients were treated with slow release formulation 18 mm Bx-Velocity stents, quantitative angiography and 3-D IVUS were performed at implantation and 6 months follow-up. All stent implantations were successful. One patient died on day 2 due to cerebral hemorrhage and 1 patient had subacute stent occlusion due to edge dissection. At 9 months follow-up no further adverse events had occurred and all patients were angina free. QCA revealed essentially no change (in stent, late loss 0.00 mm, DS 13.7%) at 6 month follow-up. 3-D IVUS showed that intimal hyperplasia volume and percent obstruction volume at follow-up were negligible with 5.3 mm^3 and 1.8%, respectively.[39] However the question remains whether the early promising results will persist at long term follow-up. In the Rotterdam registry, 2 years clinical follow-up has been performed. Through 6-month follow-up and up to average 20 months repeat catheterization, no additional event occurred. QCA analysis revealed no significant change in stent minimal lumen diameter, percent diameter stenosis, and 3-D-IVUS showed no significant deterioration in lumen and edge volumes (Figure 7). In 2 patients, additional stenting was performed because of significant lesion progression remote from the sirolimus eluting stent.[40]

Ravel trial

RAndomized study with the sirolimus-coated bx VElocity balloon-expandable stent in the treatment of patients with de novo *native coronary artery Lesions*

The trial included 238 patients at 19 medical centers. The primary end point was in-stent late luminal loss (the difference between

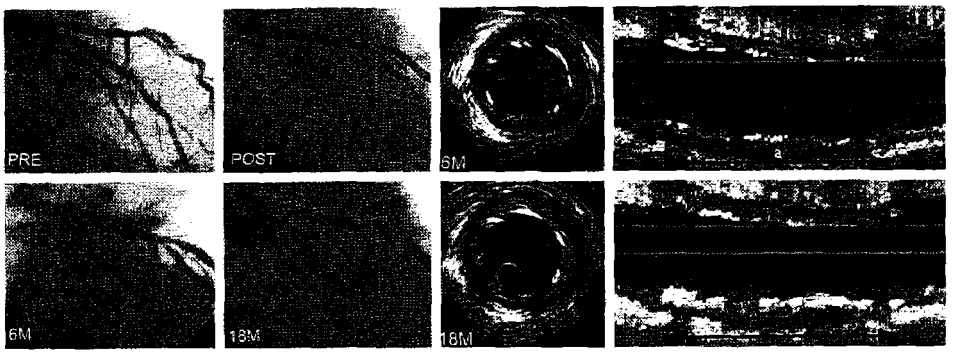

Fig. 7.—Persistent inhibition of neointimal hyperplasia at 18 months follow-up.

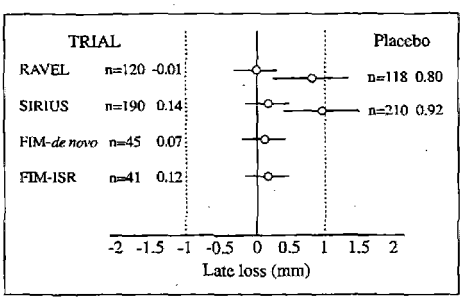

Fig. 8.—Late lumen loss at 4/6-month follow-up angiography in clinical trials of sirolimus eluting stent.

the minimal luminal diameter immediately after the procedure and the diameter at 6 months). Secondary end points included the percentage of in-stent stenosis of the luminal diameter and the rate of restenosis (luminal narrowing of 50% or more). A composite clinical end point consisting of death, myocardial infarction, and percutaneous or surgical revascularization at 1, 6, and 12 months was also analyzed. At 6 months, the degree of neointimal proliferation, manifested as the mean (±SD) late luminal loss, was significantly lower in the sirolimus-stent group (-0.01±0.33 mm) than in the standard-stent group (0.80±0.53 mm, p<0.001), (Figure 8). None of the patients in the sirolimus-stent group, as compared with 26.6% of those in the standard-stent group, had a diameter stenosis of >50% or more at follow-up (p<0.001). There were no episodes of stent thrombosis. Up to 1 year follow-up, the overall rate of major cardiac events was 5.8% in the sirolimus-stent group and 28.8% in the standard-stent group (p<0.001). The difference was entirely due to a higher rate of revascularization of the target vessel in the uncoated-stent group.[22]

A subgroup analysis of RAVEL study also showed that Sirolimus eluting stents prevent neointima formation growth and late luminal loss irrespective of the vessel size (Figure 9).[41] At 6 month follow-up, the restenosis rate was 0% for small, intermediate and large vessels, while the uncoated stent group showed the classical relationship between vessel size with a increasing restenosis rate (20%, 21% and 37%) for large, intermediate and small vessels. Side branch analysis after implantation of sirolimus eluting stents in RAVEL trial, showed that the coating thickness of eluting stent did not adversely affect the side branches, which originated in the lesion and covered by sirolimus eluting stents. The intravascular ultrasound investigation of RAVEL trial was performed in a subset of 95 patients (Sirolimus eluting stent=48 patients, Uncoated stent=47 patients) at 6 month follow-up. Stent volumes, total vessel volumes, and plaque behind stent volumes were comparable between the two groups. However, the difference in neo-intimal hyperplasia (2±5 *vs* 37±28 mm^3) and percent volume obstruction (1±3 *vs* 29±20%) at 6 months between the two groups was highly significant

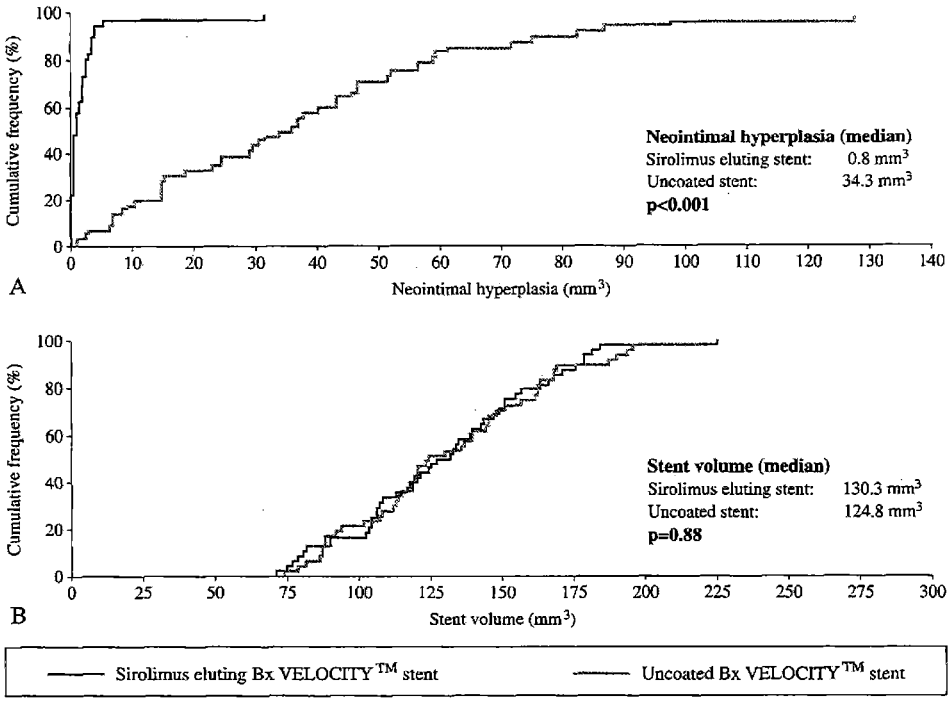

Fig. 9.—Cumulative distribution curve in stent neointimal hyperplasia and stent volumes at follow-up for the patients treated with sirolimus eluting stent patient (black line) and uncoated stent (gray line) in the RAVEL trial.

(<0.001), emphasizing the nearly complete abolition of the proliferative process inside the drug-eluting stent. Analysis of the proximal and distal edge volumes showed no significant difference between the two groups in EEM, lumen and plaque volume at the proximal and distal edges. Patients with sirolimus elutings stents revealed 21% (10/48) incomplete stent apposition *versus* 4% (2/47) of patients with uncoated stents. IVUS was not done immediately postprocedure thus, it is impossible to say whether these ISA observed at 6 month follow-up are the result of late acquired malapposition or persistence of acute incomplete deployment. Although there was a higher incidence of incomplete stent apposition in the sirolimus group compared to the uncoated stent group (p<0.05), it was not associated with any adverse clinical events at 1 year.[42]

SIRIUS trial

Multicenter, randomized, double blind study of the SIRolImUS-*eluting Bx-Velocity™ balloon expandable stent in the treatment of patients with* de novo *coronary artery lesions*

The SIRIUS trial is an ongoing study conducted in 53 centers in the US that randomized 1100 patients with *de novo* native coronary arterial lesions (2.5 to 3.5 mm diameter, 15 to 30 mm lesion length) in to treatment with rapamycin coated or bare metal Bx Velocity™ balloon expandable stents. The primary endpoint of the SIRIUS trial is target vessel failure (death, myocardial infarction, target lesion revascularization) at 9 months. In addition, secondary endpoints are core laboratory analysis of angiographic and intravascular ultrasound data to deter-

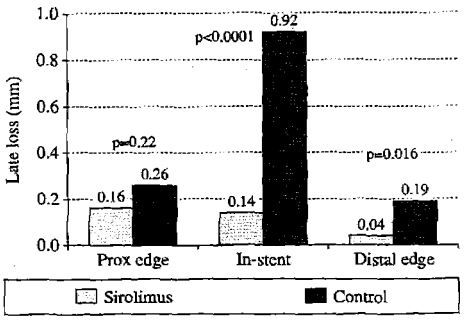

Fig. 10.—Comparison of late luminal loss (in the stent and peri-stent margins) between sirolimus eluting stent and uncoated stent at 8 months follow-up.

mine treatment effects on neointimal hyperplasia and in-stent restenosis. The preliminary results of the study (n=400) have been presented in the Euro PCR meeting in May 2002. In this patient population, repeat revascularization at 9 months follow-up was 4.1% in the sirolimus eluting stent group *versus* 16.7% in the placebo group. In stent restenosis (2% *versus* 31%) and late loss (0.14 mm *versus* 0.92 mm) in the sirolimus eluting stent were substantially lower than placebo group DS (31%) and late loss (0.92 mm). However, in-lesion restenosis rate was 7.2% and mostly was seen at the proximal edge (5.7%) possibly, due to failure to cover the entire injured segment by eluting stent (Figure 10). Final results will be presented by the end of 2002.

In-stent restenosis

The potential of using sirolimus eluting stent to treat recurrent in-stent restenosis performed in Sao Paulo and Rotterdam. Forty-one patients were enrolled to receive sirolimus eluting Bx Velocity stent for recurrent in-stent restenosis lesion.

Rotterdam experience for treatment of complex in-stent restenosis

Sixteen patients with severe, recurrent ISR in a native coronary artery (average lesion length 18.4 mm) and objective evidence of ischemia were recruited. They received one or more 18 mm slow release sirolimus-eluting Bx VELOCITY stents. Sirolimus-eluting stent implantation (n=26) was successful in all 16 patients. Quantitative angiographic and 3-D IVUS follow-up was performed at 4 months, and clinical follow-up at 9 months (Figure 11). Four patients had recurrent restenosis following brachytherapy, and 3 had totally occluded vessels before the procedure. The in-hospital course was uneventful. At 4 months follow-up, 1 patient had died and 3 patients had angiographic evidence of repeat restenosis, (1 in-stent and 2 in-lesion). In-stent late lumen loss was 0.21 mm and the mean percent volume obstruction of the stent was 1.2% by IVUS. At 9 months clinical follow-up, 3 patients had experienced 4 major adverse cardiac events (2 deaths, 1 acute myocardial infarction

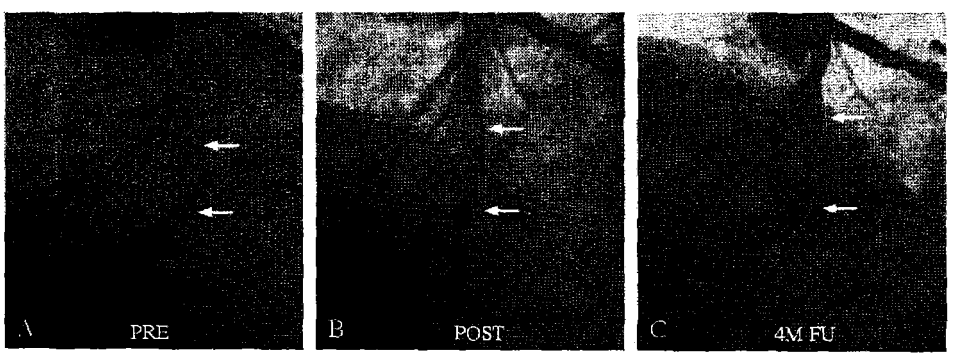

Fig. 11.—Clinical example of sirolimus eluting stent implantation in patients with in-stent restenosis.

necessitating repeat target vessel angioplasty). Sirolimus-eluting stent implantation in patients with severe ISR lesions effectively prevents neointima formation and recurrent restenosis at 4-month angiographic follow-up. The 9 month clinical follow-up showed a relatively low rate of major adverse cardiac events in a patient population with highly vascular disease.[43]

Sao-Paulo registry in patients with ISR

Twenty-five patients with recurrent in-stent restenosis were treated with slow release sirolimus eluting stent in Sao-Paulo and submitted to angiographic and IVUS follow-up at 4 month follow-up. Nine months clinical follow-up was uneventful in all patients and all vessels were patent. Angiographic late loss (-0.05 mm in lesion, 0.07 mm in stent) and IVUS percent volume obstruction (0.8%) were similar to the result of *de novo* studies (FIM and RAVEL). There was no evidence of either in-stent or edge restenosis. Intimal hyperplasia by 3-D IVUS was 0.9 mm^3 and the percent volume obstruction was 0.8% at 4 month follow-up.[44]

Conclusions

These first clinical results of sirolimus eluting stents are very promising, as they convincingly demonstrate the inhibition of neointimal proliferation in all patients at 1 year after coronary stent implantation, a phenomenon which has never been reported in the past. In the light of these results, we are witnessing the onset of a new era in interventional cardiology and the revolution of catheter based coronary intervention. Some concerns such as drug toxicity, vessel healing, excessive inflammation or haemorrhage, and re-endothelialization, need to be addressed in ongoing clinical trials for any type of drug eluting stents. The data for the sirolimus eluting stent so far do not support these concerns. However, clinical results were obtained mostly from a patient population at low risk. Thus, a lot of questions and theoretical concerns remain to be answered. These include different lesion subsets and clinical conditions such as long lesions (>18 mm-50 mm), bifurcation lesions, left main disease, small vessel, chronic total occlusion, acute coronary syndromes, etc. Some ongoing studies are addressed to answer those clinical problems (Table I). In our center RESEARCH (Rapamycin Eluting Stent Evaluated At Rotterdam Cardiology Hospital) study is ongoing since April 2002, first preliminary results will be present in November 2002.

TABLE I.—*Unanswered questions are being resolved.*

1) Long lesion (18-50 mm) (Sirius)
2) Small vessel (<2.5 mm) (Research)
3) Acute myocardial infarction (Research)
4) Chronic total occlusion (Sicto)
5) Multi-vessel disease (ARTS-2, freedom)
6) Bifurcation (Bifurcation)
7) Main stem (Ultima)
8) Vein graft, LIMA (Research)
9) Diabetic (Diabetic Ravel)
10) Renal insufficiency (Research)

After those promising findings of eluting stent, sirolimus eluting stent began to challenge the classical indications for CABG surgery. Previous studies which compared CABG surgery with balloon angioplasty (CABRI) [45] and coronary stenting (ARTS-1) [46] in patients with multivessel coronary artery disease, revealed 32% and 14% difference respectively, in favor of surgery for event free survival, mostly due to poor results of diabetic patients treated by percutaneous coronary interventions (Figure 12). However, the RAVEL trial provided 96.5% event free survival and essentially no late intimal hyperplasia in either diabetic or non-diabetic patients. Accordingly, the main problem of increased restenosis in diabetics may have an imminent solution and for diabetic patients with multivessel coronary disease may no longer be the first choice anymore. The questions regarding this problem will be answered with the results of ARTS-2 (Arterial Revascularization Therapies Study part II of the sirolimus-eluting Bx VELOCITY™ balloon expandable stent in the treatment of patients with *de novo* coronary

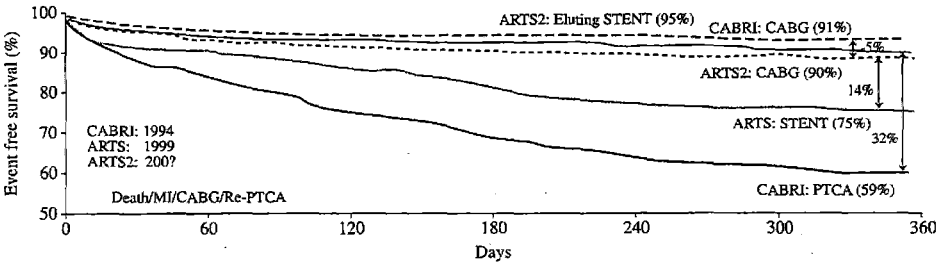

Fig. 12.—Comparison of event free survival after treatment by bypass surgey, balloon angioplasty and coronary stent implantation in patients treated for multivessel coronary artery disease.

artery lesions). However, cost effective analysis will be the next issue to address and hopefully, this treatment modality will be cost effective.

Riassunto

Uso di stent a rilascio di sirolimus («sirolimus eluting stent») per il trattamento delle occlusioni coronariche

Attualmente l'applicazione di stent è l'intervento coronarico più utilizzato. Tuttavia resta da risolvere il problema della stenosi intrastent dovuta ad un'esagerata iperplasia neointimale. Quest'ultima è dovuta alla risposta del vaso alle lesioni provocate dallo stent e consiste essenzialmente nella proliferazione di cellule muscolari lisce. I meccanismi molecolari alla base della restenosi vengono spiegati in questo articolo. Recentemente l'applicazione di uno stent a rilascio controllato di farmaci («drug eluting stent») è stato proposto come un possibile metodo per evitare la restenosi intrastent. Studi su animali hanno confermato la sicurezza e l'efficacia dell'applicazione *in vivo* di uno stent a rilascio di sirolimus («sirolimus eluting stent»). Nella sperimentazione FIM — il primo studio clinico sull'uso per lesioni primitive di stent rilascianti sirolimus — il tasso di restenosi è risultato sorprendentemente pari allo 0%. Nella sperimentazione RAVEL — il primo studio prospettico a doppio cieco multicentrico — sono stati scelti, in 19 centri, 238 pazienti con lesioni primitive e divisi in modo casuale in 2 gruppi: l'uno trattato con uno stent rilasciante sirolimus e l'altro con un Bx velocity stent non rivestito da farmaci. Dopo 6 mesi il tasso di stenosi nel gruppo con stent rilasciante sirolimus era sempre 0% rispetto al 26,6% del controllo. Inoltre le complicanze angiografiche tardive e quelle cardiache erano nettamente inferiori nel gruppo con stent rilasciante sirolimus. La sperimentazione SIRIUS è attualmente in atto in 53 centri degli Stati Uniti e studia 1100 pazienti con lesioni primitive coronariche divisi in modo casuale in 2 gruppi: uno trattato con stent rilasciante sirolimus e l'altro con stent non rivestito. I risultati preliminari mostrano una riduzione dei tassi di restenosi, di perdita tardiva e di necessità di ripetere la procedura di rivascolarizzazione. Lesioni primitive a parte, i primi studi non random sono stati condotti anche sull'applicazione di stent rilasciante sirolimus per la restenosi intrastent ed hanno fornito risultati promettenti: gli interventi di rivascolarizzazione necessari hanno raggiunto tassi inferiori al 10%. Confrontato con gli stent coronarici standard, lo stent rilasciante sirolimus mostra di poter prevenire in modo efficace la proliferazione neointimale, la restenosi e le complicanze cliniche associate.

Parole chiave: Stent - Malattia coronarica - Aterosclerosi.

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CHAPTER 5

INTRAVASCULAR ULTRASOUND FINDINGS IN THE MULTICENTER, RANDOMIZED, DOUBLE-BLIND RAVEL TRIAL

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Circulation 2002; 106: 798-803

Intravascular Ultrasound Findings in the Multicenter, Randomized, Double-Blind RAVEL (RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions) Trial

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Background—The goal of this intravascular ultrasound investigation was to provide a more detailed morphological analysis of the local biological effects of the implantation of a sirolimus-eluting stent compared with an uncoated stent.

Methods and Results—In the RAVEL trial, 238 patients with single de novo lesions were randomized to receive either an 18-mm sirolimus-eluting stent (Bx VELOCITY stent, Cordis) or an uncoated stent (Bx VELOCITY stent). In a subset of 95 patients (sirolimus-eluting stent=48, uncoated stent=47), motorized intravascular ultrasound pullback (0.5 mm/s) was performed at a 6-month follow-up. Stent volumes, total vessel volumes, and plaque-behind-stent volumes were comparable. However, the difference in neointimal hyperplasia (2 ± 5 versus 37 ± 28 mm^3) and percent of volume obstruction ($1\pm3\%$ versus $29\pm20\%$) at 6 months between the 2 groups was highly significant ($P<0.001$), emphasizing the nearly complete abolition of the proliferative process inside the drug-eluting stent. Analysis of the proximal and distal edge volumes showed no significant difference between the 2 groups in external elastic membrane or lumen and plaque volume at the proximal and distal edges. There was also no evidence of intrastent thrombosis or persisting dissection at the stent edges. Although there was a higher incidence of incomplete stent apposition in the sirolimus group compared with the uncoated stent group ($P<0.05$), it was not associated with any adverse clinical events at 1 year.

Conclusions—Sirolimus-eluting stents are effective in preventing neointimal hyperplasia without creating edge effect and without affecting the plaque burden behind the struts. (***Circulation.*** **2002;106:798-803.**)

Key Words: stents ■ restenosis ■ ultrasonics ■ drugs

The main limitation of the percutaneous techniques of revascularization remains the phenomenon of restenosis, which is an exaggerated healing response to the vessel wall injury that occurs as a result of mechanical dilatation. The 3 processes involved in restenosis are immediate elastic recoil, late constrictive remodeling, and neointimal hyperplasia. The scaffolding properties of a stent can control the first 2 processes but lead to an increase in neointimal hyperplasia.

Pilot studies testing the safety, feasibility, and efficacy of the sirolimus-eluting stent have demonstrated a near complete abolition of neointimal hyperplasia.[1,2] These pilot studies have been conducted on patients with Benestent type lesions in large vessels, and the stents were implanted under intravascular ultrasound (IVUS) guidance.

The RAVEL trial is a multicenter randomized study involving patients with more complex lesions in smaller vessels in whom IVUS guidance was not used during stent implantation.[3] In a subset of the enrolled patients, quantitative 3-dimensional IVUS assessment was performed at follow-up. The goal of this investigation was to provide a more detailed morphological analysis of the local biological effects of the implantation of a sirolimus-eluting stent.

Sirolimus has potent antiproliferative and antimigratory effects.[4] Intravascular brachytherapy also has antiproliferative and antimigratory effects but has been associated with certain side effects, including edge restenosis,[5,6] persisting dissection,[7,8] increased plaque burden outside the struts of the stent with expansion of the external elastic membrane,[8,9] late malapposition,[10] late thrombotic occlusion,[11] and "black holes."[12,13]

Received March 4, 2002; revision received May 22, 2002; accepted May 23, 2002.

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Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/01.CIR.0000025585.63486.59**

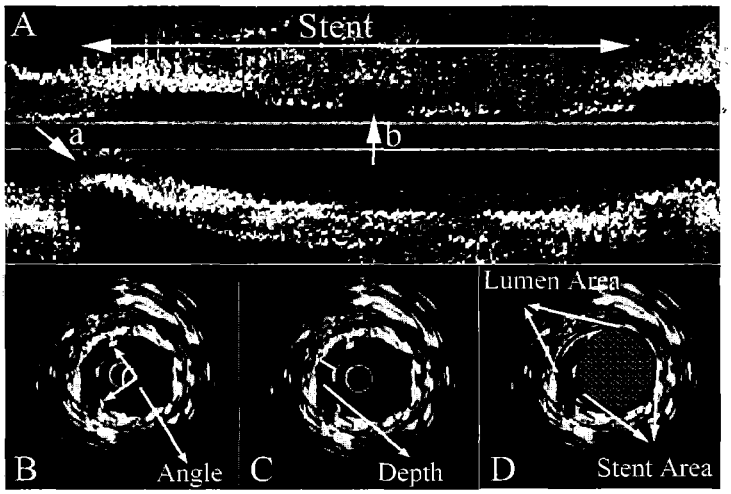

Figure 1. Methodology used to evaluate incomplete apposition at follow-up by IVUS. The figures illustrate the variety of measurements performed to quantify the incomplete apposition observed: location of incomplete apposition (arrows a and b) on a longitudinal view (A), circumferential extent in angular degree (B) maximal depth, distance between the vessel wall and the most incompletely apposed strut (C), and the area of incomplete apposition (lumen area−stent area=incomplete apposition area) in a single IVUS cross section (D).

On the basis of the previous experience with brachytherapy, we specifically looked for any evidence of these harmful effects in the patients enrolled in the RAVEL trial.

Methods

Patient Selection

The RAVEL trial enrolled 238 patients at 19 European and South American medical centers, and a subset of 95 patients enrolled at 6 centers underwent an IVUS investigation of their stents at 6 months. The study was reviewed and approved by each participating institution's Ethics Review Committee. All randomized patients signed a specific written informed consent mentioning the follow-up IVUS investigation. Patients were eligible if they had a diagnosis of stable or unstable angina pectoris or documented silent ischemia and if they had a single de novo target lesion of a native coronary artery in a vessel between 2.5 and 3.5 mm in diameter that could be covered by an 18-mm stent. Patients were not eligible for enrollment if they had an evolving myocardial infarction; an unprotected left main coronary artery stenosis ≥50%; an ostial target lesion; a calcified lesion that could not be successfully predilated; an angiographically visible thrombus within the target lesion; a left ventricular ejection fraction below 30%; or intolerance to aspirin, clopidogrel, or ticlopidine.

Study Procedures

After successful predilatation, patients were randomized 1:1 in a double-blind fashion to undergo the implantation of either an uncoated metal Bx VELOCITY Balloon-Expandable Stent or a sirolimus-eluting Bx VELOCITY Balloon-Expandable Stent (Cordis Corp, Johnson & Johnson). The sirolimus-eluting stents were indistinguishable from the uncoated metal stents to the naked eye. Postdilatation was performed as necessary to achieve a residual stenosis below 20% with a TIMI grade III flow. In case of dissection or of incomplete coverage of the lesion, additional study stents from the same randomization assignment were used as necessary.

Heparin was administered in intravenous boluses to maintain an activated clotting time >250 seconds for the duration of the procedure and was discontinued within 12 hours. Aspirin, at least 100 mg, was administered 12 hours before the procedure and continued indefinitely. A loading dose of 300 mg of clopidogrel was administered, preferably 48 hours before the procedure, followed by 75 mg once daily for 8 weeks. Alternatively, ticlopidine 250 mg twice daily was begun 1 day before the procedure and continued for 8 weeks.

Patient Follow-Up

At 30 days, 6 months, and 12 months, patients underwent evaluation of anginal status according to the Canadian Cardiovascular Society Classification of angina[14] and the Braunwald Classification for unstable angina,[15] as well as monitoring of major adverse cardiac events or additional revascularization of the index target lesion. A 12-lead ECG was performed at each visit; follow-up angiography and an IVUS investigation was performed at 180±30 days.

Quantitative Coronary Angiography

Coronary angiograms were obtained in multiple views after patients had received an intracoronary injection of nitrates. Quantitative analyses of all pre-, peri-, and postprocedural angiographic data were performed by an independent core laboratory (Cardialysis, Rotterdam, the Netherlands) and analyzed quantitatively by edge-detection techniques.[16] These data have been reported previously.

Quantitative Intravascular Ultrasound

At a 6-month follow-up, stented vessel segments were examined with mechanical IVUS (CardioVascular Imaging System, CVIS) using automated pullback at 0.5 mm per second. A coronary segment beginning 5 mm distal to and extending 5 mm proximal to the stented segment was also examined. A computer-based contour detection program was used for automated 3D reconstruction of the stented segment from up to 200 cross-sectional images. Lumen, stent boundaries, and external elastic membrane were detected using a minimum cost algorithm.[17,18] Total vessel volume (TVV), stent volume (SV), and lumen volume (LV) were calculated as $V=\Sigma^{n}_{i=1} A_i \cdot H$, where V is volume, A is total vessel, stent, or lumen area (as desired) in a given cross-sectional image, H is thickness of the coronary artery slice, and n is the number of slices. Lumen volume did not include the incomplete apposition spaces, and in absence of neointimal hyperplasia, lumen volume was delineated by the boundaries of the struts. Total plaque volume (TPV), plaque volume behind the stent (PBS), and neointimal hyperplasia (NIH) were calculated as TVV−LV, TVV−SV, and SV−LV, respectively. Percentage of

TABLE 1. Comparison of Baseline Demographic and Angiographic Data of the Population Undergoing IVUS Investigation at Follow-Up With the Entire Cohort of Randomized Patients

	Sirolimus-Coated Stent (n=48)	Uncoated Stent (n=47)	All Randomized (n=238)
Age, y	62.2±10.7	58.4±9.7	60.7±10.4
Men	72.9	85.1	75.6
Diabetes mellitus	14.6	14.9	18.5
Hypercholesterolemia	45.8	52.2	51.5
Hypertension	45.8	53.3	49.2
Previous MI	41.7	27.7	35.7
Previous CABG	2.1	2.1	1.7
Previous PTCA	18.8	8.5	18.1
Current smoker	31.3	40.4	29.8
Unstable angina	58.6	57.4	50.2
Stable angina	32.6	31.9	38.7
Silent ischemia	8.7	10.6	11.1
RVD before procedure, mm	2.59±0.61	2.66±0.55	2.62±0.53
DS after procedure, %	65±10	62±9	64±10
MLD before procedure, %	0.90±0.29	1.01±0.38	0.95±0.33
RCA/LAD/CX, %	22.9/54.2/22.9	23.9/52.2/23.9	26.8/49.8/23.4

Values are given as mean±SD or percentage.

The difference between demographics and angiographic preprocedure measurements was tested by Fisher's exact and unpaired *t* tests (*P*=NS). MI indicates myocardial infarction; CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty; RVD, reference vessel diameter; DS, diameter stenosis; and MLD, minimal luminal diameter.

obstruction volume was calculated as neointimal volume/stent volume × 100 at the 6-month follow-up. For the segments proximal and distal to the stent, the vessel volume was measured at each cross section as the area lying within the external elastic lamina.

Feasibility, reproducibility and inter- and intra-observer variability of this system have been validated in vitro and in vivo.[17,18] The quantitative ultrasound analyses were performed by an independent core laboratory (Cardialysis BV, Rotterdam, the Netherlands).

Qualitative IVUS parameters assessed in the study included persisting edge tears and incomplete stent apposition. Edge tears were defined as disruption of plaque immediately adjacent to the stent ends, where the flap could be clearly differentiated from the underlying plaque. Incomplete stent apposition was defined as 1 or more struts clearly separated from vessel wall with evidence of blood speckles behind the strut,[19,20] and because it was based on the consensus of 3 independent analysts, the determination was blind for the type of stent used. The measures of agreement by Kappa analysis between 3 observers were 0.87, 0.85 and 0.80, respectively (*P*=NS).

The number of loci exhibiting areas of incomplete stent apposition per stent was determined by cross-sectional IVUS images. The total length of these single or multiple areas of incomplete apposition were calculated from the number of frames involved. The maximal number of struts separated from the vessel wall on 1 single cross section, as well as the maximal depth (distance between the most incompletely apposed strut and the vessel wall) and the maximal circumferential extent of incomplete apposition (expressed in angular degrees) are reported. Finally, the volume of the incompletely apposed segments was quantified in mm^3 and related to the stent volume-in percent (Figure 1).

End Points

The primary end point of the study is angiographic in-stent late loss at a 6-month follow-up as determined by quantitative coronary angiography. The secondary clinical end point of the study was a composite of major adverse cardiac events, including cardiac and noncardiac death, Q-wave and non–Q-wave myocardial infarctions, coronary artery bypass grafts, or target lesion or vessel revascularizations at 30 days, 6 months, and 12 months after the index procedure.[3]

Statistical Analysis

All analyses were performed on an intention-to-treat basis. Treatment group differences were tested by ANOVA or Wilcoxon rank sums scores for continuous variables. Discrete variables were described by counts and percentages and tested with Fisher's exact test.

The differences in event-free survival were compared by log-rank tests. A 2-sided *P* value <0.05 was considered statistically significant. To identify potential causative factors responsible for incomplete apposition, a multivariate analysis was performed including all the conventional pre, peri-, and postprocedural factors recorded in the frame of this trial.

Results

The baseline demographic and angiographic data of this subset of patients were similar to those observed in the entire cohort of the patients randomized in the RAVEL trial, and the IVUS population was not the result of a biased selection of patients (Table 1).

Follow-up IVUS was obtained in 80% (95 of 118) of the eligible patients. The analysis of the 2 groups within the IVUS population shows that the stent volumes were comparable. At follow-up, there was no difference in the TVV or PBS volume, suggesting that the eluted drug did not affect the plaque burden located outside the stent structure (Table 2).

The differences in neointimal hyperplasia and percent of volume obstruction between the 2 groups were highly significant, emphasizing the near complete abolition of the proliferative process inside the stent (Figure 2).

The analysis of the proximal and distal edge volumes showed no significant difference in EEM, lumen, and plaque volume at the proximal and distal edges (Table 2).

TABLE 2. IVUS Measurements at 6-Month Follow-Up

Lesion Parameters Measured	Sirolimus-Eluting Stent (n=48)			Uncoated Stent (n=47)		
	Proximal	Stent	Distal	Proximal	Stent	Distal
Total vessel volume	64±27	280±69	51±24	59±24*	280±75*	49±21*
Plaque and NIH	31±15	152±47	21±12	30±13*	183±53†	24±14*
Plaque behind stent	NA	150±44	NA	NA	146±43*	NA
Stent volume	NA	131±35	NA	NA	132±36*	NA
Neointimal volume	NA	2±5	NA	NA	37±28‡	NA
Lumen volume	33±16	129±34	30±14	30±15*	95±41‡	25±11*
% Stent volume obstruction	NA	1±3	NA	NA	29±20‡	NA

*Not significant; †$P<0.05$; ‡$P<0.001$.
NA indicates not applicable.

Qualitative assessment by IVUS did not reveal any evidence of intrastent thrombosis or persisting dissection at the stent edges, but showed a 21% incidence of incomplete apposition in the sirolimus group compared with a 4% incidence in the uncoated stent group. Table 3 provides a quantitative evaluation of the extent of incomplete apposition by the number of individual segments that were incompletely apposed, as well as their total length, maximal depth, circumferential extent, and volume of incomplete apposition. There was no significant difference between the 2 groups other than the frequency of the occurrence of this finding (21% versus 4%).

Correlation Between Quantitative Coronary Angiography and Incomplete Apposition Detected by IVUS

The binary restenosis rate and the late angiographic loss in the sirolimus group followed up with IVUS were 0% and 0.06±0.30 mm, respectively, whereas the restenosis rate and the late loss in the uncoated stent group were 23.4% and 0.91±0.58 mm.

The quantitative coronary angiography analysis of the 48 patients who received a sirolimus-eluting stent showed that the mean diameter of the stent segment remained unchanged 2.87±0.46 versus 2.87±0.49, whereas the mean diameter of the 47 patients treated with an uncoated stent decreased significantly from 2.90±0.42 to 2.17±0.48 ($P<0.001$). The mean diameter of the stents in the 10 patients who received a sirolimus-eluting stent and had incomplete apposition at follow-up was on average 3.16±0.57 mm and was significantly larger than the mean diameter of the stents of the 38 patients who had their stents well apposed at follow-up (2.79±0.43 mm, $P<0.05$). Incomplete apposition was more likely to occur in larger vessels. Stent diameter, however, was not used in the multivariate analysis of incomplete apposition.

Clinical Events at 1-Year Follow-Up

In the subset of patients (n=95) investigated with IVUS, the event-free survival rates at 1 year (98% in the sirolimus group versus 72% in the uncoated stent group, $P<0.001$) are very similar to the rates observed for the entire cohort of randomized patients (94% in the sirolimus group versus 72% in the uncoated stent group, $P<0.0001$). The 10 patients with incomplete stent apposition in the sirolimus group were asymptomatic and event-free at 1 year, whereas 1 of the 2 patients with incomplete apposition in the placebo group underwent percutaneous target lesion revascularization.

Discussion

The present results confirm the volumetric ultrasound analysis performed in the First In Man (FIM) trial at 4, 6, and 12 months.[1,2] The percent of stent volume obstruction and the volume of neointimal hyperplasia in the sirolimus group are comparable to those observed in the FIM trial and are markedly different from those measured in the control group of the RAVEL trial. The cumulative frequency curve of the NIH shows that almost 75% of the stented segments do not exhibit NIH, and the term naked struts has been coined to describe the IVUS appearance of the sirolimus-eluting stent struts. It should be emphasized that the axial resolution of IVUS is in the range of 150 to 200 μm and does not permit any assessment of the reendothelialization. The volume of PBS and the total vessel volume at follow-up were similar in both groups, suggesting that no significant plaque shrinking or positive/negative remodeling occurred as a result of sirolimus elution. This contrasts with what has been seen with intravascular brachytherapy, where both positive remodeling of the vessel and plaque progression have been reported after a 6 to 8-month follow-up.[8,9]

The quantitative and qualitative assessments in this trial have demonstrated the absence of an edge effect in drug-eluting stents when compared with the placebo, the absence of persisting intimal tears at the stent edges, and the absence of parietal thrombi or "black holes" inside the stent.

Because of the initial report that there were more cases of late incomplete apposition detected by IVUS in the sirolimus group, this observation has created a great deal of interest. It therefore seemed important to evaluate this phenomenon carefully to determine whether there were any clinical sequelae to put it in the proper perspective. Because IVUS assessment of the completeness of apposition immediately after deployment was not performed, it is not possible to determine whether these few cases of incomplete apposition observed at follow-up are the result of late acquired malapposition or the consequence of an acute incomplete deployment. Therefore, we have used the broader term "incomplete apposition." The completeness of apposition may be highly dependent on the presence or absence of intravascular guidance at the time of deployment; in the FIM trial, performed with IVUS guidance, only 2 cases of late

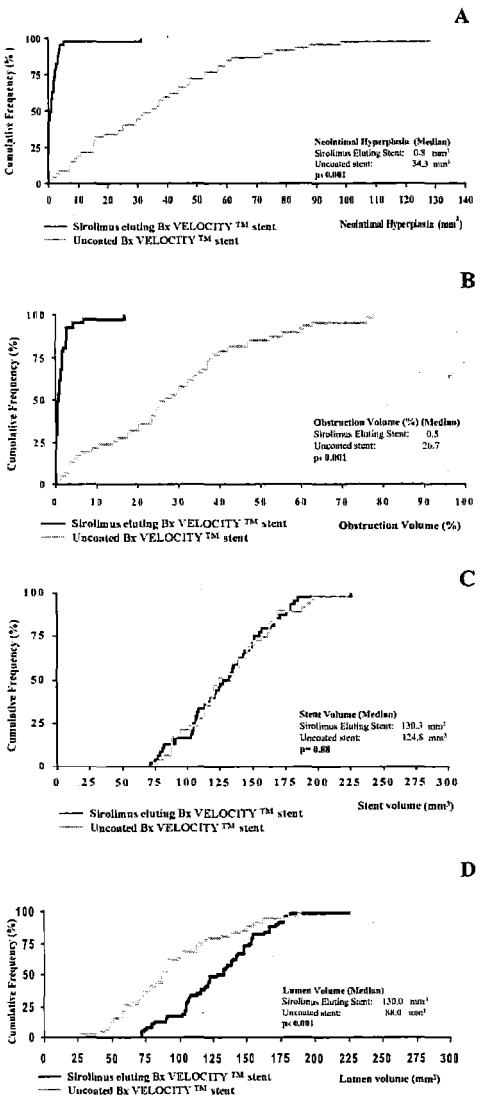

Figure 2. Cumulative distribution curve of in-stent neointimal hyperplasia volume at follow-up (A), percent obstruction volume of the stent at follow-up (B), stent volume at follow-up (C), and in-stent lumen volume at follow-up (D) for the 48 patients treated with sirolimus-eluting stent (black lines) and the 47 placebo patients treated with an uncoated Bx VELOCITY stent (gray line). Although stent volume after the procedure is similar, the neointimal and percent of obstruction volume curves are significantly shifted to the left for the sirolimus group.

acquired malapposition at follow-up were recorded out of 45 patients enrolled in this pilot study. A 17% incidence of acute incomplete apposition has been reported in a recent series of 62 patients in which bare metal stent deployment, judged optimal by angiography, was systematically evaluated by IVUS. In the IVUS-guided trials Stent Treatment Region assessed by Ultrasound Tomography (STRUT) and Angiography-directed Versus IVUS-Directed coronary stent placement trial (AVID), the incidences of malapposition are 22% and 13%, respectively.[20,21] Although the observed frequency of 21% in the sirolimus group is not very different from those reported with bare stents, it does not explain the difference seen between the 2 randomized groups in RAVEL.

Several purely speculative hypotheses may be raised to explain this general phenomenon. The first is that the antiproliferative action of the drug may preclude the growth of tissue in the void between struts and the vessel wall initially created by an incomplete deployment. The observation that larger vessels were more likely to exhibit this phenomenon seems to support this hypothesis. Second, the antimetabolite effect of the drug may induce phenomena such as necrosis or apoptosis, which may generate a new empty space between the struts and the vessel wall, which were originally in close contact. Third, the antimigratory and antiproliferative mechanism of action may prevent myoblasts from colonizing and proliferating in an organized thrombus (for example, in an unstable patient), which will dissolve at follow-up, creating a new empty space. A multivariate analysis considering conventional pre-, peri-, and postprocedural factors recorded in this trial did not identify any causative factors other than a large minimum luminal diameter after the procedure, elution of sirolimus, and absence of diabetes as predictors of incomplete apposition. The more proliferative nature of the healing process in the diabetic patients, although adequately inhibited by sirolimus (late loss 0.08 mm in diabetics), may be sufficient to fill in the gap between the sirolimus-eluting stents and the vessel wall when stents are initially incompletely deployed. This may explain why this finding was not present in any of the diabetics in this study.

Similar observations will undoubtedly be made with stents that elute drugs other than sirolimus. Serial IVUS observations from the first human experience with the QP_2-eluting polymer stent system have indicated that mild incomplete stent apposition and persistent edge tears were observed in 5% and 10%, respectively, of the 20 cases studied in this registry,[19] despite the fact that the dose of taxane analogue used in this registry seems to possess less potent antimigratory and antiproliferative properties than sirolimus (mean neointimal area of 1.16 ± 1.35 mm^2 versus of 0.09 ± 0.26 mm^2 in the present study). The angiographic late loss results reported for TAXUS I (a Feasibility Study Evaluating Safety of the NIRx Paclitaxel-Coated Conformer Coronary Stent for the Treatment of De Novo Coronary Lesions) (0.35 ± 0.47 mm), the ASian Paclitaxel-Eluting stent Clinical Trial (ASPECT) study highest dose (0.29 ± 0.72 mm) and European EvaLUation of PacliTaxel-Eluting Stents (ELUTES) highest dose (0.10 ± 0.68 mm), when the range of standard deviation is factored in, suggest the occurrence of negative late loss (or late gain) compatible with late malapposition in some patients, while at the same time suggesting in other patients substantially more neointimal hyperplasia than observed in the present study. The clinical significance of these observations in these trials remains to be determined.

It is of paramount importance to emphasize that in the sirolimus group, the incomplete apposition detected in some patients at 6 months did not translate into any subacute or late (1 year) clinical events. Furthermore, late (18-, 24-, and 36-month)

TABLE 3. Characteristics and Quantification of Incomplete Apposition of Stent

	Sirolimus-Eluting Stent	Uncoated Stent	*P*
Frequency per patient (%)	10/48 (21)	2/47 (4)	0.001
Frequency of incomplete stent apposition as a function of nominal stent size (patients can have more than 1 stent)			
2.5 mm	1/10 (10)	0/3 (0)	NS
3.0 mm	4/27 (15)	3/36 (8)	NS
3.5 mm	5/13 (38)	0/9 (0)	NS
Number of sites per stent exhibiting incomplete apposition	1.9 (1–3)	2 (2–2)	NS
Localization of incomplete apposition sites			
Proximal edge of the stent, %	5/19 (27)	1/4 (25)	NS
Middle part of the stent, %	12/19 (63)	3/4 (75)	NS
Distal edge of the stent, %	2/19 (10)	0/4 (0)	NS
Maximal number of struts separated from vessel wall on one single cross-section	3.6 (2–5)	4.0 (3–5)	NS
Total length on one single or multiple longitudinal views, mm	6.7 (3.5–13.5)	6.9 (5.3–8.4)	NS
Maximal depth, mm	0.75 (0.3–1.2)	0.62 (0.6–0.7)	NS
Maximal circumferential extent, arc°	154° (63–270)	131° (104–158)	NS
Volume per stent, mm^3	20 (3–66)	27 (16–39)	NS
Volume per stent volume, %	14 (2–42)	14 (7–20)	NS

Values are mean (%) or mean (range).
NS indicates not significant.

IVUS investigation of cases of malapposition after brachytherapy has shown that this phenomenon may disappear at follow-up (unpublished data, personal communication of J. Ligthart, MSc, January, 2002). Therefore, the significance of this phenomenon may be trivial and clinically irrelevant, but longer-term follow-up will be necessary to answer this question definitively.

Acknowledgments

This study was supported by a grant from Cordis Corporation, a Johnson & Johnson Company. We appreciate the constructive suggestions and assistance of Dr Brian Firth in reviewing this manuscript.

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CHAPTER 6

SIROLIMUS ELUTING STENT FOR THE TREATMENT OF COMPLEX IN-STENT RESTENOSIS: THE FIRST CLINICAL EXPERIENCE

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J Am Coll Cardiol 2003; 41: 184-189

Journal of the American College of Cardiology
© 2003 by the American College of Cardiology Foundation
Published by Elsevier Science Inc.

Vol. 41, No. 2, 2003
ISSN 0735-1097/03/$30.00
PII S0735-1097(02)02704-3

CLINICAL STUDIES **Interventional Cardiology**

Sirolimus-Eluting Stent for Treatment of Complex In-Stent Restenosis

The First Clinical Experience

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OBJECTIVES In this study, we assess the value of sirolimus eluting stent (SES) implantation in patients with complex in-stent restenosis (ISR).

BACKGROUND The treatment of ISR remains a therapeutic challenge, since many pharmacological and mechanical approaches have shown disappointing results. The SESs have been reported to be effective in de-novo coronary lesions.

METHODS Sixteen patients with severe, recurrent ISR in a native coronary artery (average lesion length 18.4 mm) and objective evidence of ischemia were included. They received one or more 18 mm Bx VELOCITY SESs (Cordis Waterloo, Belgium). Quantitative angiographic and three-dimensional intravascular ultrasound (IVUS) follow-up was performed at four months, and clinical follow-up at nine months.

RESULTS The SES implantation (n = 26) was successful in all 16 patients. Four patients had recurrent restenosis following brachytherapy, and three patients had totally occluded vessels preprocedure. At four months follow-up, one patient had died and three patients had angiographic evidence of restenosis (one in-stent and two in-lesion). In-stent late lumen loss averaged 0.21 mm and the volume obstruction of the stent by IVUS was 1.1%. At nine months clinical follow-up, three patients had experienced four major adverse cardiac events (two deaths and one acute myocardial infarction necessitating repeat target vessel angioplasty).

CONCLUSIONS The SES implantation in patients with severe ISR lesions effectively prevents neointima formation and recurrent restenosis at four months angiographic follow-up. (J Am Coll Cardiol 2003;41:184–9) © 2003 by the American College of Cardiology Foundation

Coronary stent implantation is the main therapeutic approach to coronary stenosis in interventional cardiology. Consequently the most common form of restenosis today is in-stent restenosis (ISR). The treatment of ISR remains a therapeutic challenge, as all pharmacological and mechanical treatment modalities have shown disappointing results. The recurrence of ISR was reported to be in the range of 20% to 40% (1,2).

Intracoronary radiation is the only therapy for ISR proven to be effective in randomized clinical trials (3,4). However, restenosis is not eliminated. The wide spread use of brachytherapy is limited by logistic requirements and potential side effects (5,6).

Attention is now focusing on the concept of local pharmacologic intervention by drug-eluting stents. Sirolimus has been shown to be effective in de-novo lesions with a remarkable restenosis rate of 0% in some studies (7,8). These findings provoked considerable enthusiasm (9), but also profound skepticism (10). The major criticism focused on the lack of data in *complex lesions* and on the lack of *long-term* data.

The aim of our study was to evaluate the effectiveness of sirolimus eluting stents (SESs) in preventing neointimal formation in patients with severe ISR.

METHODS

Patient population. Patients with recurrent ISR in a native coronary artery and objective evidence of ischemia were included. The vessel size had to be >2.5 mm and <3.5 mm. Between March and June 2001, 16 consecutive patients were included. All patients signed a written informed consent. The Medical Ethics Committee at our institution had approved the study protocol.

ISR definition. In-stent restenosis was defined as >50% diameter stenosis (DS) by quantitative coronary angiography (QCA) within a previously (at least four months) stented vessel segment. In-stent restenosis was classified as focal (<10 mm long), diffuse (>10 mm long), proliferative (>10 mm long and extending outside the stent edges), or totally occluded (11).

Procedure. All ISR lesions were predilated. Then, a SES Bx VELOCITY (Cordis Waterloo, Belgium) was im-

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Manuscript received May 29, 2002; revised manuscript received July 30, 2002, accepted August 19, 2002.

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Abbreviations and Acronyms

DS = diameter stenosis
ISR = in-stent restenosis
IVUS = intravascular ultrasound
NIH = neointimal hyperplasia
QCA = quantitative coronary angiography
SES = sirolimus eluting stent
TIMI = Thrombolysis In Myocardial Infarction

planted using conventional techniques. The stent was loaded with 140 μg sirolimus/cm^2 metal surface area in a slow release formulation (>28 days drug release). All stents were 18 mm long and 2.5 to 3.5 mm in diameter. Postdilatation was performed as required.

All patients received aspirin (325 mg/day, indefinitely) and clopidogrel (300 mg loading dose immediately after stent implantation followed by 75 mg/day for two to four months at the discretion of the operator).

QCA and intravascular ultrasound (IVUS) analysis. Serial coronary angiography was performed at baseline (before and after intervention) and at four months follow-up. In-stent and in-lesion (stent plus 5 mm proximal and 5 mm distal to the stent) restenosis was defined as >50% DS at follow-up.

The QCA analysis was performed by an independent core laboratory (Brigham and Women's Hospital, Boston, Massachusetts).

Serial IVUS was performed using motorized pullback at a constant speed of 0.5 mm/s postprocedure and at four months follow-up. The quantitative ultrasound analyses were performed by an independent core laboratory (Cardialysis BV, Rotterdam, The Netherlands).

Statistical analysis. Continuous variables are expressed as mean ± standard deviation. Because of the small sample size no statistical comparison was performed. Only the IVUS data were expressed as mean and 95% confidence interval.

Table 1. Baseline Clinical Characteristics

Variable	n (%)
Patients	16
Male gender	12 (75)
Age, yrs	56.9 ± 13.9
Unstable angina pectoris	5 (31)
Multivessel disease	11 (68.7)
Diabetes mellitus	4 (25)
Hypertension	9 (56.2)
Hyperlipidemia	8 (43.7)
Previous MI	9 (56.2)
Previous brachytherapy	4 (25)
Previous CABG	1 (6.2)
Previous heart transplantation	1 (6.2)

Values are n (%) or mean ± SD.
CABG = coronary artery bypass graft surgery; MI = myocardial infarction.

RESULTS

Baseline characteristics. Sixteen patients were included in the study. The patients' demographics are summarized in Table 1. Five patients presented with unstable angina and four patients had diabetes mellitus. Four patients with recurrent ISR after intracoronary beta-brachytherapy and one heart transplant recipient with proliferative ISR were included.

Procedural data. Lesion and procedural characteristics are shown in Table 2. The average length of the restenotic segment was 18.4 ± 13.1 mm: three lesions were focal, five diffuse, five proliferative, and three showed total occlusion of the stent.

A total of 26 SESs were implanted. Nine patients received a single stent, and six patients received two stents to cover long lesions. In one patient with a totally occluded vessel, five SESs were implanted. All patients were discharged without complication one day after the procedure.

Angiographic outcome and three-dimensional IVUS analysis. The QCA data are presented in Table 3 and the IVUS data are shown in Table 4. Satisfactory angiographic results were achieved in 15 out of 16 patients. Representative sequences of angiograms and IVUS from a single patient are shown in Figure 1.

In one patient who received two SESs in an occluded obtuse marginal branch of the circumflex artery, adequate stent expansion could not be achieved despite the use of high pressure (24 atm), noncompliant balloon inflation. The final QCA revealed a residual stenosis of 34%. At follow-up, this patient showed restenosis with silent target vessel occlusion.

Two other patients showed 59% and 62% in-lesion DS, respectively, at follow-up without evidence of cardiac ischemia. The first patient had received two SESs. Both IVUS and angiographic analysis revealed a gap of ~2.2 mm between the two SESs. Neointimal hyperplasia (NIH) occurred precisely at the bare segment between the two

Table 2. Lesion and Procedural Characteristics

Treated vessels	
Left anterior descending	6 (37.5)
Left circumflex	4 (25)
Right coronary artery	6 (37.5)
In-stent restenosis type	
Focal	3 (18.7)
Diffuse intra-stent	5 (31.2)
Proliferative	5 (31.2)
Total occlusion	3 (18.7)
Lesion length, mm	18.4 ± 13.1
Lesion length >10mm	13 (81.2)
Number of previous PCI per lesion	1.68 ± 0.87
Previous implanted stent length (mm)	20.1 ± 6.1
Number of SES per lesion	1.62 ± 1.02
Implanted SES (mm)	28.5 ± 18.0
Implanted SES diameter (mm)	3.01 ± 0.38
Max. inflation pressure (atm)	16.1 ± 3.58

Data are presented as numbers, (relative percentages), or mean ± SD.
PCI = percutanenus coronary intervention; SES = sirolimus eluting stent.

Table 3. Quantitative Coronary Analysis by Core Laboratory

Parameters	15 Patients*
Pre-procedure	
RD, mm	2.68 ± 0.33
MLD, mm	0.59 ± 0.50
DS, %	77.2 ± 18.9
Lesion length, mm	18.4 ± 13.1
Post-procedure	
RD, mm	2.74 ± 0.38
In-lesion MLD, mm	2.23 ± 0.41
In-stent MLD, mm	2.58 ± 0.37
In-lesion DS, %	18.4 ± 10.0
In-stent DS, %	5.44 ± 11.3
Follow-up	
RD, mm	2.73 ± 0.40
In-lesion MLD, mm	1.97 ± 0.82
In-stent MLD, mm	2.36 ± 0.80
In-lesion DS, %	26.9 ± 27.0
In-stent DS, %	11.6 ± 27.3
Restenosis	
In-lesion (%)	2 (13.3)
In-stent (%)	1 (6.7)
Change in MLD	
In-lesion late loss	0.26 ± 0.67
In-stent late loss	0.21 ± 0.62
In-lesion late loss index	0.14 ± 0.38
In-stent late loss index	0.09 ± 0.30

Data are presented as number relative percentages or mean value ± SD. *One patient, who died 3.5 months after the procedure, was not included in this analysis.
DS = diameter stenosis; MLD = minimal luminal diameter; RD = reference diameter.

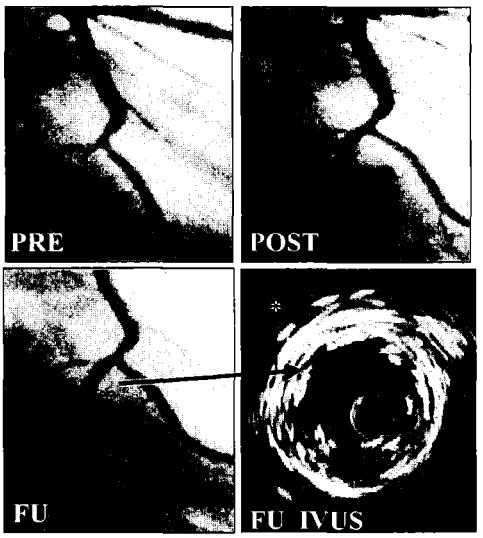

Figure 1. A chronically occluded left circumflex due to in-stent restenosis (PRE) was treated with a sirolimus eluting stent (POST). Follow-up (FU) angiography showed no restenosis; intravascular ultrasound (IVUS) revealed no neointimal hyperplasia with the clear appearance of double stent struts. * indicates the position of the IVUS catheter.

stents (Fig. 2). A repeat intervention was not performed because the patient was asymptomatic, intracoronary pressure measurement showed a fractional flow reserve of 0.80, and the stenosis was assessed as 50% DS by online QCA. The second case was the heart transplanted recipient who had a 62% DS proximal to the stent. The vessel, which had Thrombolysis In Myocardial Infarction (TIMI) grade 1 flow prior to implantation of the SESs, had been extensively ballooned during the procedure and the injured area was not completely covered by SES. As the patient had no evidence of ischemia by radionuclide scintigraphy, repeat revascularization was not performed. All other patients showed only minimal late lumen loss.

In one patient who had previously undergone brachytherapy and showed recurrent ISR associated with a "black hole" (12) (echolucent tissue, rich in proteoglycans and poor in mature collagen and elastin) prior to SES implantation, IVUS showed reappearance of the "black hole" four months after SES implantation without significant stenosis. The eccentric, nonobstructive, echolucent luminal tissue was situated in the proximal portion of the stent.

Nine months clinical outcome. The major adverse cardiac events are summarized in Table 5. One patient with severe three-vessel disease died suddenly 3.5 months after successful implantation of two overlapping SESs in the right coronary artery. Unfortunately, no clinical or autopsy information is available.

The second patient, who had received five SESs, showed no late lumen loss at five months follow-up, but developed an inferior myocardial infarction seven months after the index procedure. This event occurred after the follow-up angiogram three weeks after discontinuing clopidogrel. Angiography revealed a proximal total occlusion of the artery. The patient was treated with thrombus aspiration. Intravascular ultrasound after thrombectomy showed a well-expanded stent without NIH.

Table 4. Volumetric Intravascular Ultrasound Measurements by Core Laboratory

	Post-Procedure		4-Month Follow-Up	
N = 11	Mean	(−95% CI/+95% CI)	Mean	(−95% CI/+95% CI)
Stent length (mm)	20.5 ± 5.9	(16.5/24.4)	20.3 ± 6.3	(16.1/24.5)
Stent volume (mm^3)	159.7 ± 57.3	(121.2/198.2)	158.6 ± 69.3	(112.1/205.2)
Lumen volume (mm^3)	159.7 ± 57.3	(121.2/198.2)	157.1 ± 69.9	(110.1/204.1)
NIH (mm^3)	NA		1.5 ± 3.3	(−0.71/3.73)
Volume obstruction (%)	NA		1.1 ± 2.6	(−0.61/2.85)

CI = confidence interval; NIH = neointimal hyperplasia.

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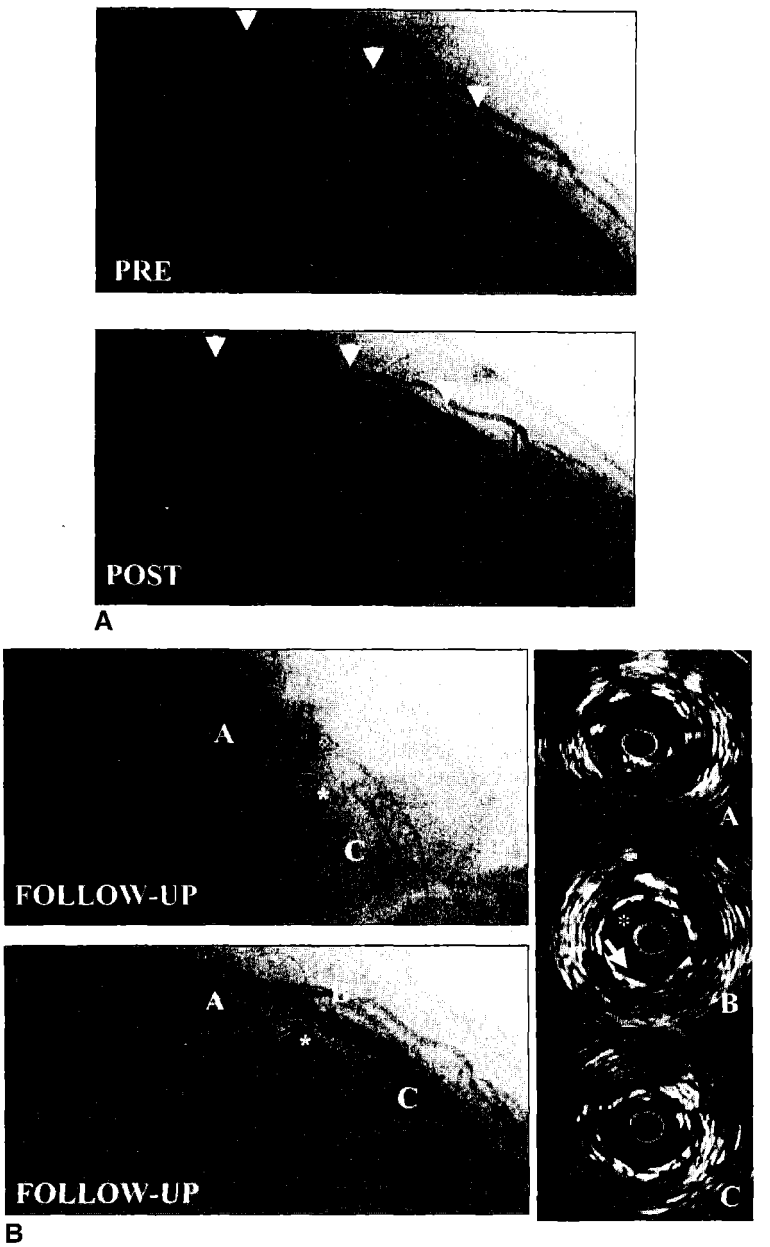

Figure 2. **(A)** Angiograms: the long proliferative in-stent restonsis (ISR) (PRE) was treated with two sirolimus eluting stents (SESs) (POST). The follow-up angiogram showed focal-repeat ISR (62% DS) in the gap **(arrow)**, which was not covered by the SES. No neointimal hyperplasia (NIH) was evident in the two SESs **(A and C)**. **(B)** Intravascular ultrasound (IVUS): follow-up IVUS showed no NIH in the proximal **(A)** and distal **(C)** SES with images of two layers of stent struts. Neointimal hyperplasia was noted in the gap region **(B)** where only one layer of (bare) stent struts can be seen. * indicates the position of the IVUS catheter at the gap segment.

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Table 5. Individual 9-Month Outcome in 16 Patients Treated With Sirolimus Eluting Stent for ISR

Case	ISR Pattern	Number of Previous PCI	Brachytherapy Failure	Length of SES (mm)	30-Day Events	4-Month Events	4-Month Restenosis	9-Month Events*
1	Diffuse	4	Yes	18	No	Death	—	Death
2	Total occlusion	1	No	18	No	No	No	No
3	Focal	3	No	36	No	No	No	Death
4	Total occlusion	1	No	90	No	No	No	Q-MI
5	Focal	2	No	18	No	No	No	No
6	Focal	2	Yes	18	No	No	No	No
7	Proliferative	1	No	36	No	No	No	No
8	Proliferative	1	No	18	No	No	No	No
9	Diffuse	1	No	18	No	No	No	No
10	Proliferative	1	No	18	No	No	No	No
11	Diffuse	1	No	18	No	No	No	No
12	Diffuse	2	Yes	18	No	No	No	No
13	Diffuse	2	No	36	No	No	In-lesion†	No
14	Proliferative	1	No	36	No	No	No	No
15	Total occlusion	2	Yes	36	No	No	In-stent†	No
16	Proliferative	2	No	36	No	No	In-lesion†	No

*Events are death, myocardial infarction (MI), target vessel revascularization (percutaneous transluminal coronary angioplasty/coronary artery bypass graft surgery). †No repeat percutaneous coronary intervention (PCI) was performed. Treatment strategies for restenotic vessels are explained in the Results section.
ISR = in-stent restenosis; SES = sirolimus eluting stent.

The third patient, who had failed brachytherapy, had no evidence of NIH at a four months follow-up IVUS, but died due to congestive heart failure 9.5 months after the index procedure. This 79-year-old man with left main coronary artery disease and congestive heart failure had undergone bypass surgery twice and had percutaneous coronary intervention four times before the index procedure.

DISCUSSION

In this study, we describe the application of SESs in a subset of patients presenting with extremely *complex lesions* and one of the most challenging therapeutic problems today, which is ISR. Notwithstanding the challenging population treated, we found strikingly similar results in terms of suppression of neointimal proliferation to that reported previously in lower-risk patient populations (13). The acute procedural and in-hospital outcome was uneventful. At a four months angiographic follow-up, only one patient with prior total occlusion showed repeat ISR due to silent total reocclusion of the vessel. In the remaining patients, late lumen loss averaged 0.08 mm and volume obstruction within the stent was 1.1%. This is extremely low compared to other treatment strategies, including brachytherapy. By contrast, contemporary studies report a restenosis rate of 45% for bare stent–in-stent implantation with a late lumen loss of 1.36 mm (2). A registry of patients undergoing rotational atherectomy followed by beta-radiation revealed a restenosis rate of 10% with a late lumen loss of 0.37 mm (14).

Important clinical findings. Despite our relatively small patient population, we witnessed some remarkable phenomena. First, we observed NIH in a gap between two SESs and at a site of injury that was not completely covered by the SES. This case illustrates the therapeutic power of SESs, since the patient serves as his own control (Fig. 2).

Second, we monitored the treatment of a patient with severe transplant vasculopathy. The patient presented with a small, diffusely diseased vessel and impaired flow (TIMI grade 1) and received two sequential, overlapping 2.5 mm diameter SESs at the site of ISR. The vessel segment proximal to the stents was treated by balloon dilation. At follow-up there was only minimal NIH within the SESs, and angiographic restenosis occurred at the proximal adjacent vessel segment, outside the stents.

Third, we examined the treatment of patients after failed brachytherapy. We treated four patients who had failed brachytherapy, two of whom developed clinical events. The third patient revealed a reappearance of the "black hole" at follow-up IVUS; nonetheless, no significant stenosis was seen at follow-up angiography. Brachytherapy failure patients were responsible for one-third of all adverse events and represent a particular challenge. These patients can have prolonged endothelial dysfunction that can increase the risk of thrombosis; there are no current data available on the combined effect of radiation and cytostatic drug therapy in coronary arteries.

Late vessel occlusion occurred in two additional patients who had not been treated with brachytherapy. One patient with five drug-eluting stents experienced acute vessel closure and developed myocardial infarction after follow-up angiography and IVUS three weeks after discontinuing clopidogrel. Intravascular ultrasound performed at the time of the acute myocardial infarction showed no evidence of NIH within the stents and thrombus formation as the cause for the occlusion. The second patient who had received two SESs died suddenly and we have to consider this as an acute cardiac and possibly thrombotic event. Therefore, it seems wise to propose that patients receiving more than one SES for the treatment of ISR, particularly in the setting of failed brachytherapy, total vessel occlusion, or poorly deployed stents, should receive clopidogrel for an extended period.

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January 15, 2003:184–9

Study limitations. This is a small observational study and only lesions with vessel diameter between 2.5 to 3.5 mm were enrolled. Therefore, the results need to be confirmed by randomized and multicenter trials. Additionally, the study comprises four months angiographic and IVUS follow-up. However, the recently reported long-term data, which demonstrated that the four months results are preserved at one year in de-novo lesions, support the notion that our four months data may be predictive of the long-term findings (13).

Conclusions. Sirolimus eluting stent implantation is an effective treatment for patients with complex ISR, even when they are at an intrinsically high risk for complications. As the use of drug-eluting stents increases, their complexity and the range of indications will expand towards higher risk patient populations. In this setting, stenting the whole area injured by the balloon, overlapping SESs properly, and good stent deployment with low residual stenosis, as well as an appropriate anti-platelet regimen will be the keys to successful treatment. When more than one eluting stent is used to treat long in-stent restenotic lesions, IVUS guidance may be advisable to optimize complete coverage of previously implanted bare metal stents and to ensure that the edges of implanted stents are overlapped.

Acknowledgments

The authors thank Mrs. J. van Wijk-Edelman, Mr. P. Cummins, Mr. A. Ruiters, and E. Wuelfert for their continuous support and Dr. B. Firth for his critical review of this manuscript.

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CHAPTER 7

FATE OF SIDE BRANCHES AFTER CORONARY ARTERIAL SIROLIMUS-ELUTING STENT IMPLANTATION

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Am J Cardiol. 2002; 90(9):937-941

Fate of Side Branches After Coronary Arterial Sirolimus-Eluting Stent Implantation

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The sirolimus-eluting stent (SES) is emerging as a potential solution for the prevention of restenosis. Although the outcome of side branches after stenting with an uncoated metal stent (UMS) has been reported, the fate of side branches after SES implantation is unknown. Furthermore, the absence of spontaneous recanalization of occluded side branches following intracoronary brachytherapy has been previously described and has been related to a delayed healing process. We assessed the procedural and 6-month follow-up angiograms of 238 patients enrolled in the RAVEL study, a double-blind controlled trial of the SES versus the UMS. Any side branch seen on the preprocedure angiogram and subsequently covered by the stent was evaluated. The side branch Thrombolysis In Myocardial Infarction (TIMI) flow grade was assessed at baseline and at follow-up by 2 observers. One hundred twenty-eight patients with ≥1 side branches were identified (63 patients in the SES group with 118 side branches, 65 patients in the UMS group with 124 side branches). Side branch occlusion occurred after stenting in 12 branches (10%) in the SES group and in 9 branches (7%) in the UMS group (p = NS). Of these occluded branches, spontaneous recanalization was observed in 11 branches (92%) in the SES group and in 6 branches (67%) in the UMS group at follow-up angiography (p = NS). Thus, the fate of side branches after SES implantation is favorable and at least as good as after UMS implantation. ©2002 by Excerpta Medica, Inc.

(Am J Cardiol 2002;90:937–941)

The sirolimus-eluting stent (SES) is emerging as a potential solution for the prevention of restenosis.[1,2] It has been recently demonstrated that treatment of native de novo coronary lesions with the SES was associated with no in-stent restenosis at 6 months in the RAndomised, double-blind study with the Sirolimus-eluting Bx VElocity balloon expandable stent in the treatment of patients with de novo native Coronary artery Lesions (RAVEL) trial.[3] However, the fate of side branches after SES implantation is unknown. Side branch occlusion, a well-recognized complication of percutaneous coronary stenting, was reported to develop in up to 19% of cases.[4–11] However, the incidence of spontaneous recanalization at follow-up of occluded side branches is controversial. The reported rate varies from 35% to 100%.[4,7,8,10,12] Furthermore, Cottin et al[13] demonstrated the absence of spontaneous recanalization of occluded side branches in patients with in-stent restenosis followed by intracoronary radiation therapy. Debruyne et al[14] also reported that the rate of spontaneous recanalization following stent implantation with brachytherapy was lower than that observed without brachytherapy. In addition, they described a higher rate of delayed side branch occlusion in the brachytherapy group. Sirolimus is a potent immunosuppressive agent that induces cell-cycle arrest in the late G1 phase, which inhibits the proliferation of smooth muscle cells and reduces intimal thickening.[15–17] Thus, the hypothesis tested in this study is that sirolimus might potentially behave the same way as brachytherapy, and have the potential to cause a delayed healing process. We consequently also hypothesized that the rate of spontaneous recanalization of side branches occluded after SES implantation would be lower than that after uncoated metal stent (UMS) implantation.

METHODS

Patient group: From August 2000 to January 2001, 238 patients were enrolled in the RAVEL trial.[3] They had a single de novo lesion of a native coronary artery that could be covered by a single 18-mm stent. Patients were excluded if they had a target lesion involving a side branch >2.5 mm in diameter that would require side branch stenting. Enrolled patients were randomized 1:1 in a double-blind manner to receive either an uncoated metal Bx VELOCITY stent or a sirolimus-eluting Bx VELOCITY stent (Cordis Corp., Johnson & Johnson, Warren, New Jersey). The angiographic follow-up at 6 months after stent deployment included 211 patients, 128 of whom had ≥1 side branches covered by a stent and were part of this

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analysis. All randomized patients signed a written informed consent statement before enrollment.

Study protocol: Lesions were treated by means of conventional interventional techniques. Direct stenting was not allowed. Postdilation was performed as required to achieve a residual stenosis of <20%. Patients received ≥100 mg aspirin daily, indefinitely in addition to either clopidogrel (75 mg once daily) or ticlopidine (250 mg twice daily) for 8 weeks.

Angiographic analysis: Quantitative coronary angiography of the target lesion was performed by an independent core laboratory (Cardialysis BV, Rotterdam, The Netherlands).[18] The reference vessel diameter, minimal lumen diameter, and percent diameter stenosis were measured at baseline and at 6-month follow-up angiography. Late loss was calculated as the difference between the minimal lumen diameter after the procedure and that at follow-up.

Any side branch that was seen on the angiogram before the procedure and subsequently covered by the stent was analyzed by 2 observers who were blinded to allocation. The Thrombolysis In Myocardial Infarction (TIMI) grade flow in the side branch was assessed before and after the procedure. Side branch occlusion was defined as TIMI flow grade 0. The TIMI flow in the side branch was also evaluated on the follow-up angiogram. Spontaneous recanalization was defined as an increase in flow from TIMI grade 0 to ≥1. The side branch was considered to exhibit delayed occlusion if its TIMI flow grade was ≥1 after the procedure, but decreased to 0 at follow-up. Side branches were classified into 4 types by visual assessment: type A (arising within the lesion, with ostial narrowing); type B (arising within the lesion, without ostial narrowing); type C (arising from outside the lesion, with ostial narrowing); and type D (arising from outside the lesion, without ostial narrowing) (Figure 1) Side branches were also classified visually according to their take-off angle from the parent vessel (≤45° or >45°).

Intravascular ultrasound (IVUS) analysis: Fifty-eight patients with 114 side branches in the stented segment underwent IVUS imaging at 6-month follow-up. All images were obtained using an automated pull-back system at 0.5 mm/s. A complete IVUS run was recorded on videotape for off-line 3-dimensional reconstruction. A computer-based contour detection program was used. Stent and lumen boundaries were detected using a minimum cost algorithm. Total stent and lumen volumes were calculated using Simpson's rule. Neointimal hyperplasia volume was calculated as stent volume minus lumen volume.[19] This analysis was performed by the same independent core laboratory.

Statistical analysis: Continuous variables were expressed as mean ± SD and were compared using the 2-tailed Student's *t* test or variance using the Bonferroni adjustment. The chi-square test was used for categorical variables. Logistic regression analysis was performed on all clinical and procedural characteristics to identify the determinants of side branch occlusion. Because there were multiple side branches per lesion, the p values reported for side branch characteristics predictive of occlusion ignore this intracluster correlation effect. A p value <0.05 was considered statistically significant. All analyses were performed using the SPSS for Windows (version 10.0, SPSS Inc., Chicago, Illinois) statistical software package.

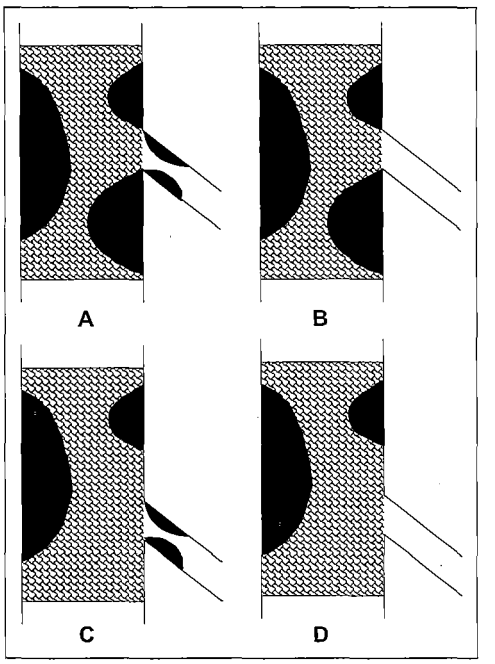

FIGURE 1. Side branch type classification: type A (arising within the lesion, with ostial narrowing); type B (arising within the lesion, without ostial narrowing); type C (arising from outside the lesion, with ostial narrowing); and type D (arising from outside the lesion, without ostial narrowing).

RESULTS

Patient characteristics: Sixty-three patients, who had 63 target lesions and 118 involved side branches, were randomized to receive a SES; 65 patients, who had 65 target lesions and 124 involved side branches, were assigned to the UMS group. With the exception of a higher percentage of men in the UMS group (85% vs 68%, p = 0.03), there were no significant differences between the 2 groups in terms of baseline clinical characteristics such as age, coronary risk factors, prior myocardial infarction, prior coronary angioplasty, and prior coronary bypass surgery.

Angiographic and IVUS characteristics of target lesions: Nearly all treated lesions were American College of Cardiology/American Heart Association type B1 or B2 (91% in the SES group vs 98% in the UMS group, p = 0.14). The reference lumen diameter after the procedure in the SES group (2.63 ± 0.53 mm) was similar to that in the UMS group (2.68 ± 0.58 mm, p = 0.62). The minimal lumen diameters after the procedure in the SES group and in the UMS group were

TABLE 1 Baseline Angiographic and Procedural Characteristics of Side Branches

	SES Group (n = 118)	UMS Group (n = 124)	p Value
TIMI flow before procedure			0.67
0	0 (0%)	0 (0%)	
1	3 (3%)	2 (2%)	
2	6 (5%)	4 (3%)	
3	109 (92%)	118 (95%)	
Side branch classification			0.29
A	45 (38%)	36 (29%)	
B	38 (32%)	52 (42%)	
C	2 (2%)	4 (3%)	
D	33 (28%)	32 (26%)	
Take-off angle >45°	80 (67%)	76 (61%)	0.29
Stent size (mm)	3.1 ± 0.3	3.1 ± 0.3	0.36
Maximal balloon size (mm)	3.2 ± 0.4	3.3 ± 0.4	0.42
Maximal inflation pressure (atm)	14.9 ± 3.1	14.9 ± 2.5	0.97
No. of inflations	3.1 ± 1.5	2.9 ± 1.1	0.19
Duration of inflations (s)	102.6 ± 54.2	84.8 ± 48.5	<0.01*

Data are presented as the mean ± SD or the number (%) of side branches.
*Statistically significant.

TABLE 2 Fate of Side Branches

	SES Group (n = 118)	UMS Group (n = 124)	p Value
Occlusion postprocedure	12 (10%)	9 (7%)	0.42
TIMI flow postprocedure			
Improved	2/9 (22%)	1/6 (17%)	0.79
Deteriorated	25/118 (21%)	16/124 (13%)	0.09
Recanalization at follow-up	11/12 (92%)	6/9 (67%)	0.15
Flow at follow-up			
Improved	24/30 (80%)	13/19 (68%)	0.36
Deteriorated	2/106 (2%)	4/115 (4%)	0.47
Delayed occlusion	2/106 (2%)	0/115 (0%)	0.14

Data are presented as the number (%) of side branches.
TIMI flow after the procedure is compared with that before procedure. The denominator in the "improved" category represents the number of side branches with TIMI flow before the procedure of <3, because TIMI 3 flow cannot improve further. TIMI flow at follow-up is compared with that after the procedure. The denominator in the "improved" category represents the number of side branches with TIMI flow after the procedure of <3. Similarly, the denominator in the "deteriorated" category represents the number of side branches with TIMI flow after the procedure of >0. In the category of "recanalization at follow-up," the denominator represents the number of side branches originally occluded after procedure.

also similar (2.48 ± 0.41 and 2.42 ± 0.46 mm, respectively, p = 0.46). In contrast, the minimal lumen diameter at 6-month follow-up was significantly greater in the SES group (2.40 ± 0.48 mm) than that in the UMS group (1.63 ± 0.59 mm, p <0.001). Thirty patients in the SES group and 28 patients in the UMS group underwent IVUS examination at follow-up. The quantitative IVUS analysis demonstrated that neointimal hyperplasia volume was significantly less in the SES group than in the UMS group (1 ± 1 and 37 ± 26 mm^3, respectively, p <0.001).

Baseline characteristics of side branches: Table 1 lists the baseline characteristics of the side branches. Although the duration of balloon inflation was longer in the SES group, the other characteristics were not different.

Fate of side branches: The fate of the side branches is described in Table 2. Immediately after intervention, occlusion was seen in 12 branches (11 patients) in the SES group versus 9 branches (9 patients) in the UMS group. Myocardial infarction (defined as an increase in creatine kinase enzyme to more than twice the upper limit of normal, accompanied by increased creatine kinase-MB) was documented in 2 patients (1 non–Q-wave myocardial infarciton in the SES group and 1 Q-wave myocardial infarction in the UMS group). Both patients were discharged without anginal complaints. There were no significant differences between the 2 groups in either flow improvement or flow deterioration after the procedure. At 6-month follow-up angiography, 11 of 12 occluded side branches in the SES group showed spontaneous recanalization. Contrary to our hypothesis, this recanalization rate (92%) was not lower than that in the UMS group (67%). Furthermore, the percentage of patients with improvement in TIMI grade flow at follow-up in the SES group was comparable to that in the UMS group. The percentage of side branches in which the flow deteriorated at follow-up was also similar in both groups, including 2 side branches in the SES group that showed delayed occlusion. However, 1 of these had TIMI 2 flow and the other had TIMI 1 flow immediately after the procedure. Table 3 lists the quantitative coronary angiography and IVUS variables in the parent vessels and relates them to the change in side branch flow at follow-up. The side branches were classified into 3 groups based on the flow change during the follow-up period (deteriorated, unchanged, and improved). These data reveal no difference in quantitative analysis among the 3 subgroups.

Predictive factor: By multivariate analysis, the presence of type A side branch morphology was the only independent predictor of side branch occlusion (odds ratio 9.7, 95% confidential interval 3.1 to 30.4). None of the factors examined detected predicted spontaneous recanalization of occluded side branches, even by univariate analysis.

DISCUSSION

The major findings of the present study are as follows: (1) the frequency of side branch occlusion after SES implantation and UMS implantation was similar; (2) SES implantation did not adversely affect the spontaneous recanalization rate of occluded side branches or flow improvement at follow-up; (3) there was no significant difference between the SES group and the UMS group in the rate of delayed side branch occlusion or the rate of flow deterioration at follow-

TABLE 3 Quantitative Coronary Angiography and IVUS Variables in the Parent Vessels in Relation to the Change in Side Branch Flow at Follow-up

	TIMI flow at Follow-up			
	Deteriorated	Unchanged	Improved	p Value
Quantitative coronary angiography at follow-up	(n = 6)	(n = 199)	(n = 37)	
Minimal lumen diameter (mm)	1.90 ± 1.12	2.01 ± 0.63	2.05 ± 0.56	0.84
Late loss (mm)	0.62 ± 1.07	0.45 ± 0.54	0.32 ± 0.46	0.31
IVUS data at follow-up	(n = 5)	(n = 96)	(n = 13)	
Stent volume (mm^3)	140 ± 32	131 ± 35	144 ± 24	0.36
Lumen volume (mm^3)	107 ± 56	114 ± 39	127 ± 35	0.50
Neointimal volume (mm^3)	33 ± 37	17 ± 24	18 ± 28	0.38

Data are presented as the mean ± SD.
TIMI flow at follow-up is compared with that after the procedure.

up; (4) the change in side branch flow during the follow-up period was not directly associated with late loss or neointimal hyperplasia volume in the parent vessel; and (5) the presence of type A side branch morphology was the most powerful predictor of side branch occlusion, and there were no factors that predicted side branch recanalization.

The putative mechanisms of side branch occlusion may include the presence of spasm, dissection, thrombus formation, embolization of plaque debris, ostial compromise by displaced stent struts, and the "snow plow" effect, where the plaque is shifted into the ostium of the side branch from the parent vessel. Because intracoronary nitroglycerin was given to our patients before angiography, spasm is an unlikely explanation. Although SES might have a slightly larger surface area than UMS due to the 5- to 10-μm thick coating, there was no difference in the incidence of side branch occlusion or flow deterioration after the procedure between the 2 treatment groups.

Previous studies have not shown consistent findings with respect to the rate of spontaneous recanalization of occluded branches.[4,7,8,10,12] These inconsistencies may be due to differences in stent design. However, most investigators reported that >60% of side branches that were occluded immediately after stenting had recanalized spontaneously at follow-up. In the present study, both the recanalization rate and the rate of flow improvement were >60% in both groups. Conversely, delayed side branch occlusion was seen in 2 branches (2%) in the SES group and in 0 branches in the UMS group, both of which are consistent with the reported rate of 4% with bare metal stents.[8,10]

This is the first study to evaluate the correlation between the neointimal hyperplasia volume and the change in side branch flow during the follow-up period (Table 3). Neointimal hyperplasia does not seem to play an important role in determining the side branch flow at follow-up because no formal statistical correlation could be demonstrated between these 2 phenomena. Therefore, we speculate that healing of dissection or disappearance of thrombus and emboli may play a role in recanalization of occluded side branches. It is clear that the SES does not adversely affect this process. Conversely, brachytherapy has been associated with a lower rate of spontaneous recanalization in previous studies, probably due to a delayed healing process.[13,14] Furthermore, because brachytherapy delays re-endothelialization, it may predispose to a continued risk of thrombosis of the ostia of side branches. This may explain the higher rate of delayed side branch occlusion following brachytherapy. The fact that no differences were seen in delayed occlusion or flow deterioration during the follow-up period between the SES group and the UMS group is consistent with the observation in animal studies that the SES does not delay re-endothelialization.[20] However, the conclusion that drug-eluting stents do not impair re-endothelialization cannot be generalized to other drug-eluting stents and should be restricted to the particular form of SES with slow release of the specific dose used in this trial. In this regard, it is worth noting that in the First In Man (FIM) and RAVEL trials, not a single case of acute, subacute, or late thrombosis or silent occlusion of the stented vessel occurred despite postprocedural administration of clopidogrel for only 2 months.[1–3]

Study limitations: The main limitation of this study is that it involves a relatively small number of patients and that side branches >2.5 mm were not assessed due to the exclusion criteria of the RAVEL trial. However, in the clinical setting, it is generally necessary to maintain patency of a side branch that is > 2.5 mm in diameter by appropriate techniques. The value of the SES for the treatment of true bifurcation lesions should be prospectively assessed in the future.

Acknowledgment: We greatly appreciate the assistance provided by Brian Firth, MD, PhD, in reviewing and editing this manuscript.

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CHAPTER 8

PERSISTENT INHIBITION OF NEOINTIMAL HYPERPLASIA AFTER SIROLIMUS ELUTING STENT IMPLANTATION: LONG-TERM (UP TO 2 YEARS) CLINICAL, ANGIOGRAPHIC AND INTRAVASCULAR ULTRASOUND FOLLOW-UP

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Circulation 2002;106(13):1610-3

Brief Rapid Communications

Persistent Inhibition of Neointimal Hyperplasia After Sirolimus-Eluting Stent Implantation

Long-Term (Up to 2 Years) Clinical, Angiographic, and Intravascular Ultrasound Follow-Up

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Background—Early results of sirolimus-eluting stent implantation showed a nearly complete abolition of neointimal hyperplasia. The question remains, however, whether the early promising results will still be evident at long-term follow-up. The objective of our study was to evaluate the efficiency of sirolimus-eluting stent implantation for up to 2 years of follow-up.

Methods and Results—Fifteen patients with de novo coronary artery disease were treated with 18-mm sirolimus-eluting Bx-Velocity stents (Cordis) loaded with 140 μg sirolimus/cm^2 metal surface area in a slow release formulation. Quantitative angiography (QCA) and intravascular ultrasound (IVUS) were performed according to standard protocol. Sirolimus-eluting stent implantation was successful in all 15 patients. During the in-hospital course, 1 patient died of cerebral hemorrhage after periprocedural administration of abciximab, and 1 patient underwent repeat stenting after 2 hours because of edge dissection that led to acute occlusion. Through 6 months and up to 2 years of follow-up, no additional events occurred. QCA analysis revealed no significant change in stent minimal lumen diameter or percent diameter stenosis, and 3-dimensional IVUS showed no significant deterioration in lumen volume. In 2 patients, additional stenting was performed because of significant lesion progression remote from the sirolimus-eluting stent.

Conclusion—Sirolimus-eluting stents showed persistent inhibition of neointimal hyperplasia for up to 2 years of follow-up. **(*Circulation*. 2002;106:1610-1613.)**

Key Words: stents ■ restenosis ■ ultrasonics ■ drugs

Coronary stents provide a mechanical scaffolding that virtually eliminates recoil and remodeling, but they do not reduce neointimal growth. Sirolimus-eluting stents may provide a definitive solution for in-stent restenosis in the short term.[1,2,3] Histological follow-up in the porcine model, however has indicated that late neointimal hyperplasia can recur at 90 and 180 days (Andrew J. Carter, DO, unpublished data, 2001). Thus, there are sufficient concerns about delayed healing with consequent risks of late restenosis[4] and thrombosis,[5] late malapposition,[6] edge effect,[7] and, on the other hand, delayed restenosis,[8] to warrant additional late follow-up catheterization. The objective of this study was to determine angiographic, intravascular ultrasound (IVUS), and clinical outcome up to 2 years after implantation of sirolimus-eluting stents in de novo coronary lesions.

Methods

Patients and Stent Implantation

The patient population consisted of 15 patients who were included at our center between February and May of 2000 in the First in Man clinical trial on sirolimus-eluting stents (FIM). The methodology has been published previously.[3]

In brief, patients with short (<15 mm) de novo coronary lesions received a single 18-mm sirolimus-eluting Bx-Velocity stent (Cordis). All lesions were predilated before stent implantation. The sirolimus coating was a slow-release formulation (≈28-day drug release with 140 μg of sirolimus per cm^2 stent surface area). All patients received aspirin (325 mg/d, indefinitely) and clopidogrel (300 mg loading dose immediately and 75 mg/d for 8 weeks).

Angiographic and IVUS Analysis

Serial coronary angiography was performed at baseline, 6 months, and late follow-up (mean 20.3±2.4; range 18 to 24 months). Two

Received May 6, 2002; revision received July 30, 2002; accepted August 5, 2002.

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TABLE 1. Baseline Characteristics

Male	10
Age, y	60.2±14.3 (35–80)
Unstable angina	9
Treated vessel	
LAD	6
CX	5
RCA	4
No. of diseased vessels	
1	13
2	2
Catheterization follow-up period, mo	20.3±2.4 (18–24)
Clinical follow-up period, mo	23.3±1.0 (22–25)

Values are n or mean±SD (range). n=15.

LAD indicates left anterior descending artery; CX, circumflex artery; and RCA, right coronary artery.

coronary segments were subjected to quantitative angiography (QCA), one in stent and one in lesion. The in-stent segment encompassed only the 18-mm segment covered by the stent. The in-lesion segment was defined as the stent plus 5 mm proximal and 5 mm distal to the edge or the nearest side branch. In-stent and in-lesion stenosis was defined as >50% diameter stenosis. QCA analysis was done by an independent core laboratory (Brigham and Women's Hospital, Boston, Mass).

Stented vessel segments were examined with mechanical IVUS, using automated pullback at 0.5 mm per second. A coronary segment beginning 5 mm distal to and extending 5 mm proximal to the stented segment was also examined. A computer-based contour detection program was used for automated 3-dimensional reconstruction of the stented segment from up to 200 cross-sectional images.[9]

Clinical Follow-Up

We assessed the clinical outcome during the hospital stay, at 6 months, and up to 2 years later. Major adverse cardiac events were defined as death, acute myocardial infarction, and repeat revascularization of the target lesion and/or vessel by coronary artery bypass graft or percutaneous coronary intervention.

Statistical Analysis

Quantitative data are presented as mean±SD. Multiple comparisons between postprocedural 6- and 20-month follow-up measurements were performed by ANOVA. Paired comparisons were performed by Student's *t* test.

Results

Six-month outcomes of the original 15 patients have been described earlier.[2] Baseline characteristics are shown in Table 1. In brief, between 6 months and up to 2 years after stent implantation, no additional clinical events occurred. Complete sets of postprocedural, 6-month, and late follow-up cardiac catheterizations were obtained in 10 of 14 surviving patients. Four asymptomatic patients refused to undergo a second diagnostic investigation for scientific purposes only.

TABLE 2. Major Adverse Cardiac Events

	6 Months	6 to 24 Months	Up to 24 Months
Death	1†	0	1
MI*	1	0	1
TLR*	1	0	1
TVR	0	2	2
CABG	0	0	0

n=15.

MI indicates myocardial infarction; TLR, target-lesion revascularization; TVR, target-vessel revascularization; and CABG, coronary artery bypass graft.

*The same patient (periprocedural MI).

†Due to cerebral hemorrhage in hospital.

At 18 months after the procedure, 1 patient demonstrated a significant stenosis (60% diameter stenosis; fractional flow reserve 0.65) located distally to the sirolimus stent (8 mm from distal edge by quantitative IVUS) that was treated by direct stenting. Another patient presented with effort angina 22 months after the index procedure and underwent stenting because of progression of a preexisting atherosclerotic lesion 12 mm from the distal edge of the sirolimus stent (minimal lumen area by IVUS 3.5 mm^2 after the procedure and 3.0 mm^2 at 22-month follow-up). Volumetric IVUS measurements showed no neointimal hyperplasia (NIH) in the stented segment. Lumen volume of both 5-mm proximal and distal edges of the sirolimus stent revealed virtually no changes when comparing postprocedural, 6-month, and 22-month follow-up measurements.

At almost 2 years of follow-up, 1 death (noncardiac) and 1 target-lesion revascularization occurred, both of which were in the early in-hospital period (Table 2).

Quantitative Coronary Angiography and IVUS Analysis

Quantitative coronary angiography data are shown in Table 3. Twenty-month in-stent minimum lumen diameter (2.74±0.41 mm) and percent DS (3±13%) remained unchanged compared with 6-month follow-up data

TABLE 3. Quantitative Coronary Angiography Analysis

	Before Procedure	After Procedure		6-Month Follow-Up		20-Month Follow-Up	
		In Lesion	In Stent	In Lesion	In Stent	In Lesion	In Stent
RD, mm	2.97±0.51	3.01±0.43		3.02±0.38		2.85±0.40	
MLD, mm	0.81±0.24	2.58±0.43	2.90±0.33	2.32±0.37	2.69±0.30	2.50±0.51	2.74±0.41
Stenosis, %	72±8	14±10	1.5±7	23±7	11±8	12±15	3±13
Late loss, mm				0.25±0.31	0.25±0.28	0.08±0.46*	0.20±0.24*
Late loss index				0.13±0.20	0.12±0.11	0.02±0.30*	0.10±0.13*

Values are mean±SD. n=10.

RD indicates reference diameter; MLD, minimal lumen diameter.

*P=NS (6-month vs 20-month follow-up). P=NS between groups (after procedure, 6-month, and 20-month follow-up). Comparison by ANOVA.

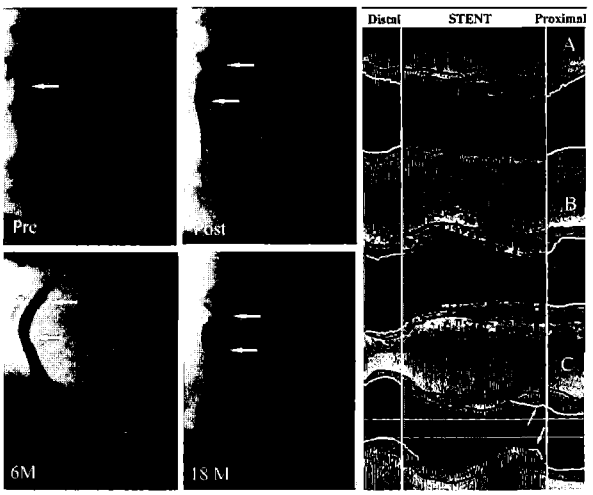

Figure 1. A 38-year-old male with unstable angina and mid-right coronary artery lesion (arrow) treated with sirolimus-eluting Bx-velocity stent. No lumen deterioration was observed at 6- and 18-month follow-up (6M and 18M). Longitudinal IVUS reconstructions demonstrate absence of NIH at 6-month follow-up (B), with minimal NIH (C, arrows) at 18 months compared with after the procedure (A).

(2.69±0.30 mm and 11±8%, respectively; P=NS). Representative sequences of angiograms from a single patient are shown in Figure 1.

IVUS analysis demonstrated persistent inhibition of NIH at long-term follow-up (Table 4). FIM study data from Sao Paulo cohort are also shown in Table 4. Between the 6- and 20-month follow-ups, a small change in NIH (1.4±1.6 mm^3 and 5.9±5.3 mm^3, respectively) and in percent volume obstruction of the stent (1.1±1.2% and 4.4±3.1%, respectively) was observed. Only 1 patient reached 10% NIH of stent volume as shown by IVUS, which corresponded with an actual luminal loss of 0.29 mm at the 18-month follow-up (Figure 1). In addition, no significant change in lumen or vessel volume was observed in either proximal or distal edges of the stent (Figure 2). No late stent malapposition was detected.

Discussion

First clinical applications of sirolimus-eluting stents in de novo lesions were shown to be safe and feasible in preventing NIH at 6 months and 1 year, with a complete abolition of restenosis.[1–3] Such findings have provoked considerable interest but have also raised concerns about the long-term follow-up[10,11]

TABLE 4. Volumetric IVUS Measurements

	Rotterdam (n=10)		Sao Paulo (n=14)*	
Follow-up period, mo	6	20	4	12
Stent volume	133±31	132±29	138±21	127±30
Lumen volume	132±31	126±28	137±22	124±30
NIH volume	1.4±1.6	5.9±5.3†	0.3±0.9	2.5±3.4
% Volume obstruction	1.1±1.2	4.4±3.1†	0.3±0.8	2.2±3.4

*Data from Sao Paulo[3] (slow-release formulation stent group).
†P<0.05, 6-month vs 20-month follow-up.

In the present study, NIH assessed by IVUS at both 6 and 20 months was not substantially different from the 12-month follow-up data presented by Sousa et al[3] (Table 3). In addition, the percent volume obstruction of the stent detected by volumetric IVUS in our study (4.4%) at 20-month follow-up is importantly less than those observed at 6-month follow-up in other trials (36% and 25%) using uncoated stents.[12,13] Similarly, in-stent late loss and late loss index (LLI; 0.20 mm and 0.10, respectively) at a 20-month follow-up is markedly lower than with bare metal stents, in which late loss averages were 1.04 to 0.61 mm (LLI 0.59 to 0.39) at a 6-month[12,13] and 0.46 mm (LLI 0.30) at a 36-month follow-up.[14] Therefore, our findings provide considerable reassurance with regard to persistent inhibition of late restenosis or rebound hyperplasia, such as was previously observed with radioactive stents.[8]

In fact, minimal hyperplasia in humans up to 2 years after the procedure constitutes the first evidence that behavior in humans is at variance with the porcine model, where 90-day data actually demonstrate the recurrence of considerable NIH (Andrew J. Carter, unpublished data). For the first time in interventional cardiology, a new antirestenosis therapy performs better in humans than in the animal models.

Concern about potential late complications, such as late occlusion, thrombosis, late malapposition, aneurysm, and edge restenosis as reported in patients treated with brachytherapy,[13] has not been observed in our patient population during up to 2 years of follow-up.

It has to be emphasized that short-term (8-week) antiplatelet therapy as used here and in the RAndomized study with the sirolimus-eluting Bx VELocity balloon-expandable stent (RAVEL)[15] provides adequate protection against subacute and late thrombotic occlusion. Nonetheless, generalization of these findings to treatment of long and complex lesions, total chronic occlusion, left main stem, etc, needs to be specifically evaluated in clinical trials.

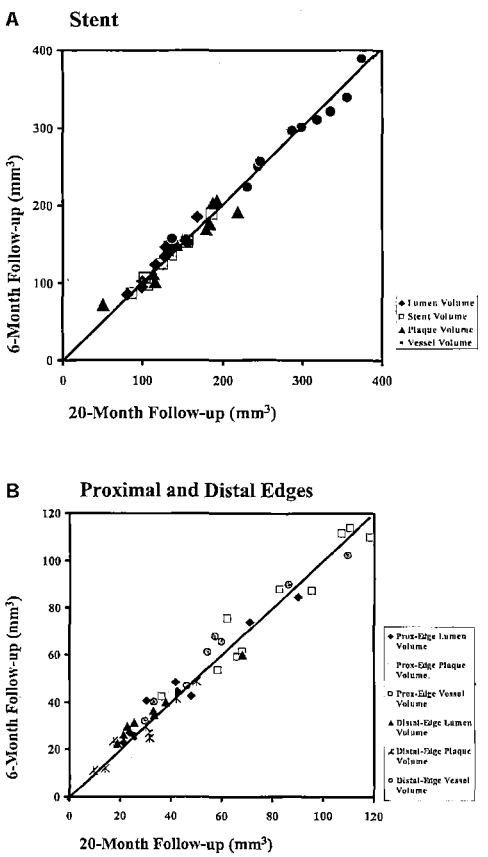

Figure 2. Changes in vessel, plaque, and lumen volume at the sirolimus-eluting stent (A) and peri-stent margins (5-mm proximal and 5-mm distal edges of the stent) (B). Individual data are presented in relation to the line of identity. *P*=NS for 6-month versus 20-month follow-up

The need for late target-vessel revascularization in 2 patients in lesions remote from the sirolimus stent again emphasizes the indolent nature of atherosclerosis in some patients. Although this study confirms that sirolimus-eluting stents constitute a major advance in restenosis prevention, the problem of atherosclerosis itself remains a considerable challenge.

Limitations

This is a small observational study and the results need to be confirmed by long-term follow-up in larger patient series. Lack of complete QCA and IVUS follow-up was unfortunate but was not prespecified in the study protocol. The virtual absence of NIH in the 10 patients studied at 20 months renders the data quite compelling because the remaining 4 patients were completely asymptomatic.

Conclusion

Sirolimus-eluting Bx-Velocity stents demonstrated persistent inhibition of neointimal hyperplasia and absence of restenosis in single de novo coronary lesions for up to 2 years of follow-up.

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CHAPTER 9

INTRAVASCULAR ULTRASOUND EVALUATION AFTER SIROLIMUS ELUTING STENTS IMPLANTATION FOR DE NOVO AND IN-STENT RESTENOSIS LESIONS

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European Heart Journal in Press

Intravascular Ultrasound Evaluation After Sirolimus Eluting Stent Implantation For De Novo And In-Stent Restenosis Lesions

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ABSTRACT

Aims: The aim of this study is to compare the efficacy of sirolimus-eluting stents (SES) on neointimal growth and vessel remodeling for in-stent restenosis versus de novo coronary artery lesions using serial intravascular ultrasound (IVUS).

Methods and Results: The study population consisted of 86 patients with in-stent restenosis (ISR) (n=41) or *de novo* lesions (n=45) treated with SES and evaluated by IVUS post-procedure and at follow-up. One 18-mm SES was used for *de novo* lesions while 16 patients with ISR received > 1 SES (total stented length 17.9mm vs 22.0mm respectively; p=0.004). At follow-up, no differences were observed between the ISR and *de novo* groups with respect to changes in the mean external elastic membrane (1.7% vs 1.3%; p=0.53), plaque behind the stent (1.2 % vs 3.4%; p=0.49), and lumen areas (0.7% vs 1.9%; p=0.58). No positive remodeling or edge effect was observed. A gap between stents was observed in 2 patients with ISR, where more prominent, though non-obstructive, neointimal proliferation was noted.

Conclusion: Sirolimus-eluting stenting is equally effective at inhibiting neointimal proliferation in *de novo* and ISR lesions without inducing edge restenosis or positive vascular remodeling.

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Introduction

Coronary stenting has reduced restenosis compared with balloon angioplasty; however stent restenosis is still a major problem in interventional cardiology [1-3]. Intracoronary radiation has emerged as an effective treatment for restenosis after coronary stent implantation.[4-6] However, the widespread use of intracoronary radiation therapy is limited by considerable logistic requirements, and potential side effects such as edge effects, geographic miss, delayed healing and late thrombosis[7-9].

Recently, sirolimus-eluting stents (SES) have been demonstrated to significantly reduce late luminal re-narrowing after coronary intervention, both for *de novo* lesions[10,11] and for in-stent restenosis (ISR)[12,13]. This favorable effect is accomplished by a potent and sustained inhibition of neointimal tissue growth by the anti-proliferative drug applied to the stent in a polymer. However, the treatment of ISR with placement of a new, drug-eluting stent presents different challenges compared to the treatment of *de novo* lesions. The repeat stent implantation has to be performed in the presence of a previously placed stent obstructed by soft neointimal tissue. ISR lesions have different histological features and proliferation profiles from the de novo lesions[14]. In an animal re-injury model, it has been shown that the accumulation of extracellular matrix is a major factor in repeat restenosis formation and the cellular content in the vessel wall is different from that observed in *de novo* lesions.[15,16] Therefore, ISR lesions may respond differently from *de novo* lesions, particularly since this represents a second episode of barotraumas to the vessel. [17] Although SES have been shown to be effective at inhibiting neointimal hyperplasia (NIH) in both *de novo* [11,18] and ISR[12] [13] lesions, the influence of SES on vascular remodeling and edge effects have not previously been evaluated in patients with ISR.

The aim of this study is to compare the vessel responses of *de novo* and ISR lesions treated with SES implantation, as assessed by serial volumetric intravascular ultrasound (IVUS).

Methods

Patient Population

Patients with either *de novo* coronary lesions or ISR assigned to receive sirolimus eluting stent in the respective First-In-Man (FIM) registries were compared[11,18]. In the FIM *de novo* group, eligible patients had stable or unstable angina or documented silent ischemia, with a single *de novo* lesion of a native coronary artery in a vessel between 3.0 and 3.5 mm in diameter that could be covered by a single 18mm stent. In the FIM ISR group, patients with ISR in a native coronary artery and objective evidence of ischemia were included. The vessel size had to be > 2.5mm and <3.5mm. In-stent restenosis in saphenous vein grafts was excluded.

All lesions were predilated before implantation of a sirolimus-eluting Bx VELOCITY‘ stent (Cordis Waterloo, BL) using conventional techniques. All ISR patients and 30 of 45 patients from the FIM de novo group received the slow release formulation

SES. Fifteen patients in the FIM de novo trial received the fast release formulation SES. All stents were 18mm long and 2.5-3.5 mm in diameter.

All patients received aspirin (325 mg/d, indefinitely) and clopidogrel as a 300 mg loading dose immediately after stent implantation followed by 75 mg/d for 2 months in patients with *de novo* lesions and 2 to 4 months, according to discretion of the operator, in the ISR patients.

IVUS Analysis and Quantitative Measurements

IVUS imaging was performed after administration of intracoronary nitroglycerin (150-200μg) using motorized catheter pullback at a speed of 0.5 mm/sec. Ultrasound images were recorded on s-VHS tape for off-line analysis. The lumen, stent, and external elastic membrane (EEM) contours were detected with the CURAD QCU analysis software (Curad BV, Wijk Bij Duurstede, The Netherlands) applying 3-D reconstruction of the stented segment, as described elsewhere.[19] Quantitative IVUS analysis included the stent segment and the coronary segment beginning 5mm proximal to and extending 5mm distal to the stented segment. Lumen, stent boundaries and external elastic membrane were detected using a minimum cost algorithm. Mean external elastic membrane area (EEMA), stent area (SA) and lumen area (LA) were calculated. Mean total plaque area (TPA), mean plaque behind stent area (PBSA) and neo-intimal hyperplasia area (NIHA) were calculated as 'EEMA minus LA', 'EEMA minus SA', 'SA minus LA', respectively.

Delta values (D) for each measurement were calculated as follow up minus post-procedure. To eliminate the influence of the vessel size and the length of the analyzed segment, which affects area calculations, percent change [(Darea / post-procedure area)*100] was also calculated.

Incomplete stent apposition (ISA) was defined as one or more stent struts clearly separated from the vessel wall with evidence of blood speckles behind the strut.[20]

Qualitative analysis was performed by reviewing all post-procedure and follow-up IVUS videotapes to identify the ISA.

Quantitative coronary angiographic analysis

Serial coronary angiography was performed at baseline (before and after intervention) and at 4 or 6-month follow-up. In-stent stenosis was defined as >50% diameter stenosis (DS) at follow-up. Quantitative angiographic analysis was performed by an independent core laboratory (Brigham and Women's Hospital, Boston, Mass)

Statistical Analysis

Statistical analysis was performed using the SPSS software (version 10.0, Statistical Package for the Social Sciences, Chicago). Continuous variables are presented as mean ± SD and compared using paired or unpaired Student`s t test, as appro-

priate. Categorical variables are presented as counts and frequencies and compared using chi-square test or Fisher's exact test. IVUS parameters among diabetics and non-diabetics with de novo or ISR lesions were analyzed using one-way analysis of variance (ANOVA) and post hoc comparisons were made with the Tukey–Kramer HSD (honestly-significant-difference) test for multiple group comparisons. Multivariate linear regression analyses were performed to evaluate the independent value of baseline and procedural variables in predicting the IVUS outcomes at follow-up. All variables presented in Tables 1, 2, and 3 were tested and the final models were built by stepwise selection, with probabilities for entry and removal of factors set to 0.05 and 0.10, respectively. All tests were two-tailed and a p value <0.05 was considered as statistically significant.

Results

Patient demographics are shown in Table 1. In the ISR group, 4 patients had failed previous brachytherapy treatment, 11 patients had recurrent percutaneous coronary interventions and 3 patients had totally occluded vessels before SES implantation. In the *de novo* group, all patients had 1 SES but in the ISR group, 16 of 41 patients received more than 1 stent (range:2-5 stents). The mean length of predilation balloons was 17.9± 4.2mm in the ISR group, and 17.9± 3.1mm in de novo group. Longer than 20mm balloon was not used in any case and 44% of the balloons used for predilation were ≤16mm.

Follow-up cardiac catheterization was performed at 4 months (n=30) or 6 months (n=13) in the *de novo* group and at 4 months (n=40) in the ISR group. Baseline, post-procedure, and follow-up angiographic characteristics are shown in Table 2. When compared to the *de novo* group, the ISR group showed smaller reference vessel diameters, as well as post-procedure and follow-up minimal lumen diameters (MLD). However, follow-up % DS and late loss was not different there was not a significant difference between post-procedure and follow-up MLD in either the de novo or ISR patients.

Table 3 shows post-procedure and follow-up IVUS results. Serial IVUS was performed in 43 of 45 patients with de novo coronary lesions and 37 of 41 with ISR lesions. The total stented length was longer in the ISR group than in the de novo group. No differences were found between the 2 groups with respect to mean EEMA, SA, LA, and PBSA, both post-procedure and at late follow-up.

EEM and PBS area measurements showed no significant changes between the 2 periods, in patients with ISR or *de novo* lesions. There was also no significant difference in NIH area at follow-up (Figure-1). Two patients in the ISR group had a gap between two stents and these patients had increased NIH in the gap segment.

Late acquired ISA was not observed at 4 months in any studied patient. Two patients (1 in the *de novo* and 1 in the ISR) showed persisting ISA at late follow-up.

IVUS analyses were performed in 16 (7 from de novo, 9 from ISR group) out of 18 diabetic patients. There was no significant difference between diabetics and non-diabetics with respect to in-stent mean NIH area (0.07mm^2 vs 0.04mm^2, p=0.24). Also, there was no difference in the mean percent area obstruction among diabetics with *de novo* and with ISR, and non-diabetics with de novo and with ISR (0.4% vs 1.6% vs 0.5% vs 0.7%, respectively; p=NS by ANOVA). Serial edge segment analysis was possible at 34 distal and 24 proximal edges in the ISR group and at 37 distal and 39 proximal edges in the *de novo* group, respectively. Edges were excluded from analysis when there was a side-branch take off within 5mm of the stent, inadequate image quality or incomplete image acquisition. Table 4 shows post-procedure and follow-up IVUS findings for edge segments. No significant difference was observed at follow-up in the *de novo* or ISR groups. There was no significant difference in lumen area changes between patients with and without diabetes mellitus both at the proximal (+0.3mm^2 vs -0.2 mm^2 p=NS) and the distal edges (+0.3mm^2 vs +0.2mm^2 p=NS).

Multivariate regression analyses have identified post-procedure lumen area to be high correlated and to be the only independent predictor of follow-up IVUS mean lumen area (coefficient 0.90; p-value <0.001; r^2 of the model 0.84). Importantly, neointimal area and mean percent area obstruction at follow-up could not be predicted by any the tested variables.

Clinical Follow-up

Clinical follow-up of patients with de-novo and ISR have been previously presented in detail[11,18,35]. Briefly, in de-novo group, 1 patient died (in hospital; cerebral hemorrhage), 1 patient developed non-Q myocardial infarction and 2 patients underwent target vessel revascularization. No patient presented with in-stent restenosis and major adverse clinical events (death, cerebrovascular accident, myocardial infarction, or re-intervention) free survival was 91% at 2 years follow-up. In ISR group, 2 patients died (1 sudden death, 1 due to congestive heart failure), 1 patient, who had received 5 SESs, showed no late lumen loss at five months follow-up, but developed an inferior myocardial infarction seven months after the index procedure. Only 2 patients presented with in-stent restenosis were asymptomatic. Therefore, repeat revascularization was not performed. Adverse clinical events free survival was 92.7% after 1 year.

Discussion

In the present study we report for the first time a comparative analysis of the effects of sirolimus-eluting stent implantation in patients with *de novo* lesions versus those with in-stent restenosis, as evaluated by serial angiographic and volumetric intravascular ultrasound. We observed that: 1) SES were equally and highly effective at preventing neointimal proliferation in both *de novo* and ISR lesions, 2) no significant changes were observed in external arterial dimensions between immediately post-

procedure and late follow-up in patients with *de novo* or ISR lesions, 3) SES were equally effective at inhibiting NIH in diabetics and non-diabetics in both groups 4) late acquired incomplete stent apposition was not observed at 4 or 6 month follow-up in either group of lesions.

The restenotic and de novo atherosclerotic lesions differ considerably between each other, reflecting the distinct physiopathological background involved in both situations [16]. Moreover, re-dilatation of restenotic lesions (i.e. exposure to "double injury") is associated with a peculiar local vascular response, distinct from that observed after the first dilatation[17]. Accordingly, in practice treatment of restenotic lesions presents a different behavior as compared to de novo lesions. Late luminal renarrowing had been observed to be consistently more frequent after treatment of restenotic than of de novo lesions, with re-restenosis rates >70% in its most severe forms[3,21]. Several pharmacological and mechanical treatment modalities have shown disappointing results for the prevention and treatment of restenosis. So far, vascular brachytherapy is the only therapy proven in randomized clinical trials to be effective for the treatment of ISR, although post-brachytherapy failures have been reported to occur in up to 30- 40% of cases [21,22]. After brachytherapy for ISR, the late lumen loss was observed to range from 0.38 to 0.64mm in studies with either _ or _ radiation [6,23,24]. However, late lumen loss after SES implantation for ISR was 0.12mm, the amount of NIH close to zero (0.05 mm^2) and lumen area obstruction at IVUS examination was only 0.8%. Notably, in our series SES implantation equalized the IVUS-assessed NIH between de novo and ISR lesions. Interestingly, as SES had virtually eliminated NIH post-procedure and follow-up mean lumen areas were almost the same, which explains the high correlation observed between these 2 parameters. Furthermore, since NIH was almost eliminated in all patients, IVUS neointimal area and percent lumen area obstruction at follow-up had an almost uniform value close to zero in all included cases, which may justify the absence of predictive value for all tested characteristics.

Concerns have been raised whether SES could significantly affect the vascular architecture behind the stent struts, as previously reported following coronary radiation.[25-27] However, in our series no significant vessel enlargement was observed in either de novo or in-stent restenotic lesions. Indeed, the percent change in vessel area in both de novo (1.7%) and in ISR (1.3%) after SES implantation was highly comparable to that previously reported after bare metal stent implantation (2%).[28]

"Edge effect", or restenosis at the stent margins, has occurred most notably with radioactive stents, as a combined effect of radiation dose fall-off and vessel injury outside the stent.[29-31] IVUS analysis of edge stenosis with radioactive stents has shown that this results predominantly from negative remodeling with exaggerated neointimal hyperplasia. In our series, no "edge effect" was observed. In both de novo and restenostic lesions, the luminal dimensions were maintained at both stent edges, which is in

accordance with the IVUS findings of the RAVEL trial, where a trend toward larger lumen areas at distal edge was reported. The possible reasons for more beneficial effect of the drug at the distal edge might be a higher downstream concentration of the drug.

Diabetic patients have higher restenosis and recurrent ischemic event rates than non- diabetics even with aggressive revascularization strategies.[3] With serial IVUS Kornowski et al[32] demonstrated that late loss following angioplasty among diabetics is predominantly due to exaggerated NIH. However, in our study, SES had virtually equalized the degree of NIH growth in patients with and without diabetes. Percent area obstruction did not differ among diabetics and non-diabetics, both in the de novo (0.4% vs 0.5%, p=ns) and ISR groups (1.6% versus 0.7%, p=ns). Our data are similar with the observations in the diabetic subgroup of the RAVEL trial, which demonstrated almost no NIH growth after SES implantation for de novo lesions (0.08mm late lumen loss), with no binary restenosis occurrence (personal communication of A.Abizaid, MD PhD 2002).

Late acquired incomplete stent apposition (LAISA) is another potential concern with drug- eluting stents,[20] and recently published data have demonstrated that in bare stents is due to positive vascular remodeling.[33] Although post-procedure ISA persisted in 2 patients at 4 month follow-up, no LAISA was observed in either the *de novo* or ISR groups in the present study. This is consistent with our quantitative IVUS measurements which showed no significant vessel size change at follow-up as well as and in the amount of plaque behind the stent. These findings suggest that the therapeutic effect of SES is solely due to inhibition of NIH without inducing positive vascular remodeling in either *de novo* or ISR lesions.

Apart from the well-known high rates of recurrence after treatment of ISR lesion, length (and the stented length) has been identified as one of the most important predictors of restenosis.[34,35] In the current study, the ISR group had a longer stented segment than the *de novo* lesion group. Nevertheless, the amount of NIH did not significantly differ between *de novo* lesions, treated with shorter stented lengths, and ISR in which multiple stents were more often implanted. Interestingly, in two patients with ISR, NIH was observed to be limited to the site of a gap between two stents. Taken together, these findings suggest that the therapeutic power of SES, is not adversely affected by the length of the stented segment as long as there is not a gap left between two adjacent stents during the index procedure.

Study Limitations

This is a non-randomized comparison of sirolimus-eluting stents and the current report is limited as only the data from single de novo and relatively less complex ISR lesions in vessels with a diameter between 2.5 and 3.5 mm were enrolled. Therefore, results need to be confirmed by randomized trial with larger series of patients. The results in the diabetic subgroup are remarkable. However, due to the relatively small

number of patients some of the interpretations may be highly speculative and may or may not be borne out in larger studies. Mid-term IVUS evaluation was performed at different time-points, at 4 months ("São Paulo cohort") or at 6 months ("Rotterdam cohort"). Nonetheless, no major differences in NIH were detected throughout the follow-up period, indicating that mid-term 4-month and 6-month IVUS results may be interchangeable. The average duration of follow-up is short and longer-term follow-up is needed. However, the recently reported long-term data demonstrated that the IVUS findings in the FIM trial at 4 months remained essentially unchanged at 12 months[11] and up to 2 years[36] supporting the notion that early findings may be predictive of the findings at long-term follow-up.

Conclusion

Sirolimus-eluting stents appear to be as effective at inhibiting neointimal hyperplasia in ISR lesion as it is in de novo lesions without inducing edge effect or positive vascular remodeling.

Acknowlegment

We would like to thank Brian Firth MD.PhD for his critical review of this manuscript.

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TABLE 1:
Patient Demographics

	De novo (n=45)	ISR (n=41)	p value
Age	57.4± 11	57.8 ± 12	0.87
Male, %	69	80	0.48
Hypertension,%	49	63	0.17
Diabetes Mellitus,%	16	27	0.19
Hypercholesterolemia,%	62	71	0.40
Smoking, %	58	56	0.87
Previous MI, %	29	56	0.01
Unstable Angina, %	40	27	0.19
Treated Vessel			
LAD, %	53	39	0.13
CX,%	20	22	0.51
RCA,%	27	39	0.25

ISR; in-stent restenosis, MI; myocardial infarction, LAD; left anterior descending artery, CX; circumflex artery, RCA; right coronary artery

TABLE 2:
Quantitative Coronary Angiographic Results

	De novo (n=43)	ISR (n=40)	p value
Reference Diameter, mm	2.94±0.38	2.74±0.3	0.015
Pre-Procedure MLD,mm	0.96±0.35	0.87±0.44	0.35
Pre-Procedure DS,%	67.3±11.3	67.8±15.8	0.86
Post-Procedure (in-stent) MLD, mm	2.89±0.35	2.66±0.33	0.003
Post-Procedure (in-stent) DS, %	3.27±7.37	3.66 ±9.9	0.83
Follow-up (in-stent) MLD,mm	2.82±0.38	2.54± 0.58	0.009
Follow-up (in-stent) DS, %	6.04±6.8	8.8±17.8	0.34
Late loss (in-stent), mm	0.07±0.30	0.12±0.41	0.50

Values are mean± SD. MLD; minimal lumen diameter, DS; diameter stenosis

TABLE 3:
Serial Intravascular Ultrasound Measurement

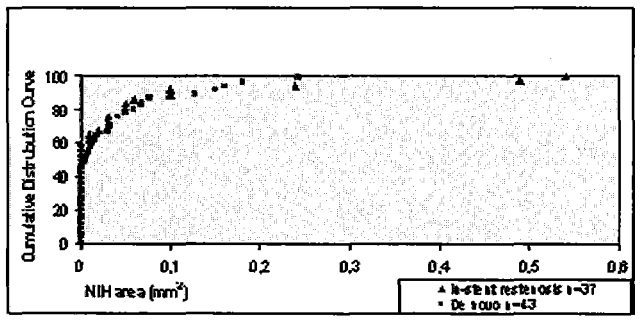
	De novo (n=43)	ISR (n=37)	p value
Post-Stent Implantation			
Stent length, mm	17.9± 1.2	22.0±7.6	0.004
EEM mean area, mm^2	16.4±4.4	16.5±4.1	0.9
PBS mean area, mm^2	9.1±3.3	9.3±2.9	0.76
Lumen mean area, mm^2	7.4±1.6	6.9±1.7	0.19
Stent mean area, mm^2	7.4±1.6	6.9±1.7	0.17
Minimum lumen area, mm^2	6.1±1.6	5.5±1.6	0.41
Follow-up			
Stent length, mm	18.2±1.2	22.5±10.3	0.015
EEM mean area, mm^2	16.7 ±4.1	16.6±3.9	0.93
PBS mean area, mm^2	9.1± 3.1	9.4± 2.6	0.72
Lumen mean area, mm^2	7.6±1.9	7.1±1.9	0.21
Stent mean area, mm^2	7.7±1.8	7.2±1.9	0.21
Minimum lumen area, mm^2	6.1±1.8	5.6±1.7	0.51
NIH mean area, mm^2	0.03±0.06	0.05±0.12	0.33
% Area Obstruction	0.4±0.7	0.8± 2.1	0.21
Area Change at Follow-up			
% Lumen mean area	0.7± 8.3	1.9±10	0.58
% EEM area	1.7±7.1	1.3±7.4	0.53
% PBS area	1.2±11.6	3.4±11.4	0.49

Values are mean± SD. ISR; in-stent restenosis, EEM; external elastic membrane, PBS; plaque behind the stent, NIH; neointimal hyperplasia.

TABLE 4:
Intravascular Ultrasound Measurements at The Edge Segments

Proximal Edge:	**Lumen area (mm^2)** Post / Follow-up	*p-value	**Plaque area (mm^2)** Post / Follow-up	*p-value	**EEM area (mm^2)** Post / Follow-up	*p-value
De novo	9.1±3.0 8.8±3.4	0.17	6.8±2.8 6.9±2.9	0.42	15.9±4.1 15.7±4.4	0.57
ISR	7.3±2.1 7.7±2.5	0.13	7.9±3.1 8.1±3.3	0.56	15.2±3.6 15.8±3.9	0.14
#p-value	0.005 0.29		0.08 0.75		0.53 0.12	
Distal Edge:	**Lumen area (mm^2)** Post / Follow-up	*p-value	**Plaque area (mm^2)** Post / Follow-up	*p-value	**EEM area (mm^2)** Post / Follow-up	*p-value
De novo	7.6±2.5 7.8±3.0	0.53	5.0±2.4 5.1±2.2	0.79	12.6±3.9 12.9±4.3	0.40
ISR	7.0±2.3 7.2±2.4	0.34	6.1±3.6 5.9±3.5	0.69	13.1±5.1 13.2±4.9	0.71
#p-value	0.37 0.44		0.21 0.14		0.71 0.64	

Values are mean± SD. Post; post procedure, FU; follow-up, ISR; in-stent restenosis. *p-value; post-procedure vs follow-up, #p-value; de novo vs in-stent restenosis



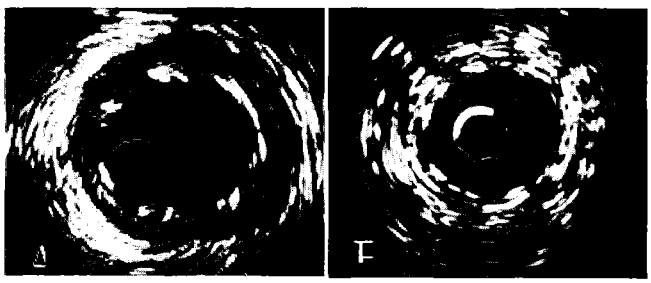
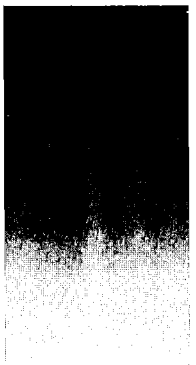


Figure 1 : Cumulative distribution curve of neointimal hyperplasia (NIH) area at follow-up for the patients with in-stent restenosis and de novo coronary lesions. Lower part shows inhibition of neointimal hyperplasia at follow-up IVUS cross section images of SES in de-novo lesion (A) and in –stent restenotic lesion with two layers of stent struts (B).



CHAPTER 10

EVALUATION OF CORONARY REMODELING AFTER SIROLIMUS ELUTING STENT IMPLANTATION: A SERIAL 3D-INTRAVASCULAR ULTRASOUND STUDY

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Am J Cardiol. 2003; 91: 1046-1050

Evaluation of Coronary Remodeling After Sirolimus-Eluting Stent Implantation by Serial Three-Dimensional Intravascular Ultrasound

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This study evaluates the response of the coronary vessel wall to implantation of the sirolimus-eluting stent (SES), Bx-VELOCITY, by using serial intravascular ultrasound. SESs have a major impact on the inhibition of in-stent neointimal hyperplasia. However, changes in the vessel wall and behind stent struts in animal models and humans have not been evaluated after SES implantation. Thirty-four patients who received a SES (n = 24) or a Bx-VELOCITY bare stent (BS) (n = 10) for single de novo coronary lesions and had serial motorized pullback 3-dimensional intravascular ultrasound were included. Stent, lumen, and vessel volumes were similar in the 2 groups at baseline. At follow-up, significantly larger lumen and lower neointimal hyperplasia volumes (0.7 vs 33 mm^3, p = 0.001) were seen in the SES group compared with the BS group. There was no significant difference between SES and BS in either the vessel volume (+2.4% vs +0.7%, p = NS) or the plaque behind stent volume change (+3.4% vs +2.5%, p = NS) from after the procedure to late follow-up. The stent edges also showed no significant difference between postprocedural and follow-up measurements, either in patients receiving SESs or BSs. No stented or edge segment required redilatation in the SES group, whereas 2 patients underwent repeat percutaneous coronary angioplasty in the BS group. In the SES group, 1 patient (4%) showed late acquired incomplete stent apposition. Thus, the SES is effective in inhibiting neointimal hyperplasia without affecting vessel volume and plaque behind the stent. ©2003 by Excerpta Medica, Inc.

(Am J Cardiol 2003;91:1046–1050)

The effects of sirolimus-eluting stents (SESs) on the vessel wall have not been fully investigated in humans using serial volumetric intravascular ultrasound (IVUS) follow-up. A subanalysis of the RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions (RAVEL) trial that included all patients with IVUS investigation during 6-month follow-up revealed a 21% incidence of incomplete stent apposition in the SES group compared with 4% in the bare stent (BS) group (p <0.001).[1] Although the interpretation of these data are limited by the lack of a baseline IVUS immediately after stent implantation, these findings raised the question whether, and to what extent, the SES affects the plaque burden behind the stent struts as well as vascular remodeling. This study evaluates the effect of SESs on the coronary vessel wall and remodeling by serial 3-dimensional IVUS investigation.

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METHODS

Patient population: We included all patients who underwent implantation for a native coronary lesion using the Bx-VELOCITY SES (Cordis Corp., Johnson & Johnson, Warren, New Jersey) or BS. Patients were eligible if they had a diagnosis of stable or unstable angina pectoris or documented silent ischemia and if they had a single target lesion of a native coronary artery in a vessel between 2.5 and 3.5 mm in diameter that could be covered by an 18-mm stent. Total occlusion, ostial or thrombus-containing lesions, unprotected left main coronary artery disease with >50% stenosis, and myocardial infarction within the preceding 72 hours were major exclusion criteria. Stents that could not be completely analyzed for vessel, stent, and lumen volumes were excluded. The study protocol was approved by the Medical Ethics Committee and all patients gave written informed consent.

Stent and implantation technique: The Bx VELOCITY stent is a laser-cut, 316-L stainless steel, balloon-expandable stent. The sirolimus-eluting Bx VELOCITY stents were coated with a polymer containing 140 μg of sirolimus per squared centimeters of stent surface area, of which approximately 80% is delivered within 30 days. All stents were 18-mm long and 2.5 to 3.5 mm in diameter. All target lesions were predilated before stent implantation. Postdilatation was performed as needed to achieve <10% residual diameter

TABLE 1 Patient Characteristics

Variable	SES Group (n = 24)	BS Group (n = 10)	p Value
Age (yrs)	61.2 ± 10.8	61.3 ± 11.7	0.99
Men	15 (62%)	9 (90%)	0.21
Previous myocardial infarction	4 (17%)	2 (20%)	1.0
Unstable angina pectoris	5 (21%)	2 (20%)	1.0
Diabetes mellitus	2 (8%)	0 (0%)	0.34
Systemic hypertension	9 (37%)	4 (40%)	0.64
Hypercholesterolemia	15 (62%)	5 (50%)	0.3
Smoker	9 (37%)	2 (20%)	0.32
Family history of coronary artery disease	4 (17%)	2 (20%)	0.38
Treated coronary artery			
Left anterior descending	12 (50%)	5 (50%)	1.0
Circumflex	5 (21%)	4 (40%)	0.39
Right	7 (29%)	1 (10%)	0.38
Nominal stent size (mm)	3.2 ± 0.25	3.1 ± 0.21	0.14
Maximum inflation pressure (atm)	14.8 ± 2.5	14.4 ± 2.7	0.87

*Total cholesterol >200 mg/dl.
Values expressed as number of patients (%), mean, or mean ± SD.

stenosis as assessed by on-line quantitative coronary angiography. Heparin (10,000 U) was given at the start of the procedure and activated clotting time was maintained at >300 seconds. All patients received aspirin (325 mg/day, indefinitely) and clopidogrel (300-mg loading dose immediately and 75 mg/day for 8 weeks).

IVUS analysis and quantitative measurements: At baseline and follow-up, IVUS was performed with motorized catheter pullback at a speed of 0.5 mm/s and recorded on s-VHS tape for off-line 3-dimensional reconstruction. A computer-based contour detection program was used for automated 3-dimensional reconstruction of the stented segment from ≤200 cross-sectional images. Quantitative IVUS analysis included the stent segment and the coronary segment beginning 5 mm proximal to and extending 5 mm distal to the stented segment. Lumen, stent boundaries, and external elastic membrane were detected using a minimum cost algorithm.[2] Total vessel, stent, and lumen volumes were calculated as: $V = \Sigma_{i=1}^{n} A_i \cdot H$, where V = volume, A = total vessel, stent, or lumen area in a given cross-sectional image, H = thickness of the coronary artery slice, and n = number of slices. Total plaque volume, plaque volume behind the stent volume, and neointimal hyperplasia volume were calculated as "total vessel volume minus lumen volume," "total vessel volume minus stent volume," and "stent volume minus lumen volume," respectively. Percentage obstruction volume of the stent was calculated as neointimal volume/stent volume × 100 at follow-up. For the segments proximal and distal to the stent, the vessel volume was measured at each cross section as the area lying within the external elastic lamina. To assess the volumetric changes in the vessel structure over time, the Δ value (follow-up, postprocedure) for each measurement was calculated. To eliminate the influence of the vessel size and the length of the analyzed segment, which affects volume calculations, percent Δ change (Δ volume/postprocedural volume) was also calculated.

Incomplete stent apposition: Incomplete stent apposition was defined as ≥1 stent struts clearly separated from the vessel wall with evidence of blood speckles behind the strut.[1,3] Qualitative analysis was performed by reviewing all postprocedural and follow-up IVUS videotapes to identify the incomplete stent apposition.

Statistical analysis: Quantitative data are presented as mean ± 1 SD. Comparisons between postprocedural and follow-up measurements were performed with a 2-tailed, paired *t* test. Comparisons between groups were performed using the unpaired Student's *t* test. A value of p <0.05 was considered statistically significant.

RESULTS

Patients: Thirty-four patients who received a SES (n = 24) or BS (n = 10) for single de novo coronary lesions were enrolled. Baseline demographics were similar between the 2 groups (Table 1). Two patients in the BS group underwent target lesion revascularization due to restenosis. No patient died or experienced myocardial infarction during the follow-up period (5.5 ± 0.9 months).

Stent segment analysis and vessel remodeling: Volumetric IVUS data are listed in Table 2. At follow-up, a significantly larger lumen (135 vs 99 mm^3, p = 0.02) and lower neointimal hyperplasia volume (0.7 vs 33 mm^3, p = 0.001) was seen in the SES group compared with the BS group. The stent and vessel volume remained basically unchanged over time in both groups. The volumetric changes in the 2 groups for lumen, stent, vessel, and plaque behind the stent are demonstrated in Figure 1. There were no significant changes between SES and BS in either the vessel volumes (+2.4% vs +0.7%, p = NS) or the plaque behind stent volume change (+3.7% vs +2.5%, p = NS).

Incomplete stent apposition: At baseline, all stents showed complete apposition of the stent struts against the vessel wall over the entire length of the stent in both groups. At follow-up, 1 patient (4%) in the SES group showed late acquired incomplete stent apposition with a change in vessel volume (324 mm^3 at baseline, 438 mm^3 at follow-up) and in plaque behind stent volume (from 146 to 250 mm^3), indicative of positive vessel remodeling. IVUS of the patient with incomplete stent apposition revealed blood speckling behind 4 struts. The maximum depth between stent struts and the vessel wall measured 0.75 mm. No patient in the BS group revealed incomplete stent apposition.

Stent edges: Edge segment analysis was not possible at 3 edges (2 distal, 1 proximal) in the BS group

TABLE 2 Three-dimensional Intravascular Ultrasound (IVUS) Measurements of the Stents

	Vessel Volume (mm^3)		Plaque Behind Stent Volume (mm^3)		Stent Volume (mm^3)		Lumen Volume (mm^3)		Neointimal Hyperplasia Volume (mm^3)
	Post/Follow-up		Post/Follow-up		Post/Follow-up		Post/Follow-up		Follow-up
SES	289 ± 76/296 ± 77*		156 ± 57/161 ± 59*		132 ± 28/135 ± 27*		132 ± 28/135 ± 27*		0.7
BS	255 ± 62/257 ± 65*		123 ± 35/124 ± 32*		132 ± 34/132 ± 38*		132 ± 34/99 ± 40†		33
p Value	NS	NS	0.048	0.029	NS	NS	NS	0.025	0.001

*p = NS for values after procedure versus follow-up
†p = 0.001 for after procedure versus follow-up.
Values expressed as mean or mean ± SD.
Post = after procedure.

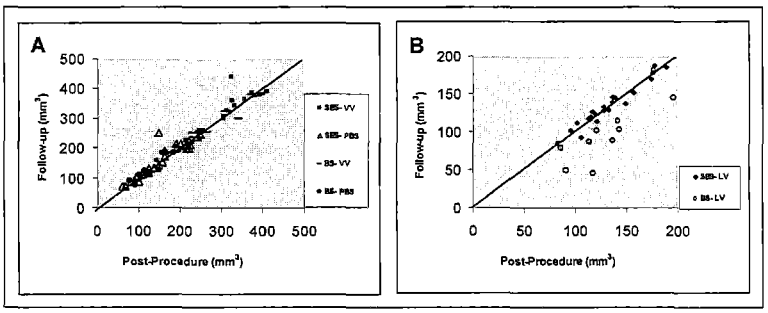

FIGURE 1. Volumetric IVUS follow-up of sirolimus eluting (SES) and bare (BS) stents. Changes in vessel volume (VV), plaque behind stent volume (PBS) *(A)*, and lumen volume (LV) *(B)* are presented in relation to line of identity. p = NS for VV and PBS volume change; p = 0.025 for LV change.

TABLE 3 Three-dimensional Intravascular Ultrasound (IVUS) Measurement of Edges Proximal and Distal to the Stent

	Vessel Volume (mm^3)	Plaque Volume (mm^3)	Lumen Volume (mm^3)
	Post/Follow-up	Post/Follow-up	Post/Follow-up
Proximal edge			
SES	77 ± 28/78 ± 26	34 ± 17/38 ± 17	42 ± 19/41 ± 15
BS	80 ± 18/74 ± 16	35 ± 14/33 ± 10	44 ± 14/41 ± 13
Distal edge			
SES	67 ± 23/68 ± 23	31 ± 17/31 ± 16*	37 ± 10/37 ± 10
BS	57 ± 15/57 ± 13	25 ± 9/28 ± 12	33 ± 11/29 ± 11

p = NS
Values pressed as mean ± SD.
Abbreviation as in Table 2.

and at 9 edges (5 distal, 4 proximal) in the SES group. Edges were excluded from analysis due to side branch take off, inadequate image quality, and incomplete image acquisition. At baseline IVUS, lumen, plaque, and vessel volume at both edges were similar in the 2 groups. There was no significant difference between proximal and distal edges in either the SESs or BSs (Table 3).

SESs and BSs showed similar volumetric IVUS changes at follow-up with respect to lumen volume loss (−3.6% vs −2.8%, p = NS) at the proximal edge. Plaque and vessel volume changes in the SES and BS groups were +11.8% versus −4.5% (p = 0.054) and +1.7% versus −6.4% (p = 0.057), respectively. A trend toward a negative vascular remodeling pattern was observed in the BS group (Figure 2).

In the distal edges, the SES showed almost no luminal loss (tendency toward enlargement) compared with the BS (+1.5% vs −8.0%, p = NS). Vessel (+1.6% vs +1.6%, p = NS) and plaque volumes (+6.5% vs +13.9%, p = NS) showed similar patterns with slight increases in volumetric measurements (Figure 2).

DISCUSSION

This is the first study focusing on vascular remodeling by using serial 3-dimensional IVUS analysis after SES implantation. The main findings of our study are: (1) lumen, plaque, and vessel volume remain stable over 6-month follow-up after SES implantation; (2) the SES does not induce a significant vessel response at the edge of the segment; and (3) clinically silent late acquired incomplete apposition was detected in only 1 patient who received a SES.

Sirolimus has potent anti-inflammatory, immunosuppressive, and antiproliferative effects.[4,5] These potent biologic effects raise theoretic concerns about potential side effects, such as incomplete healing, increased thrombogenicity, necrosis, apoptosis, and positive remodeling. The recent experience with intracoronary radiation therapy, where such phenomena became clinically relevant in individual patients, justify a meticulous search

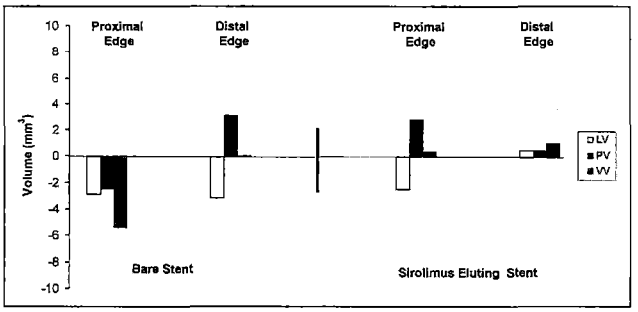

FIGURE 2. Volume changes at the proximal and distal edge of the SES and BS at follow-up. There were no significant differences between the SES and BS. The SES revealed minimal lumen enlargement at the distal edges (p = NS). PV = plaque volume; other abbreviations as in Figure 1.

for these phenomena after the implantation of all new drug-eluting stents.[6-8]

Vascular response to stenting: No significant change in stent, plaque behind stent, and vessel volume were described after conventional balloon-expandable stent implantation by Mudra et al.[9] The findings in that study, which showed no changes in vessel dimensions behind the stent in the BS group, are in agreement with the present report.

Our study demonstrates that the vessel dimensions remained stable after SES implantation. Plaque behind stent and vessel volumes (+3.7% and +2.4%, respectively) remained largely unchanged when comparing postprocedural and follow-up IVUS findings. Furthermore, no difference was found between the BS and SES groups. Our findings derived from serial IVUS analysis are in agreement with the IVUS substudy of the RAVEL trial at follow-up, which found no differences in plaque behind the stent and vessel volume in either the BS or the SES groups.

Edge remodeling: Conventional balloon-expandable stents do not show significant changes in lumen, plaque, or vessel volume adjacent to the stent.[9] However, edge effect accounts for treatment failures with radioactive stents and intravascular brachytherapy.[10,11] IVUS analysis of radioactive stents has demonstrated that this significant late loss at the stent margins was caused by both neointimal hyperplasia and vessel shrinkage.[12]

In our study, the SES showed no edge effect or significant lumen narrowing of the vessel segments adjacent to the stent. At the proximal edges only minimal changes over time were seen after SES and BS implantation. Although these changes failed to be statistically significant, the pattern of lumen loss at the proximal edge is potentially different. Increase in plaque volume (+11.8% vs −4.5%, p = 0.054) is the predominant mechanism for the lumen loss in the SES group, whereas a trend toward negative remodeling was observed within the BS group. The lumen loss change observed in the proximal stent edge may be due to injury from the stent deployment balloon in conjunction with the limited diffusion and absence of drug in the adjacent area. Ideal results "without any late loss" could potentially be achieved if the proximal edge injury could be minimized by avoiding damage to the vessel wall with postdilatation. In addition, a higher drug concentration at the proximal part of the stent may have some impact on lumen loss in the proximal edge.

At the distal edges, SESs showed almost no change (slight increase, +1.4%) in lumen volume. Although this effect did not reach a statistically significant level when compared with the BS, it is consistent with angiographic observations made in the RAVEL[13] and the US multicenter, Randomized Double Blind Study of the SIROLIMUS-eluting stent in de novo native coronary lesions (SIRIUS) trials. In contrast with the proximal edge, a trend toward positive remodeling was noted, possibly due to some wash-off of the sirolimus from the stent and a slightly higher downstream concentration of the drug.

Incomplete stent apposition: A subgroup analysis of the RAVEL trial has revealed a significantly higher incidence of late incomplete stent apposition in the SES than in the BS (21% vs 4%).[1] The mechanistic interpretation of these data were hampered by the fact that no IVUS analysis had been performed during the baseline procedure. Thus, it is not clear whether the stents were already incompletely apposed against the vessel wall during the index procedure or whether this was a late acquired effect. These findings prompted us to scrutinize stent expansion and stent wall contact at baseline and at follow-up in the present series of patients. There was evidence of late acquired incomplete stent apposition in only 1 patient (4%) in our study group.

Acknowledgment: We would like to thank Brian G. Firth, MD, for his critical review of this manuscript.

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CHAPTER 11

TRUE THREE-DIMENSIONAL RECONSTRUCTED IMAGES SHOWING LUMEN ENLARGEMENT AFTER SIROLIMUS-ELUTING STENT IMPLANTATION

Kengo Tanabe, Frank J.H. Gijsen, Muzaffer Degertekin, Jurgen M.R. Ligthart, Remko M. Oortman, Patrick W. Serruys, and Cornelis J. Slager

Circulation 2002 106: 179e-180e.

Images in Cardiovascular Medicine

True Three-Dimensional Reconstructed Images Showing Lumen Enlargement After Sirolimus-Eluting Stent Implantation

Kengo Tanabe, MD; Frank J.H. Gijsen, PhD; Muzaffer Degertekin, MD; Jurgen M.R. Ligthart, BSc; Remko M. Oortman, BSc; Patrick W. Serruys, MD, PhD; Cornelis J. Slager, PhD

A 69-year-old woman with stable angina pectoris was enrolled in the randomized, double-blind RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions (RAVEL) trial. Coronary angiography revealed a proximal stenosis in the left circumflex coronary artery (Figure 1A). A 3.0×18 mm sirolimus-eluting Bx VELOCITY stent (Cordis Corp, Johnson & Johnson) was implanted with a satisfactory result (Figure 1B). Intravascular ultrasound (IVUS) images were then obtained with ECG-gated pullback, showing stent struts well apposed to the vessel wall (Figure 1D). At 6-month follow-up, angiography showed no restenosis (Figure 1C), whereas IVUS images revealed good stent apposition with minimal neointimal hyperplasia and some tissue disappearance between stent struts (Figure 1E and 1F). To further evaluate these observations, we combined biplane angiography and IVUS (ANGUS) for a true 3-dimensional reconstruction of the stented region. Figure 2 shows the intimal thickness color-coded on the stent surface. The blue area seen on the proximal stent surface after the procedure (Figure 2A and 2B) relates to a side branch. The images at follow-up (Figure 2C and 2D) identify additional blue areas, indicating disappearance of tissue between stent struts and lumen enlargement. Localized neointimal hyperplasia (red area) was also observed. In addition, there are small changes in 3D stent shape. In the RAVEL trial, the late loss averaged −0.01±0.33 mm, consistent with the presence of lumen enlargement in some patients.

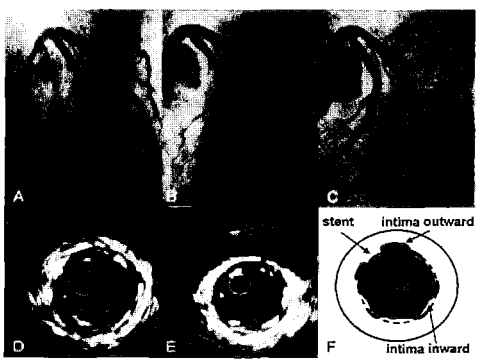

Figure 1. Coronary angiograms in left anterior oblique projection showing stenosis in the proximal segment of the left circumflex coronary artery (A), a good final result of angioplasty (B), and no restenosis at 6-month follow-up (C). The IVUS images show the stent well apposed to the vessel wall both after the procedure (D) and at follow-up (E). The schema of the IVUS image at follow-up (F) depicts minimal neointimal hyperplasia and the disappearance of tissue between stent struts.

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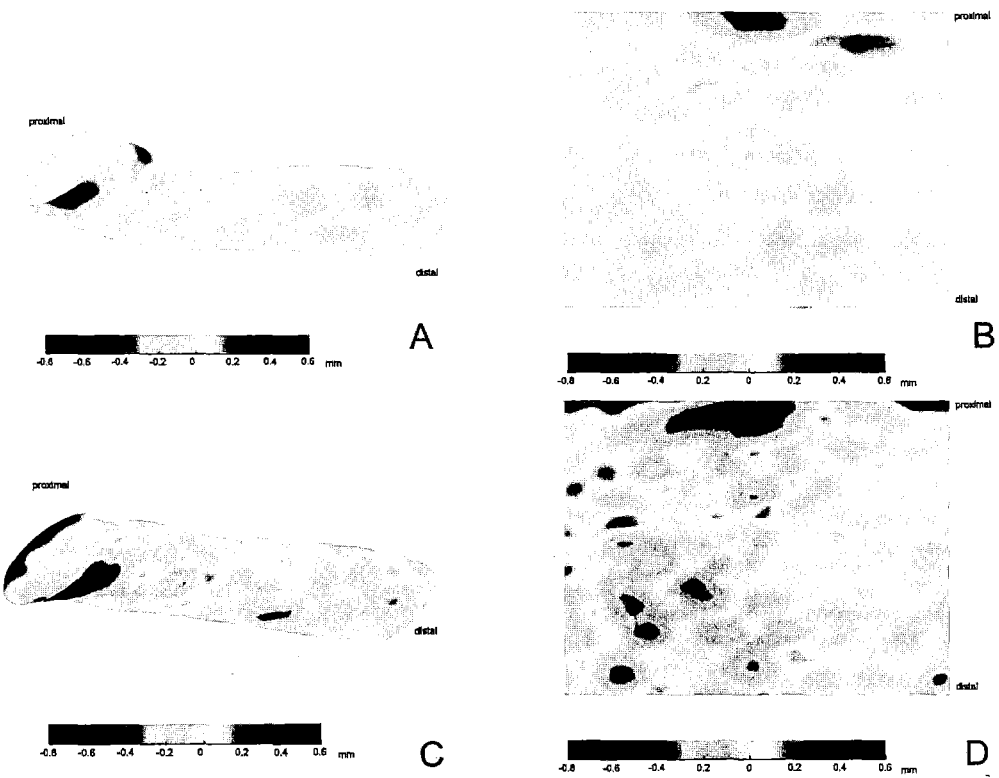

Figure 2. Local intimal thickness color-coded and projected on the stent surface. The color code indicates the relative position of lumen surface to the stent surface as defined in Figure 1F and ranges from −0.8 mm (blue) to 0.6 mm (red). A and C are the 3D-reconstructed images after the procedure and at follow-up, respectively. B and D are the unfolded images of A and C, respectively. The post-procedure image (A) shows a small thrombus (orange) opposite the side branch. At follow-up, the yellowish to orange areas demarcate the individual stent struts covered by some intimal hyperplasia.

CHAPTER 12

INCIDENCE AND CLINICAL OUTCOME OF INCOMPLETE STENT APPOSITION AND CORONARY ANEURYSM FORMATION AFTER DRUG ELUTING STENT IMPLANTATION

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Submitted for publication

Incidence And Clinical Outcome Of Incomplete Stent Apposition And Aneurysm Formation After Drug Eluting Stent Implantation In De Novo Coronary Artery Lesions

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Objectives: The aim of this study was to evaluate the incidence of incomplete stent apposition (ISA) and coronary artery aneurysm (CAA) formation as well as their clinical impact after DES implantation.

Background: Drug eluting stents (DES) significantly reduce the rate of in-stent restenosis. However, there are concerns that the drugs used for elution may induce ISA and CAA.

Methods: Patients from 3 DES trials (ACTION –Actinomycin-D eluting stent, RAVEL-sirolimus eluting stent, TAXUS-II-Paclitaxel eluting stent) with de novo coronary artery lesions, randomly assigned to receive DES or bare stents (BS), were included. ISAs were detected by intravascular ultrasound (IVUS) and coronary aneurysms were documented by angiography. IVUS videotapes and angiograms were analyzed by a blinded core lab.

Results: The overall incidence of post-procedure ISA in ACTION and TAXUS-II trials was not significantly different between the DES group (8.5%) and the BS group (10.7%). The combined rate of ISA in DES group at 6-month follow-up in all 3 trials, revealed slightly higher rates than BS (11.4%vs 7.7% p=0.07), late acquired ISA fol-

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lowing Actinomycin-D and Paclitaxel eluting stents (6.9% vs 4.8% p=NS) was comparable to BSs (8.9% vs 5.4% p=NS). For the entire study population CAA was observed in 1.3% of the DES group, and in 1.3% of the BS group.

Conclusions: DES trials did not reveal increased incidence of ISA when compared to BS. DESs do not increase the risk of CAA formation in native de novo coronary lesions. Clinical outcome is not affected by the development of ISA and CAA.

Introduction

Although some studies such as SCORE (Taxane QP2 coated quanam stent) and ACTION (Actinomycin-D Eluting Stent Improves Outcomes By Reducing Neointimal Hyperplasia) have been prematurely terminated or unblinded, due to poor outcome and lack of efficacy respectively, Sirolimus and Paclitaxel eluting stents have shown promising results with dramatic reduction of in-stent restenosis. However, there are concerns that the drugs used for elution may have detrimental effects on the vessel wall and induce incomplete stent apposition (ISA) or coronary artery aneurysm (CAA) formation. Coronary aneurysm and late acquired ISA (LAISA) may occur not only after brachytherapy but also after bare metal stent (BS) implantation [1-4]and there was concern that ISA may contribute to late stent thrombosis[5]. Accordingly the incidence and clinical significance of ISA and CAA developing after DES implantation deserves special attention. The aim of this study is (1) to evaluate the incidence of ISA and CAA formation after DES implantation, (2) compare the incidence of ISA in DESs and BSs and (3) determine the clinical significance of ISA and aneurysm formation.

METHODS

Patient Population and Inclusion Criteria

IVUS videotapes and coronary angiograms acquired from 3 multicenter randomized trials were analyzed by a blinded core lab (Cardialysis BV, Rotterdam, The Netherlands) in order to establish the incidence of ISA and CAA after DES or BS implantation.

1) ***RAVEL***[6](RAndomized study with the sirolimus-eluting Bx-Velocity stent): 18mm Bx-Velocity stent coated by 140μg sirolimus/cm^2 per unit of meatl area, 2) ***ACTION:*** 18mm Multilink-Tetra^{TM} stent coated by either 2.5 or 10μg mm^2 Actinomycin-D, 3) ***TAXUS-II***[7] (A Randomized, Double-Blind, Controlled, Study of the TAXUS' NIRx Paclitaxel-eluting Stent) 15mm TAXUS' NIRx stent coated by 1μg Paclitaxel.

Eligible patients had stable or unstable angina or documented silent ischemia, with a single de novo lesion of a native coronary artery in a vessel between 2.5 and 3.5 mm

in diameter that could be covered by 15mm or 18mm stent. All lesions were predilatated before stent implantation. Patients received Aspirin >75 mg/day indefinitely and Clopidogrel 75mg/day for 2 months in RAVEL, 6 months in ACTION and TAXUS-II.

IVUS imaging and evaluation of ISA and coronary aneurysm

At baseline and follow-up, IVUS was performed with motorized catheter pullback at 0.5 mm/sec. ISA was analyzed from IVUS videotapes and defined as one or more struts clearly separated from the vessel wall with evidence of blood speckling behind the stent struts without overlapping side branches[8] (Figure-1). ISA was evaluated post-procedure (except in the RAVEL) and at 6 month follow-up. Follow-up ISA was divided into 3 subgroups on the basis of serial IVUS 1) Resolved: ISA present at post-procedure but no longer present at follow-up. 2) Persisting: ISA present both at post-procedure and follow-up. 3) Late Acquired: ISA not present at baseline but is present at follow-up.

Coronary aneurysm was analyzed from coronary angiograms and defined as areas of localized coronary artery dilatation $\geq$ 1.5 times the diameter of the normal reference segment[2,9].

Statistical Analysis

Comparable qualitative data for ultrasound and angiography was analyzed using chi-square test. A value of $p<0.05$ was considered statistically significant.

RESULTS

Serial IVUS was available in 425 DES patients and in 282 BS patients respectively. The type and incidence of ISA in the 3 randomized trials is summarized in Table 1. At post-procedure, the combined incidence of ISA in ACTION and TAXUS-II trials was 8.5% (44/515) in DES group and 10.7% (39/365) in BS group (p=ns). At follow-up, the overall incidence of ISA in the 3 trials was slightly higher in the DES group than in BS group (11.4% [55 /482] versus 7.7% [26 / 339] p=0.07). Paclitaxel and Actinomycin –D eluting stents showed no difference in terms of follow-up ISA compared to each other and to BSs. However, in RAVEL, a higher incidence of follow-up ISA was observed. The follow-up ISA findings of RAVEL trial could not be further sub-categorized as no post-procedure IVUS was done.

Serial IVUS of the Paclitaxel and Actinomycin-D-eluting stents revealed that more than 50% of post-procedure ISA had been resolved. There was no significant difference in persistent and late acquired ISA compared to BS (Table-1).

For the entire study population CAA was observed in 1.3% (8 /615) of the DES group, and in 1.3% (6/ 453) of the BS group (Table-2). No significant difference

between the 3 trials in incidence of CAA was observed. An example is shown in Figure 2.

Death, myocardial infarction and stent thrombosis

Clinical events are presented in Table-3. In RAVEL, 1 patient presented with CAA at 18 months follow-up angiography and was successfully treated with a covered stent. In DES group of ACTION, 11of 13 target lesion revascularization (TLR) were performed due to either in-stent or edge stenosis during 6 month follow-up. In TAXUS-II, no patient developed clinical events between 6-months and 12 months follow-up. There was no difference in clinical events between patients with and without ISA in both DES and BS groups. Patients with CAA did not experience any thrombotic events. However, 4 of 5 patients with CAA from DES arm of ACTION and 1 of 4 patient from BS arm of TAXUS-II underwent TLR at 6-month due to severe in-stent restenosis.

DISCUSSION

This comparative analysis evaluates the incidence of ISA and CAA after implantation of different DES in 3 randomized trials. The main findings are 1) ISA occurs both after BS and DES implantation irrespective of drug elution 2) DESs do not induce excessive coronary aneurysm formation when compared to BSs 3) ISA seen immediately post stent implantation may resolve during follow-up 4) ISA and aneurysm formation are not associated with late stent thrombosis, myocardial infarction and death.

Recently, the POST registry suggested that acute and sub-acute thrombotic events after BS implantation were particularly associated with ISA, as well as stent under expansion, inflow/outflow disease, dissection or thrombus. As expected, we observed comparable rates of ISA at the time of the index procedure in both DESs (10.7%) and BSs (8.5%). However, in contrast to the POST registry, we did not see an increase in thrombotic events related to post-procedure ISA in BSs, nor in DESs. Furthermore, more than 50% of post-procedure ISA has been found to resolve at follow-up in both DES and BS. The occurrence of ISA, even those in whom it was persistent or late acquired were not associated with an increased rate of adverse clinical events at 1 year follow-up.

The pathogenesis of LAISA is not fully understood. Theoretically, some possible explanations are dissolution of thrombotic material behind the stent struts, apoptosis, necrosis, and regional vascular remodeling. However, further assessment of this phenomenon is beyond the scope of our study. The rate of LAISA in the BS groups (4.8%-5.4%) correlates well with that recently reported by Shah et al.[1]The rate of LAISA of Actinomycin-D and Paclitaxcel-eluting stents was 6.9% and 8.9% respectively, com-

parable to the sirolimus group (10%) in SIRIUS (Multicenter, randomized, study of the SIRolImUS –eluting Bx-Velocity^{TM} stent) trial. Without serial IVUS analysis in RAVEL, it is impossible to categorize the different types of ISA in this study. However, the rate of 21% ISA at follow-up in sirolimus-eluting stents is highly comparable to that seen in SIRIUS (19%) suggesting that a similar rate of LAISA may have occurred in RAVEL[8].

Coronary artery aneurysms have been reported to occur after BS implantation, balloon angioplasty and directional coronary atherectomy with a frequency of 3.9% to 10%. [2,9] Additionally, gamma radiation in de novo lesions has resulted in CAA in 20%[4], and in one study, the use of adjuvant anti-inflammatory drugs such as steroids and colchicines resulted with CAA in 32% of patients receiving stent implantation[10]. Possible mechanisms of CAA formation are intramural hemorrhage, inflammatory reactions, polymorphism in matrix metalloproteinase genes associated with increased proteolysis in the vessel wall and weakening of the media.[11-13]. Thus, the use DES with potential antiproliferative and immunosuppressive effects raises concerns that CAA might be induced. However, our study demonstrated no difference in incidence of CAA for DESs compared to BS (1.5% versus 1.3%) which is less than the rate of previous studies that evaluated BSs and other treatment modalities such as balloon angioplasty and directional coronary atherectomy. Furthermore, the clinical outcome of these patients has been so far benign as previously reported in the literature [2,13].

Finally, it should be emphasized that ISA and CAA may also be documented even when the drug delivery system failed to be efficacious: patients from DES arm in ACTION developed in-stent and edge stenosis concomitantly with ISA and CAA.

Limitations

In ACTION trial, the relatively small number of patients with BS at follow-up may have biased the results. Lack of serial IVUS in the RAVEL study precludes any accurate assessment of LAISA. In absence of equivalency trials, we restrained ourselves from comparing the statistical incidences of ISA and CAA between the 3 different DES.

Conclusion: DESs did not reveal significant increased incidence of ISA when compared to BS. DESs do not increase the risk of CAA formation in native de novo coronary lesions. In addition, clinical outcome is not affected by the development of ISA and CAA.

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TABLE 1:
Incidence of incomplete stent apposition after drug eluting stent implantation

	RAVEL trial			ACTION trial			TAXUS-II trial		
ISA	**DES**	**BS**	**p**	**DES**	**BS**	**p**	**DES**	**BS**	**p**
Post-procedure	N/A	N/A	—	27/229 (11.8%)	17/109 (15.6%)	0.3	17/256 (6.6%)	22/256 (8.6%)	0.5
Follow-up	10/48 (21%)	2/47 (4%)	0.02	19/194 (9.8%)	3/45 (6.6%)	0.7	26/240 (10.8%)	21/247 (8.5%)	0.44
Resolved	N/A	N/A	—	16/188 (8.5%)	8/34 (19.0%)	0.05	11/237 (4.6%)	11/240 (4.6%)	1.0
Persistent	N/A	N/A	—	6/ 188 (3.2%)	1/34 (2.4%)	1.0	5/237 (2.1%)	8/240 (3.3%)	0.57
Late Acquired	N/A	N/A	—	13/188 (6.9%)	2/42 (4.8%)	1.0	21/237 (8.9%)	13/ 240 (5.4%)	0.15

ISA: incomplete stent apposition, DES: drug eluting stent, BS: Bare metal stent.

TABLE 2
Incidence of coronary artery aneurysm in three randomized trials

RAVEL		ACTION		TAXUS-II	
Drug Eluting Stent	**Bare Stent**	**Drug Eluting Stent**	**Bare Stent**	**Drug Eluting Stent**	**Bare Stent**
0 / 120	0 / 118	5 / 230	2 / 65	3/ 265	4 / 270
(0 %)	(0%)	(2.2%)	(3.1 %)	(1.1%)	(1.5%)

TABLO 3:
Clinical outcome in patients with incomplete stent apposition

	RAVEL		ACTION		TAXUS-II	
	Bare (n=2)	DES (n=10)	Bare (n=19)	DES (n=40)	Bare (n=45)	DES (n=48)
Death	0% (0/2)	0% (0/10)	0% (0/19)	0% (0/40)	2.2% (1/45)	0 % (0/48)
Q-Myocardial Infarction	0% (0/2)	0% (0/10)	0% (0/19)	0% (0/40)	0% (0/45)	0% (0/48)
Non-Q Myocardial Infarction	0% (0/2)	0% (0/10)	0% (0/19)	2.5% (1/40)	0% (0/45)	4.8% (2/48)
Target lesion revascularization	0% (0/2)	10% (1/10)	9.5 % (2/19)	32.5% (13/40)	4.4 %(2/45)	2.1% (1/48)
Target vessel revascularization	0% (0/2)	0% (0/10)	0% (0/19)	0% (0/40)	8.9% (4/45)	2.1% (1/48)
Stent Thrombosis	0% (0/2)	0% (0/10)	0% (0/19)	0% (0/40)	0% (0/45)	0% (0/48)
Any Events	0% (0/2)	10% (1/10)	9.5 % (2/19)	35% (14/40)	11.1% (5/45)	6.2 %(3/48)

In RAVEL 2 years follow-up, in ACTION and TAXUS-II 1 year follow-up was given.

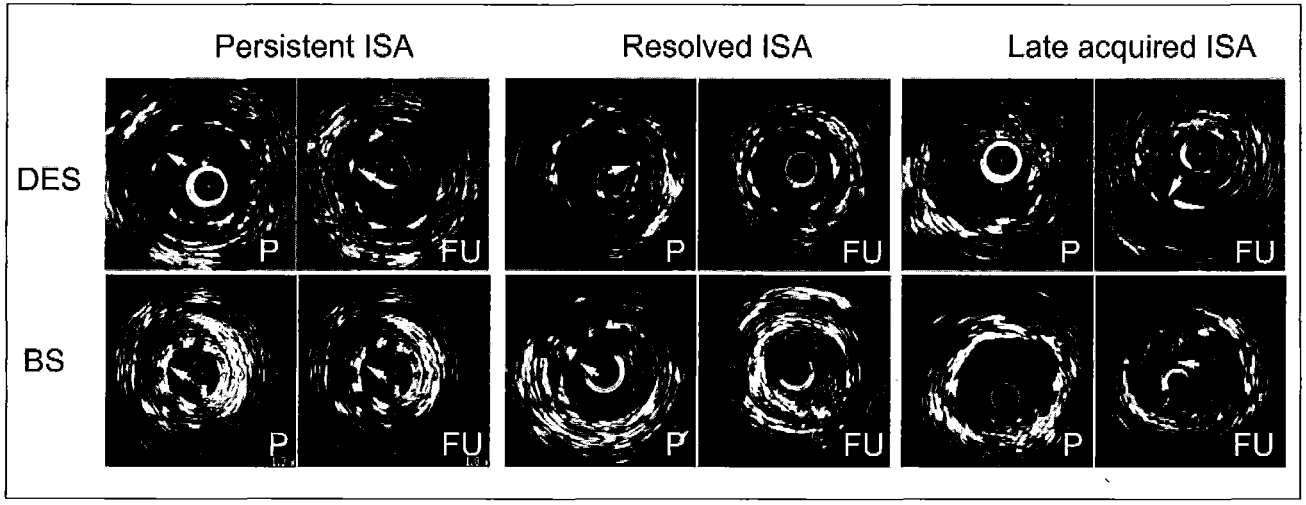

Figure 1 : Paired Post-procedure (P) and follow-up (FU) IVUS images demonstrate different types of incomplete stent apposition (ISA) in both bare (BS) and drug eluting stents (DES).

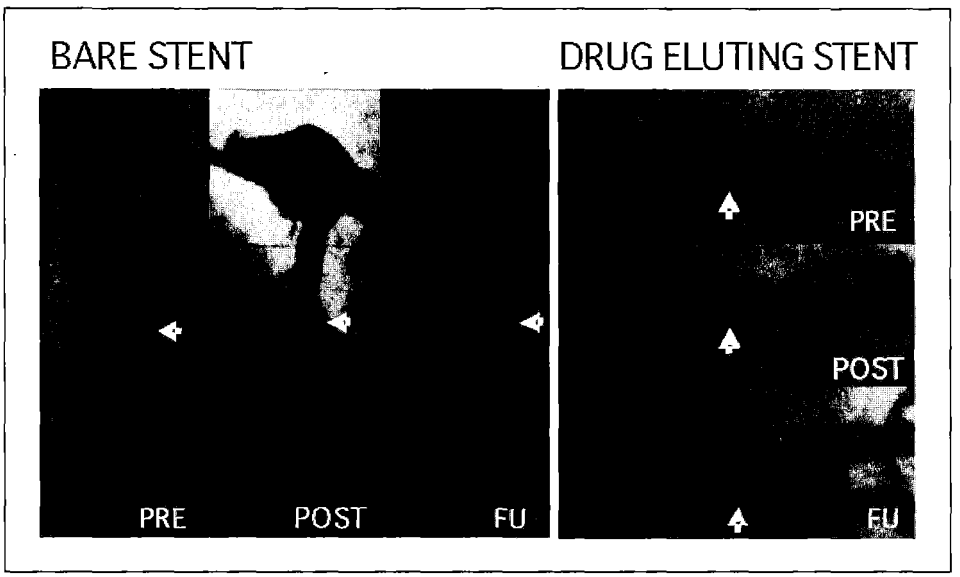

Figure 2 : Angiography shows lesions in the left anterior coronary artery which were treated with either bare (left) or drug eluting stents (DES) (right) and coronary aneurysms at 6-month follow-up (6M FU).

CHAPTER 13

LONG-TERM FOLLOW-UP OF INCOMPLETE STENT APPOSITION IN PATIENTS WHO RECEIVED SIROLIMUS ELUTING STENT FOR DE NOVO CORONARY LESIONS

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Circulation in press

Long-Term Follow-Up Of Incomplete Stent Apposition In Patients Who Received Sirolimus Eluting Stent For De Novo Coronary Lesions

An Intravascular Ultrasound Analysis

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Background: Incomplete stent apposition (ISA) has been previously documented after sirolimus-eluting stent (SES) implantation. The aim of this study was to investigate the long-term intravascular ultrasound (IVUS) findings of ISA in patients who received SES.

Methods and Results: A total of 13 patients who received SES and showed ISA at follow-up IVUS (Follow-up-I) were investigated. IVUS were performed on all of these patients 12 months later (Follow-up-II). Quantitative ISA area measurement was also performed at follow-up-I and II. No vascular remodeling was observed in the vessel segment with ISA; external elastic membrane area (EEMA) was 19.4±6.6 mm^2 vs 19.5±6.4 mm^2, at follow-up-I and II, respectively. There was also no significant change in EEMA between vessel segment with ISA and without ISA (+1.5% vs -3.0%, respectively, p=0.27) at late follow-up. The ISA area, either including (2.5±1.7mm^2 vs 3.8±6.3 mm^2; p=NS) or excluding (2.5±1.8mm^2 vs 2.4±1.7 mm^2; p=NS) a single patient with aneurysm formation was not significantly different between follow-up-I and II. One patient manifested a coronary aneurysm in the stented segment at late follow-up, that was probably present at the initial follow-up but masked by thrombus. It was successfully treated with a covered stent. All patients were asymptomatic, and no patient experienced late thrombotic occlusion.

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Conclusions: Vessel dimensions and area of ISA did not change over time, except for one coronary aneurysm which became apparent. ISA after implantation of a SES was not associated with adverse events at late follow-up.

INTRODUCTION

The RAVEL (***RA***ndomized study with the sirolimus-eluting Bx-***VEL***OCITY ™ stent) trial recentlty demonstrated that sirolimus-eluting stent (SES) effectively inhibits neointimal hyperplasia (NIH) without showing edge narrowing, thrombotic occlusion or persistence of dissection[1,2]. However, incomplete stent apposition (ISA) was observed during follow-up intravascular ultrasound (IVUS) in patients who received SES[2].

ISA has been shown to occur after brachytherapy, as well as in patients who receive bare metal stents (BS)[3,4]. Clinical outcomes of patients who developed ISA remains controversial. Furthermore, there is no data on serial IVUS evaluation of ISA in the long-term follow-up. As drug-eluting stents (DES) may potentially become a routine therapy in interventional cardiology, information on the long-term effects of ISA with DES are eagerly awaited. The aim of our study was to investigate the long-term quantitative IVUS findings of ISA in patients who received SES.

METHODS

Patient Population

In the RAVEL[1] and FIM[5] trials, 168 patients received SES for single de novo coronary lesions and a subset of 91 patients underwent IVUS investigation at follow-up. In this report, a total of 13 patients who showed ISA at 6 or12 months follow-up (Follow-up-I) were included and quantitative IVUS were performed on all of these patients 12 months later (Follow-up-II).

Evaluation of ISA, Quantitative IVUS and Coronary Angiography Analysis

IVUS was performed with automated pullback at 0.5mm/s. All IVUS procedures were recorded on VHS videotapes. ISA was defined as one or more than one stent struts clearly separated from the vessel wall with evidence of blood speckles behind the strut without overlapping side branches[2]. As previously reported, the maximum number of struts separated from the vessel wall, maximal depth and angle of the ISA were documented[2]. The length of ISA site was measured from single or multiple longitudinal views. When the patient had >1 ISA sites separated from each other by completely well apposed stented segment, the total length of ISA was defined as the sum of the lengths of each ISA segment.

In the segment with ISA, the "lumen contours" were delineated within and outside the stent strut boundaries (stent area: SA) (Figure 1). The QCU (quantitative coronary

ultrasound) analysis software (Curad BV, Wijk Bij Duurstede, The Netherlands) was modified in order to calculate the fraction of the lumen area that lies outside of the stent, e.g. ISA area.[6] ISA is thus conceptually considered as a part of an "effective" lumen. Therefore, two types of lumen area are reported: the ***"intra-stent"*** lumen area (SA *minus* the intra-stent neointimal hyperplasia area) and the ***"effective"*** lumen area which is the sum of ISA area and intra-stent lumen area. In addition, in the segment with ISA, external elastic membrane area (EEMA), and plaque behind stent area (PBSA='EEMA-SA-ISA area), were measured (Figure 1).

Coronary artery aneurysm (CAA) was defined as a maximum lumen area >50% larger than the proximal reference lumen area, which is a cross section of normal appearance within 5mm proximal to the stent.[7] Quantitative coronary angiography (QCA) was performed by independent core lab, as previously described[1,5].

Statistical Analysis

Quantitative data are presented as mean ±1SD and compared using paired Student`s t-test. Treatment group differences were tested by analysis of variance of Wilcoxon Rank Sums Scores. Consecutive QCA measurements were analyzed by general linear modeling with repeated measures considering various times as factors. A value of $p<0.05$ was considered statistically significant.

RESULTS

Of 13 patients, 8 were male (age, 58.4±11.6years). Cardiac risk factor included hypercholesterolemia in 4, hypertension in 5. No patient had diabetes. All patients were asymptomatic and none of them experienced late thrombotic occlusion or in-stent restenosis one year after the diagnosis of ISA. Coronary angiography demonstrated persistent minimal late loss at late follow-up (Table-1).

Table 2 shows serial IVUS measurements of stented segments with ISA. There was no significant difference in either EEMA or PBSA between follow-up-I and II. NIH remained minimal at late follow-up. There was also no significant change in EEMA between vessel segment with ISA and without ISA (+1.5% vs -3.0%, respectively, p=0.27) at late follow-up.

Figure-2A illustrates individual data on ISA volume at the two time points. At follow-up-I, 22 ISA sites were found; 1/13 patient (4.5%) had 3, 7/13 patients (31.8%) had 2 separate ISA sites. At follow-up-II, the patient who had 3 ISA sites had developed an aneurysm covering the previous 2 ISA sites; apart from this patient, no new ISA sites were observed. Indeed, 4 ISA sites had resolved at follow-up-II.

The ISA area, either including ($2.5\pm1.7mm^2$ vs $3.8\pm6.3mm^2$; p=NS) or excluding ($2.5\pm1.8mm^2$ vs $2.4\pm1.7mm^2$; p=NS) a single patient with aneurysm formation was not significantly different between follow-up-I and II. In this patient with aneurysm the

border of external elastic membrane could not be delineated on 6-month IVUS. However, serial IVUS examinations suggesting dissolution of thrombotic material in a pre-existing aneurysm (Figure-2B). This aneurismal sac with a depth of 5.9mm was successfully treated by implanting a covered stent.

DISCUSSION

The main findings of our analysis are 1) ISA after implantation of a SES is not associated with adverse clinical events 1 year after the diagnosis; 2) The vessel segment surrounding the incompletely apposed stent does not show positive vascular remodeling over time 3) ISA area does not significantly change at late follow-up 4) inhibition of in-stent NIH persists during long-term follow-up.

ISA after implantation of SES has been a major concern since it was first described.[2] The present report demonstrated that clinical course of ISA observed after SES implantation was benign: none of the patients with ISA experienced stent thrombosis or myocardial infarction. The absence of events, even in the presence of ISA, is also consistent with the observation that endothelialization after implantation of SES and BS is similar, and that SESs are less thrombogenic than BSs[8].

The underlying mechanism for ISA remains largely unknown. Several hypotheses have been postulated: plaque regression, regional positive vascular remodeling, late dissolution of thrombotic material trapped behind the stent, cell necrosis, apoptosis, and allergic reaction to sirolimus[4,9-11].

Any dilatation of the vessel lumen raises concern about progressive dilatation over time, aneurysm formation, and ultimately the potential of rupture, as is seen with aortic aneurysms. We observed one case of CAA in the SES stented segment 1 year after the diagnosis of ISA. Although there was no IVUS image from the index procedure, the angiograms after the index procedure and at 6-month follow-up were similar (Figure-2). Therefore, we suspected that there was a pre-existing CAA filled with thrombus at the time of the index procedure and this thrombotic material had been resolved at 18 months. Based on the fact that elution of sirolimus from the stent struts continues for only 6 weeks with a half-life of sirolimus in the tissue of 60 hours (personal communication of R Falotico PhD,2002), sirolimus itself is unlikely to induce structural vessel wall changes in the longer-term. Nevertheless, it remains difficult to rule out formation of CAA after SES implantation. It is worth noting that, CAA is well known after BS implantation, balloon angioplasty and coronary atherectomy.[12,13]

Excluding the aneurysm case, the vessel segment related to the incompletely apposed stent did not significantly alter in size (+1.5% change in EEMA) at late follow-up and mean ISA area also did not significantly change. Moreover, negligible amount of NIH at late follow-up showed that the efficacy of SES in inhibiting neointimal tissue migration and proliferation was not affected by the presence of ISA.

Therefore, since ISA per se was not associated with any additional adverse events, we suggest that there is no need for late mechanical correction of these cases of ISA.

Conclusion

ISA after implantation of a SES was not associated with adverse events 1 year after the diagnosis. ISA area and vessel dimensions in the segments including ISA did not change over time.

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TABLE 1:
Serial Quantitative Coronary Angiography

Parameters (N=13)	**Post**	**Follow-up-I**	**Follow-up-II**
Reference Diameter, mm	2.98±0.48	3.00±0.46	2.93±0.49
Minimum Lumen Diameter, mm	2.72±0.46	2.64 ±0.53	2.46±0.61
Diameter stenosis, %	8.9±6.7	11.9±10.5	16.0±14.6
In-stent late lumen loss, mm	0.07±0.29	0.26±0.46*	

Data are presented as number relative percentages or mean value ±SD.
*p=0.04 follow-up-I versus follow-up-II.

TABLE 2:
*Serial quantitative intravascular ultrasound analysis of vessel segment showing incomplete stent apposition (n=12)**

	Follow-up-I	**Follow-up-II**	**P value**
Length of the ISA segment, mm	5.1±3.5	4.8±2.6	0.36
External elastic membrane area, mm^2	19.4±6.6	19.5±6.4	0.86
Maximal depth of the ISA segment, mm	0.8±0.3	0.9±0.4	0.63
Maximal circumferential extent of the ISA, (arc°)	138±66	144±66	0.83
Max. number of struts separated from vessel wall on one single cross-section	3.3±0.8	3.25±1.4	0.79
Mean ISA area,mm^2	2.5±1.8	2.4 ±1.7	0.60
Plaque behind stent area, mm^2	9.02±4.2	9.2±3.9	0.95
Stent Area (Struts Boundaries), mm^2	7.95±2.40	8.15±2.31	0.57
Intra-stent neointimal hyperplasia area (NIHA), mm^2	0.02±0.01	0.05±0.04	0.047
"Intra-stent" lumen area (Stent area *minus* NIHA), mm^2	7.92±2.39	8.09±2.33	0.42
"Effective" lumen area, mm^2 (Lumen area within the stent plus ISA area)	10.4±3.6	10.3±3.4	0.88

Values are mean±SD. *Patient who showed coronary aneurysm is not included due to lack of external elastic membrane measurement. ISA, incomplete stent apposition area.

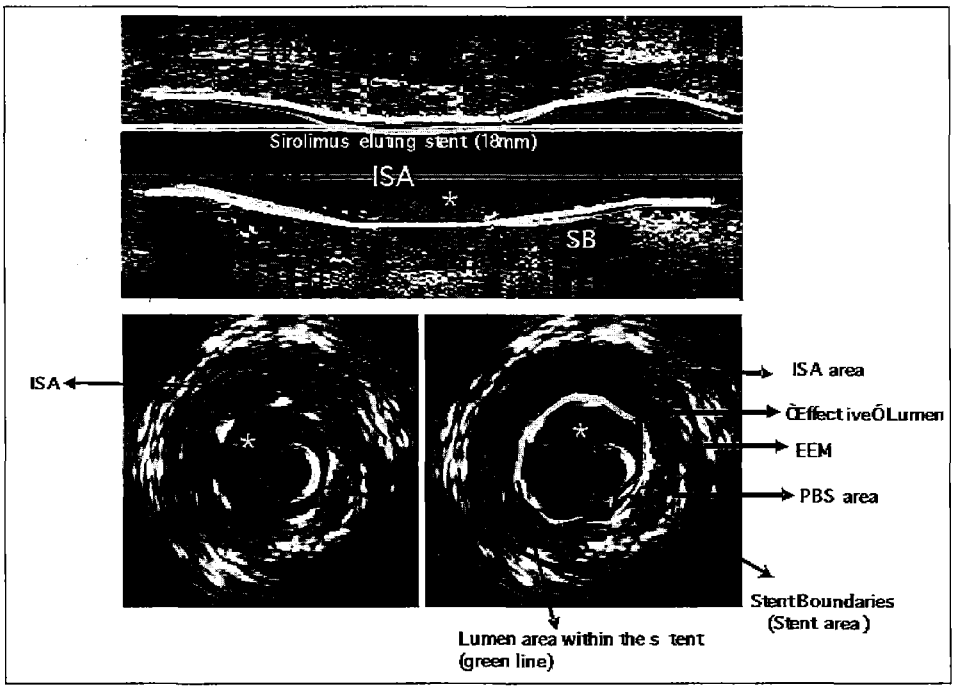


Figure 1 : The longitudinal IVUS image of a patient who has a segment with incomplete stent apposition (ISA). The cross-sectional views correspond to the "*" section of the longitudinal view showing the red, yellow, blue, and green lines that indicate the external elastic membrane (EEM) contour, the stent contour, ***"effective"*** lumen area contour, and ***"intra-stent"*** lumen area contour, respectively. PBS; plaque behind the stent.

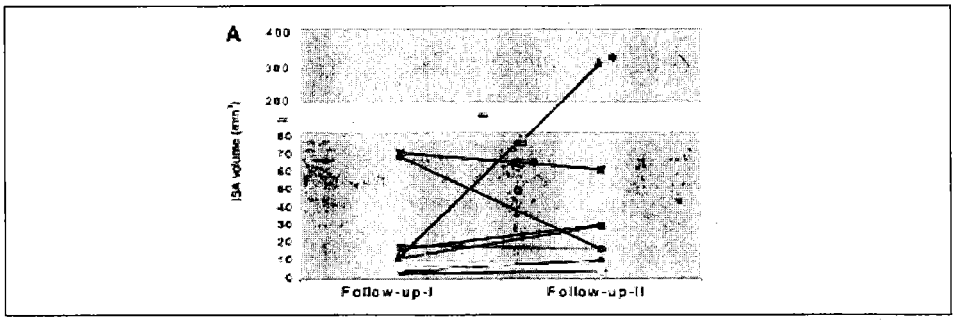


Figure 2A: Volume changes of incomplete stent apposition (per-patient) between two time intervals.
*Patient who showed coronary aneurysm

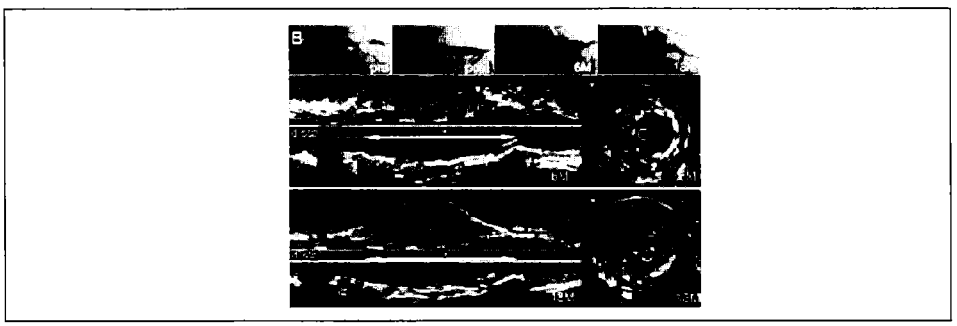
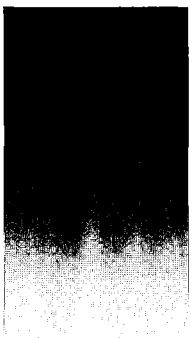


Figure 2B: Serial coronary angiography shows small pouching (arrow) at 6-month follow-up (6M). At 18- month follow-up (18M), coronary aneurysm exists at the same locality of pouching. In the IVUS (lower part), at 6M, homogeneous, low echogenic solid mass suggesting thrombus behind the stent struts, 18M IVUS shows this mass dissolved with blood flow at the same (*) area consistent with aneurysm formation suggesting,-dissolution of thrombotic material.



CHAPTER 14

VASCULAR RESPONSES AT PROXIMAL AND DISTAL EDGES OF PACLITAXEL-ELUTING STENTS – SERIAL IVUS ANALYSIS FROM THE TAXUS II TRIAL

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Circulation in press

Vascular Responses at Proximal and Distal Edges of Paclitaxel-Eluting Stents – Serial IVUS Analysis from the TAXUS II Trial

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ABSTRACT

Background: Based on brachytherapy experience, edge stenosis has been raised as a potential limitation for DES. We used serial intravascular ultrasound (IVUS) to prospectively analyze vessel responses in adjacent reference segments after implantation of polymer controlled Paclitaxel eluting stents.

Methods and Results: TAXUS II was a randomized, double-blind trial with two consecutive patient cohorts that compared slow (SR) and moderate-release (MR) Paclitaxel-eluting stents with control bare metal stents (BMS). By protocol, all patients

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had post-procedure and 6-month follow-up IVUS. Quantitative IVUS analysis was performed by an independent core laboratory, blinded to treatment allocation in 5 mm vessel segments immediately proximal and distal to the stent. Serial IVUS was available for 106 SR, 107 MR, and 214 BMS patients. For all three groups, a significant decrease in proximal edge lumen area at 6-months was observed. The decrease was comparable (by ANOVA, p = 0.194) for SR (-0.54±2.1mm^2,) and MR (-0.88±1.9mm^2) compared with BMS (-1.02±1.9mm^2). For the distal edge, a significant decrease in lumen area was only observed with BMS (-0.91±2.0mm^2,p<0.0001); this decrease was significantly attenuated with SR (+0.08±2.0mm^2) and MR (-0.19±1.7mm^2) stents (p<0.0001 by ANOVA). Negative vessel remodeling was observed at the proximal (-0.48±2.2mm^2,p=0.011) but not the distal edges of BMS and at neither edge of SR or MR stents.

Conclusion: The marked reduction in in-stent restenosis with SR or MR stents is not associated with increased edge stenosis at 6-month follow-up IVUS. In fact, when compared to BMS there is instead a significant reduction in late lumen loss at the distal edge with TAXUS stents.

INTRODUCTION

In-stent restenosis related to neointimal hyperplasia after stent implantation remains a major clinical problem[1,2]. Over the last decade, both systemic pharmacological and novel mechanical treatment strategies to prevent in-stent neointimal hyperplasia have been unsuccessful[3-5]. Only intracoronary radiation therapy has emerged as a promising modality to attenuate the neointimal hyperplasia after stent placement[6,7]. However, initial enthusiasm in the use of radiation therapy has been limited by the occurrence of stenosis in the segments adjacent to the proximal and distal edge of the stent (so called 'edge stenosis')[8,9].

Recently, stent based local drug delivery with a number of pharmacological agents has been demonstrated to reduce in-stent neointimal hyperplasia. Randomized clinical safety and feasibility trials with Sirolimus- and Paclitaxel-eluting stents have shown very promising results preventing in-stent restenosis in de novo coronary and in-stent restenosis lesions[10,11]. However, initial enthusiasm has been tempered by concerns regarding potential untoward effects. Among these concerns is the possibility that edge effects, analogous to those observed with radioactive stents and following intravascular brachytherapy, might limit the effectiveness of drug eluting stents. In the initial trials with Sirolimus eluting stents (SES), FIM[12] and RAVEL[11] trials, no edge effect was reported. Edge stenosis was however observed in the high dose group of the prematurely terminated ACTION (Actinomycin-D Eluting Stent for Coronary Revascularization) trial, which tested Actinomycin-D eluting stents, compared to low dose and BMS groups. In the SIRIUS (a multicenter study of the ***SIR***o***I***m***US***-eluting

Bx-Velocity stent in the treatment of patients with de novo coronary artery lesions) trial, which evaluated SES in a more complex population than RAVEL, a higher rate of significant (>50% diameter stenosis) stenosis was observed at the proximal edge of the SES compared to either the stented region or its distal edge (M.B. Leon unpublished data, 2002). These observations have prompted renewed concern regarding the issue of "edge" stenosis with drug eluting stent.

In the TAXUS-I trial[10], no edge restenosis were seen with a slow release Paclitaxel formulation; however, this was a feasibility study including only 61 patients. The TAXUS-II trial compared two consecutive cohorts; slow- (SR) and moderate-release (MR) polymer formulations of Paclitaxel-eluting stent with control bare metal stents (BMS) and mandated serial intravascular ultrasound (IVUS) examinations providing a unique opportunity to obtain detailed information on the outcome at vessel segments adjacent to Paclitaxel eluting stents.

METHODS

Patient Selection

The TAXUS-II was a randomised, double-blind, controlled, trial conducted in 38 centers. Patients were eligible for inclusion if 1) they had stable or unstable angina pectoris, or documented silent ischemia: 2) they were scheduled for treatment of a single significant (>50% stenosis on visual assessment) *de novo* target lesion in a native coronary artery that could be treated with a single stent (3.0 or 3.5mm diameter and 15mm long). Major exclusion criteria were; total vessel occlusion (TIMI grade 0-1) before intervention, intervention for evolving myocardial infarction, significant (>50% diameter stenosis) unprotected left main coronary artery stenosis, ostial location of the target lesion, lesion calcification that precluded successful predilatation, angiographic evidence of thrombus within the target lesion, left ventricular ejection fraction <30 percent, or intolerance to aspirin or clopidogrel. The current intravascular ultrasound (IVUS) substudy included patients who received one study stent and underwent serial IVUS examination post-procedure and at 6-month follow-up. The study was reviewed and approved by each participating institution's Ethics Review Committee and written informed consent was obtained from all patients.

TAXUS (Paclitaxel Eluting) Stent System

The stent used in this study was the NIR' Conformer stent (Boston Scientific Corporation, MA and Medinol Ltd. Jerusalem). The control bare metal stent was an uncoated steel stent (NIRx', Boston Scientific). The **TAXUS NIRx'** stent was coated with proprietary polymer (Translute') designed to control Paclitaxel release with an initial burst phase for approximately 10 days [13] All **TAXUS** stents were coated with a total loaded dose of 1.0mg /mm^2 Paclitaxel. Two Paclitaxel eluting release formulations were evaluated; slow release (SR) and moderate release **TAXUS** (MR) with an

8-fold higher release rate for the MR formulation in the first 48 hours. All stents were 15mm long and 3.0 or 3.5 in diameter on 20mm balloon delivery catheters.

Study design and Procedure

To evaluate the safety and performance of the TAXUS NIRx^{TM} stent patients in 2sequential cohorts were randomized (1:1ratio), after successful predilatation, to receive either the TAXUS or a control NIRx' bare metal stent (BMS). In Cohort1, patients were randomised to -SR or BMS. In Cohort2, patients were randomised to -MR or BMS.

Stents were deployed at10 to16 atmospheres and post dilatation was performed as necessary to achieve a residual stenosis below 20 percent.

Heparin was administered in intravenous boluses to maintain an ACT greater than 250 sec for the duration of the procedure, and discontinued within 12 hours. Aspirin, at least 100 mg, was begun 12 hours before the procedure and continued indefinitely. A loading dose of clopidogrel, 300 mg was administered, preferably 48 hours prior to the procedure, followed by 75 mg once daily for 6 months.

Quantitative Intravascular Ultrasound and Angiographic analysis

Serial IVUS (post-procedure and 6-month follow-up) procedures were performed after administration of 200 µg of intracoronary nitroglycerin using an automated pull-back at 0.5 mm per second. All IVUS procedures were recorded on VHS videotapes and images were digitized for analysis. A computer based contour detection were performed using QURAD QCU analysis software (Curad BV, Wijk Bij Duurstede, The Netherlands) for 3-D reconstruction, as described elsewhere[14]. In the quantitative analysis of the edge segments; the vessel segment beginning 5 mm distal to and extending 5 mm proximal to the stented segment were examined. In where branches or calcification was present, the entire 5 mm segment could not be analyzed. For this reason and to clarify the mechanism of possible edge responses to drug elution at different distances from the stent struts, we also performed IVUS analysis for each 1mm sub-segment as well as for the entire 5mm edge segments. Therefore, both proximal and distal vessel segments were further divided into 1 mm sub-segments and numbered from 1(nearest the stent) to 5. For each sub-segment, vessel, lumen and plaque area were calculated from each available cross sectional slice (up to 50 slices for each mm) obtained after digitizing the video tapes and expressed as mean values. Area changes (D values) for each measurement were calculated as follow up – post procedure. To eliminate the influence of vessel size, percent change (_ area / post-procedure area)* 100 was also calculated.

The quantitative ultrasound and coronary angiographic (QCA) analyses were performed by an independent core laboratory that remains blind to treatment allocation during follow-up (Cardialysis, Rotterdam, The Netherlands).

Statistical analysis

The BMS groups of the two cohorts were combined because the baseline and 6-month follow-up data showed no significant differences, as previously described.[15] Therefore, 3 groups are reported in this study: the combined BMS, the TAXUS-SR, and the TAXUS-MR groups. Discrete variables are displayed as percentages and tested with Fisher's exact test. Continuous variables are expressed as mean ± standard deviation. Changes for each measurement were calculated as 'follow-up – post-procedure'. When comparing 3 groups, overall p values were derived from one-way ANOVA. Comparisons between post-procedure and 6-month follow-up were performed with a 2-tailed paired t test. Whereas, comparisons between 2 groups were performed with Fisher's Least Significant Difference (LSD) test. A value of $p<0.05$ was considered statistically significant.

RESULTS

Overall **536** patients, (270 BMS, 135-MR, and 131-SR) were randomized in TAXUS-II trial. IVUS edge analysis could not be performed either in part or all of the predefined 5mm edge segment in some patients (n = 162) due to one or more of the following reasons;- incomplete image acquisition (23%), inadequate image quality (9%), or the presence of major side branches (68%). Of the 536 patients, 427 with 1 stent and paired IVUS edge analysis (214 BMS, 106 -SR, and 107-MR) entered in this sub-study. Baseline clinical, demographic, and angiographic characteristics were similar among BMS, SR, and MR groups (Table-1). Serial IVUS was available for the proximal edge in 161 BMS, 84 SR, and 84 MR patients and for the distal edge in 191 BMS, 97SR and 98MR patients.

Mean changes within the entire 5mm section at proximal and distal edges

Mean vessel area, plaques area and lumen area of the entire 5 mm edge segment (proximal and distal) was comparable without statistically significant differences between the three groups immediately after the procedure (baseline) as well as during the 6 month follow-up (Table 2A and 2B). At the proximal edge, only the control group showed significant constructive vascular remodeling with a decrease in mean vessel are of the entire proximal edge from baseline to follow-up (p=0.011) whereas both the SR and MR group did not show any differences (SR p=0.689, MR p=07.82). With a comparably significant increase in mean plaque area in all three groups, this still translated into a significant decrease in mean lumen area all three groups (Figure 1).

At the distal edge the mean plaque and vessel area remained comparable between all three groups. However, the lumen area of the entire distal edge differed significantly between control (7.6±2.8mm^2) and SR (8.4±2.9mm^2; p=0.0185). From baseline to fol-

low-up, the vessel area of the distal edge decreased in the control group while increased in SR and MR group. With a comparably increase in mean plaque area in all three groups, this translated into a significant decrease in mean lumen area in the control compared to a stable lumen area in both the SR and MR group (Figure 1).

The correlation between intra stent neointimal area and change in proximal/distal plaque area were separately investigated for all three groups. The statistical analysis showed that the intra stent neointimal area is correlated with the distal plaque area in each group and correlated with the proximal plaque area in MR and control but not in SR. These relationships would suggest that the vascular responses at the proximal and distal edges reflect a global responsiveness of the vessel to the degree of neointimal inhibition induced by the drug with both eluting formulations.

Analysis of the vascular response at the proximal or at the distal edges of the stent in the three groups (MBS, MR, SR) were also carried out for the patients having undergone post dilatation of the stent or for those who exhibited an early or late malapposition of the stent. No level of statistical significance could be detected between the groups with and without post dilatation, with or without malapposition.

The changes in EEM volume and area, in lumen volume and area, in plaque volume and area at the proximal and distal edge of the stent were not statistically different between the MR and SR group and there is no statistical argument suggesting the superiority of one eluting formulation over the other.

Subsegmental analysis of longitudinal changes at 5mm edge segment of proximal and distal edges

On a per segment analysis analyzing five consecutive 1 mm segments adjacent to the stent, vascular remodeling proximal to SR and MR stents differs within the first 1 mm subsegment. While vessel area, plaque area and lumen area did not differ between the different segments and different groups at baseline, positive vascular remodeling reflected by an increase in vessel area was more pronounced within this first subsegment in the SR and MR group than in the control group ($p=0.0052$, Figure 2). Together with a comparable increase in plaque area in all three groups, this resulted in significantly less lumen area loss in the SR and MR group (-0.55 ± 2.1 mm^2 and $-0.78\pm2.0mm^2$) than in the control group ($-1.42\pm2.2mm^2$,$p=0.0055$). Beyond the first proximal segment, the change in lumen area, plaque area, and vessel area did not differ significantly between SR, MR and control (Figure 2).

At the distal edge, the beneficial effect of SR and MR stents on change in lumen area was evident on all five 1mm subsegments distal to the stent. The comparable decrease in plaque area in the first two subsegments in all three groups was balanced in the SR and MR group by positive vascular remodeling reflected by an increase in

vessel size. This resulted in stable lumen area in all subsegments in both SR and MR whereas the control group exhibited a significant decrease along all five subsegments of the distal edge ($p<0.001$ versus SR and MR).

Difference between proximal and distal edges

There were no significant differences between proximal and distal edges with respect to % changes in either vessel or plaque area among groups. However, although there were no significant differences in % lumen area change between proximal and distal edges in BMS (-9.6% versus –8.9% respectively, $p=0.91$), for TAXUS stents, a significant decrease in lumen area at proximal compared with distal edges was seen in both MR (-7.6% versus +0.04% respectively, $p=0.01$) and SR (-4.4% versus +3.1% respectively, $p=0.03$).

DISCUSSION

In the present study, we evaluated the behavior of vessel segments adjacent to polymer controlled slow and moderate release Paclitaxel eluting stents (TAXUS) by serial IVUS. The major finding of the study was that the use of TAXUS stents was not associated with a significant increase in edge stenosis compared to BMS. Indeed, the luminal area at the distal edge of TAXUS stents was significantly greater than that of BMS at follow-up due to the occurrence of positive vascular remodeling..

Edge Effects and Restenosis

The inevitable arterial injury due to balloon deployment of a stent coupled with the presence of a metallic foreign body causes an inflammatory and proliferative responses[16]. Animal studies have shown that this results in neointimal hyperplasia not only within the stent but also at the edges in the adjacent reference segments[17].

The concerns regarding edge effects with drug eluting stent reflect potential similarities between the effects of intracoronary radiation therapy and those of drug eluting stent such as local inhibition of neointimal growth and delayed endothelial healing[18]. In patients treated with intracoronary brachytherapy, edge stenosis has proved to be an important clinical problem, occurring in between 3 and 12% of patients[19,20].With radioactive stents the incidence of edge stenosis was an unacceptable 30%[8,21].

TAXUS II confirmed that no "edge effect" greater than that found in BMS occurs with either MR or SR. As previously reported, the term "edge effect" is used to connote an effect greater than would be seen with Bare Metal Stent [8,21].

In fact, there was a slight but non-significant decrease in edge stenosis compared to BMS. Edge stenosis (diameter stenosis greater than 50%) rates for BMS were 3.4% (proximal) and 3.1% (distal) whereas for SR and MR groups the rates were 1.6% and 2.3% at both proximal and distal edges.

In Sirolimus eluting stent trials, no edge stenosis was reported in the FIM and RAVEL trials. However, in the SIRIUS trial, which included patients with more complex lesions than either the RAVEL[11] or TAXUS-II trials, although the in-stent restenosis rate (3.2%) was similar to that in TAXUS-II, edge stenosis, which were more frequently observed at proximal than at distal edges and in smaller (<3 mm) vessels, occurred in 5.8% of patients.

Remodeling in segments adjacent to the stent (Insights from Intracoronary Ultrasound)

Although stent edge lumen narrowing can be detected by quantitative coronary angiography, angiography can only provide information regarding the vessel lumen. IVUS, on the other hand can be used to analyze the mechanisms of such narrowing. Thus, serial IVUS analyses of stent edges provide important insights into potential "edge" effects associated with drug eluting stents.

Previous serial IVUS studies reported that significant lumen loss occurs at the proximal segment after BMS implantation. However, there is controversy as to the mechanism(s) involved. Hoffmann et al[2] and Weissmann et al[22] reported that this luminal loss was predominantly related to negative remodeling whereas Mudra et al[1] suggested that it was related to an increase in plaque burden. In the present study, both BMS and TAXUS stents showed a significant decrease in lumen area in the proximal reference segment at follow-up. While this was due to both negative remodeling and plaque increase in BMS, it was related to plaque increase without significant vessel remodeling in TAXUS stents. Sub-segment analysis for BMS demonstrated that in the 2mm proximal to the stent, lumen loss was due exclusively to plaque increase, whereas more proximally it reflected both plaque increase and negative remodeling. With TAXUS stents, lumen loss was significantly less than for BMS. This was due to the fact plaque increase was compensated by positive remodeling.

Previous studies regarding distal edge behavior in BMS have produced conflicting results. Mudra et al[1] reported no significant lumen loss or negative remodeling in the 3mm distal to BMS edges whereas Weissman et al[22] reported discordant results showing significant lumen loss throughout the distal reference segment. In the present study, BMS demonstrated significant lumen loss in the distal reference segment without negative remodeling. In detailed sub-segment analyses, we demonstrated that lumen loss in the 2 mm distal to the stent edge was related to plaque increase, in accordance with the results of Weismann et al[22].

In contrast to BMS, TAXUS stents were associated with a beneficial effect on the distal reference segment, where no significant lumen narrowing was observed at follow-up. The subsegment analysis showed that this reflects the fact that positive vascular remodeling compensated for the increase in plaque burden in the reference segment

immediately (<2 mm) adjacent to the stent. Possible reasons for the beneficial effects of the drug at the distal edge and for the difference between the behavior of proximal and distal edge segments include higher downstream concentrations of the drug or the relatively smaller distal vessel size.

The potentially higher drug concentration at distal edge of the TAXUS stent did not therefore appear to have any deleterious consequences. In addition, drug dose fall-off, different drug eluting formulations, polymer materials and exposure to different drug concentration in drug eluting stents have the potential to induce a proliferative response at the peri-stent margins. It is thus reassuring that neither TAXUS-SR nor TAXUS-MR showed increased lumen narrowing or remodeling compared with BMS at the proximal edge where there is drug concentrations are potentially lower.

Previous drug eluting stent trials

Although no detailed IVUS results have been published, no edge stenosis were reported on quantitative angiography in the TAXUS-I trial[10]. Our IVUS findings in TAXUS-II are consistent both with the quantitative angiographic results reported in TAXUS I and II (Table 1) and with the results of the Sirolimus eluting stent trials, all of which showed a decrease in lumen loss, compared to BMS, at the distal edge of the stent.

No IVUS edge analysis has been reported from the SCORE study. Only two studies (QUANAM[23] and ASPECT[24]) reported serial IVUS edge analysis in small numbers of patients. In the ASPECT study, there were no significant changes at either edge whereas in the QUANAM[23]study there was significant lumen loss at the distal edge. This observation in the QUANAM[23] study is contrary to the findings of the present study. We have recently evaluated edge responses after SES by serial IVUS in a subset of the RAVEL and FIM patients and found no significant changes between implantation and follow-up at either proximal or distal edges in any of the parameters studied.

Study Limitations

Patients included to the study had simple de novo coronary lesion and low risk profiles reflecting the inclusion criteria of the TAXUS-II trial. The study results can not be extrapolated to more complex coronary lesions. Furthermore, the follow-up period is relatively short and no conclusions can be drawn regarding the ultimate long term behavior at the stent edges.

Conclusion

These results suggest that concerns regarding edge stenosis with TAXUS eluting stents are unfounded. Indeed, compared to BMS, TAXUS stents appear to have a sig-

nificant protective effect against distal edge "restenosis" compared to BMS; a similar trend was noted for the proximal edge. These effects were observed both with SR and MR formulations.

Acknowledgement

We would like to Eugene McFadden MB ChB for his critical review in preparing this manuscript.

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TABLE 1:
Baseline Clinical and Procedural Characteristics

Characteristics	Combined Control(N=214)	Taxus SR (N=106)	Taxus MR (N=107)
Age (years)	59.9±9.61	61.9±10.4	59.6±10.3
Male	78.5%	69.8%	72.9%
Current Smoker	27.6%	20.8%	22.4%
Diabetes Mellitus	14.5%	11.3%	15.0%
Hypertension	61.2%	61.3%	59.8%
Hypercholesterolemia	73.7%	81.1%	77.6%
Unstable Angina	34.3%	34.0%	29.2%
Prior MI	45.8%	39.6%	37.4%
Target Lesion Vessel:			
LAD	46.7%	39.6%	42.1%
LCA	14.5%	19.8%	22.4%
RCA	38.8%	40.6%	35.5%
RVD Pre, (mm)	2.73±0.44	2.78±0.44	2.73±0.45
Max Balloon:Artery, Ratio	1.1±0.2	1.1±0.2	1.1±0.2
Max Inflation Pressure, atm	12.4±2.7	12.7±2.7	12.2±2.8
Quantitative angiography at follow-up			
Proximal edge late loss, (mm)	0.33 ±0.40	0.18±0.33*	0.16±0.37*
Binary restenosis %	2.8 (6/214)	1.9 (2/106)	2.8 (3/107)
Distal edge late loss, (mm)	0.20 ±0.38	0.07±0.32*	0.05±0.31*
Binary restenosis %	2.3 (5/214)	1.9 (2/106)	0.9 (1/107)
In stent late loss, (mm)	0.74 ±0.44	0.30±0.30*	0.25±0.35*
Binary restenosis %	15.9 (34/214)	0.9 (1/106)	0.9 (1/107)

Numbers are % (Count/Sample Size) or Mean±SD.
LAD indicates left anterior descending artery; RCA, right coronary artery; LCX, left circumflex artery
*$p < 0.05$ versus the control group

TABLE 2:
Serial IVUS results of proximal and distal edges

A- PROXIMAL EDGE	Control (BMS) N=161	Taxus-SR N=82	Taxus-MR N=85	p-value overall
Vessel Area (mm^2)				
Post-Procedure	16.9±4.3	16.8±4.8	16.6±4.0	0.82
6-M Follow-Up	16.4±4.2	16.9±4.5	16.5±4.0	0.70
P value	**<0.01**	**0.689**	**0.782**	
Plaque Area (mm^2)				
Post-Procedure	7.7±2.9	7.6±2.9	7.5±2.7	0.81
6-M Follow-Up	8.2±2.9	8.2±2.9	8.3±2.9	0.97
P value	**<0.0005**	**<0.0005**	**<0.0005**	
Lumen Area (mm^2)				
Post-Procedure	9.2±3.0	9.2±2.9	9.1±2.6	0.93
6-MFollow-Up	8.3±2.9	8.7±3.0	8.2±2.4	0.47
P value	**<0.0001**	**<0.02**	**<0.0001**	
B- DISTAL EDGE	**Control (BMS) N=187**	**Taxus-SR N=94**	**Taxus-MR N=96**	**p-value overall**
Vessel Area (mm^2)				
Post-Procedure	14.7±4.5	14.4±4.3	14.1±4.3	0.54
6-M Follow-Up	14.5±4.3	14.8±4.5	14.4±4.1	0.74
P value	0.115	**0.064**	**0.103**	
Plaque Area (mm^2)				
Post-Procedure	6.3±3.1	6.1±2.8	5.8±2.7	0.45
6-M Follow-Up	6.9±3.0	6.4±2.7	6.3±2.7	0.14
P value	**< 0.0001**	**0.073**	**<0.02**	
Lumen Area (mm^2)				
Post-Procedure	8.4±2.9	8.4±2.7	8.3±3.0	0.88
6-M Follow-Up	7.6±2.8	8.4±2.9	8.0±2.8	0.05
P value	**<0.0001**	**0.767**	**0.190**	

Numbers are Mean±SD p= NS for MR vs SR.
Overall p-values are from one-way ANOVA for continuous variables

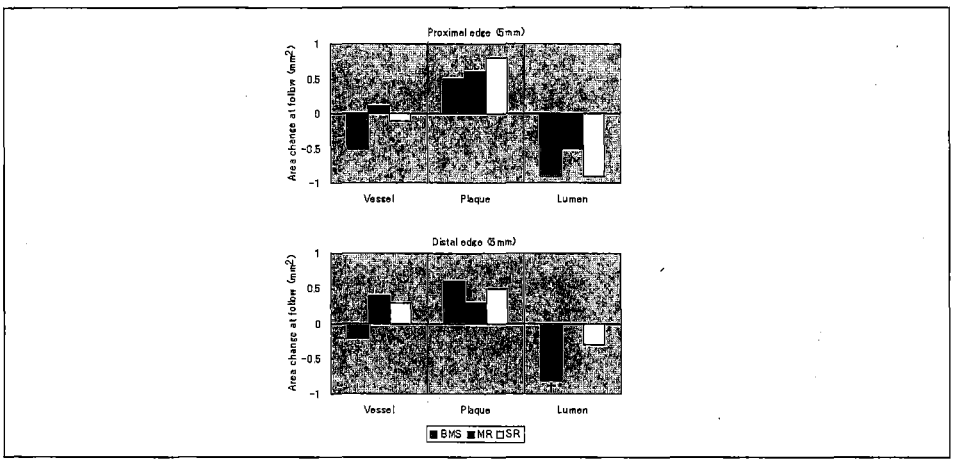

Figure 1 : Averaged area changes (follow-up – post-procedure) for entire 5mm edge segment in lumen, plaque and vessel at proximal and distal edge segments, BMS=bare metal stent, SR= TAXUS stent slow release formulation, MR= TAXUS stent moderate release formulation.
* $p < 0.05$, †$p<0.0005$ by one way ANOVA

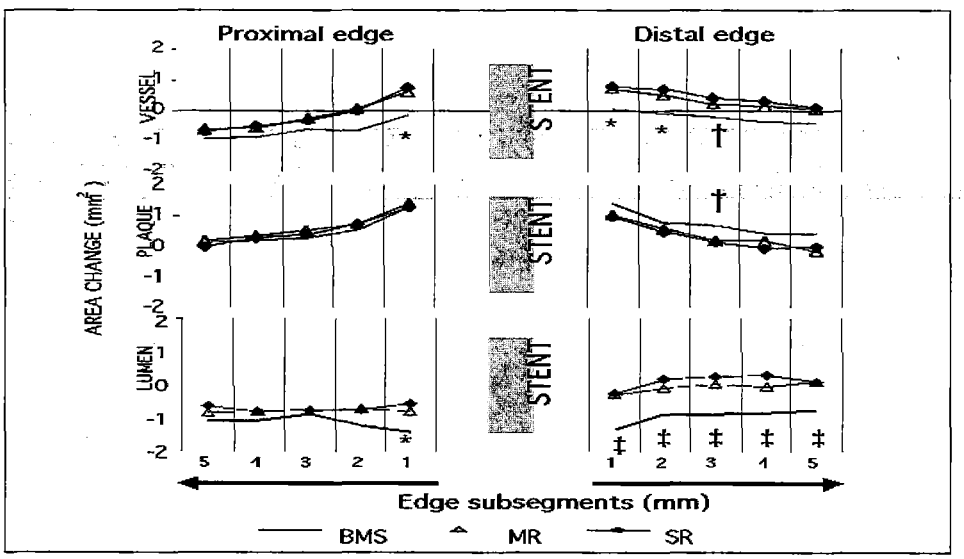

Figure 2 : Every 1mm mean area changes (follow-up – post-procedure) in lumen, plaque and vessel at proximal and distal edge sub-segments, BMS=bare metal stent, SR= TAXUS stent slow release formulation, MR= TAXUS stent moderate release formulation.
* $p <0.05$, ‡$p <0.01$ by one way ANOVA, †$p = 0.0052$ BMS vs -SR.

CHAPTER 15

CHRONIC ARTERIAL RESPONSES TO POLYMER-CONTROLLED PACLITAXEL-ELUTING STENTS: COMPARISON WITH BARE METAL STENTS BY SERIAL INTRAVASCULAR ULTRASOUND ANALYSES DATA FROM THE RANDOMIZED TAXUS-II TRIAL

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Circulation in press

Chronic Arterial Responses to Polymer-Controlled Paclitaxel-Eluting Stents: Comparison with Bare Metal Stents by Serial Intravascular Ultrasound Analyses.

Data from the Randomized TAXUS-II Trial

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Abstract

Background: Polymer-controlled Paclitaxel-eluting stents have shown a pronounced reduction in neointimal hyperplasia compared to bare metal stents (BMS). The aim of this substudy was to evaluate local arterial responses using serial quantitative intravascular ultrasound (IVUS) analyses in the TAXUS II trial.

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Methods and Results: TAXUS II was a randomized, double-blind study with 536 patients in 2 consecutive cohorts comparing slow release (SR; 131 patients) and moderate release (MR; 135 patients) paclitaxel-eluting stents to BMS (270 patients). This IVUS substudy included patients treated with one study stent that underwent serial IVUS examination post-procedure and at 6-month follow-up (BMS 152 patients, SR 81, MR 81). The analyzed stented segment (15mm) was divided into 5 subsegments where mean vessel area (VA), stent area (SA), lumen area (LA), intra-stent neointimal hyperplasia area (NIHA), and peri-stent area (VA-SA) were measured. NIHA was significantly reduced in SR (0.7±0.9 mm^2, $p<0.001$) and MR (0.6±0.8mm^2, $p<0.001$) compared to BMS (1.9±1.5mm^2) with no differences between the two paclitaxel-eluting release formulations. Longitudinal distribution of neointimal hyperplasia throughout the paclitaxel-eluting stent was uniform. Neointimal growth was independent of peri-stent area at post-procedure in all groups. There were progressive increases in peri-stent area from BMS to SR to MR (0.5±1.7mm^2, 1.0±1.8mm^2, 1.4±2.0mm^2, respectively, $p<0.001$). The increase in peri-stent area was directly correlated with increases in VA.

Conclusion: Both slow and moderate release paclitaxel-eluting stents prevent neointimal formation to the same degree compared to BMS. However, the difference in peri-stent remodeling suggests a release-dependent effect between SR and MR.

Introduction

Stent based local drug delivery with a number of different types of pharmacologic agents has been demonstrated to reduce neointimal hyperplasia within the stent.[1-3] However, late chronic arterial responses to drug-eluting stents have not yet been fully characterized. Even the arterial responses to bare metal stents remain controversial as to whether peri-stent remodeling occurs after stent implantation.[4-8] Furthermore in studies detecting peri-stent remodeling, its relationship to the amount of neointimal hyperplasia is controversial.[5,6]

Paclitaxel interferes with microtubule function, which leads to the inhibition of cell division and migration, thereby interrupting the restenotic cascade.[9] Early clinical feasibility trials suggested paclitaxel-eluting stents as a safe and potentially efficacious way to treat de novo lesions and in-stent restenosis.[10,11] These promising preliminary results were confirmed by the randomized double-blind TAXUS II trial which showed significant improvement in clinical, quantitative angiography and intravascular ultrasound (IVUS) parameters of restenosis.[2] The aim of this study was to evaluate the arterial responses to paclitaxel-eluting stents using serial quantitative IVUS analyses in the TAXUS II trial.

Methods

Patient selection

Between June 2001 and January 2002, the TAXUS II trial at 38 sites enrolled 536 patients randomized (1:1) into 2 consecutive and independent cohorts. Patients in the first cohort received either the TAXUS-NIRx slow release formulation (SR) paclitaxel-eluting stent or the control bare metal stent (BMS). Those in the second cohort were randomized to either the TAXUS-NIRx moderate release formulation (MR) paclitaxel eluting stent or the BMS. Patients were eligible if they had a single de novo target lesion of a native coronary artery with an estimated stenosis between 50 and 99 %, lesion length < 12mm, and vessel diameter between 3.0 and 3.5mm. The current IVUS substudy included patients who received one study stent and underwent serial IVUS examination post-procedure and at 6-month follow-up. The study protocol was approved by the ethics review committees for all participating centers. All patients gave written informed consent prior to enrollment.

Study Device and Procedure

The stent used in this study was the NIR‘ Conformer stent (Boston Scientific Corporation, Natick, MA and Medinol Ltd., Jerusalem). All stents were 15 mm long and 3.0 or 3.5 mm in diameter. The paclitaxel-eluting stent (TAXUS NIRx) was identical to the BMS except it was coated with a total load of 1.0 mg/mm^2 of paclitaxel incorporated into a proprietary polymer (Translute‘) that provides controlled biphasic release. For both stents, the initial burst release over the first 48 hours after implantation is followed by a low-level release phase for approximately 10 days. The difference between both stents is an 8-fold higher release rate in the initial burst of the TAXUS-MR stent when compared to the TAXUS-SR stent.

Balloon pre-dilatation was performed followed by study stent implantation using standard techniques. Post-dilatation was performed if necessary. There were no objective angiographic or IVUS criteria for ensuring optimal stenting. During the procedure, intravenous heparin was given to maintain an activated clotting time ≥ 250 seconds. All patients received clopidogrel 300 mg loading dosage followed by 75 mg daily (or ticlopidine 250 mg twice daily) for 6 months and aspirin 75 mg daily indefinitely.

Quantitative Angiographic and Intravascular Ultrasound Analysis

Quantitative coronary angiographic (QCA) and IVUS analyses were performed by an independent core laboratory that continues to be blinded to treatment allocation (Cardialysis, Rotterdam, The Netherlands). IVUS was performed using automated pullback at 0.5mm/sec to examine the stented vessel segments. The lumen, stent, and external elastic membrane (EEM) contours were detected using the CURAD QCU

analysis software (Curad BV, Wijk Bij Duurstede, The Netherlands) applying 3-D reconstruction, as described elsewhere.[12] If the EEM could not be detected (due to extensive calcification with acoustic shadowing), that patient was excluded from this substudy. For the analysis of the longitudinal distribution, the stented segment was arbitrarily divided into 5 sub-segments, each 3 mm long as previously described.[13-15] In the stented segment and in each subsegment, mean total vessel area (VA), mean stent area (SA), and mean lumen area (LA) were measured. Mean neointimal hyperplasia area (NIHA) and peri-stent area (PSA) were derived by 'SA-LA' and 'VA-SA' respectively. Percentage of NIHA and PSA were calculated as 'NIHA/SA × 100' and 'PBSA/VA × 100', respectively.

Statistical analysis

Pooling of the BMS groups of the two cohorts were combined because the baseline and 6-month follow-up data showed no significant differences. Therefore, 3 groups are reported in this study: the combined BMS, the TAXUS-SR, and the TAXUS-MR groups. Discrete variables are displayed as percentages and tested with Fisher's exact test. Continuous variables are expressed as mean ± standard deviation. In general, analyses were performed on a per patient basis; if indicated analyses were performed on a per segment basis. Delta values (D) for each measurement were calculated as 'follow-up – post-procedure'. When comparing 3 groups, overall p values were derived from one-way ANOVA. Comparisons between post-procedure and 6-month follow-up were performed with a 2-tailed paired t test. Comparisons between 2 groups were performed with Fisher's Least Significant Difference (LSD) test. Linear regression was performed on a per segment basis to assess the correlation between IVUS indices. A value of $p<0.05$ was considered statistically significant.

Results

Baseline characteristics

Of the 536 randomized patients, 314 with serial and analyzable IVUS entered this substudy (BMS 152, SR 81, MR 81). There were 5 subsegments analyzed per patient yielding a total of 1570 subsegments. The patients' baseline clinical and procedural characteristics are shown in Table 1. In this subgroup, the left circumflex coronary artery was more frequent as a target vessel in the TAXUS-MR group compared to the BMS ($p=0.015$). The other baseline characteristics were comparable among the 3 groups.

Quantitative IVUS data

Table 2 summarizes quantitative IVUS parameters analyzed on a per patient basis. IVUS parameters at post-procedure were comparable among the 3 groups. At 6-month

follow-up, both the TAXUS-SR (0.7 ± 0.9 mm^2) and the TAXUS-MR (0.6 ± 0.8 mm^2) groups showed a significant reduction in mean NIHA compared with the BMS (1.9 ±1.5 mm^2; $p<0.001$). As shown in Figure 1, there was a statistically significant increase in mean VA in all groups between post-procedure and follow-up (BMS < TAXUS-SR < TAXUS-MR, ANOVA $p<0.001$). Second, there was an increase in PSA showing the same ranking (ANOVA $p<0.001$). Finally, there were decreases in LA between baseline and follow up for all groups. This decrease was significantly larger in the BMS (-1.7 ± 1.7 mm^2) than in the SR (-0.6 ± 1.1 mm^2; $p<0.001$) and MR (-0.5 ± 1.3 mm^2; $p<0.001$). However, there were no release dependent differences in lumen reduction between the SR and the MR groups.

Distribution of neointimal hyperplasia

The distribution of neointimal hyperplasia among the 5 subsegments at follow-up in each group is shown in Figure 2A. There was no predilection for neointimal growth to occur within any 3 mm subsegments either in the TAXUS-SR or the TAXUS-MR group nor in the BMS (ANOVA; P=0.95, 0.80, and 0.35, respectively). As shown in Figure 2B, the distribution of PSA post-procedure was not uniform. Therefore, the correlation between IVUS indices including PSA and VA was analyzed on a per segment basis.

Correlation between IVUS parameters

Table 3 summarizes regression analyses performed between IVUS parameters. In all groups, there was no significant correlation between PSA post-procedure and NIHA at follow-up, suggesting that residual plaque burden post-procedure does not affect neointimal formation. There was a significant positive correlation between DVA and DPSA in all groups ($P<0.0001$). DVA did not correlate with NIHA in either group.

Discussion

The major findings of this study are the following: 1) Both slow and moderate release paclitaxel-eluting stents inhibit neointimal growth to the same degree when compared with BMS; 2) Peri-stent remodeling occurs in BMS as well as the TAXUS groups. There are progressive increases in peri-stent area from BMS to SR to MR; 3) The degree of peri-stent remodeling (change in peri-stent area) is not quantitatively related to the amount of neointimal hyperplasia; 4) Finally, there is no correlation between plaque burden post-procedure and subsequent neointimal hyperplasia.

Inhibitory effect of paclitaxel on neointimal hyperplasia

The SR and MR stents showed a significant reduction in neointimal area compared to the BMS by 73% and 79%, respectively and this inhibition was uniformly distrib-

uted along the stent (Figure 2A), indicating the homogeneous longitudinal diffusion pattern of paclitaxel from the stent. Paclitaxel has been shown to exert dose-dependent, anti-proliferative effects on smooth muscle cells in vitro and in in-vivo models.[9,16] In the standard risk, de novo lesions treated in the TAXUS II, there was no difference in the neointimal reduction between the 2 release formulations with differing kinetic profiles. The comparable reduction in neointimal hyperplasia suggests that the critical paclitaxel threshold to interrupt the restenotic cascade had been reached with the SR formulation in this low risk lesion subset. These 2 release formations differ in that the polymer matrix regulates the amount of paclitaxel that is released in the early burst phase (first 48 hours) with an 8-fold increase in the MR compared with SR.

Effect of paclitaxel on stented tissue growth (intra and peri-stent)

Paclitaxel may allow an increase in cells or matrix behind the stent, while preventing smooth muscle cells from proliferating and migrating into the stent. Figure 4 shows the comparison of the value of "DPSA + NIHA" among the 3 groups. This measure of stented tissue growth (intra and peri-stent) increased from: SR < MR < control. This suggests that the increase in cells and/or matrix is less pronounced in the slow-release formulation. Ongoing studies (TAXUS V and VI) will address the issue of whether different release profiles will alter restenosis outcomes in higher risk lesions.

Peri-stent remodeling following stent implantation

There is controversy as to whether peri-stent remodeling occurs after bare stent implantation. In 3 retrospective studies evaluating a total of 121 patients, Mudra et al, Koyama et al, and König et al independently reported that remodeling did not occur.[4,7,8] Conversely, the presence of remodeling was reported by 2 groups (Hoffman et al and Nakamura et al) from an aggregate of ~100 patients.[5,6] In this TAXUS II IVUS substudy with more than 300 patients, we establish unequivocally that peri-stent remodeling occurs in BMS as well as TAXUS stents and there were increases in peri-stent area from BMS to SR to MR.

Relationship between Peri-stent Remodeling and Neointimal Hyperplasia

In the previous studies where peri-stent remodeling was detected, the relationship to the amount of neointimal hyperplasia is conflicting. Nakamura et al. reported an inverse correlation, while Hoffmann et al. demonstrated a positive correlation. [5,6] In our large, randomized, blinded study with core lab analysis, the IVUS data establishes that neointimal hyperplasia is not quantitatively correlated with peri-stent remodeling in either BMS or TAXUS stents.

Impact of Plaque Burden at Baseline on Neointimal Hyperplasia

Initial plaque burden, referred to as peri-stent area (PSA) in this study, has been suggested to be important in restenosis because it correlated with neointimal hyperplasia in previous IVUS studies.[7,17,18] However, there are more recent reports showing contrasting results. [19,20] Plaque burden may play any number of roles in tissue responses within and out of the stent. On one hand, it may serve as a source for cells and growth factors involved in the restenotic process. On the other hand, it may be a physical barrier that buffers the medial injury caused by stent struts and thus it may attenuate neointimal formation. These opposite facets may counteract each other, leading to the disparity in IVUS findings. The TAXUS II data set establishes the absence of a relationship between plaque burden and neointimal growth in the BMS group.

It is of paramount importance to investigate whether plaque burden affects the efficacy of drug-eluting stents. The size and composition of the plaque may effect drug diffusion, penetration and activity. We found that for both the SR and MR, there was no relationship between plaque burden and neointimal hyperplasia. Since the plaque has no predictive value with respect to neointimal hyperplasia, IVUS assessment of the plaque burden will have no decision making utility in customizing drug-eluting stents with differing potencies.

Study Limitations

First, the analyses were limited to the patients with serial IVUS where the EEM could be well visualized raising the possibility of selection bias in IVUS sampling. However, this is a randomized, blinded study with a large IVUS sample size compared to previous IVUS studies, which minimizes this bias. Second, patients had relatively low risk profiles and simple lesions related to the inclusion criteria of the TAXUS II trial. Therefore, the results can not be extrapolated to a general population of diverse patients. Third, this represents a time frame of only 6 months that may not predict subsequent findings or relationships identified in this data set.

Conclusion

This study strongly supports the notion that there is no quantitative relationship between plaque burden and neoinimal hyperplasia following stent implantation. This would argue that the amount of post-procedural plaque burden has no predictive value for the anticipated restenosis rate in the long term follow-up. By using the sensitivity of IVUS technology in a large cohort of patients, we show that both slow and moderate release of paclitaxel eluting stents reduce neointimal hyperplasia to the same degree. However, by studying peri-stent remodeling we demonstrate release-dependent effects on the global vessel wall response within and around the stent.

Acknowledgments

We thank all of the investigators, their staff and the study staff at PPD and BSC. We thank Dr. Wijatyk for her contributions in the design, execution, and analysis. We appreciate the assistance provided by Dr. Hoye in drafting and reviewing this manuscript.

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TABLE 1:

Baseline Clinical and Procedural Characteristics

	BMS	Taxus SR	Taxus MR
Number of patients	152	81	81
Age	59.2 ± 9.8	60.5 ± 10.2	59.1 ± 10.2
Male (%)	78.9	71.6	74.1
Current Smoker (%)	26.3	25.9	25.9
Diabetes Mellitus (%)	13.8	11.1	14.8
Hypertension (%)	60.5	61.7	58.0
Hypercholesterolemia (%)	73.0	80.2	72.8
Unstable Angina (%)	32.2	32.1	31.3
Prior MI (%)	44.7	42.0	35.8
Target vessel (%)			
LAD	48.7	37.0	42.0
LCx	11.8	19.8	24.7*
RCA	39.5	43.2	33.3
Balloon artery ratio	1.1 ±0.2	1.1 ± 0.2	1.1 ±0.2
Maximal inflation pressure (atm)	12.1 ± 2.6	12.4 ± 2.8	12.0 ± 3.0
Stent Size (mm)	3.23 ± 0.25	3.30 ± 0.25	3.22 ± 0.25
Reference vessel diameter (mm)	2.71 ± 0.38	2.81 ± 0.43	2.72 ± 0.43

Values are presented as relative percentages or mean value ± SD.

LAD indicates left anterior descending artery; RCA, right coronary artery; LCx, left circumflex artery

*$p < 0.05$ versus the BMS group

TABLE 2:

Quantitative IVUS data

	BMS	Taxus SR	Taxus MR
Number of patients	152	81	81
Post-procedure			
mean VA (mm^2)	16.3 ± 3.4	16.9 ± 3.6	16.2 ± 3.7
mean SA (mm^2)	8.2 ± 1.6	8.6 ± 1.8	8.4 ± 1.9
mean LA (mm^2)	8.2 ± 1.6	8.6 ± 1.8	8.4 ± 1.9
mean PSA (mm^2)	8.1 ± 2.5	8.3 ± 2.3	7.8 ± 2.4
% PSA (%)	48.9 ± 7.7	48.5 ± 6.3	47.5 ± 6.8
6-month follow-up			
mean VA (mm^2)	16.9 ± 3.4	18.0 ± 4.0	17.7 ± 4.2
mean SA (mm^2)	8.3 ± 1.6	8.7 ± 1.9	8.5 ± 2.0
mean LA (mm^2)	6.5 ± 2.0	8.1 ± 1.9*	7.8 ± 2.1*
mean PSA (mm^2)	8.6 ± 2.4	9.3 ± 2.8	9.3 ± 2.7
% PSA (%)	50.0 ± 6.7	50.8 ± 6.9	51.6 ± 6.3
mean NIHA (mm^2)	1.9 ± 1.5	0.7 ± 0.9*	0.6 ± 0.8*
% NIHA (%)	22.8 ± 17.4	7.4 ± 9.6*	7.7 ± 9.8*

Values are presented as mean value ± SD.

VA indicates vessel area; SA, stent area; LA, lumen area; PSA, peri-stent area; NIHA, neointimal hyperplasia area

*$p < 0.05$ versus the BMS group

TABLE 3:

Summary of Regression Analysis

	BMS			Taxus SR			Taxus MR		
	coefficient	p value	R-square (%)	coefficient	p value	R-square (%)	coefficient	p value	R-square (%)
PSA post vs NIHA fup	-0.02	0.47	0.07	0.02	0.39	0.18	-0.02	0.25	0.32
DVA vs DPSA	0.94	<0.00	68.6	1.01	<0.00	67.0	1.10	<0.00	80.6
DVA vs NIHA fup	0.04	0.38	0.1	0.02	0.82	0.01	0.04	0.79	0.01

R-square is presented as percentage.

NIHA indicates neointimal hyperplasia area; PSA, peri-stent area; VA, vessel area.

"fup" indicates follow-up; "post", post-procedure.

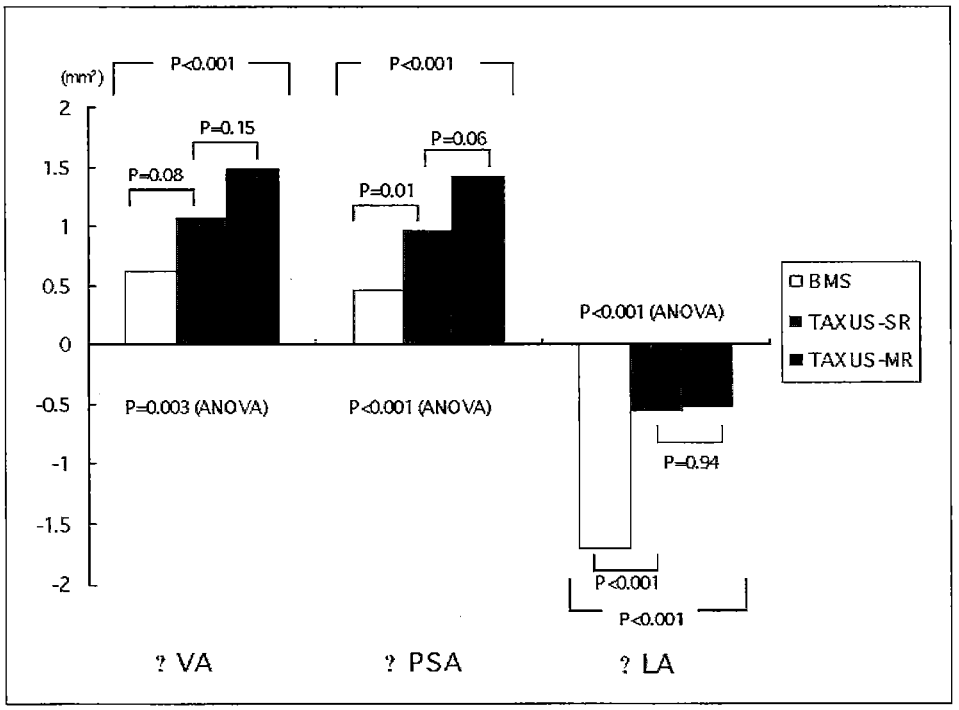

Figure 1 : Changes of quantitative intravascular parameters between post-procedure and 6-month follow-up. VA indicates vessel area; PSA, peristent area; LA, lumen area.

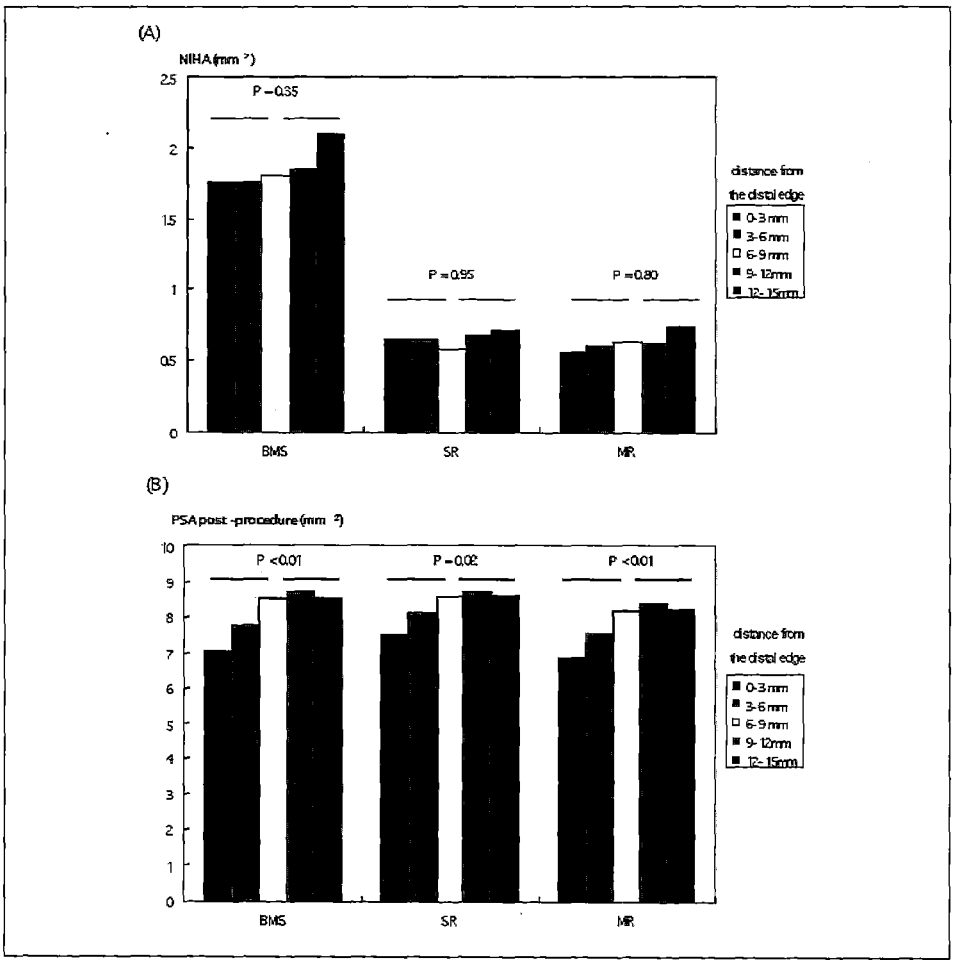

Figure 2 : (A) Distribution of NIHA at follow-up along the length of the stent. (B) Distribution of PSA post-procedure along the length of the stent. NIHA indicates neointimal hyperplasia area; PSA, peri-stent area

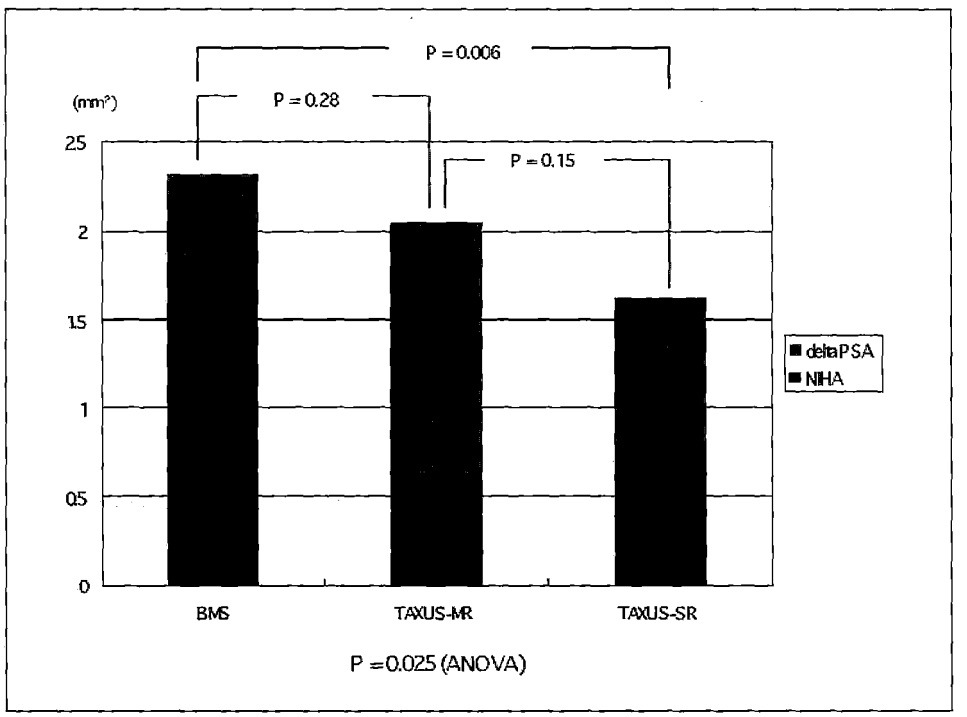

Figure 3 : Comparison of the value of "D PSA + NIHA" among the 3 groups. PSA indicates peri-stent area; NIHA, neointimal hyperplasia area.

CHAPTER 16

EARLY OUTCOME AFTER SIROLIMUS-ELUTING STENT IMPLANTATION IN PATIENTS WITH ACUTE CORONARY SYNDROMES

INSIGHTS FROM THE RAPAMYCIN-ELUTING STENT EVALUATED AT ROTTERDAM CARDIOLOGY HOSPITAL (RESEARCH) REGISTRY

Pedro A. Lemos, Chi-Hang Lee, Muzaffer Degertekin, Francesco Saia, Kengo Tanabe, Chourmouzios A. Arampatzis, Angela Hoye, Joost Daemen, Marco van Duuren, Georgios Sianos, Pieter C. Smits, Pim J. de Feyter, Willem van der Giessen, Ron T. van Domburg, Patrick W. Serruys

J Am Coll Cardiol 2003; 41:2093-9

Journal of the American College of Cardiology
© 2003 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 41, No. 11, 2003
ISSN 0735-1097/03/$30.00
doi:10.1016/S0735-1097(03)00429-7

EXPEDITED REVIEW

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

Insights From the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) Registry

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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 implantation in patients with a high risk for early thrombotic complications is currently unknown.

METHODS Sirolimus-eluting stents 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 four months of enrollment, 198 patients with ACS had been treated exclusively with SES (64% of those treated in the period) and were compared with a control group composed of 301 consecutive patients treated with bare stents in the same time period immediately before this study. The incidence of major adverse cardiac events (MACE) during the first month was evaluated (death, nonfatal myocardial infarction [MI], or re-intervention).

RESULTS Compared with control patients, 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 glycoprotein IIb/IIIa inhibitor utilization (27% vs. 42%; $p < 0.01$). The 30-day MACE rate was similar between both groups (SES 6.1% vs. control patients 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 control patients ($p = 0.4$). In multivariate analysis, SES utilization did not influence the incidence of MACE (odds ratio 1.0 [95% confidence interval: 0.4 to 2.2]; $p = 0.97$).

CONCLUSIONS Sirolimus-eluting stent implantation for patients with ACS is safe, with early outcomes comparable with bare metal stents. (J Am Coll Cardiol 2003;41:000–000) © 2003 by the American College of Cardiology Foundation

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 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 owing 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 in unselected complex cases is presently not known. Sirolimus has been reported 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 aim of this study was to investigate the impact of SES implantation on the occurrence of early adverse events (30 days) in a consecutive series of unselected patients with ACS enrolled in the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry.

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Manuscript received February 12, 2003; revised manuscript received March 15, 2003, accepted March 20, 2003.

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June 4, 2003:000–000

Abbreviations and Acronyms

ACS	= acute coronary syndromes
CI	= confidence interval
MACE	= major adverse cardiac events
MI	= myocardial infarction
OR	= odds ratio
RESEARCH	= Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital registry
SES	= sirolimus-eluting stent
TIMI	= Thrombolysis In Myocardial Infarction

METHODS

The RESEARCH registry. The SES (Cypher; Johnson & Johnson-Cordis unit, Cordis Europa NV, Roden, the Netherlands) received Conformité Européenne mark approval in April 2002, since then being commercially available for routine use in Europe. From April 16, 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 aim 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 before this study. Therefore, the control and the RESEARCH groups are constituted by two 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.

The postprocedural antiplatelet regimen consisted of aspirin lifelong and clopidogrel 75 mg/day for one month (control group and patients treated with bare stent only) or three months (patients treated with SES). Prolonged clopidogrel prescription (six 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.

During the RESEARCH period, according to the actual SES utilization, three 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 nonutilization 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 compared with 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 one year of follow-up. Additionally, the following secondary objectives have also been predefined: 1) short-term (30-day) safety in patients with ACS; 2) survival free of MACE at six-month follow-up; 3) cost-effectiveness analysis at six months and one year; 4) anginal status and medication usage at six months and one year; and 5) quality of life and work status at six months and one year.

In the present study, we report on the 30-day outcomes of patients with ACS treated with SES implantation compared with 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.

ACS substudy: patient population. 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 four months of the RESEARCH registry (from April 16, 2002 to August 15, 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%) were not included in the present analysis. Among patients not included, nonutilization of SES was due to unavailability of an appropriate SES size (diameter or length) in 73% of cases, inclusion in another study in 5%, and impossibility to cross the lesion with the SES in 1%. In the remaining 21% of cases, SES was not utilized owing to a variety conditions related to the operator's personal choice or other "medical/technical issues" (for instance, balloon dilation instead of stent implantation in a small coronary branch, mechanical thrombectomy without stent implantation for vessels with a high thrombotic burden, or heparin-coated stents owing to contraindication for antiplatelet therapy). A control group was comprised of 301 consecutive patients with ACS treated with bare stent implantation during the last four months (from December 16, 2001 to April 15, 2002) before 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 h of an acute MI were classified as rescue or primary angioplasty, if preceded or not by (failed) intravenous thrombolysis, respectively. Patients treated after 24 h but before discharge of an episode of MI were classified as post-MI unstable angina (Braunwald class C).

End point definitions and follow-up. Major adverse cardiac events were defined as: 1) death; 2) nonfatal MI; or 3)

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repeat target lesion revascularization or target vessel revascularization. A definite diagnosis of MI 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 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 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 (Thrombolysis In Myocardial Infarction [TIMI] flow grade 0 or 1) or flow-limiting thrombus (TIMI flow grade 1 or 2) occurring after the procedure (after removal of the guiding catheter) in an artery treated with angiographic success (TIMI flow grade 3 immediately after stent placement and percent in-lesion diameter stenosis ≤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 which they were discharged shortly after the procedure unless a periprocedural complication occurred and/or specialized surveillance was required. In total, patients have been referred from a group of 14 local hospitals. Postprocedure 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 postprocedure MI was suspected. For elective outpatient cases, it has been our practice to discharge the patients after a mean period of observation of 3 ± 1 h (unpublished data), provided no postprocedural 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 not available only for patients in whom the likelihood of postprocedure MI 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 postprocedural 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 six months and one year to all living patients with information regarding postdischarge anginal status, medication usage, and the occurrence of clinical events. Furthermore, a psychological questionnaire was sent and included forms with the Short Form-36 quality of life (17), the Hospital Anxiety and Depression Scale (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.

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. Therefore, a patient can contribute to one, two, or more person-time. This design is of particular interest in a study like the RESEARCH, which intends to evaluate two 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 ACS substudy.

Discrete variables were presented as percentages and compared with Fisher exact tests. Continuous variables were presented by their means and standard deviations and compared with Student *t* test or one-way analysis of variance. 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 of <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 summarized in Table 1. As compared with the control patients, patients treated with SES had

Table 1. Baseline and Procedural Characteristics of Patients Treated With Bare Stents Versus Patients Treated With Sirolimus-Eluting Stents

	Bare Stent (n = 301)	SES (n = 198)	*P* Value
Age, yrs, mean ± SD	60 ± 12	62 ± 11	0.21
Male gender, %	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 CABG, %	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 CK-MB, U/l ± SD‡	317 ± 256	217 ± 236	0.04
Glycoprotein IIB/IIIA 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 of all lesions, %	97	96	0.48

*Relative to the number of patients with unstable angina; total sum may not result in 100% because of rounding; †relative to the number of patients with acute MI; ‡upper limit of normal = 24 U/l.

CABG = coronary artery bypass graft surgery; CK = creatine kinase; LAD = left anterior descending artery; LCx = left circumflex artery; LMC = left main coronary; MI = myocardial infarction; RCA = right coronary artery; SES = sirolimus-eluting stent.

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 U/l vs. 317 ± 256 U/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 one 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; $p = 0.8$ by log-rank test), with most complications occurring in the first week after the procedure (Fig. 1). Stent thrombosis occurred in one patient (0.5%) in the SES group and in five 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 four significant predictors of 30-day MACE identified in the final model. The presence of multivessel disease (odds ratio [OR] 4.4 [95% confidence interval {CI}: 1.8 to 10.8]; $p < 0.01$), cardiogenic shock (OR 3.9 [95% CI: 1.2 to 12.8]; $p = 0.02$), and acute MI at presentation (OR 3.3 [95% CI: 1.4 to 7.6]; $p < 0.01$) were associated with an increased risk of MACE, while right coronary angioplasty

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Table 2. Incidence of Adverse Events at 30 Days in Patients Treated With Bare Stents Versus Patients Treated With Sirolimus-Eluting Stents

	Bare Stent (n = 301)	SES (n = 198)	*P* Value
Death, %	3.0	3.0	1.0
Nonfatal MI, %	1.0	3.0	0.17
TLR, %	2.7	1.0	0.33
TVR (includes TLR), %	2.7	1.0	0.33
Total MACE, %	6.6	6.1	0.85
Thrombotic stent occlusion, %	1.7	0.5	0.41

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

(OR 0.4 [95% CI: 0.2 to 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 to 2.2]; p = 0.97) did not predict the occurrence of adverse events, with virtually no influence on the predictive strength of the model (Fig. 3).

DISCUSSION

In this study, we analyze for the first time the impact of SES implantation on the early outcomes of patients with ACS. Compared with 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.

Patients treated with SES differed in some aspects from patients 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 exposed these patients to a higher procedural risk (23). It seems unlikely that the lower utilization of glycoprotein IIb/IIIa blockers in this group could be explained by a lower risk profile perceived during the procedure because both the control and SES populations were equally composed predominantly of 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 rule out an effect of the drug vehicle (8). Additionally, sirolimus has been reported 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 $\alpha_{IIb}\beta_3$ (9,10,24). Regardless of these contradictory laboratory findings, SES was 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

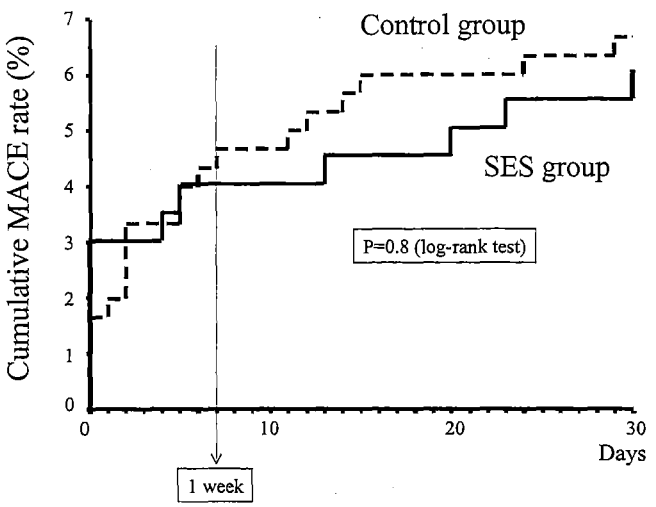

Figure 1. Cumulative major adverse cardiac events (MACE) rate (death, nonfatal myocardial infarction, or re-intervention) during the first month for control patients (bare stent) and patients treated with sirolimus-eluting stents (SES). Note that >50% of events occurred during the first week in both groups.

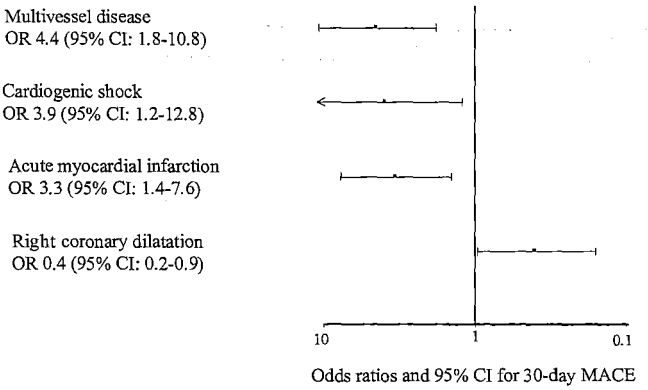

Figure 2. Multivariate independent predictors of 30-day major adverse cardiac events (MACE) rate (death, nonfatal myocardial infarction, and re-intervention) derived from the final logistic regression model. The odds ratios (OR) are shown on logarithmic scale together with their 95% confidence interval (CI).

postprocedural complications compared with control patients, 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.

STUDY LIMITATIONS

The present investigation suffers from the inherent limitations of a nonrandomized 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 daily clinical practice. Postprocedure cardiac markers were not collected routinely for all patients (available for 42% of control patients 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 patients with and without postprocedure enzymes collected, the 30-day death rate was 7.1% versus 0% ($p < 0.001$) and the re-intervention rate was 4.7% versus 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 glycoprotein IIb/IIIa 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).

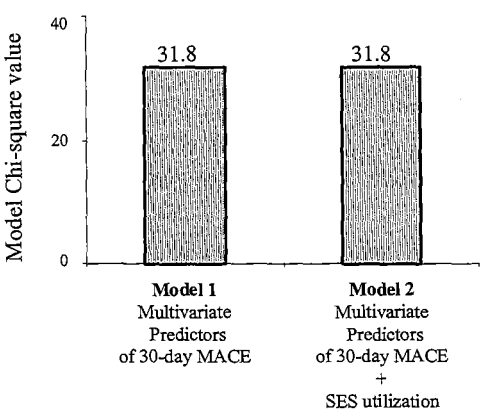

Figure 3. Comparison of the strength (chi-square values) for the prediction of 30-day major adverse cardiac events (MACE) rate (death, nonfatal myocardial infarction, and re-intervention) of multivariate models. Model 1 is the final model selected in the logistic regression analysis and included the variables displayed in Figure 2. The forced inclusion of sirolimus-eluting stent (SES) utilization (Model 2) did not enhance the predictive strength of the model, as reflected by the negligible change in the chi-square values.

CONCLUSIONS

Sirolimus-eluting stent implantation for patients with ACS 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 the treatment of complex cases, such as those commonly found in daily practice. Further evaluation in the context of randomized trials is warranted to confirm the results observed in the present study.

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CHAPTER 17

VERY LONG SIROLIMUS-ELUTING STENT IMPLANTATION FOR DE NOVO CORONARY LESIONS: A PROSPECTIVE CLINICAL AND ANGIOGRAPHIC STUDY FROM THE RESEARCH REGISTRY

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Submitted

Very Long Sirolimus-Eluting Stent Implantation for de novo Coronary Lesions: A Prospective Clinical and Angiographic Study From the RESEARCH registry

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ABSTRACT

Long length stenting has a poor outcome when bare metal stents (BMS) are utilized. The safety and efficacy of SES in longer stented segments has not yet been evaluated. Therefore, the aim of the present study was to evaluate the clinical and angiographic outcomes of sirolimus eluting stent (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, stents were available in lengths of 8, 18, and 33 mm. The present report included a predefined 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 a 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). 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 overall incidence of major cardiac events was 8.3%. As a conclusion; sirolimus eluting stent implantation appears safe and effective for *de novo* coronary lesions requiring multiple stent placement over a very long vessel segment.

INTRODUCTION

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 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 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 longer than 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 (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital) registry. Further details of the methodology has been previously described [10].

Study group and Stent Implantation: During the RESEARCH, sirolimus-eluting stents were available at lengths of 8, 18, and 33 mm. The present report included a pre-defined study population composed by 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 com-

posed 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 study protocol was approved by the hospital ethics committee 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). 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 minimal luminal diameter immediately after the procedure and at follow-up.

Statistical Analysis: Discrete variables were presented as counts and percentages. Continuous variables were presented as mean±SD deviation and compared by Student's T test.

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 arery (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 are summarized in Table 3.

Two patients died. One patient died during the in-hospital period after emergent bypass surgery for procedure related left main stem dissection. The other was admitted with post-myocardial infarction angina with cardiogenic shock. 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 can not 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 nitroprusidde infusion. At 6 months follow-up angiography, patient was asymptomatic with patent long stented segment.

Two patients underwent emergency bypass surgery for left main dissection. The patient who died in hospital (mentioned above). The other patient had also left main stem dissection during the index procedure with cardiogenic shock and underwent successful emergent bypass surgery.

A total of 4 patients were successfully treated with repeat PCI electively for focal restenotic lesions. Follow-up IVUS were available in 3 out of 5 patients presented with in-stent restenosis and in 1 patient the focal restenotic segment were located at the overlapped stented segment. 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 restenosis and 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 BMS for long segments, ranging from 0.79 to 1.41 mm[1,3-5] (Table 4). 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 BMS.

Longer stented segment length using BMS is an independent predictor of restenosis and adverse events [1]. Long stenting is frequenlty 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 (61 mm on average).

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 easier to treat successfully with repeat PCI. Since all patients with angiographically visible gaps between stents were exluded 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 of thrombosis might increase after implantation of long length of stent. In current study, no documented thrombotic stent occlusion was observed, although we can not rule out stent thrombosis in the patient that suddenly died 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.

Study Limitations: 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. Additionally, Not having a follow-up IVUS for all restenotic patients is unfortunate to exactly evaluate the mechanism and localization of restenosis in all patients with restenosis.

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

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TABLE 1:
Baseline patient demographics and procedural data

		Patients with longer stented segment n=96 (102 lesions)
Age (years)		64±12
Male (%)		62
Diabetes (%)		18
Current smoking (%)		26
Hypercholesterolemia (%)		57
Hypertension (%)		45
Previous MI (%)		32
Previous Balloon Angioplasty (%)		19
Target vessel	LAD (%)	47
	LCX (%)	9
	RCA (%)	44
Chronic Total Occlusion (%)		20
Primary PCI,(%)		8
Glycoprotein IIb/IIIa inhibitor use (%)		31
Mean number of SES per lesion		2.66±0.9 (range 2-6)
Mean length of SES per lesion, (mm)		61.2±21.4 (range, 41-134mm)
Mean diameter SES (mm)		2.82 ± 0.24

MI: myocardial infarction, PCI: percutaneous coronary artery, LAD: left anterior descending artery, LCX: left circumflex artery, RCA: right coronary artery, SES: sirolimus-eluting stent.

TABLE 2:
Quantitative coronary angiography analysis post-procedure and at 6-months of the patients with follow-up data (n=67).

Post-procedure	**Proximal 5mm**	**In-stent**	**Distal 5mm**
Vessel reference diameter (mm)	3.17 ± 0.55	2.68± 0.51	2.45 ± 0.51
Minimal lumen diameter (mm)	2.76 ± 0.54	2.17 ± 0.47	1.94 ± 0.53
% diameter stenosis	12	18	20
6-month follow-up			
Vessel reference diameter (mm)	3.30±0.61	2.82 ± 0.59	2.63 ± 0.62
Minimal lumen diameter (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

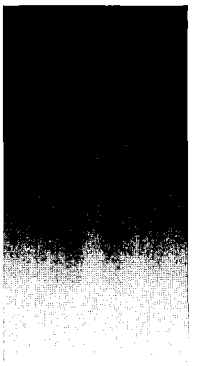
TABLE 3:
Major Adverse Cardiac Events (n=96)

Mean 320 Days follow-up	**N (%)**
Death	2 (2.1)
Non-fatal myocardial infarction	1 (1.0)
Target vessel revascularization	6 (6.2)
Target lesion revascularization	4 (4.2)
CABG	2 (2.1)*
Any major adverse cardiac event	8 (8.3)

CABG; coronary artery bypass graft surgery
* One of 2 patients who underwent emergency CABG for left main stem dissection died in hospital.

TABLE 4:
RESEARCH data compared with published data of long stenting procedure performed using bare metal stent

Trials	Number of Patient	The Length of Implanted Stent (mm)	Reference Vessel Diameter (mm)	Late Lumen Loss (mm)	Restenosis Rate (%)
IMPULSE (4)					
Single Stent Grp	62	32	3.04	1.18	37
Two stents Grp	62	33	3.04	1.14	38
TULIP (5)					
IVUS Guided Grp	73	42	2.95	1.20	23
Angiography Grp	71	35	2.96	1.33	46
ADVANCE (3)	124	—	2.80	0.79	27
Kobayashi (1)	247	52	2.95	1.41	47
RESEARCH	**67**	**61**	**2.68**	**0.13**	**12**



CHAPTER 18

ACTINOMYCIN ELUTING STENT FOR CORONARY REVASCULARIZATION: A RANDOMIZED FEASIBILITY AND SAFETY STUDY (THE ACTION TRIAL)

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Submitted for publication

Actinomycin Eluting Stent for Coronary Revascularization: A Randomized Feasibility and Safety Study (The ACTION Trial)

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ABSTRACT

Background- Drug-eluting stents (DES) releasing sirolimus or paclitaxel almost abolish restenosis. The antiproliferative drug, Actinomycin-D, highly effective in reducing neointimal proliferation in preclincal studies was selected for clinical evaluation.

Methods and Results- The multi-center, single blind, 3-armed Action Trial, randomized 360 patients to receive a DES (2.5 or 10 mcg/cm^2 of Actinomycin-D per stent), or a metallic stent (MS). The primary endpoints at 30 days were Major Adverse Cardiac Events (MACE), and at 6 months diameter stenosis by angiography and tissue effects and neointimal volume by Intravascular Ultrasound (IVUS). When early monitoring revealed an increased rate of repeat revascularization the protocol was amended to allow for additional follow-up for DES patients. Angiographic control of MS patients was no longer mandatory. The biased selection of the DES patients undergoing IVUS follow-up invalidated the interpretation of IVUS findings.

The late lumen loss in-stent and at the proximal and distal edges was higher in both DES groups when compared with MS and resulted in higher six months and one year MACE (34.8 % and 43.1% vs 13.5%) driven exclusively by target vessel revascularisation (TVR) without excess death or MI.

Conclusions: the results of the Action trial indicate that all antiproliferative drugs will not uniformaly show a drug class effect in the prevention of restenosis.

Introduction

Restenosis after Percutaneous Coronary Intervention (PCI) remains a major limitation of efficacy[1]. The concept of further reducing restenosis by coating a stent with an appropriate medication that elutes has great appeal. The stent can abolish recoil and negative remodeling while a drug can be delivered in sufficient concentration directly to the injured site potentially limiting the intimal hyperplastic component of restenosis[2].

Delivery platforms incorporating sirolimus[3,4] and paclitaxe[5,6] almost completely abolish restenosis in simple lesions but efficacy has yet to be demonstrated in more complex lesions.

Actinomycin-D affects the "S"phase of the cell cycle by forming a stable complex with double-stranded DNA inhibiting RNA synthesis and is a powerful inhibitor of cell proliferation. To create the Actinomycin-D stent, Actinomycin was coated onto the stainless steel Multilink Tetra stent in a polymer.

Following preclinical studies, the ACTION Trial (Actinomycin eluting stent Improves Outcomes by reducing Neointimal hyperplasia), the first clinical evaluation of the Multi-Link Actinomycin-D coronary stent system aimed to test the safety and efficacy of 2 doses of Actinomycin-D compared with the MULTI-LINK TETRA MS.

Methods

Study design

This was a prospective, randomized, parallel, 3-arm, single-blind trial with two doses of Actinomycin-D (2.5 and 10 mcg/cm^2) coated on the Actinomycin eluting stent compared with the uncoated MULTI-LINK TETRA stent as the control. The protocol was approved by the ethics committees of each of the 28 participating institutions (appendix) and all patients gave written informed consent.

Endpoints

The primary safety endpoints were MACE at 30 days, and local tissue effects at 6 months (incomplete stent apposition, persisting dissection, edge stenosis and thrombus formation). MACE was defined as a composite of death, Q-wave myocardial infarction (QMI), non-Q-wave myocardial infarction (NQMI), more than 3 times the upper limit of normal CK levels and revascularization by surgery (CABG) or repeat PCI attributed to the target site (the stented segment including 5 mm proximal and distal to the stent). When target vessel (vessel containing the target site) revascularization was included in MACE, the composite end-point was re-named target vessel failure (TVF).

The primary performance endpoints were, at 6 months, the reduction of in-stent volumetric burden assessed by IVUS and reduction of target site angiographic diameter stenosis.

The secondary performance endpoints were TVF at 6 and 12 months and angiographic binary restenosis at 6 months.

Power calculation and sample size

To detect a difference of 6.6% in diameter stenosis and of 11.5mm^3 in intimal hyperplasia with a significance level of 0.05 and 90% power, 110 patients would be needed in each of the 3 arms. A sample size of 120 patients was chosen.

Patient selection

Patients were eligible for the study if they were able to comply with the study protocol, were over 18 years of age, and had angina pectoris or silent ischemia. Additional eligibility criteria were the presence of a single de novo ≥ 50-< 100% diameter stenosis, in a native coronary artery that was ≥ 3.0 mm and ≤ 4.0 mm in diameter by visual estimate, that could be covered by an 18mm stent. Blood flow was required to be TIMI grade 1 or higher. Patients were ineligible if they had an evolving MI, had an unprotected left main coronary stenosis equal to or greater than 50 percent, an untreated lesion of 40% diameter stenosis proximal or distal to the target site, an aorto-ostial lesion, a calcified lesion without successful predilatation, or had intolerance of aspirin, clopidogrel or ticlopidine.

Randomization was done by a telephone allocation service.

Study device

The 3 components of the investigational device were the Multilink Tetra stent, a polymeric coating and an anti-proliferative drug, Actinomycin-D [7,8].

The flat phenoxazone and large polypeptide rings of Actinomycin-D form a stable complex with double-stranded DNA (via deoxyguanosine residues), thus inhibiting DNA-primed RNA synthesis. The 2.5 and 10 micrograms (mcg) per cm^2 of metal stent surface area of Actinomycin-D used in the polymer-coated stent is equivalent to <1% to <2% of the recommended daily total chemotherapy dose of 500 mg given intravenously for 5 days to adults. The eluting profile of Actinomycin-D is targeted to release 80% of drug in 28 days.

Stenting procedure

Stents were 18 mm in length and 3.0, 3.5 or 4.0 mm in diameter.To avoid vessel damage outside the stent predilatation and postdilatation balloons shorter than the stent were recommended. For major dissections or abrupt occlusions in the DES arms, a single bailout stent from the same randomization arm was allowed. Clopidogrel 75 mg daily was to be administered for 6 months and aspirin 100-325 mg daily for at least 1 year after the procedure.

Quantitative Coronary Angiographic Evaluation

In quantitative angiographic analyses, binary restenosis and late loss were determined in-stent and within the target site [4]. The "vessel segment" was defined as that portion of artery bounded by side-branches proximal and distal to the target site. Coronary aneurysms were defined on angiography as localised coronary artery dilatation ≥ 1.5 x reference diameter. [9]

Quantitative Intravascular Ultrasound

Target site IVUS evalutation was performed as previously described. [10,11,12]

Statistical analysis

All analyses were based on the intent to treat principle. For continuous variables, differences between the treatment groups were evaluated by analysis of variance or Wilcoxon's rank-sum test. For discrete variables, differences were expressed as counts and percentages and were analysed with Fisher's exact test.

Event free survival times were analyzed using the Kaplan-Meier method. Differences between each of the doses and the MS were compared with the use of the Wilcoxon and log-rank test.

All tests are 2-sided and unadjusted for multiple comparisons.

Study organization

The Data and Safety Monitoring Board (DSMB), and the Clinical Events Committee were separate groups independent from the study, that monitored safety and adjudicated clinical endpoints respectively. The angiographic and ultrasound core laboratory (Cardialysis BV, Rotterdam, the Netherlands) was blinded to the treatment and clinical outcomes and assessed each imaging modality independently. The trial sponsor was Advanced Cardiovascular Systems, Inc., a subsidiary of Guidant Corporation, Santa Clara, CA.

Results

Patient baseline characteristics

Between August 2001 and November 2002, 360 patients were randomly assigned to receive a DES with a dose of 2.5 mcg/cm^2 (120 patients) or 10 mcg/cm^2 (121 patients), or a MS (119 patients). Three patients (1 in the MS arm and 2 in the 10 mcg DES arm) were deregistered as they did not receive either a DES or control stent. Baseline clinical and angiographic characteristics (Table 1) did not differ between treatment groups except that there were fewer diabetic patients in the MS group. The significant difference in minimal lumen diameter (MLD) post procedure between the MS and DES groups could not be accounted for by procedural differences.

Patient enrolment, procedural characteristics, and clinical outcomes in-hospital and at 1 month

There was adherence to the randomization in all but one patient. Post dilatation was performed in 37% of the patients with an average pressure of 14.8 atmospheres. The procedural success was 99%. Platelet glycoprotein IIb/IIIa inhibitors were administered to 16% of patients.

A second DES for a suboptimal result was implanted in 15 patients who were analysed on an intention to treat basis.

The in-hospital MACE were confined to the 4 patients (1.1%) with non-Q MI. MACE rates at 30 days ranged between 0.8 and 2.5%, without differences between groups.

However, early monitoring of a subset of 39 DES patients angiography revealed an increased rate of TSR suggesting that the investigational device was not performing as intended. After the sponsor informed the principal investigator and the DSMB, the following recommendations were made: 1. Accelerated angiographic follow-up for DES patients. 2. A second angiographic and clinical follow-up 6 months later. 3. Possible re-intervention for moderate restenosis (>30% DS). 4. Extension of clopidogrel administration for at least a further 6 months for DES patients. 5. Angiographic and IVUS follow-up was no longer mandatory for MS patients as primary performance endpoints could not be reached. Consequently, only 65 of 118 MS patients underwent imaging and 101 clinical follow-up at 6 months.

Angiographic outcomes

The late loss and restenosis at 6-months in-stent and in-lesion were higher in both DES groups compared with MS (Table 2). Aneurysm formation was infrequent with 2 (3.1%) in MS and 5 (2.2%) in DES patients.

Clinical outcomes at 12 months

At 12 months, MACE and TVF were higher in the DES than in the MS patients due mainly to increased TSR (Table 3). Of the 2 deaths, the one with a MS was sudden at 44 days and the one with low-dose DES was due to MI at 306 days. After 30 days, there were 2 additonal non-QMIs in the low dose and 1 in the high dose DES arms. To 1 year, there were 14 DES patients who had a second reintervention and in 2 a third reintervention.

IVUS outcomes

There was late-acquired incomplete stent apposition (ISA) in 6 patients in the low dose and 7 in the high dose group but there was late persisting dissection in only 1 patient who was from the high dose group.

At variance with the angiographic findings, there were apparently no differences between groups in volumetric obstruction measured by IVUS. This discrepancy may result from a biased selection of the DES patients undergoing IVUS during follow-up (Table 4), as demonstrated by the higher binary "vessel segment" restenosis rate (32% and 47.8%) in the DES patients who did not undergo IVUS follow-up, when compared with those who did (25.8% and 23.7%). This biased selection of the DES patients undergoing IVUS during follow-up invalidated interpretation of the IVUS findings. Directional atherectomy, a standard treatment for in stent restonosis, retrieved restenotic material in 7 patients. Histopathological analysis revealed presence of proteoglycan matrix and smooth muscle cells interspersed with collagen type III. There were rare foci of CD68 positive macrophages and T lymphocytes (CD45 Ro). Cell proliferation identified by Ki 67 antigen staining was also rare. Incidentally some areas showed the presence of persisting fibrin consistent with delayed healing.) (See Figure 2)

Discussion

Summary

The results of this trial showed that while in-hospital and 1 month outcomes were similar in each group, by 6 months there was increased restenosis, late lumen loss, and target site revascularization in the DES arm. Despite this increased rate of restenosis, mortality and rate of myocardial infarction were very low in ACTION, contrasting with the medium or long-term follow-up of the SCORE study (unpublished data, personal communication from M. Russel MD) showing high incidence of late death and myocardial infarction. In addition, the relatively benign nature of the restenotic pathological material retrieved by DCA contrasts with that from patients treated with QuaPDs stents, where in some specimens there were large aggregates of macrophages and T-lymphocytes suggesting a persisting active inflammation process with a high proliferation index (Ki-67 immunostaining) [13].

Preclinical Studies

The safety of the polymer, was demonstrated in the porcine coronary model, where the histological response was similar to MS to 180 days.

DES with 4 doses of Actinomycin-D (2.5, 10, 40 and 70 mcg/cm2) were evaluated in preclinical studies in the porcine coronary model by angiography, histomorphometry and histopathology at 28 days. At this time, all vessels were patent and there was marked suppression of neointimal formation above the stent with all doses. Neointimal thickness above the internal elastic lamina was equivalent to that with the MS. Medial thinning and necrosis was observed in the high dose groups, as was positive remodeling. Intimal fibrin deposition and inflammation were present with all doses but most marked with the higher doses. Based on these preclinical findings, the two lower doses were considered safe for further evaluation in humans with 3 months data pending.

Long-term animal data and lessons learned from this trial

At the time of the design of this trial it was current practice for MS, which was extended to DES, to commence clinical investigation following analysis of 28-day animal data.[3] As soon as the sponsor became aware of the clinical events and the outcomes of long-term animal data, immediate action, as previously described, was taken. This trial has demonstrated that 28-day animal data do not provide sufficient information to judge safety and efficacy of DES. In the light of animal results at 3 months and the results of the Action trial, it is now reasonable to conclude that medial necrosis and inflammation at 28 days are predictors of poor outcomes at 3 months. Efficacy may not be predictable from 28 day data and 3 month data may be needed especially if the balloon-to-artery ratio for stent deployment is 1.1:1.

Methodological implications of an early detection of lack of efficacy

Traditionally it has been believed that the histological results observed in pigs at 30 days correspond to the anatomo-morphologic change documented in humans at 6-months and similarly animal observations made at 3 months should be correlated to some extent with the anatomical findings made in humans at 18 to 24 months. Since there was deterioration in the histological findings in animals between 30 and 90 days, there was a concern that there would be deterioration in patients between 6 and 18 months. Therefore, a policy of accelerated angiographic follow-up (before 6 months) with possible intervention for moderate restenosis >30% DS even in asymptomatic patients were implemented and a second angiographic investigation 6 months later was recommended. As a consequence, a bias toward MACE (re-intervention) in the DES patients cannot be excluded.

As primary performance endpoints could not be reached, angiographic and IVUS follow-up was no longer mandatory for MS patients. This lead to bias in the MS group towards higher MACE because of selection of symptomatic patients for follow-up angiography. Counterbalancing this there may be a bias towards lower MACE in the MS group, because of lower angiography driven repeat intervention in asymptomatic patients [14].

IVUS in restenotic lesions in the DES groups was not pursued with the same assiduity as seen in a trial with favourable outcome resulting in a disproportionately low number of severe restenoses studied with IVUS. This latter phenomenon led us to declare invalid the comparison of neointimal volume and percent volume obstruction between the 3 groups. However, serial IVUS analyses, although biased towards patients without restenosis, revealed significant increase in the plaque behind the stent struts which was higher in the 10 mcg group (32±39 mm^3 $p<0.001$, n=55) than in the 2.5 mcg (21±29 mm3 $p<0.001$, n=52) and control MS (18±45 mm^3 $p=0.11$, n=17) group. In addition, the serial analysis of the 5mm proximal and distal edges of the stent in the 10mcg group showed a significant increase (+7±10 mm^3 and +7±13 mm^3,

$p<0.001$) in plaque (vessel volume-lumen volume) resulting in a decrease (-4±12 mm^3 and -6±14 mm^3,$p<0.01$) in lumen volume in absence of change in vessel volume. Since cell culture experiments did not show signs of paradoxically increased proliferation of smooth muscle cells with Actinomycin-D concentrations down to of 10^{-12} Molar these IVUS findings may be interpreted as signs of cytotoxicity with late inflammatory and proliferative response.

Conclusion

The impressive results observed in the first drug-eluting stent trials with sirolimus and paclitaxel have led to speculation that any antiproliferative DES would have a beneficial effect on restenosis. However, the ACTION trial shows that there is no class effect and all antiproliferative drugs are not effective in the prevention of restenosis. It has become clear that promise in early pre-clinical studies (30 days) does not necessarily translate into clinical effectiveness at 6 months and that late safety animal data (90 days) is a prerequisite for clinical investigation [15].

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TABLE 1:
Baseline clinical and angiographic characteristics of each study group

	MS (n=118)	2.5 mcg (n=120)	10 mcg (n=119)
Age, years (mean ± SD)	60 ± 10	61 ± 11	60 ± 11
Gender, male	78	78	80
Previous MI	41	38	37
Diabetes mellitus*	5	15	11
Treated dyslipidemia	53	58	54
Treated hypertension	50	49	45
Current smoker	30	23	29
Angina pectoris†			
CCS Class I	7	4	4
CCS Class II	34	34	35
CCS Class III	21	21	23
CCS Class IV	15	14	13
Target coronary artery			
LAD	37	44	42
RCA	42	40	35
LCX	21	16	23
Lesion type			
A	7	7	2
B1	23	21	29
B2	66	64	64
C	4	8	5
Reference vessel diameter, (mm)	2.83	2.84	2.91
Lesion length, (mm)	11.3	11.6	10.7
MLD pre, (mm)	1.00	1.01	1.04
MLD post, (mm)	2.64	2.78	2.82
Diameter stenosis pre	64	64	63

Plus-minus value are means ±SD; Unless indicated otherwise, all data are presented as percent of patients.
MI = myocardial infarction; LAD = left anterior descending; RCA = right coronary artery; LCX = left circumflex.; MLD = minimal luminal diameter
* Difference and 95% CI in incidence of diabetes; Control vs 2.5 mcg/mm^2: –9.9% [-17%, -2.3%]; Control vs 10 mcg/ mm^2: –5.8% [-12%, 1.02%]. † Angina was defined according to the system of the Canadian Cardiovascular Society (CCS). In the 2.5 and in the 10 mcg groups there were 7 and 8 lesions receiving 2 Actinomycin-D-stents respectively.

TABLE 2:
Serial QCA analyses

	MS (n=65)	2.5 mcg (n=114)	P	10 mcg (n=115)	P
In-Stent					
MLD Post mm	2.64±0.34	2.77±0.45	0.02	2.82±0.43	0.002
MLD FUP mm	1.88±0.58	1.76±0.70	0.25	1.90±0.68	0.87
Late loss mm	0.76±0.43	1.01±0.58	0.001	0.93±0.58	0.03
Restenosis %	11	25	0.03	17	0.38
Edges					
Prox MLD Post mm	2.60±0.53	2.73±0.58	0.12	2.79±0.56	0.02
Prox MLD FUP mm	2.32±0.60	2.22±0.67	0.35	2.26±0.76	0.58
Prox Late loss mm	0.28±0.38	0.51±0.52	0.002	0.53±0.61	<0.001
Prox Restenosis %	3	5	0.71	14	0.02
Distal MLD Post mm	2.31±0.56	2.40±0.58	0.32	2.41±0.58	0.25
Distal MLD FUP mm	2.23±0.53	2.05±0.61	0.05	1.99±0.64	0.009
Distal Late loss mm	0.08±0.31	0.35±0.50	<0.001	0.43±0.57	<0.001
Distal Restenosis %	2	4	0.65	6	0.26
Target site*					
DS %	35±15	40±18	0.08	40±19	0.05
Restenosis %	14	26	0.06	28	0.04
Vessel segment					
IRD FUP mm	2.76±0.58	2.71±0.55	0.58	2.78±0.48	0.81
DS %	37±13	41±18	0.11	41±18	0.06
Restenosis rate	14	27	0.04	28	0.04
Median time of angio-fup days	162±53	161±40	NS	160±41	NS

Continuous variables: T-Test (two sided) compared to MS control arm. Discrete varaibles: Fishers exact two sided test compared to MS control arm.* Target site diameter stenosis- primary performance endpoint; intention to treat analysis. MLD = minimal luminal diameter; Prox = proximal; DS = diameter stenosis; IRD = … Reference Diameter

TABLE 3:

Most severe (hierarchical) and total count of cardiac events up to 12 months in each treatment group

	MS n=104*	2.5mcg n=120 ±	P Value	10mcg n=119±	P Value
Death, n (%)	1 (0.8)	1(0.8)	ns	0 (0.0)	ns
Myocardial infarction					
Q-wave, n (%)	0 (0.0)	0 (0.0)	ns	0 (0.0)	ns
Non Q-wave, n (%)	1 (1.0)	2 (1.7)	ns	4 (3.4)	ns
Target Site Revascularization					
CABG, n (%)	1(1.0)	0 (0.0)	ns	5 (4.2)	ns
PCI, n (%)	11 (10.6)	37(30.8)	<0.001	41 (34.5)	<0.001
Hierarchical MACE: n (%)±	14 (13.5)	40 (33.3)	<0.01	50 (42.0)	<0.001
Event-free survival, n (%)	90 (86.5)	80 (66.7)		69 (58.0)	
Target Vessel Revascularization (CABG and PCI) n (%)	3 (2.9)	4 (3.3)	ns	1 (0.8)	ns
Target vessel failure, n, (%) §	17 (16.3)	44 (36.7)	<0.001	51 (42.9)	<0.001
Total count of events, n (%)	16	45		61	

CABG = coronary artery bypass graft; PCI; percutaneous coronary intervention; MACE = major adverse events

* Follow-up no longer mandatory for MS group, therefore for 14 patients no follow-up available.

† For 5 and 3 patients in the 2.5 and 10 mcg group respectively no follow-up case report forms have been received, however, these patients have been contacted and all are alive and had no other MACE at 12 months follow up timeframe.

‡ Includes Death, MI, Target Site Revascularization

§ Includes Death, MI, Target Site Revascularization and / or Target Vessel Revascularization

p-values are displayed for descriptive purposes only since they were not the result of formally planned statistical hypothesis testing, and have not been adjusted for multiple comparisons

TABLE 4:

Incidence of vessel segment restenosis in patients with and without IVUS

	MS	2.5 mcg	10 mcg
Vessel segment restenosis			
Patients with IVUS n (%)	4/39 (10.3)	23/89 (25.8)	22/93 (23.7)
Patients without IVUS n (%)	5/26 (19.2) *p = 0.47	8/25 (32.0) p = 0.61	11/23 (47.8) p = 0.037

*Fischer's exact test

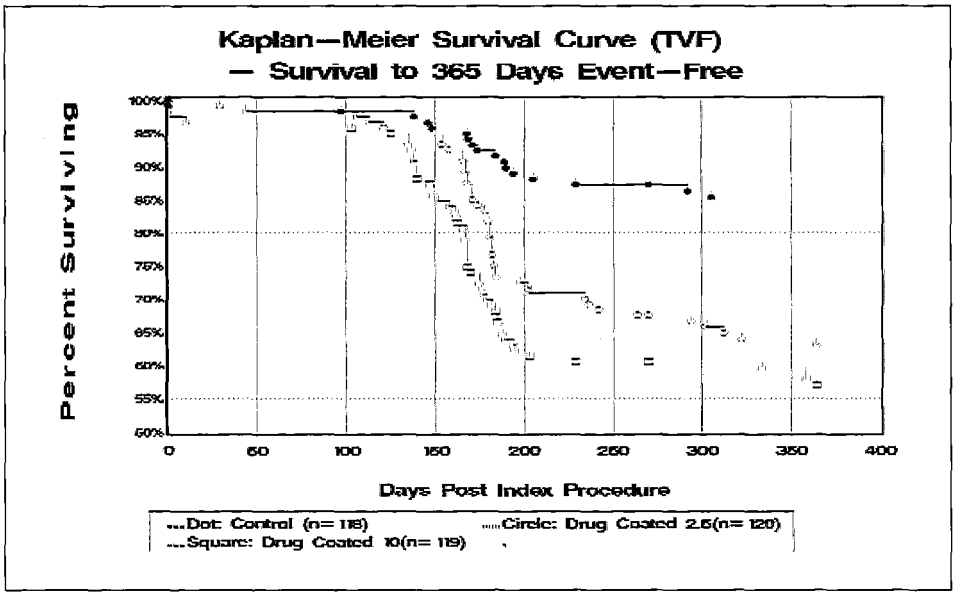


Figure 1: Kaplan-Meier estimates of survival free of repeated target site revascularization among patients who received Actinomycin-eluting 2.5 and 10 mcg stents and those who received standard stents.
The rate of event-free survival was significantly higher in the control stent group than in the Actinomycin stent group (P < by the Wilcoxon and log-ranks tests).

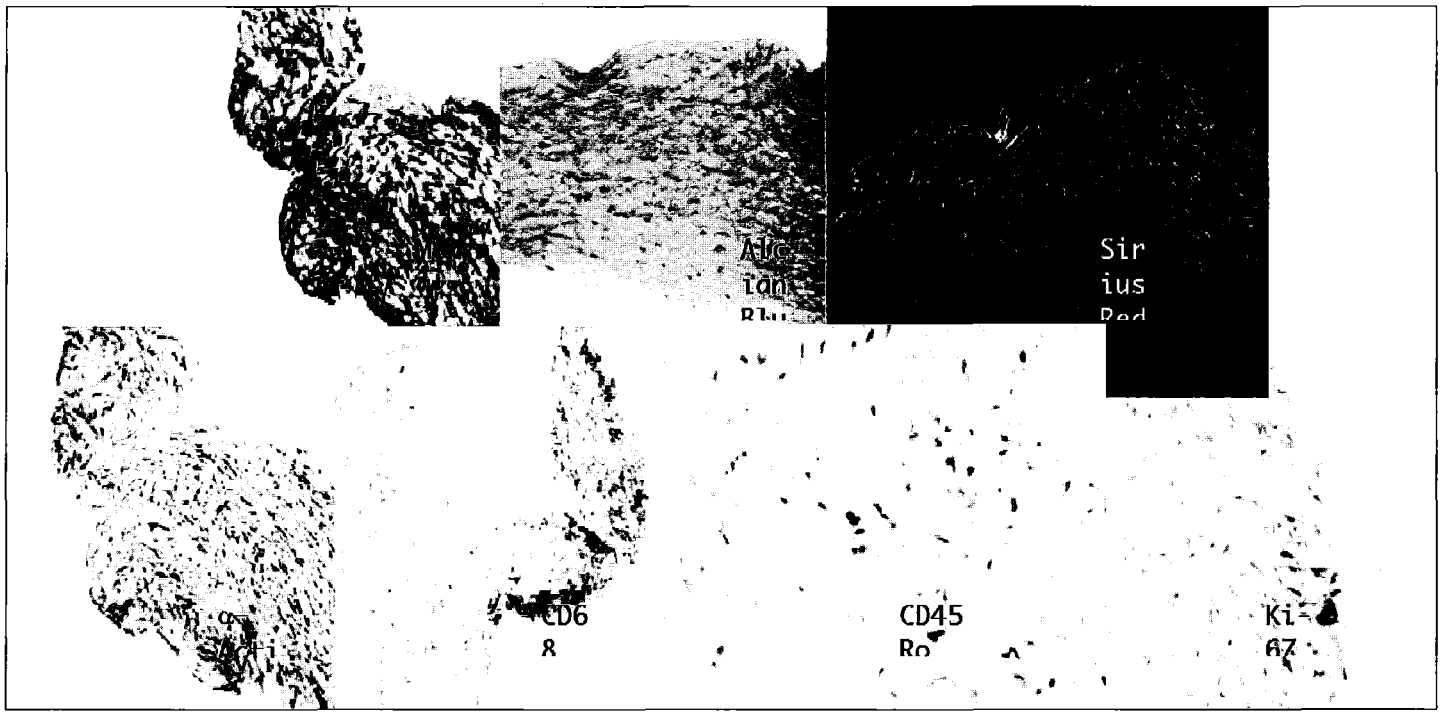
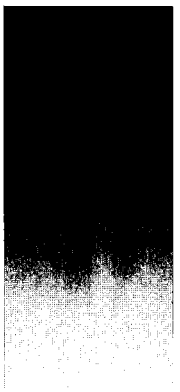


Figure 2: Atherectomy specimen of restenosis tissue. The Movat pentachrome stain shows a tissue fragment consisting mostly of SMCs proteoglycan matrix and focal fibrin accumulation (arrows). Alcian blue stain demonstrating proteoglycans.
Sirius red shows a green birefringence consistent with collagen type III. There were rare foci of CD68-positive macrophages andT-lymphocytes (CD45Ro). Cell proliferation identified by Ki-67 antigen staining was also rare.



SUMMARY AND CONCLUSIONS

Coronary stent implantation represents a major advance in the treatment of obstructive coronary artery disease since the development of balloon angioplasty. However, in-stent restenosis (ISR) remains the most important limitation after stent implantation. An enormous number of studies had been devoted to the prevention of ISR. Attempts to reduce the risk of restenosis using different pharmacological and mechanical methods were unsuccessful. Recently, drug eluting stents (DES) have been emerged as a novel technology in reducing restenosis. In this thesis, we report the first clinical application of DES and detailed three dimensional intravascular ultrasound (IVUS) analysis after implantation of DES.

In-stent restenosis (Part-I)

In the first part of this thesis the evolution of percutaneous coronary intervention and the role of coronary stenting in the treatment of coronary artery disease were summarized. In chapters 1 and 2, we overview ISR problem of bare metal stents and the complex restenosis phenomenon. Stents provide mechanical scaffolding that virtually eliminates recoil and remodeling and that neointimal hyperplasia is the major reason for in-stent restenosis.

Drug eluting stents: A potential solution (Part-II)

As a new strategy to tackle the problem of ISR, the concept of using stents coated with different drugs that potentially inhibit neointimal hyperplasia has been evaluated. In the second part of this thesis (chapters 3 and 4), we endeavour to summarize the ongoing researches and technological improvement in the field of the DES. Preclinical studies of sirolimus and paclitaxel eluting stent demonstrated a significant reduction in in-stent neointimal hyperplasia. Recently, these preclinical findings were confirmed by promising data from clinical studies using sirolimus and paclitaxel.

First clinical experiences with sirolimus eluting stents (Part-III)

When a new technology emerges, assessing its safety, efficacy and clinical impact is of utmost importance to implement this treatment modality into routine clinical practice. Sirolimus eluting stents (SES) have been proved to be able to significantly reduce ISR in de-novo lesions. However, there are some concerns regarding long-term follow-up and detailed IVUS findings of this new technology.

The goal of the chapter 5 was to provide a more detailed morphological analysis of the local biological effects after implantation of a SES versus an uncoated (bare) stent by intravascular ultrasound. The difference in amount of in-stent neointimal hyperplasia at 6 months between SES and bare stents was highly significant, reflecting the nearly complete abolition of the in-stent proliferative process after DES implantation. Although the incidence of incomplete stent apposition at 6 months was higher in the SES group, the interpretation of the data is limited by the lack of baseline IVUS data immediately after stent implantation.

Side branch occlusion, a well-recognized complication of percutaneous coronary stenting, was reported to occur in up to 19% of cases after bare metal stent implantation. However, the fate of side branches after SES implantation remains unknown. In chapter 6, we investigated the

issue that sirolimus might potentially behave the same way as brachytherapy; and have the potential to delayed the healing process which may lead to a higher rate of side branches occlusion. In contrast to brachytherapy, we have shown that the SES did not adversely affect the spontaneous recanalization. The fate of side branches after SES implantation is favorable and at least as good as after bare metal stent implantation.

We also investigated the efficacy of SES in subsets of patients with complex lesions and high risk of restenosis. ISR lesions may respond differently from *de novo* lesions, particularly since this represents a second episode of barotraumas to the vessel. In chapters 7 and 8, we showed that the SES implantation for the treatment of severe ISR lesions effectively prevents neointima formation and recurrent ISR. In particular, IVUS analysis have demonstrated that sirolimus-eluting stenting is equally effective at inhibiting neointimal proliferation in de novo as well as in ISR lesions. Stent edge restenosis or positive vascular remodeling were not observed.

Preclinical studies have suggested that although restenosis may be prevented at 6 months, DESs may be associated with delayed restenosis and late catch-up phenomenon. In chapter 8, we demonstrated persistent inhibition of neointimal hyperplasia with SES for up to 2 years of follow-up. These preliminary results of longer follow-up are encouraging. Larger randomized studies with adequate and complete longer-term follow-up will provide definitive data regarding durability of the anti-restenotic effect of DES.

Evaluation of vessel wall response to drug eluting stents (Part-IV)

Sirolimus eluting stents have a major impact on the inhibition of in-stent neointimal hyperplasia. However changes in the vessel wall and behind stent struts in animal models and humans have not been evaluated by serial IVUS. In chapters 10and 11, Three-Dimensional Reconstructed Images have been performed in order to clearly understand the IVUS images obtained from the new therapeutic device. In serial IVUS, we have shown that SES is effective in inhibiting neointimal hyperplasia without affecting vessel volume and plaque behind the stent.

In the sub-analysis of RAVEL trial, incomplete stent apposition was more frequent at 6-months in patients received SES (21%) than in the control group (4%). Although, the lack of serial IVUS was limiting the interpretation, these findings raised concerns regarding vascular remodeling, frequency and clinical outcome of this phenomenon. In chapter 12-13, we showed that DES implantation was not associated with increase in coronary aneurysm formation. Moreover, ISA was not associated with adverse clinical events 1 year after the diagnosis, emphasizing the benign nature of this phenomenon. Furthermore, serial IVUS evaluation of patients with ISA have demonstrated that vessel dimension and volume of ISA did not change over time and the efficacy of SES in the inhibition of NIH was not affected by the occurrence of ISA.

Sirolimus was undoubtedly the first successful drug eluting stent. However, many other drugs including paclitaxel are currently under evaluation. The TAXUS trial demonstrated that when compared with a bare metal stent, paclitaxel-eluting stents (PES) reduced in-stent neointimal formation and restenosis and improved clinical outcome in patients with single de novo

coronary lesions. However, based on the experience with vascular brachytherapy, edge stenosis and local arterial responses have been raised as a potential limitation for DES. We used IVUS to prospectively analyze vessel responses in adjacent reference segments and behind the stent struts after implantation of PES. In chapter 14 and 15, we demonstrated that the marked reduction in ISR with stents was not associated with increased edge stenosis at 6-month follow-up. In fact, compared to bare metal stent, there was a significant reduction in late lumen loss at the distal edge with PES. In addition, this study establishes that there is no quantitative relationship between plaque burden and neointimal hyperplasia following stent implantation that has diagnostic and therapeutic implications. By using the sensitivity of IVUS, in a large cohort of patients we show that PES reduce neointimal hyperplasia to the same degree. However, by studying the peri-stent remodeling, we demonstrated release-dependent effects on the global vessel wall response within and around the stent.

Drug eluting stent in the " real world" (Part V)

The effectiveness of sirolimus-eluting stents in unselected patients treated in the daily practice is currently unknown. The RESEARCH (the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital) 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 the **"real world"** daily practice.

In chapter 16, we evaluated the early outcomes of patients with acute coronary syndromes treated with SES. We found that SES implantation for patients with acute coronary syndromes is safe, with early outcomes comparable to bare metal stents. In chapter 17, despite the treatment of challenging coronary lesions, we found that SES implantation was also safe and an effective treatment for de novo coronary lesions requiring multiple stent placement over a very long (>36mm) vessel segment.

The failure: Actinomycin-D eluting stents (Part-VI)

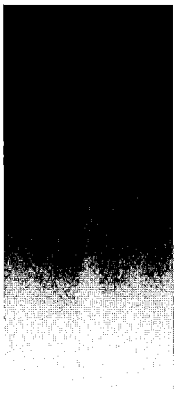
Although drug-eluting stents releasing sirolimus or paclitaxel represent a effective tool of abolishing restenosis, unsuccessful experience of using other drugs seems inevitable. The antiproliferative drug, Actinomycin-D, effective in reducing neointimal proliferation in preclincal studies was evaluated in clinical trial. Actinomycin eluting stent for coronary revascularization (The ACTION Trial) (Chapter 18) was aimed at assessing the feasibility and safety of implanting Actinomycin-D eluting stent in comparison with bare stent. However, because of a high incidence of repeat revascularization in the treated arm, the study was interrupted prematurely. The results of the ACTION trial indicated that not all antiproliferative drugs will show a class effect in the prevention of restenosis.

Conclusion and Perspectives:

The development of the stent as a local drug-delivery vehicle with no systemic effects looks promising. Given the results being available, safety, feasibility and efficacy seem to prove the drug eluting stent concept and its success story, even in long term results; and this concept will certainly further impact on fate of cardiovascular bypass surgery and interventional cardiology.

Despite promising results have been obtained with drug eluting stent in many trials, we have to know that drug eluting stents could not be totally eliminated in-stent restenosis. However, further understanding mechanism of restenosis occurring following the use of drug-eluting stents will contribute to development of new lesion and/or patients specific stents which might provide controlled release of different agents (e.g antiproliferative, antitrombotic, anti-inflammatory) with more lesion coverage may provide cure for in-stent restenosis.

Drug eluting stents have lead to a new **"era"** of interventional cardiology and the future of DES seems promising. However, development atherosclerosis is a generalized disease process which is not curtailed by drug-eluting stents. In the future, selective detection of vulnerable plaques with need for drug eluting stents to block the biological activity might be essential. Thermographic mapping, evaluation of genotypes and local catheter based gene therapy will be another area of investigation.



SAMENVATTING EN CONCLISIES

Samenvatting en conclusies

Coronaire stents vormen een belangrijke vooruitgang bij de behandeling van coronaire vaatziektes, waarbij de vaten dicht groeien, sinds de toepassing van ballon angioplastie.

Het wederom dichtgroeien van het vat binnen de stent is de meest beperkende factor bij het toepassen van stents bij coronaire vaatziektes. Een groot aantal onderzoekers hebben zich gestort op het onderzoek naar dit dichtgroeien van de stents. Het resultaat van deze onderzoeken is de ontwikkeling geweest van stents voorzien van medicijnen, als een mogelijke oplossing om het dichtgroeien van de stent tegen te gaan. In dit proefschrift rapporteren we de eerste klinische toepassingen en de bevindingen van gedetaileerde, drie dimensiolale, weergave met behulp van intravasvulair ultrageluid (IVUS) van deze met medicijnen voorziene stents.

Deel I: In het eerste deel van dit proefschrift is een samenvatting gegeven van de ontwikkeling van percutane coronaire interventies en de rol van het plaatsen van stents bij de behandeling van coronaire vaatziektes. In de hoofdstukken 1 en 2 wordt een overzicht gegeven van de problemen met betrekking tot het weer opnieuw dichtgroeien of restenoseren van een bloedvat bij toepassing van normale stents en de complexe verschijnselen die hierbij optreden. Stents zouden een mechanische belemmering moeten vormen voor het krimpen en remodeleren en het opnieuw dicht groeien van deze stents. Het blijkt echter, dat de formatie van veel nieuw intima weefsel de belangrijkste oorzaak is van het opnieuw dichtgroeien van een stent.

Deel II: Teneinde het probleem van het opnieuw dichtgroeien van stents te voorkomen, is het gebruik van stents voorzien van een laag met medicijnen, die dit dichtgroeien op zijn minst remmen, sterk ontwikkeld. In het tweede deel van dit proefschrift (de hoofdstukken 3 en 4) wordt een samenvatting gegeven van de steeds voortdurende onderzoeken en technische ontwikkelingen op het gebied van deze medicijn afgevende stent. Studies voorafgaande aan de klinische studies hebben aangetoond, dat stents voorzien van sirolimus en paclitaxel een aanzienlijke vermindering geven van het ontstaan van instent restenose. Tot nog toe beantwoorden de resultaten van de eerste klinische studies met stents voorzien van sirolimus en paclitaxel volledig aan de resultaten die aan deze klinische studies vooraf gingen.

Deel III: Wanneer nieuwe technologieën toegepast gaan worden, moeten de veiligheid en doeltreffendheid ervan aangetoond worden, verder moet nagegaan worden welke gevolgen het heeft op de routine matige werkzaamheden binnen een interventie kamer. Stents voorzien van sirolimus hebben bewezen dat zij het ontstaan van instent restenose aanzienlijk kunnen reduceren. Echter er zijn nog bedenkingen met betrekking tot de lange termijn resultaten en de resultaten van ultrageluid analyses van deze nieuwe technologie.

Het doel van hoofdstuk 5 was om een gedetailleerde morfologische analyse te geven van de lokale biologische effecten tengevolge van een geïmplanteerde met sirolimus voorziene stent ten opzichte van een normale stent met behulp van intervasculaire ultrageluid technieken.

Het verschil na 6 maanden in de nieuw weefsel vorming in de intima tussen de met sirolimus voorziene stent en de normale stent was aanzienlijk, waarbij vooral de afwezigheid

van het proces met ongeregelde celvermeerdering binnen de met medicijnen voorziene stent opvallend was. Verder bleek bij de controle na 6 maanden, dat de medicijn afgevende stents minder goed in de vaatwand opgenomen waren, dan de normale stents. Echter de interpretatie van deze resultaten is beperkt, aangezien direct na het plaatsen van de stents geen ultrageluid opnamen gemaakt zijn.

Het blokkeren van zijtakken is een zeer bekende complicatie bij het plaatsen van stents, in coronaire vaten werd dit in 19 % van de onderzochte gevallen aangetroffen. De oorzaak van dit verschijnsel na het plaatsen van stents met sirolimus is niet bekend.

In hoofdstuk 6 wordt de stelling onderzocht of stents voorzien van sirolimus hetzelfde effect hebben als intra vasculaire brachytherapie en of ze de mogelijkheid bezitten om het herstelproces te vertragen, en een grotere kans op het blokkeren van zijtakken tot gevolg hebben. In tegenstelling tot de brachytherapie wordt aangetoond, dat met sirolimus voorziene stents het spontane rekanaliseren van een bloedvat niet negatief beïnvloeden. Het open houden van zijtakken na het implanteren van een met sirolimus voorziene stent is op zijn minst even goed als bij een normale stent.

We onderzochten ook de doeltreffendheid van met sirolimus voorziene stents bij een groep patiënten met complexe leasies en een groot risico voor restenose. Instent restenose leasies kunnen anders reageren dan de novo leasies vooral omdat ze een tweede reactie in het vat oproepen. In de hoofdstukken 7 en 8 wordt aangetoond, dat bij patiënten met ernstige instent restenose verschijnselen, de met sirolimus voorziene stents de vorming van nieuw intima weefsel effectief tegen gaat en dus ook instent restenose. Ultrageluid analyses hebben aangetoond, dat stents voorzien van sirolimus eveneens een effectieve invloed hebben op de remming van nieuw intima weefsel in de novo en instent restenose leasies zonder rand restenose effecten of herstelgroei in het vat.

Uit eerdere studies zou afgeleid kunnen worden, dat, ofschoon het optreden van restenose binnen 6 maanden tegen gegaan wordt, de met medicijnen voorziene stents het ontstaan van restenose alleen maar vertragen. In hoofdstuk 8 wordt aangetoond, dat bij patiënten met een met sirolimus geïmplanteerde stent na 2 jaar nog steeds geen neo intimale hyperplasia gevormd is. Dergelijke resultaten na een periode van 2 jaar zijn zeer bemoedigend. Gerandomiseerde studies en studies waarbij de patiënten nog langer onder controle blijven zullen een definitiever beeld geven van de lange termijn effecten van stents die van medicijnen voorzien zijn.

Deel IV: Stents voorzien van sirolimus hebben een belangrijke bijdrage geleverd bij de bestrijding van instent restenose. Echter veranderingen in de vaatwand en structuren achter de stent zijn noch bij dieren noch bij patiënten grondig onderzocht. In de hoofdstukken 10 en 11 zijn reële drie dimensionale modellen onderzocht teneinde dit na te gaan en om een duidelijk en betrouwbaar inzicht te krijgen in de ultrageluid metingen, volgens de nieuwste technieken. Uit diverse ultrageluid metingen is gebleken, dat met sirolimus voorziene stents effectief zijn bij de bestrijding van neointimale hyperplasia en dat daarbij de vaatwand en plakvorming achter de stent structuren niet beïnvloed worden.

In een afgeleide analyse van de RAVEL studie werd gevonden, na een controle van 6 maanden, dat het niet juist positioneren van stents met sirolimus meer optrad (21%), dan bij patiënten met een normale stent (4%). Alhoewel er geen uitgebreide ultrageluid gegevens beschikbaar waren voor deze groep van patiënten, waren de resultaten toch van dien aard, dat enige bedenkingen op hun plaats waren met betrekking tot het remodeleren van het vat en de frequentie waarmee dit femomeen optrad.

In de hoofdstukken 12 en 13 wordt aangetoond, dat de met medicijnen voorziene stents geen belangrijke verhoging geven in de vorming van coronaire aneurismata in de oorspronkelijke vaten ten opzichte van de gewone stents. Veeleer kan gesteld worden, dat instent restenose niet gecorreleerd kan worden met negatieve klinische bevindingen na 1 jaar. Uitgebreide ultrageluid studies bij patiënten hebben aangetoond, dat de afmetingen van de vaatwand en het volume in de loop der tijd niet veranderd zijn.

Sirolimus mag de eerste succesvolle medicijn zijn waarmee stents voorzien worden, echter de ontwikkeling van andere medicijnen staat niet stil. In de TAXUS studie is aangetoond, dat in vergelijking met normale stents, bij de met paclitaxel voorziene stent de nieuwe weefsel vorming in de stent minder is en dat het totale klinische resultaat beter is bij patiënten met de novo leasies. Echter gebaseerd op de bevindingen uit de diverse brachystudies dient rekening te worden gehouden met onvoorziene effecten zoals de randeffecten bij een stent en lokale effecten tengevolge van reacties van de vaatwand binnen een stent, die de resultaten van met medicijnen voorziene stents negatief kunnen beïnvloeden.

Met behulp van ultrageluid analyses zijn de reacties van de vaatwanden geanalyseerd, vooral in aangrenzende segmenten en achter de stent structuren, bij stents met paclitaxel. In de hoofdstukken 14 en 15 wordt aangetoond, dat vermindering van instent restenose niet gekoppeld kan worden met een toename van randrestenose na 6 maanden. Ten opzichte van de normale stent is er in feite een sterke reductie van restenose verschijnselen aan het distale eind van de met paclitaxel voorziene stent.

Bovendien heeft deze studie laten zien dat er geen kwantitatieve relatie bestaat tussen de plak vorming en de neointimale hyperplasia na een stent implantatie, die diagnostische en therapeutische implicaties hebben. Door gebruik te maken van de zeer gevoelige ultrageluid apparatuur bij een groot aantal patiënten kon aangetoond worden dat stents met paclitaxel de vorming van neointimale hyperplasie verminderde. Echter bij het bestuderen van de peristent kan aangetoond worden, dat de reactie van de totale vaatwand afhankelijk is van de hoeveelheid medicijnen die vrij komt.

Deel V: De effectiviteit van de stent voorzien van sirolimus bij niet geselecteerde patiënten is op dit moment nog niet bekend. Op dit moment loopt in het Academisch Ziekenhuis in Rotterdam de RESEARCH studie (stent met het rapamycin medicijn), waarbij met sirolimus voorziene stents bij patiënten ingebracht worden, zonder selectie. (dagelijkse praktijk situaties)

In hoofdstuk 16 zijn de resultaten gegeven van eerdere studies van patiënten met acute coronaire syndromen, die behandeld zijn met stents met sirolimus. Aangetoond kan worden, dat

deze patiënten op deze manier veilig behandeld kunnen worden. Het resultaat is vergelijkbaar met patiënten die een normale stents geïmplanteerd gekregen hebben.

In hoofdstuk 17 zijn de resultaten gegeven van behandeling van lastige leasies en het plaatsen van meerdere met sirolimus voorziene stents. Gebleken is dat zelfs leasies met een lengte van meer dan 36 mm veilig en met positief resultaat behandeld kunnen worden.

Deel VI: Stents met het medicijn sirolimus of paclitaxel hebben de vorming van restenose nagenoeg tot staan gebracht. Ook het groeiremmende medicijn Actinomycin- D, dat effectief is om de neointimale groei te remmen, is eveneens geselecteerd voor klinische evaluatie.

Ten einde de haalbaarheid en de veiligheid van stents voorzien van Actinomycin-D na te gaan is de ACTION studie opgezet (zie hoofdstuk 18). Echter tengevolge van het herhaald optreden van bloedvatverstoppingen in de behandelde arm is de studie stop gezet.De resultaten van de ACTION studie lijken erop te duiden, dat alle groeibelemmerende medicijnen geen uitkomst zullen geven bij de preventie van restenose.

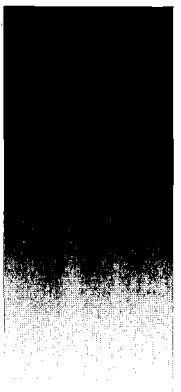
Conclusies en toekomstverwachtingen.

De ontwikkeling van een stent die lokaal een medicijn afgeeft lijkt zeer belovend. De resultaten die beschikbaar zijn, lijken te bewijzen dat de stents voorzien van medicijnen veilig en doeltreffend gebruikt kunnen worden. Tevens lijken zij op lange termijn een goed resultaat te waarborgen. Deze resultaten zullen in de toekomst zeker een grote invloed hebben op het gebied van coronaire vaatchirurgie en coronaire interventies.

Ondanks het feit dat er uitstekende resultaten behaald zijn met stents voorzien van medicijnen moet er toch rekening mee gehouden worden, dat deze stents het fenomeen restenose niet volledig uit kunnen schakelen. Echter verdere kennis van het mechanisme dat restenose veroorzaakt, zal bijdragen tot de ontwikkeling van nieuwe en andere medicijnen en de gecontroleerde vrijgave van meerdere (b.v. groei remmende, anti trombogene en ontstekingsremmende) medicijnen, eventueel patiënt specifiek, kunnen mogelijk de oplossing geven voor de instent stenose problematiek.

Stents voorzien van medicijnen openen een nieuw gebied binnen de interventie cardiologie en de toekomst van coronaire stents voorzien van medicijnen lijkt veel belovend te zijn. Echter we moeten ons bedenken, dat atherosclerosis niet met stents voorzien van medicijnen verholpen kan worden. In de toekomst zullen selectieve detectie naar vulnerabele plak en de noodzaak om die met stents met medicijnen te blokkeren nodig zijn, om de biologische activiteit te reduceren, mogelijk essentieel zijn.

Temperatuur weergave van de intima, het zoeken naar erfelijke eigenschappen en lokale injectie van genetische veranderd materiaal zijn richtingen van toekomstig onderzoek.



ACKNOWLEDGEMENT

Successful research is a product of collaboration and requires contributions of highly motivated people. This thesis is not an exception, and it has been completed with the continuous support, cooperation, patience and enthusiasm of many people.

I would like to take this opportunity to thank these people and recall the time spent at the Thoraxcenter. It is difficult to fully express all my feelings, gratefulness and appreciation, to the people who have helped and supported me during the course of this research. However, I am sure I will be understood.

From Turkey

I would like to start from Turkey where my story begins.

I would like to thank Prof. Fikret Turan, Assoc Prof. Yelda Basaran, and Prof. Cevat Yakut of Kosuyolu Heart&Research Hospital for encouraging me to apply for the Training Fellowship of European Society of Cardiology. I also would like to thank Prof. Ali Oto for his support in receiving this fellowship. At the beginning, I did not expect that this short term six-month long fellowship would extend to two years and turn into a unique experience at Thoraxcenter. Without your encouragement and continuous support I could not have the chance to work on this thesis.

I extend my deep appreciation to Dr. Bulent Mutlu, Dr. Kenan Sonmez, Dr. Salih Guran and people from Referans Clinic, whose never-ending moral support, encouragement and assistance from Istanbul helped me to survive in Rotterdam.

I still had a lot to do on my thesis when I returned to Turkey. Assoc.Prof. Mehmet Ozkan of Kosuyolu Hospital helped me to arrange my schedule at the hospital and made it possible for me to complete this thesis on time. Thank you.

I can not finish this section without acknowledging Ebru Topoglu. I am deeply indebted to Ebru for her unreserved support and patience. "Teşekkür ederim".

At the Thoraxcenter

My deepest gratitude goes to Prof. Serruys whose support and encouragement provided me the motivation to pursue the PhD degree at the Thoraxcenter. Dear Professor, you were an incredible mentor, and expanded my vision in clinical research with your sharp insight and valuable advice. Your incredible work ethic, enthusiasm and dedication as a researcher are beyond all imagination, and in order to realize this one must work with you, I am very lucky to have had that privilege. Every fellow at Thoraxcenter works very hard, but you work more than anyone else.

A weekend in Rotterdam: **Muzaffer**: "Kengo, do you know where the Professor is?" **Kengo**: "Today, he is coming back from Australia." **Muzaffer:** "It is OK. That means, he will be very tired and will take a rest at home. So, the previous plan working at his home is canceled." However, 15 minutes later, Professor was calling me from my mobile. **Prof. Patrick W. Serruys:** "Muzaffer, I just left the airport (Schipol). I will be at home at 11am. I will be wait-

ing for you to work on the manuscript at 12am. And don`t forget to bring your tennis racket, we can also play tennis." Dear Professor, my backhand is getting better!! Be careful....

I would not forget to acknowledge Mrs. Daniella Serruys: Thank you for your sincere hospitality and humor during my many visits to your home.

I would like to thank Prof. Pim J. de Feyter for his support. I am grateful for the opportunity to have been exposed to your scientific advice and witnessed your balanced approach to interventional cardiology. Also, I will remember your comments ***"Ohhh ohh jesus"*** during complex procedures at catch laboratory, especially during primary PTCA cases at late midnight hours.

Dr. Wim J. van der Giessen; your comments on my manuscripts are gratefully appreciated and I would like to mention one dialog. One day, Akis showed you a package of cigarette names ***"Fellows"*** at your office. Your comment was ***"Himmmm.. fellows kill seniors".*** This clearly showed your hidden wittiness and your special perspective. I am very lucky to have spent time with you. Thank you.

I first met Dr. Stephane G. Carlier at a dinner in Istanbul a year before starting my fellowship in Rotterdam. We could not imagine this short introduction would lead into a strong friendship and his un-interrupted support not only for my scientific activities, but also my social life during my stay in Rotterdam. Dear Stephane, your really helped make my time spent in Rotterdam more pleasant. I will never forget the dinners in Dienze, of course enjoying wines with your expert suggestions, and Tina`s hospitality. In addition, special thanks to both your and Tina`s parents for their kind invitations. Dear Stephane, I wish you all the success in your new position in New York.

I also wish to acknowledge other interventional cardiologists, M. van den Brand, D. Foley, P. Smits, J.Vos, G. Sianos, S. Hofma and E. Mc Fadden, for their friendship and support.

I am grateful to all the nurses and technicians; Mario, Caroline, Tineke, Gio, Emile, Janine, Jurgen, Anna-Marie, Samantha, and many others. My special thanks also go to Juin Tuin, Tittia and other secretaries for their help.

Arno Ruiter and Paul Cummins; many studies could not be completed without your hard work and serious effort in data collection. By the way, "Sir" Paul, I am impatient to see you in Istanbul...You know what I mean?? I also would like to extend my gratitude to Anja; "Prof. Serruys' secretary" for her invaluable assistance. Dear Anja, I hope I will never lose my position as your "favorite Turkish gentleman".

Fellows at the Thoraxcenter

First of all, I would like to visit room Z-120 where most of my time has been spent in Rotterdam with Kengo, Evelyn, Ronald and "Mr. van Essen".

Kengo Tanabe: the first Japanese whom I got a chance to know closely. A combination of work discipline, accuracy and strength of mind. Our productive and successful collaboration

will always be remembered. Thanks for introducing delicious Japanese cuisine to me. I will never forget Kayoko`s and your kindness, and your cute little baby Yuna.

Evelyn Regar: very well organized, creative, chic, determined as expected from a German. I am indebted for your scientific and non-scientific support. Besides, without your help I would be homeless (actually "without an address"!!!) in Rotterdam. I hope you will let me to respond to your and Frank`s kindness when you visit Turkey. Danke Evelyn.

Ronald Lee: the other member of our room from Hong Kong, hard worker, helpful writer, first reviewer of most of my papers and my dinner friend. Thank you very much for everything and also teaching me very important 3 words in your language (D.N.M.). I have to confess that I m using those words very frequently. I wish you had stayed longer at Thoraxcenter. I am sure you will have great success in Singapore.

Dirk van Essen: He was not a fellow. He was a physicist and the only Dutch in our room. He made life easier for international fellows (especially about our correspondence in dutch) just for a cup of coffee. Thank you Dirk!!!. (not Mr. van Essen).

Pedro Lemos - high research capacity, never-ending productivity, outstanding personality and beyond a "friend" from Brasil. He was a great chance for the fellows to reach our goals in our big "RESEACH". It is a privilege to know you. I am grateful for your help and data support in successfully completing my thesis.

Akis Arampatzis: Everybody was curious how two of us could get along well since you are from Greece, but for us there was no reason for concern, was there? Your sense of humor and friendship will always be treasured. I miss the way we share our thoughts.

Francesco Saia: A gentleman from Italy, my room-mate at cardiology meetings. Spending time with you in scientific and non-scientific venues was a great pleasure. I am eagerly looking forward to start "DO Landscape Of beautiful Mountains of ITaly will make us forget Eluting Stents?(*"DOLOMITES"*) trial. I think we deserve this, don't we?

Angela Hoye: Thank you for teaching us the secrets of real English. Your intelligent comments and suggestions made our papers better and more readable.

Fifth Floor and experimental cardiology

I would like to start with Sarah Fransen**:** Without your patience and continuous help, I and the other fellows from out of "European Union" (***strangers***) could not have overcome the problems with the Dutch bureaucracy about the staying permit. Now you can erase one problematic fellow from the list. I will not "disturb" you any more; promise. BEDANKT for everything.

Many thanks to Niko Bruining and Sebastian, I could not have completed most of the IVUS analysis without your support; to Ron van Domburg, a gentlemen and a patient teacher in statistics; to Jolanda Wentzel for allowing us to easily reach the files for my studies; and fellows staying at the 5th floor, Miklos Kertai, Tamas Szili-Torok, whom I shared problems of "strangers" and productive discussions, and finally to Nestor Mercado whom I wish a success-

ful career in the USA. I also have to express my gratitude to Annet Louw and Assoc. Prof. W.de Jong for properly coordinating all procedures for the printing of this thesis.

I wish to acknowledge Frank J.H. Gijsen and Prof. C. J. Slager, for explaining me the basics in "Angus" and "shear stress" which make me easier to interpret some IVUS images. Thanks also to Ayach (traveling to Belgium with you was pleasure) and Johannes Schaar, the "vulnerable plaque" and "palpogram" expert, with whom I had enlightening "political" discussions during lunch time.

Cardialysis

I learned quite a lot during the meetings at Cardialysis and got significant experience while working at IVUS and Angiography core Lab. Moreover, management of many trials presented in my thesis would not have been possible without the help of the people from Cardialysis. Many thanks goes to Gerrit- Anne van Es, Marie-Angele Morel, Bianca Backx, (it was pleasure to work with you, How is your neighbor??), Clemens Disco, Peter, Jennet, Ellen, Connie, Yvonne, Ali, Jamal, Anna-Marie, Wendy, Eline (thank you for Sushi, it was delicious) and to many other helpful people.

Getting to the end

I would like to thank Prof. J. R.T.C.Roelandt, Prof. M.L.Simoons, Prof.P.M.T. Patynama and Prof. J.Piek for their honorable presence of in the thesis committee.

I also have to acknowledge my uncle Prof. Halil Degertekin who definitely had an important influence and guidance not only during my medical education but also during my academic life.

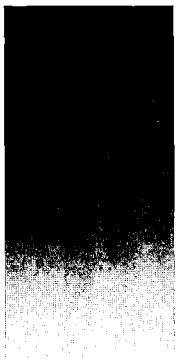
In retrospect, I think that getting to know so many nice people in Holland was a great, unforgettable experience, and it was at least as important, if not more, as my research achievements.

CURRICULUM VITAE

CIRRICULUM VITAE

Muzaffer M. Degertekin was born in Diyarbakir, Turkey on June 4th, 1965. He received his MD degree from Hacettepe University Medical School, Ankara, Turkey, in 1990, and completed his residency at Kosuyolu Heart &Research Hospital, Istanbul, Turkey, where his training included internal medicine and cardiology. Dr. Degertekin completed his cardiology training in 1995, and worked at both echocardiography and cardiac catheterization laboratories from 1996 to 1998. He started to work as an interventional cardiologist in 1999, and in 2000 he assumed his current position as a staff interventional cardiologist at Kosuyolu Heart &Research Hospital. From March 2001 to April 2003 he was on leave as a research fellow at the Interventional Cardiology Department of Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands, under the supervision of Professor Patrick W. Serruys.

Dr. Degertekin is a fellow of European Society of Cardiology and member of the Turkish Society of Cardiology.



LIST OF PUBLICATIONS

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1. **Intravascular ultrasound evaluation after sirolimus eluting stents implantation for de novo and in-stent restenosis lesions**
   Degertekin M, Lemos P, Lee CH, Tanabe K, Sousa E, Abizaid Avan der Giessen W, de Feyter P, Bruining N, Wuelfert E, Popma J, Serruys PW.
   (European Heart Journal 2003 in Press)

2. **Sirolimus-Eluting Stent Implantation in ST-Elevation Acute Myocardial Infarction. A Clinical and Angiographic Study**
   Saia F, Lemos PA, Lee CH, Arampatzis CA, Hoye A, **Degertekin M,** Tanabe K, Sianos G, Smits PC, McFadden E, Hofma SH, Van Der Giessen WJ, De Feyter PJ, Van Domburg RT, Serruys PW
   (Circulation. 2003;108:1927-1929.)

3. **Sirolimus-eluting stents for the treatment of in-stent restenosis**
   Degertekin M, Saia F, Lemos PA, Arampatzis CA, Serruys PW
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ABSTRACTS

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With thanks to

- Cardialysis
- Boston Scientific
- Johnson & Johnson