# NOVEL PERCUTANEOUS THERAPIES FOR COMPLEX CORONARY ATHEROSCLEROSIS

Chourmouzios Arampatzis

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Front cover: A Sirolimus-eluting stent.
Back cover: Alexander the Great, in the battle of Gavgamila.
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# Novel Percutaneous Therapies for Complex Coronary Atherosclerosis

## Nieuwe Ontwikkelingen in de Percutane Behandeling van Complexe Vormen van Coronaire Atheromatose

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Chourmouzios Anastasios Arampatzis
born at Serres, Greece

## PROMOTIECOMMISSIE

Promotoren: Prof.dr. P.W.Serruys
Prof.dr. P.J. de Feijter

## OTHER MEMBERS

Prof.dr.ir. A.F.W. van der Steen
Prof.dr. P.M.T. Pattynama
Prof.dr. J.J.Piek

## CO PROMOTOR

Dr. P.C. Smits

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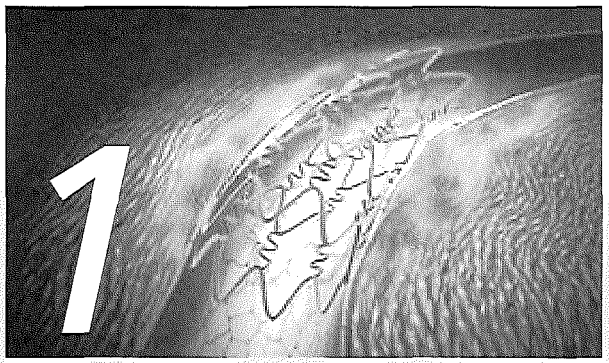

# 1 General Introduction and Outline of the Thesis

The remarkable improvements in techniques and technology have established coronary angioplasty as the dominant method of coronary revascularization in contemporary practice[1]. Despite the consequent improvement of the acute results due to the widespread use of stent implantation[2,3], restenosis and the need for repeat revascularization continues to hamper the efficacy of this strategy in the long term[4,5]. The limitations of percutaneous intervention are more evident in patients with complex coronary artery disease. This term is difficult to define in rigorous scientific terminology. Complex coronary atherosclerosis includes patients with increased risk of future cardiovascular complications[6-15], and/or complex 'anatomic' lesions[16-29].

Recently, the use of the sirolimus-eluting stent has been associated with very promising results in reducing neointimal hyperplasia and restenosis rates [30-33]. Importantly, by maintaining the mechanical properties, the late benefit observed with drug-eluting stents was accomplished without compromising the excellent procedural and acute results already obtained with conventional metallic stents. The use of this strategy has been evaluated in large randomized trials with highly homogeneous selected populations usually consisting of simple lesions in large coronary vessels. Every day clinical practice of an interventional cardiologist differs, sometimes remarkably, from this "ideal world scenario". The patient with 'complex coronary artery disease' is usually not present in these trials. Yet these patients form the majority of the patients in our current clinical practice (Table).

Evolving diagnostic modalities for coronary plaque imaging may help identify patients before cardiovascular events occur. The dream of every clinical cardiologist is to be able to prevent rather than treat acute coronary events. Therefore, the term "vulnerable patient"[34,35]has been proposed to describe a group of patients whose management poses complex challenge. The term refers to patients at risk of an acute coronary event due to plaque, blood or myocardial vulnerability (Figure). Little is known regarding the variables that underlie each of these components of vulnerability or about the interactions among them.

## PART 1

*Impact of Adjunctive Medication and New Technology on Patients with Risk Factors for Adverse Events*

The management of atherosclerotic disease in patients with powerful risk factors for future adverse events remains elusive and sub optimal. Indeed, patients with diabetes, previous bypass surgery and renal impairment compose three distinct groups deemed to have an increased risk for adverse events. Despite the similar angiographic success rates following angioplasty, they exhibit an increased incidence of in-hospital mortality, myocardial infarction and poorer event free survival compared with populations without these risk factors.

In Chapter 2 we investigate the role of adjunctive medication in patients undergoing percutaneous intervention who suffered from diabetes mellitus. We analyze, in Chapter 3, the impact of the sirolimus-eluting stent in patients with renal impairment. In Chapter 4, we explore the effectiveness of the sirolimus-eluting stent in patients with a history of previous bypass.

## PART 2

*Effectiveness of New Technology on Patients with Complex Lesions*

Surgical revascularization remains the treatment of choice in patients with complex coronary artery disease, such as diffuse coronary atherosclerosis, with disease that includes a significant left main coronary stenosis or multivessel disease, (especially involving the left anterior descending artery). In Chapter 5 and 6 we evaluate the performance of drug-eluting stent implanted in very long coronary segments and in small diameter artery sizes.

Left main stenoses are traditionally excluded from randomized trials. In Chapters 7-9 we investigate the efficacy of this strategy in patients receiving a sirolimus stent in the left main stem. In Chapter 10 we explore the effectiveness of the sirolimus-eluting stent in patients treated for multivessel stenoses. Subsequently, in Chapter 11, we analyze the impact of the utilization of the sirolimus-eluting stent in both interventional and surgical clinical practice.

## PART 3

*New Avenues, Future Directions*

Does the term "complex coronary patient" only apply to the patient with exceptionally difficult lesions and major risk factors, or should it be extended to other patients? In Chapter 12, we investigate the efficacy of different invasive and non-invasive diagnostic modalities for the evaluation of coronary plaque. In Chapter 13 we explore the impact of the sirolimus-eluting stent in a consecutive series of patients with non-flow limiting lesions.

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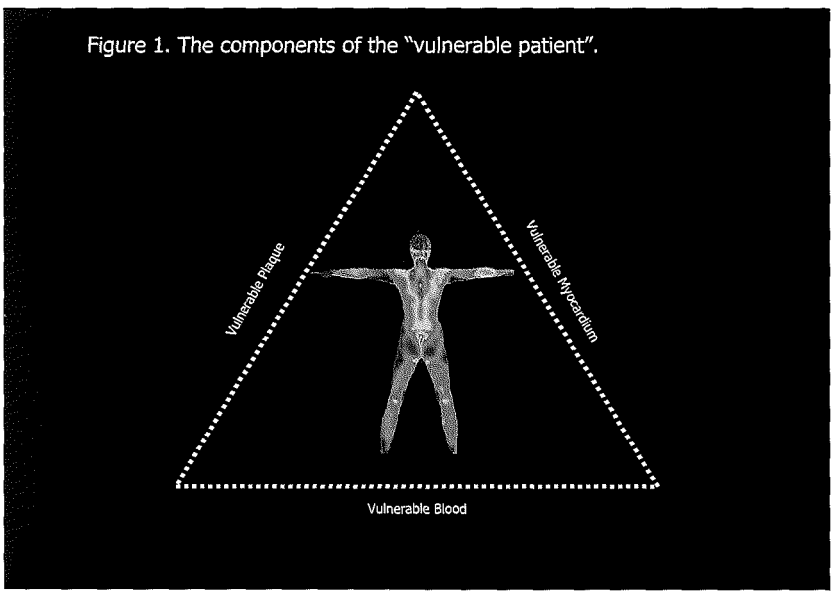
**Table. Patients treated with DES in Thoraxcentre since April 2002**

| | |
|---|---|
| Multivessel stenting | 20% |
| Very long lesions (stented > 36 mm) | 18% |
| Acute MI | 18% |
| Very small vessels (stent =2.25 mm) | 15% |
| Bifurcation stenting | 16% |
| Chronic occlusion | 8% |
| Age > 80 years | 5% |
| Main stem | 4% |
| Renal failure (creat >150 µg/L) | 4% |
| Saphenous grafts | 3% |

In total, 68% of our patients would not have been included in the randomized trials conducted to date.



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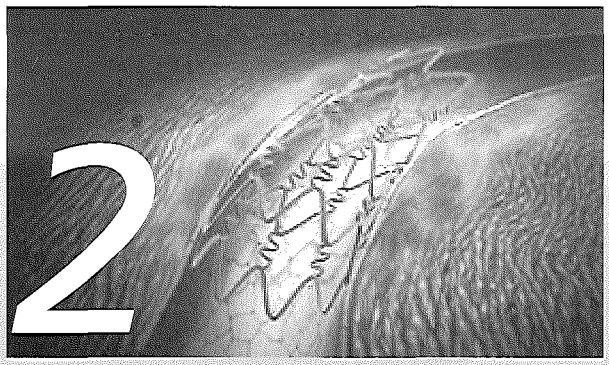

# Fluvastatin Reduces the Impact of Diabetes on Long–Term Outcome after Coronary Intervention A LIPS substudy

Chourmouzios A Arampatzis
Dick Goedhart
Patrick W Serruys
Francesco Saia
Pedro A Lemos
Pim de Feyter

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## STRUCTURED ABSTRACT

**Background:** Diabetes increases the risk of developing cardiovascular disease. Patients with diabetes undergoing percutaneous coronary intervention (PCI) show poorer outcomes compared with non-diabetic patients. The aim of this study was to determine the clinical benefit of long-term fluvastatin in patients with diabetes, who had undergone a successful PCI.

**Methods:** This subanalysis of a prospective, multicenter, randomised double blind, placebo controlled trial of patients who had undergone PCI and were treated with fluvastatin, determined the impact of fluvastatin on the survival-free period of major adverse cardiac events (MACE) (defined as cardiac death, nonfatal myocardial infarction and reintervention procedure [coronary artery by-pass grafting (CABG), repeat PCI, PCI for a new lesion]). Patients with baseline total cholesterol levels 135–270 mg/dl (3.5–7.0 mmol/L) and triglyceride levels 400 mg/dl (4.5 mmol/L) were randomised at discharge either to fluvastatin (n=844) or placebo (n=833); follow-up was 3–4 years. Among these patients 202 were diabetics (120 on fluvastatin, 82 placebo) and 1475 were non-diabetics (724 on fluvastatin, 751 on placebo). The primary clinical outcome was survival time free of MACE, and MACE excluding restenosis.

**Results:** The presence of diabetes increased the risk of MACE by almost two-fold in placebo-treated patients (RR, 1.78 95% CI, 1.20–2,64; p=0.0045). In contrast, in diabetic patients treated with fluvastatin, the risk of MACE was not significantly different from that in patients without diabetes. Fluvastatin reduced the risk of MACE in diabetic patients by 51% (p=0.0088).

**Conclusions:** Diabetes is a consistent clinical predictor of cardiovascular complications and fluvastatin reduces the increased incidence of long-term adverse complications associated with the presence of diabetes.

## INTRODUCTION

The diabetic population shows an increased risk of developing cardiovascular disease(1, 2). Moreover, a number of non-traditional factors such as levels of albumin, fibrinogen, and von Willebrand factor, factor VIII activity, and leukocyte count, are independently associated with the incidence of coronary disease in diabetic patients, in addition to traditional risk factors such as hypertension, smoking and total cholesterol levels (3). Patients with diabetes undergoing percutaneous coronary intervention (PCI) show poorer outcomes compared to non diabetic patients(4-6), while diabetic patients with multivessel disease show increased mortality and morbidity if treated with PCI rather than CABG(6, 7).

Primary and secondary prevention trials have consistently demonstrated that lipid-lowering treatment is of great benefit to diabetic patients(8-11). Accordingly, the third report of the Adult Treatment panel of the National Cholesterol Education Program, (ATP III, NCEP) (12) upgraded the guidelines for the diabetic population, without symptomatic coronary atherosclerotic disease (CAD), proposing that these patients should receive the same aggressive treatment for lowering lipids as in those with established CAD. Recently, the Lescol Intervention Prevention Study (LIPS), demonstrated that long-term treatment with fluvastatin significantly reduced the risk of major adverse coronary events (MACE) in patients undergoing a first successful PCI(13). We performed a pre-specified subgroup analysis of the effect of fluvastatin treatment on the incidence of major adverse coronary events, with or without restenosis in the subgroup of diabetic patients in the LIPS trial.

## METHODS

### *Study Design and Patient Population*

A detailed description of the LIPS study has been provided elsewhere(13, 14). Briefly, the LIPS study was a prospective, international, randomized double-blind placebo-control trial in patients undergoing a first successful PCI at 1 or more lesions in the native coronary arteries. Patients were enrolled in the study if they had a total cholesterol level of 3.5–7.0 mmol/L (135–270 mg/dl), with fasting triglyceride levels of <4.5mml/L (400 mg/dl) before undergoing PCI. The upper total cholesterol limit for eligibility was 6.0 mmol/L (232mg/dl) for patients with diabetes. Patients were classified as diabetic if they were undergoing treatment with oral hypoglycaemic agents or insulin. No distinction was made between Type I and Type II diabetes. Exclusion criteria included sustained systolic blood pressure >180 mmHg, and diastolic blood pressure >100 mm Hg despite medical therapy, left ventricular ejection fraction <30%, history of previous revascularization (PCI or CABG), severe valvular disease, idiopathic cardiomyopathy or congenital heart disease, severe renal dysfunction, obesity (body mass index >35 $Kg/m^2$), and the presence of malignant or other disease with a life expectancy of less than 4 years. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were measured for each patient at follow up visits. The ethics committee at each participating centre approved the LIPS trial, and all patients gave written informed consent. The analysis,

interpretation, and submission for publication of this sub-study were conducted independently of the trial sponsor.

A total of 1677 patients were randomized into two groups; 844 patients were randomized to receive fluvastatin (Lescol, Novartis Pharma AG Basel, Switzerland), 40mg twice daily, and 833 patients were randomized to receive placebo. Patients were randomized at discharge (median time between index procedure and first dose of fluvastatin was 2.0 days) and follow up lasted 3–4 years. Data were collected at week six after randomization, and every six months thereafter (data collected at the index procedure were identified as visit 1, and follow up was completed at visit 10).

*Follow-up and Clinical Endpoints*

The primary clinical outcome was evaluated as the time during which the patient remained free of MACE, defined as the composite of cardiac death (all deaths except those unequivocally related to a non-cardiac cause), non-fatal MI (appearance of pathological Q waves that were absent at baseline or a total creatine kinase level >2 times the upper limit of normal with presence of CK isoenzyme MB higher than the upper limit normal) and re-intervention (CABG, target lesion revascularization or PCI for a new lesion). An additional prespesified analysis was performed to evaluate the incidence of coronary atherosclerotic events, defined as the primary outcome excluding restenosis (surgical or PCI re-interventions occurring in the first 6 months of follow-up for lesions treated at the index procedure). An independent critical events committee blinded to treatment assignment reviewed all deaths and suspected non fatal MIs for adjudication, and all analyses were based on the committee's classification for the end points.

*Statistical Analysis*

All analyses were carried out on an intention-to-treat basis. Continuous variables were expressed as mean ± SD and were compared using Student's unpaired *t*-test. Fisher's exact test was used for categorical variables, and Wilcoxon scores were used for categorical variables with an ordinal scale. Discrete variables were expressed as counts and percentages and were compared in terms of relative risks (for diabetic patients when compared with non-diabetics) with 95% CI. All statistical tests were 2-tailed. Event-free survival distribution was estimated according to the Kaplan-Meier method, by using procedures for survival and regression in SAS statistical software, version 8.0 (SAS Institute, Inc., Cary, North Carolina). The overall incidence of MACE was tested using the log-rank test. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. The Cox proportional hazards model and the Cochran-Mantel-Haenszel test were used to assess risk reduction and to compare the incidences of the primary and secondary clinical endpoints, respectively. Lipid profiles were analyzed in an analysis of covariance model incorporating the baseline (at visit 1) as covariate, adding the factors treatment; visit number (visits >1) and subgroup with all possible interaction terms.

## RESULTS

*Baseline Characteristics*

Of the 1677 patients recruited into the present study, 202 (12%) had diabetes (120 on fluvastatin, 82 placebo) and 1475 were non-diabetic (724 on fluvastatin, 751 placebo). In the placebo treated diabetic patients 21 (26%) were insulin dependent, and 61 (74%) non-insulin dependent, whereas in the fluvastatin treated diabetic patients the corresponding numbers respectively were 18 (15%), and 102 (85%). It should be noted that the incidence of diabetes at baseline was significantly higher in the fluvastatin group (14.2%) compared with the placebo group (9.8%; 95% confidence interval of the difference between groups 1.3–7.5). Baseline patient characteristics showed that diabetic patients tended to be older and shorter, showed a greater incidence of hypertension and peripheral vascular disease, but were less likely to be current smokers or to have a family history of CAD (Table 1). No differences in the extent and severity of vessel disease as well as in the device used were noted at the index procedure, although diabetic patients assigned to fluvastatin treatment had more treated lesions (Table 2).

*Primary and Secondary Outcomes*

The treatment-disease interaction analysis demonstrated a possible increased effect of fluvastatin in diabetic patients (Table 3). We therefore conducted exploratory analyses in order to investigate the effect of fluvastatin in each subgroup. The presence of diabetes significantly increased the risk of experiencing a major adverse event among placebo-treated patients (RR, 1.78 95% CI, 1.20–2,64; p=0.0045). In patients treated with fluvastatin, however, the presence of diabetes was not associated with an increased risk of MACE (Table 3). The effect of fluvastatin treatment in diabetic patients was highly significant, reducing the risk of MACE by 51% (p=0.0088) (Table 3).

The survival curves for fluvastatin- and placebo-treated patients began to separate at approximately 1.5 years, and remained separate through to the end of the study (Figure 1). The same pattern was seen when procedures involving restenosis were excluded from the MACE analysis (Figure 2). Diabetes was a strong clinical predictor of long-term coronary atherosclerotic events as shown by the significantly increased incidence of such events associated with diabetes in patients allocated to placebo. Treatment with fluvastatin abolished this negative effect of the disease (Table 3).

*Lipoprotein Levels*

At baseline, diabetic patients had lower total cholesterol, LDL-C and HDL-C levels (Table 1). Fluvastatin treatment significantly reduced LDL-C levels compared to placebo in diabetic patients by 6 weeks (median change in LDL-C with fluvastatin, -29.0% [95% CI: -32.3% – -23.5%] vs. +7.8% [95% CI: +5% – +14.3%] p<0.001). Treatment with fluvastatin also reduced LDL-C levels in non-diabetic patients (-26.3% [95% CI: -28.6% – -24.4%] vs +11.1% [95% CI: +9.4% – +13.8%] p<0.001). The reduction in LDL-C achieved with fluvastatin was maintained throughout the follow-up period (Figure 3). HDL-C levels were increased to a similar extent in all subgroups, irrespective of allocated treatment. A different pattern was seen for fasting TG levels. Although a significant decrease was observed in diabetic patients randomized to fluvastatin,

(median change -18.8% [95% CI -25% – -12.5%] p<0.001) TG levels also decreased in diabetic patients receiving placebo (median change -4.1% [95%CI -13.3% – +8.3%] p<0.001), probably due to dietary factors.

## DISCUSSION

The present study shows that the presence of diabetes increased the risk of adverse cardiovascular events after a first successful PCI by almost two-fold in patients receiving placebo. In contrast, in patients receiving long-term treatment with fluvastatin, the presence of diabetes was not associated with an increased risk of events. Indeed, fluvastatin equalized the risk of long-term complications in diabetic patients to that of non-diabetic patients. Fluvastatin reduced the risk of an event in diabetic patients by 51% (p=0.0088), a finding that is consistent with previous reports (15).

### *Diabetes as a Clinical Predictor of Poorer Outcome*

Despite similar angiographic success rates following PCI, the diabetic population exhibit an increased incidence of in-hospital mortality, myocardial infarction and poorer long-term survival compared with non-diabetic patients(4-6, 16). Indeed, it is well established that diabetic patients undergoing angioplasty show disappointingly high restenosis rates that can largely be attributed to increased in-stent intimal hyperplasia(17, 18), accelerated fibrotic response(19), and enhanced predisposition to vascular thrombosis(20). Nevertheless, recent developments and technical advances in the field of interventional cardiology, such as stents(21), glycoprotein IIb/IIIa agents(22), and intracoronary gamma irradiation(23) have reduced the restenosis rate and improved outcome in diabetic patients. A new treatment approach is therefore emerging for the diabetic patient, aimed at targeting the multiple inflammatory and metabolic pathways that lead to the progression of atherosclerosis. Importantly, diabetes has been shown to be a strong predictor for accelerated progression of atherosclerosis at sites other than treated lesions. The poorer outcomes observed in diabetic patients are probably due to the hormonal and vascular abnormalities associated with the disease, which lead to problems such as small calibre vessels, more extensive atherosclerotic disease, and altered platelet function. More specifically, increased cell proliferation in diabetic patients may result from mitogens that induce cell growth, endothelial dysfunction and excessive matrix production, and thus lead to intimal hyperplasia (24-26).

### *Fluvastatin as an Anti-atherosclerotic Agent*

Long term prospective studies have shown that statin therapy safely and effectively reduces the risk of CAD morbidity and mortality in patients with or without evidence of established coronary heart disease (8-11). Pooled data from large trials suggest that although diabetic patients are at higher risk, they also experience greater clinical benefit when treated with statins compared with other subgroups (15, 27). PCI has been generally investigated in terms of immediate and short-term outcomes, with little consideration of the role of atherosclerotic progression. Patients were enrolled in the LIPS study immediately after the procedure (median time between index procedure

and first dose of fluvastatin was 2.0 days), so the well-known problem of restenosis is a factor in the present study. It has been reported that, like other statins, (28, 29) fluvastatin does not reduce the restenosis rate (30), and this is illustrated by the Kaplan-Meier curves (Figure 1). Thus immediately after the procedure, there is a similar decline in both treatment arms due to restenosis. Long-term treatment with fluvastatin clearly eliminated the poorer outcome associated with the presence of diabetes by reducing the incidence of long-term cardiovascular complications. Notably, this remarkable clinical benefit could not be attributed to the improvements observed in lipid profiles alone.

The improvement in clinical outcome after fluvastatin therapy probably involves changes in underlying pathophysiological processes. Diabetic patients are a population with complex metabolic deficits, and it therefore seems obvious that localized treatment with PCI alone will not be sufficient to achieve improvements in outcome. Adjunctive medication is of great importance in order to optimize outcome; statin treatment may provide improvements in endothelial function (31, 32), platelet aggregation and coagulation(33), and these may contribute to the overall clinical effect seen in diabetic patients. It has also been postulated that the additional pleiotropic effects of statins(34), which include antioxidant and anti-inflammatory properties, may contribute to the net clinical benefit seen with fluvastatin treatment.(35) In the present study, clear benefits of fluvastatin treatment were observed only after 1.5 years of treatment. Hence, reversal of the abnormalities seen in diabetic patients probably requires prolonged therapy.

*Limitations*

The present study is a subgroup analysis, albeit a pre-specified analysis, and therefore suffers from inherent limitations due to the small number of patients in some groups. Moreover, baseline patient characteristics showed a significantly higher prevalence of diabetes in patients randomized to receive fluvastatin compared to the placebo group, hence there is some imbalance in the subgroup sizes. It should be noted, however, that the percentage of diabetic patients in the present study is similar to that reported in several previous studies. The LIPS study population consisted only of patients who had undergone a successful PCI, so our cohort excluded various patient groups (medically treated, procedure failure and cardiac surgery patients were excluded). Nevertheless the positive impact of fluvastatin in the diabetic population, which was observed after 1.5 years of treatment and was maintained throughout the remainder of this study, is undoubtedly an important finding, which merits further investigation.

## CONCLUSION

The presence of diabetes is a consistent clinical predictor of cardiovascular complications, and patients with diabetes are at increased risk of long-term adverse events following PCI. However, recent developments in the interventional field have led to very promising reductions in restenosis (36), hence a new long-term treatment approach targeting the progression of atherosclerosis may be required in the diabetic patient. The results of the present study demonstrate that fluvastatin is a safe and effective drug that can be used to retard atherosclerotic progression and reduce the risk of long-term adverse complications in this high-risk group of diabetic patients.

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**Table 1. Baseline patient characteristics according to allocated treatment***

| | Non diabetics | | Diabetics | | p-value† |
|---|---|---|---|---|---|
| | Fluvastatin (n=724) | Placebo (n=751) | Fluvastatin (n=120) | Placebo (n=82) | |
| Age, y ± SD | 59.5 ± 10.3 | 59.7 ± 9.9 | 63.2 ± 8.2 | 62.1 ± 9.0 | 0.0001 |
| Male gender, n (%) | 615 (84) | 615 (85) | 96 (80) | 66 (80) | 0.15 |
| Height, cm ± SD | 170.1 ± 8.3 | 169.1 ± 8.3 | 168.1 ± 8.8 | 166.9 ± 8.6 | 0.0014 |
| Weight, kg ± SD | 76.9 ± 11.4 | 75.7 ± 11.5 | 78.9 ± 11.5 | 75.4 ± 10.9 | 0.16 |
| Previous MI, n (%) | 321 (45) | 337 (44) | 50 (42) | 36 (44) | 0.60 |
| Hypertension, n (%) | 272 (38) | 275 (37) | 58 (48) | 42 (51) | 0.0009 |
| Previous stroke, n (%) | 13 (2) | 24 (3) | 4 (3) | 3 (4) | 0.48 |
| Peripheral vascular disease, n (%) | 36 (5) | 48 (6) | 14 (12) | 9 (11) | 0.005 |
| Current smoker, n (%) | 189 (26) | 219 (29) | 22 (18) | 16 (20) | 0.008 |
| Family history of CAD, n (%) | 218 (30) | 232 (31) | 21 (18) | 19 (23) | 0.002 |
| Ejection fraction, % ± SD | 62.4 ± 12.0 | 62.0 ± 11.9 | 61.4 ± 12.0 | 60.4 ± 12.0 | 0.21 |
| Stable angina, n (%)‡ | 363 (51) | 368 (50) | 55 (46) | 48 (59) | 0.88 |
| Unstable angina, n (%) | 352 (49) | 373 (50) | 65 (54) | 34 (41) | 0.88 |
| Total cholesterol, mmol/l ± SD | 5.21 ± 0.80 | 5.19 ± 0.85 | 4.99 ± 0.75 | 4.88 ± 0.85 | 0.0000 |
| LDL-C, mmol/l ± SD | 3.45 ± 0.75 | .3.44 ± 0.79 | 3.22 ± 0.73 | 3.21 ± 0.77 | 0.0001 |
| HDL-C, mmol/l ± SD | 0.98 ± 0.31 | 0.97 ± 0.30 | 0.95 ± 0.29 | 0.90 ± 0.24 | 0.047 |
| Triglycerides, mmol/l ± SD | 1.75 ± 0.79 | 1.73 ± 0.74 | 1.79 ± 0.68 | 1.70 ± 0.58 | 0.76 |

*SD= standard deviation; MI = myocardial infarction; CAD = coronary atherosclerotic disease; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol

†Related to the comparison between the diabetic and non-diabetic populations, regardless of treatment allocation.

‡Includes patients with silent ischemia.

**Table 2. Procedural characteristics according to allocated treatment***

| | Non diabetics | | Diabetics | | p-value† |
|---|---|---|---|---|---|
| | Fluvastatin (n=724) | Placebo (n=751) | Fluvastatin (n=120) | Placebo (n=82) | |
| RCA, n (%) | 278 (31) | 279 (29) | 48 (26) | 31 (30) | 0.37 |
| LAD, n (%) | 438 (46) | 483 (49) | 86 (46) | 52 (50) | 0.95 |
| LCx, n (%) | 217 (23) | 216 (22) | 53 (28) | 21 (20) | 0.26 |
| Lesion type‡ | | | | | |
| A | 185 | 190 | 41 | 18 | |
| B1 | 329 | 345 | 64 | 39 | |
| B2 | 311 | 323 | 68 | 30 | |
| C | 124 | 117 | 14 | 17 | |
| Lesions treated per patient, les/pt ± SD | 1.3 ± 0.7 | 1.3 ± 0.6 | 1.6 ± 0.8 | 1.3 ± 0.7 | 0.015 |
| Number of patients treated with at lest one stent, n (%) | 470 (65) | 460 (61) | 70 (58) | 55 (67) | 0.74 |
| Number of patients treated with balloon only, n (%) | 244 (33) | 273 (36) | 43 (36) | 22 (27) | 0.74 |
| Successful procedure | 723 | 748 | 118 | 80 | |

*SD= standard deviation; RCA = right coronary artery; LAD = left anterior descending artery; LCx = left circumflex artery.

†Related to the comparison between the diabetic and non-diabetic populations, regardless of treatment allocation

‡ACC/AHA classification

**Table 3. Incidence and relative risks of MACE at follow up according to presence of diabetes at baseline and allocated treatment***

| | | Non-diabetics | | Diabetics | |
|---|---|---|---|---|---|
| | | Fluvastatin (n=724) | Placebo (n=751) | Fluvastatin (n=120) | Placebo (n=82) |
| *MACE, n (%)* | | 155 (21) | 191 (25) | 26 (22) | 31 (38) |
| Treatment/Disease interaction term † | RR 0.77 (95% CI: 0.58 - 1.03); p=0.0789 | | | | |
| Diabetes effect in patients on placebo | RR 1.78 (95% CI: 1.20 - 2.64); p=0.0045 | | | | |
| Diabetes effect in patients on fluvastatin | RR 1.06 (95% CI: 0.69 - 1.62); p=0.7879 | | | | |
| Fluvastatin effect in diabetic patients | RR 0.49 (95% CI: 0.29 - 0.84); p=0.0088 | | | | |
| Fluvastatin effect in non-diabetic patients | RR 0.82 (95% CI: 0.66 – 1.02); p=0.0738 | | | | |
| *MACE without restenosis within 6 months, n (%)* | | 112 (15) | 158 (21) | 23 (19) | 29 (35) |
| Treatment/Disease interaction term† | RR 0.85 (95% CI : 0.62-1.15) ; p=0.2887 | | | | |
| Diabetes effect in patients on placebo | RR 1.85 (95% CI : 1.22-2.80) ; p=0.0035 | | | | |
| Diabetes effect in patients on fluvastatin | RR 1.33 (95% CI : 0.84-2.11) ; p=0.2270 | | | | |
| Fluvastatin effect in diabetic patients | RR 0.50 (95% CI : 0.28-0.87) ; p=0.0144 | | | | |
| Fluvastatin effect in non-diabetic patients | RR 0.69 (95% CI : 0.54-0.88) ; p=0.0033 | | | | |

*MACE = major adverse cardiac events

p-values are unadjusted

*†The treatment/disease interaction represents the effect of fluvastatin treatment in the diabetic group relative to the treatment effect in the non-diabetic group.*

## FIGURE LEGENDS

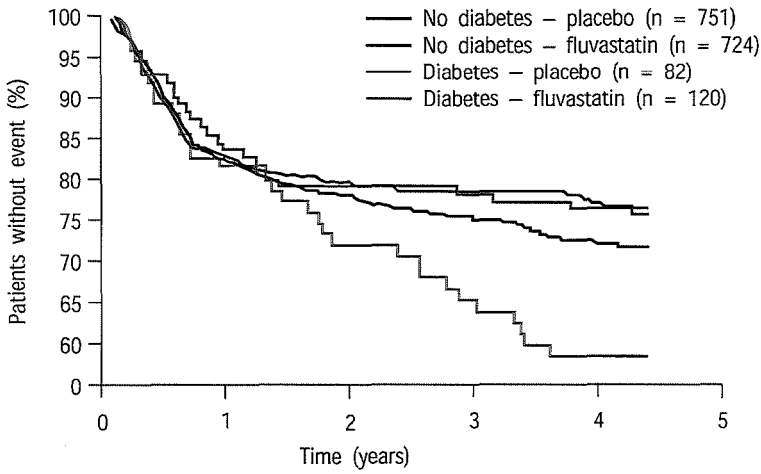



**Figure 1. Kaplan-Meier curves showing survival time free of MACE**
Survival time free of MACE (cardiac death, non-fatal myocardial infarction and reintervention) in patients with or without diabetes, randomized to receive treatment with either fluvastatin, 80 mg/day, or placebo. Event-free survival distribution was estimated as described in the text.

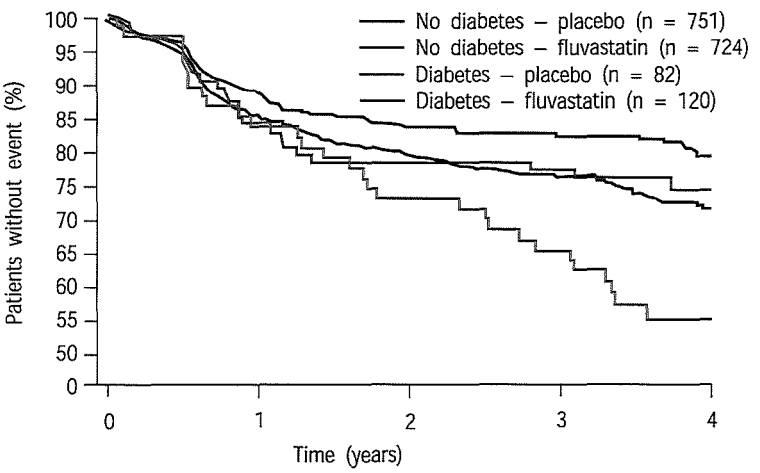



**Figure 2. Kaplan-Meier curves showing survival time free of coronary atherosclerotic events**
Survival time free of coronary atherosclerotic events (cardiac death, non-fatal myocardial infarction and all reinterventions not caused by coronary restenosis) in patients with or without diabetes, randomized to receive treatment with fluvastatin, 80 mg/day, or placebo. Event-free survival distribution was estimated as described in the text.

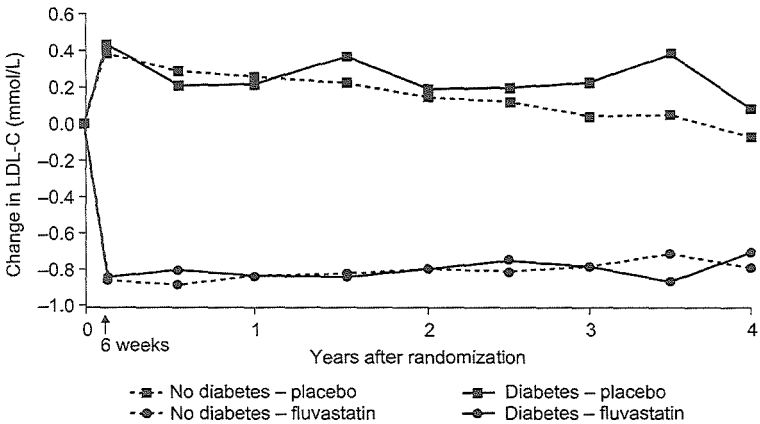
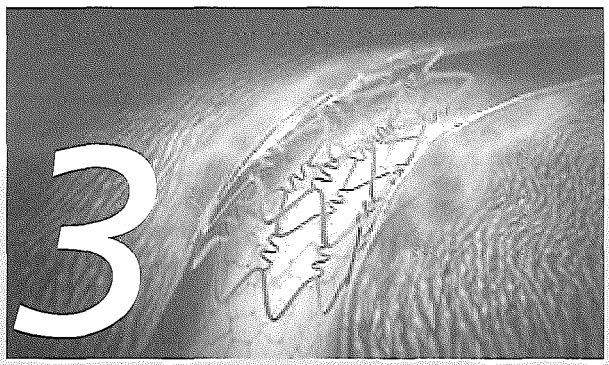



**Figure 3. Reductions in LDL-C levels with fluvastatin treatment in diabetic and non diabetic patients**
Change in LDL-C levels (mmol/L) throughout follow-up in patients with or without diabetes, randomized to receive treatment with fluvastatin, 80 mg/day, or placebo. Values are presented as mean data.

# 13



# Impact of Baseline Renal Function on Mortality after Percutaneous Coronary Intervention with Sirolimus-Eluting Stents or Bare Metal Stents

Pedro A Lemos
Chourmouzios A Arampatzis
Angela Hoye
Joost Daemen
Francesco Saia
Wim van der Giessen
Eugene McFadden
Georgios Sianos
Pieter C Smits
Pim de Feyter
Sjoerd Hofma
Ron van Domburg
Patrick W Serruys

JACC, submitted

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

Pedro A. Lemos, MD; Chourmouzios A. Arampatzis, MD; Angela Hoye, MB ChB, MRCP; Joost Daemen; Andrew T.L. Ong, MBBS FRACP; Francesco Saia, MD; Willem J. van der Giessen, MD, PhD; Eugene McFadden, MB ChB, FRCPI; Georgios Sianos, MD, PhD; Pieter C. Smits, MD, PhD; Pim de Feyter, MD, PhD; Sjoerd H. Hofma, MD; Ron T. van Domburg, PhD; Patrick W. Serruys, MD, PhD

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

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

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

Submitted for publication

## Introduction

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

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

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

## Methods

### Patient Population and Procedures

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

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

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

### Clinical Follow-up and Endpoints

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

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

### Renal Function Evaluation

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

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

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

ISR=in-stent restenosis; pt=patient; SD=standard deviation; SES=sirolimus-eluting stents
* for the comparison between patients with normal renal function and patients with renal impairment pooled over stent type group
† p<0.05 for bare stents vs. sirolimus-eluting stents pooled over renal function group
‡ p<0.01 for bare stents vs. sirolimus-eluting stents pooled over renal function group

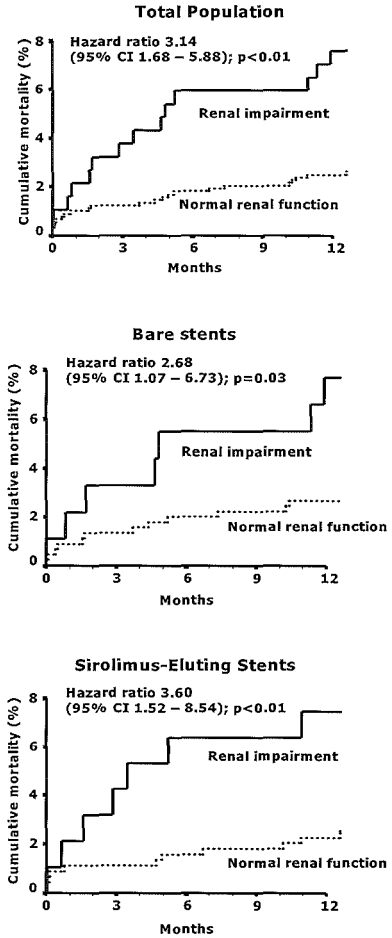



Figure 1. Incidence of all-cause death for patients with or without renal impairment. Top panel: total study population pooled over stent type. Mid panel: patients treated with bare stents. Lower panel: patients treated with sirolimus-elutings stents.

### Statistical Analysis

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

## Results

### Baseline and procedural characteristics

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

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

### 1-year mortality

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

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

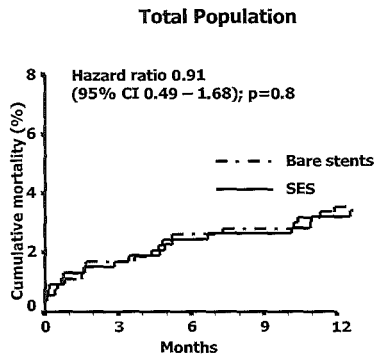



Figure 2. Unadjusted 1-year incidence of all-cause death for patients treated with bare stents vs. sirolimus-elutings stents polled over renal function.

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

### Repeat revascularization

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

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

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

## Discussion

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

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

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

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

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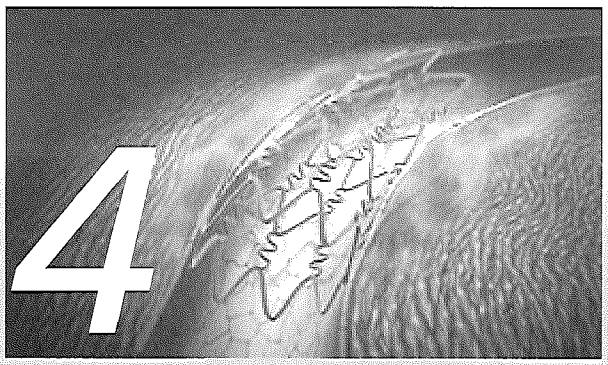

# Effectiveness of the Sirolimus-Eluting Stent in the Treatment of Patients with Prior History of Coronary Artery Bypass Graft Surgery

Angela Hoye
Pedro A Lemos
Chourmouzios A Arampatzis
Francesco Saia
Kengo Tanabe
Muzaffer Degertekin
Sjoerd Hofma
Eugene McFadden
Georgios Sianos
Pieter C Smits
Wim van der Giessen
Pim de Feyter
Ron van Domburg
Patrick W Serruys

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## ABSTRACT:

**Objective:** Percutaneous coronary intervention in patients with a history of previous coronary artery bypass grafting (CABG) is associated with an increased rate of subsequent adverse events compared to those without prior CABG. We evaluated the impact of utilizing the sirolimus-eluting stent (SES) in this high-risk population.
**Methods:** Since April 2002, SES implantation was utilized as the default strategy for all percutaneous procedures in our hospital. Consecutive patients with a history of previous CABG and *de novo* lesions (n=47) treated exclusively with SES, were compared to 66 patients who received bare stents in the 6 month period just before SES introduction.
**Results:** There were no significant differences between the groups (SES and bare stent) with respect to baseline clinical or lesion characteristics. The only difference between the groups related to the nominal diameter of stent utilized, which was smaller in the SES group than the bare stent group. (The maximum diameter of SES available was 3.0mm). At 1 year, the cumulative incidence of major adverse events (defined as death, myocardial infarction, or target vessel revascularization) was significantly lower in the SES group than the bare stent group (8.5% versus 30.3%, HR 0.37 [95% CI 0.15-0.91]; p=0.03)
**Conclusions:** The utilization of the sirolimus-eluting stent for percutaneous intervention in a high risk population with a history of previous CABG surgery, is associated with a significant reduction in the rate of major adverse cardiac events at one year.



## CONDENSED ABSTRACT:

A total of 47 consecutive patients with a history of previous coronary surgey and *de novo* lesions treated exclusively with sirolimus-eluting stents (SES) were compared to 66 patients who received bare stents in the period just before SES introduction. Baseline characteristics of both groups were similar. At 1 year, the cumulative incidence of major adverse events (defined as death, myocardial infarction, or target vessel revascularization) was significantly lower in the SES group than the bare stent group (8.5% versus 30.3%, HR 0.37 [95% CI 0.15-0.91]; p=0.03). The utilization of the sirolimus-eluting stent for percutaneous intervention in a high risk population with a history of previous coronary bypass surgery, is associated with a significant reduction in the rate of major adverse cardiac events at one year.


Key words: **Coronary artery disease; atherosclerosis; bypass; restenosis; angioplasty; drugs**

## INTRODUCTION

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

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

## METHODS AND STUDY POPULATION

From April 2002, all percutaneous coronary intervention at our centre was done with a policy of SES usage, irrespective of clinical presentation or lesion morphology, further details of the methodology are described elsewhere. [18,19] All procedures were performed with standard interventional techniques except with the use of SES as the device of choice. SES were available in lengths between 8mm and 33mm, and diameters of between 2.25-3.0mm. All patients were treated with long-term aspirin therapy and received a loading dose of 300mg clopidogrel followed by a daily dose of 75mg for at least 3 months. The procedural utilization of glycoprotein IIb/IIIa inhibitor therapy and distal protection devices was at the discretion of the operator. Angiographic success was defined as a final diameter stenosis from an on-line quantitative coronary angiography measurement of <50%.

The current study cohort comprises of 47 patients with a previous history of CABG who were treated for de novo lesions(s) solely with SES. This group was then compared with a control group (n=66) comprised of those patients who had been treated similarly in the preceding 6-months though with bare stent implantation. The

protocol was approved by the local ethics committee and is in accordance with the principles of Good Clinical Practice for Trials of Medicinal Products in the European Community and the Declaration of Helsinki. All patients signed a written informed consent.

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

**Statistical analysis:** Discrete variables are presented as percentages and compared with Fisher exact tests. Continuous variables are expressed as mean ± standard deviation and compared with Student t test. MACE-free survival curves were calculated according to the Kaplan-Meier method. Hazard ratios (and their 95% confidence intervals) of adverse events were calculated by Cox proportional hazard models. A $p<0.05$ was considered statistically significant.

## RESULTS

Baseline patient demographics and procedural data are presented in tables 1 and 2 respectively. Notably, patients were relatively old with a mean age of 69 years in the bare stent cohort, and 68 years in the SES group. In addition, there was a high rate of multivessel disease (95.5% in the bare stent group, 91.5% in the SES group), and approximately one-fifth of the patients (19.7% in the bare stent group, 21.3% in the SES group) had diabetes mellitus. There were no significant differences between the 2 groups treated with either bare stents or SES, except in the mean nominal diameter of stent utilized, which was smaller in the SES group. Intervention within native coronary arteries only, occurred in 59.9% of the bare stent group, and 63.8% of the SES group. The angiographic success rate in both groups was high at >97%.

At follow-up, there were no episodes of either acute or subacute stent thrombosis in either cohort. Table 3 presents the Kaplan-Meier estimates of the rate of major adverse cardiac events of the two groups at 1 year. There is a significantly lower rate of events in the SES group, predominantly related to a reduced need for repeat target vessel revascularization (TVR). At 1 year, 1 patient treated with SES (2.1%) required TVR for restenosis of a stent within a SVG, giving an overall TVR rate within this population of 6.3% (1 out of the 16 survivors). This compares with 15 patients (22.7%) treated with BMS who required TVR. Of these 15 patients, 9 underwent TVR for instent restenosis within a native vessel, and the remaining 6 underwent TVR (one re-do CABG) for restenosis within a SVG giving an overall TVR rate within this population of 25.0% (6 out of the 24 survivors). The Kaplan-meier curves for the cumulative incidence of major adverse cardiac events is presented in the figure.

## DISCUSSION

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

It is 20 years since Douglas et al demonstrated the feasibility of PCI in patients with a history of CABG. [20] More recently, the AWESOME randomized trial and registry demonstrated that at three years, the overall survival of patients with previous CABG and medically refractory angina, was similar whether treated with either PCI or re-do CABG. [21] Moreover, when given the choice of PCI or re-do CABG, the majority of patients preferred the former option. The Investigators concluded that PCI may be the preferred revascularization strategy.

In the present study, 40.9% in the bare stent group, and 36.2% of the SES group underwent intervention within at least one bypass graft. Compared to native vessels, percutaneous revascularization of diseased saphenous vein grafts is hampered by an increased rate of adverse events thereby contributing to the worse outcome of post-CABG patients. Procedural complications may relate to distal embolisation of friable material within the graft, and at follow-up, grafts are subject to an increased rate of restenosis. Historically, results of balloon-only therapy were disappointing. [22-24] In one study of 454 patients, procedural success was 90%, with a 5-year MACE-free survival of only 26%. [24] Subsequently, a randomized trial demonstrated the benefit of stenting over balloon-only angioplasty. At 6-months, the rate of survival free from either death, myocardial infarction, repeat CABG, or TLR was 73% in the stented group versus just 58% in the balloon-only group ($p=0.03$). [15] However, the angiographic restenosis rate remained high (37% versus 46% respectively, $p=0.24$).

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

Studies evaluating the SES have demonstrated low rates of restenosis compared with bare stents when used in relatively simple lesions. [16,17] The current study evaluated the results of PCI in a high risk population with a history of previous CABG. Both cohorts were comparable with respect to baseline clinical and lesion

characteristics, and all procedures were carried out as a consecutive series, in a single center by the same operators. The only difference between the groups was a significantly smaller mean nominal diameter of stent utilized in the SES group. This is likely to reflect the fact that the maximum nominal diameter of SES available was 3.0mm [27] (though post-dilatation was freely allowed) which is often small particularly within venous bypass grafts. A smaller stent (associated with a smaller minimal lumen diameter) is more likely to be associated with subsequent restenosis [28] which might have tended towards an increased need for target vessel revascularization in the SES group. However, at 1 year, those treated with SES had a significantly lower rate of MACE compared to those patients treated with bare stent implantation, predominantly related to a reduction in the need for repeat target vessel revascularization.

The present study is limited as it evaluated only a small cohort of patients with de novo lesions, and there was no routine angiographic follow-up. In particular, the number of patients who underwent saphenous vein graft intervention was small. In addition, the study was not randomized, and used a retrospective comparitive population. However the same operators and interventional techniques were utilized, and our study accurately reflects the "real world" practice of interventional cardiology. We have clearly demonstrated the applicability of the sirolimus-eluting stent in reducing the subsequent rate of adverse cardiac events at one year, in a high risk population with a history of previous coronary artery bypass graft surgery.

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**Table 1: Baseline patient demographics**

| | Bare stent n=66 | SES group n=47 | p value |
|---|---|---|---|
| Male sex (%) | 66.7 | 70.3 | 0.5 |
| Mean age (years) | 69.0 ± 10.9 | 68.0 ± 9.0 | 1.0 |
| Current smoker (%) | 16.7 | 10.6 | 0.4 |
| Diabetes mellitus (%) | 19.7 | 21.3 | 1.0 |
| Hypertension (%) | 54.5 | 61.7 | 0.6 |
| Hypercholesterolemia (%) | 83.3 | 89.4 | 0.6 |
| Previous myocardial infarction (%) | 47.7 | 31.9 | 0.2 |
| Previous percutaneous coronary intervention (%) | 39.4 | 42.6 | 0.9 |
| Presence of multivessel disease (%) | 95.5 | 91.5 | 0.5 |
| Clinical presentation | | | |
| Stable angina (%) | 48.5 | 63.8 | 0.2 |
| Unstable angina (%) | 43.9 | 34.0 | 0.4 |
| Acute myocardial infarction (%) | 7.6 | 2.1 | 0.4 |
| Use of glycoprotein IIb/IIIa inhibitor (%) | 36.4 | 21.3 | 0.1 |

SES: sirolimus-eluting stents

**Table 2: Procedural data**

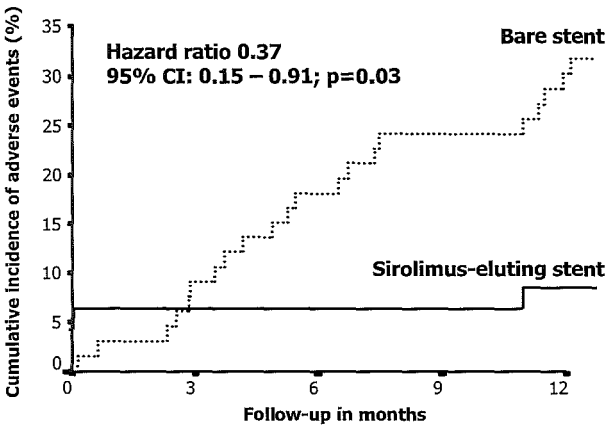
| | Bare stent n=66 | SES group n=47 | p value |
|---|---|---|---|
| Treated vessel | | | |
| Left anterior descending (%) | 34.8 | 42.6 | 0.4 |
| Left circumflex (%) | 33.3 | 29.8 | 0.8 |
| Right coronary artery (%) | 27.3 | 17.0 | 0.3 |
| Left main coronary (%) | 15.2 | 10.6 | 0.6 |
| Bypass graft (%) | 40.9 | 36.2 | 0.7 |
| Use of a distal protection device (% of those with graft intervention) | 5 (18.5) | 6 (35.3) | 0.3 |
| *Lesion type* | | | |
| Type A (%) | 16.7 | 20.6 | 0.6 |
| Type B1 (%) | 24.2 | 29.8 | 0.5 |
| Type B2 (%) | 59.1 | 50.4 | 0.3 |
| Type C (%) | 40.9 | 36.2 | 0.7 |
| Mean number of stents | 2.1 ± 1.4 | 1.9 ± 0.9 | 0.7 |
| Mean nominal diameter of stent (mm) | 3.3 ± 0.6 | 2.8 ± 0.3 | <0.001 |
| Mean length of stents per patient (mm) | 35.1 ± 24.7 | 32.6 ± 22.1 | 0.6 |
| Angiographic success (%) | 98.5 | 97.9 | 1.0 |

SES: sirolimus-eluting stents

**Table 3: Kaplan-Meier estimates of major adverse events at 1 year**

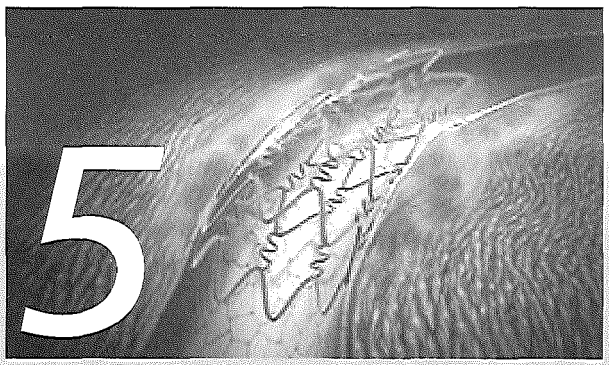
| | Bare stents | SES | HR | 95% CI | p-value |
|---|---|---|---|---|---|
| Death, % | 6.1 | 2.1 | 0.34 | 0.04 – 3.09 | 0.3 |
| Death or myocardial infarction, % | 10.6 | 6.4 | 0.80 | 0.24 – 2.71 | 0.7 |
| Target vessel revascularization, % | 23.0 | 2.1 | 0.23 | 0.07 – 0.80 | 0.02 |
| Any event, % |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

HR=hazard ratio; SES=sirolimus-eluting stents




Kaplan-meier curves for the cumulative incidence of major adverse events at one year, for patients with a history of previous coronary artery bypass surgery treated with sirolimus-eluting stent implantation versus bare stent implantation.

# 25



# Very Long Sirolimus-Eluting Stent Implantation for De Novo Coronary Lesions

Muzaffer Degertekin
Chourmouzios A Arampatzis
Pedro A Lemos
Francesco Saia
Angela Hoye
Joost Daemen
Kengo Tanabe
Chi-Hang Lee
Sjoerd Hofma
Georgios Sianos
Eugene McFadden
Wim van der Giessen
Pieter C Smits
Pim de Feyter
Ron van Domburg
Patrick W Serruys

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# Very Long Sirolimus-Eluting Stent Implantation for De Novo Coronary Lesions

Muzaffer Degertekin, MD, Chourmouzios A. Arampatzis, MD, Pedro A. Lemos, MD, Francesco Saia, MD, Angela Hoye, MB, ChB, MRCP, Joost Daemen, Kengo Tanabe, MD, Chi-Hang Lee, MD, Sjoerd J. Hofma, MD, Georgios Sianos, MD, Eugene McFadden, MB, ChB, FRCPI, Willem van der Giessen, MD, PhD, Pieter C. Smits, MD, PhD, Pim J. de Feyter, MD, PhD, Ron T. van Domburg, PhD, and Patrick W. Serruys, MD, PhD*

**Long-length stenting has a poor outcome when bare metal stents are used. The safety and efficacy of the sirolimus-eluting stent (SES) in long lesions has not been evaluated. Therefore, the aim of the present study was to evaluate the clinical and angiographic outcomes of SES implantation over a very long coronary artery segment. Since April 2002, all patients treated percutaneously at our institution received a SES as the device of choice as part of the Rapamycin Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. During the RESEARCH registry, stents were available in lengths of 8, 18, and 33 mm. The present report includes a predefined study population consisting of patients treated with >36-mm-long stented segments. Patients had a combination of ≥2 overlapping stents at a minimum length of 41 mm (i.e., one 33-mm SES overlapping an 8-mm SES) to treat native de novo coronary lesions. The incidence of major cardiac adverse events (death, nonfatal myocardial infarction, and target lesion revascularization) was evaluated. The study group comprised 96 consecutive patients (102 lesions). Clinical follow-up was available for all patients at a mean of 320 days (range 265 to 442). In all, 20% of long-stented lesions were chronic total occlusions, and mean stented length per lesion was 61.2 ± 21.4 mm (range 41 to 134). 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 ± 0.47 mm. At long-term follow-up (mean 320 days), there were 2 deaths (2.1%), and the overall incidence of major cardiac events was 8.3%. Thus, SES implantation appears safe and effective for de novo coronary lesions requiring multiple stent placement over a very long vessel segment.** ©2004 by Excerpta Medica, Inc.

(Am J Cardiol 2004;93:826–829)

Treatment of complex coronary artery stenosis with a long segment of bare metal stent 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 frequently avoided. The efficacy of the sirolimus-eluting stent (SES) implantation has been recently evaluated in the context of 2 large randomized trials. The RAndomized study with the sirolimus-eluting Bx VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions (RAVEL) trial[8] included only single lesions covered by an 18-mm-long stent and had a zero restenosis rate. In the US Multicenter, Randomized, Double-Blind Study of the SIRolImUS-eluting Bx velocity balloon expandable stent (SIRIUS) trial,[9] relatively long stent placement was allowed (maximum of 2 overlapping 18-mm-long SESs) and the restenosis rate was 9.2%. The efficacy of a SES implanted over a total coronary length >36 mm has not been tested to date. In the present study, we sought to evaluate the outcomes of patients receiving overlapping stents implanted over a length >36 mm to treat native de novo coronary lesions.

From the Department of Interventional Cardiology, Thoraxcentre, Erasmus MC, Rotterdam, The Netherlands. This study was supported in part by health care funds allotted by the Erasmus Medical Center, Rotterdam, The Netherlands, and by an institutional grant from Cordis, Johnson & Johnson, Miami Lakes, Florida. Manuscript received October 8, 2003; revised manuscript received and accepted December 4, 2003.

Address for reprints: Patrick W. Serruys, MD, PhD, Department of Interventional Cardiology, Erasmus MC Rotterdam, Thoraxcentre Bd 404, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl.

*We declare there is no conflict of interest for any of the authors.

## METHODS

Since April 16, 2002, it has been our policy to use the SES (Cypher, Cordis Europa NV, Roden, The Netherlands) as the device of choice for every percutaneous coronary intervention performed at our institution as part of the Rapamycin Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. Further details of the methods have been previously described.[10]

**Study group and stent implantation:** During the RESEARCH registry enrollement, SESs were available at lengths of 8, 18, and 33 mm. The present report includes a predefined study group composed of pa-

**TABLE 1** Baseline Patient Demographics and Procedural Data

| | Patients with Longer Stented Segment (n = 96, 102 lesions) |
|---|---|
| Age (yrs) | 64 ± 12 |
| Men | 62% |
| Diabetes | 18% |
| Current smoking | 26% |
| Hypercholesterolemia | 57% |
| Hypertension | 45% |
| Previous myocardial infarction | 32% |
| Previous balloon angioplasty | 19% |
| Target vessel | |
| Left anterior descending artery | 47% |
| Left circumflex artery | 9% |
| Right coronary artery | 44% |
| Chronic total occlusion | 20% |
| Direct stenting | 53% |
| Multivessel disease | 52.1% |
| Primary percutaneous coronary intervention | 8% |
| Glycoprotein IIb/IIIa inhibitor use | 31% |
| Mean no. of sirolimus-eluting stents per lesion | 2.66 ± 0.9 (range 2–6) |
| Mean length of sirolimus-eluting stent per lesion (mm) | 61.2 ± 21.4 (range 41–134) |
| Mean diameter of Sirolimus-eluting stent (mm) | 2.82 ± 0.24 |

tients treated with stented segments >36 mm long. Therefore, because of the availability of stent lengths, all included patients had a combination of at least 2 overlapping stents at a minimum length of 41 mm (i.e., one 33-mm SES overlapping an 8-mm SES). Patients receiving a 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 formed the present study group. The stented length was based on the cumulative length of the patient's adjacent stents. All procedures were performed according to standard interventional techniques, except with the use of the 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 Thrombolysis In Myocardial Infarction (TIMI-3) trial anterograde flow). All patients received lifelong aspirin and clopidogrel 75 mg/day for 6 months. Glycoprotein IIb/IIIa inhibitors were given at the discretion of the physician. The hospital ethics committee approved the study protocol and written informed consent was obtained from all patients.

**Definitions and follow-up:** All patients were evaluated for the occurrence of major cardiac adverse events, defined as death, myocardial infarction, target lesion revascularization, and target vessel revascularization. In-hospital outcome information was retrieved by means of an electronic clinical database for patients maintained in our hospital after the procedure and by review of the hospital records for those discharged to secondary hospitals. After discharge, recordings of all repeat interventions (surgical and percutaneous) and rehospitalizations were prospectively collected in a dedicated database. Follow-up information was obtained by regular outpatient evaluation, by phone contact, or by mail. Myocardial infarction was documented by an increase 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 postprocedural myocardial infarction was suspected. Consequently, enzymatic assessment was not available for all patients, but for those whom the likelihood of postprocedure myocardial infarction was high.[10] Target vessel revascularization was defined as either surgical or percutaneous reintervention driven by significant (>50%) luminal narrowing either within the stent or within the 5-mm 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 are presented as counts and percentages. Continuous variables are presented as mean ± SD and compared by Student's *t* test.

## RESULTS

Baseline and procedural characteristics of the 96 patients (102 lesions) are listed in Table 1. Approximately half of lesions were located in the left anterior descending coronary artery (47%) or in the right coronary artery (44%). The mean number of stents per lesion was 2.66 ± 0.9 (range 2 to 6 stents), and the average stented length was 61.2 ± 21.4 mm. The 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 segment, and 2 in the distal 5-mm adjacent vessel segment. All post-SES restenoses were focal and <10 mm 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 to 442) and is summarized in Table 3.

Two patients died. One patient died during the in-hospital period after emergent bypass surgery for a procedure related to left main stem dissection caused by the guiding catheter. The second patient was admitted in cardiogenic shock due to postinfarction un-

**TABLE 2** Quantitative Coronary Angiography Analysis After Procedure and Data at Six-month Follow-up (n = 67)

| Postprocedure | Proximal 5 mm | In-stent | Distal 5 mm |
|---|---|---|---|
| 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-mo 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) at 320 Days of Follow-up

| | |
|---|---|
| Death | 2 (2.1%) |
| Nonfatal 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%) |

*Non–Q-wave myocardial infarction peak creatine kinase 567IU (MB fraction 62IU).
†One of 2 patients who underwent emergency coronary artery bypass graft surgery for left main stem dissection died in the hospital.
CABG = coronary artery bypass graft surgery.

stable angina. He had 3-vessel disease, but the treatment was restricted to the culprit lesion. In total, six 2.25-mm diameter SESs were implanted in the left anterior artery/diagonal bifurcation. The patient died suddenly 43 days after the procedure. Although there is no clear evidence, subacute stent thrombosis cannot be ruled out in this case. Nonfatal myocardial infarction occurred in 1 patient. He developed a no-reflow phenomenon after stent placement, which was resolved after intracoronary adenosine and nitropruside infusion. At 6 months follow-up angiography, the patient was asymptomatic with a patent long-stented segment.

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

In all, 4 patients were successfully treated with repeat percutaneous coronary intervention electively for focal restenotic lesions. Overall, major adverse cardiac event-free survival was 91.7% at 320-day follow-up.

## DISCUSSION

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

Longer stented segment length using bare metal stents is an independent predictor of restenosis and adverse events.[1] Long stenting is frequently associated with prolonged intracoronary 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. The incidence of late complications has been reported to be directly proportional to the total length of stents implanted. Previously, Schalij et al[6] reported a 25% incidence of major adverse events for patients treated with bare metal stents at a mean stented length of 45 mm. In the Additional Value of NIR Stents for Treatment of Long Coronary Lesions (ADVANCE)[3] Study, the reported major adverse cardiac event rate was 23%. The present results are reassuring, because the relatively low incidence of adverse events (8.3%) presented in our series occurred in association with a markedly long length of the implanted SES (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 the angiographic pattern of restenosis of SES,[11] all our restenoses were focal and therefore easy to treat with repeat percutaneous coronary intervention. Because all patients with angiographically visible gaps between stents were excluded from the present analysis, incomplete lesion coverage was not identified as a possible mechanism of restenosis in any case.

There have been concerns that the risk for thrombosis may increase after implantation of the long length of the stent. In the present study, no documented thrombotic stent occlusion was observed, although we cannot rule out stent thrombosis in the patient who died suddenly 43 days after the index procedure. There is no consensus for the period of clopidogrel prescription after SES implantation, espe-

cially after treatment of complex lesions. Although no late thrombotic events were diagnosed after discontinuation of clopidogrel in our series (i.e., after 6 months), additional studies are warranted to further evaluate the best antiplatelet scheme for these patients.

Several limitations are noteworthy because of the small cohort of patients without a direct comparative control group. Angiographic follow-up could not be obtained in all patients. Nonetheless, not consenting to angiographic follow-up was not considered as an exclusion criterion for the RESEARCH study, which enrolled all unselected, consecutive patients treated in daily practice with percutaneous interventions. Obviously, this scenario differs substantially from that of randomized trials and limits the compliance to angiographic restudy. However, all eligible patients for whom angiographic re-evaluation was not obtained remained event free throughout the follow-up period. Postprocedure cardiac markers were not collective routinely for all patients (available for 46 of 96 patients [46%] in the study group). This was justified by the fact that high-grade enzymatic elevations (those with proved prognostic impact) rarely occur undetected in asymptomatic patients.

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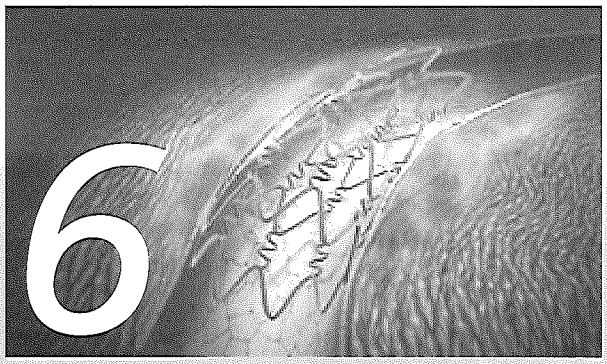

# Treatment of Very Small Vessels with 2.25mm Diameter Sirolimus-Eluting Stent (from the RESEARCH registry)

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Patrick W Serruys

Am J Cardiol. 2004;93:633-6

# Treatment of Very Small Vessels With 2.25-mm Diameter Sirolimus-Eluting Stents (from the RESEARCH Registry)

Pedro A. Lemos, MD, Chourmouzios A. Arampatzis, MD, Francesco Saia, MD, Angela Hoye, MD, ChB, MRCP, Muzaffer Degertekin, MD, Kengo Tanabe, MD, Chi-Hang Lee, MBBS, MRCP, Paul Cummins, RN, Pieter C. Smits, MD, PhD, Eugène McFadden, MB, ChB, Georgios Sianos, MD, Pim de Feyter, MD, PhD, Willem J. van Der Giessen, MD, PhD, Ron T. van Domburg, PhD, and Patrick W. Serruys, MD, PhD

**A total of 91 patients with 112 lesions received 2.25-mm sirolimus-eluting stents (SESs), and these lesions were compared with those treated with SESs of ≥2.5-mm diameter in the same procedure (n = 109). The reference diameters were 1.88 ± 0.34 and 2.52 ± 0.57 mm, respectively (p <0.01). At follow-up, the late lumen loss was 0.07 ± 0.48 mm for the 2.25-mm SES versus 0.03 ± 0.38 mm for the larger SES (p = 0.5), and the binary restenosis rate was 10.7% versus 3.9%, respectively (p = 0.1). The 12-month target lesion revascularization rate was 5.5%. In conclusion, 2.25-mm SESs were associated with low rates of clinical and angiographic late complications.** 
**(Am J Cardiol 2004;93:633–636)**

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

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

Since April 16, 2002, SES implantation (Cypher; Johnson & Johnson–Cordis Unit, Cordis Europa NV, Roden, The Netherlands) has been used as the default strategy in our institution as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) study.[10] At 6-month enrollment, a total of 91 consecutive patients (16% from the total population in that time) had been treated with 2.25-mm diameter SESs for 112 de novo lesions. Of these 91 patients, 60 patients also had lesions treated with SESs of ≥2.5 mm diameter (n = 109 lesions) (average stent diameter in these lesions was 2.9 ± 0.2 mm). The angiographic outcomes of lesions treated

**TABLE 1** Baseline and Follow-up Clinical Characteristics of Patients Treated With the 2.25-mm Diameter Sirolimus-eluting Stents (SES) (n = 91)

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

From the Department of Cardiology, Thoraxcenter, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands. This study was supported by health care funds allotted by the Erasmus Medical Center, University Medical Center Rotterdam, Rotterdam, The Netherlands, and by an institutional grant from Cordis, a Johnson & Johnson Company, Miami Lakes, Florida. Dr. Serruys' address is: Department of Cardiology, Thoraxcenter, Room Bd 408, Erasmus Medical Center Rotterdam, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl. Manuscript received September 10, 2003; revised manuscript received and accepted November 10, 2003.

**TABLE 2** Angiographic Characteristics of Lesions Treated With Sirolimus-eluting Stents (SES) of Larger Diameters and Lesions Treated With 2.25-mm Diameter SESs

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

Data are presented as numbers (percent) or mean ± SD.
*Refers to 62 patients (70% of eligible patients) with angiographic follow-up at 6 months (76 lesions in the larger SES group and 75 lesions in the 2.25-mm SES group).

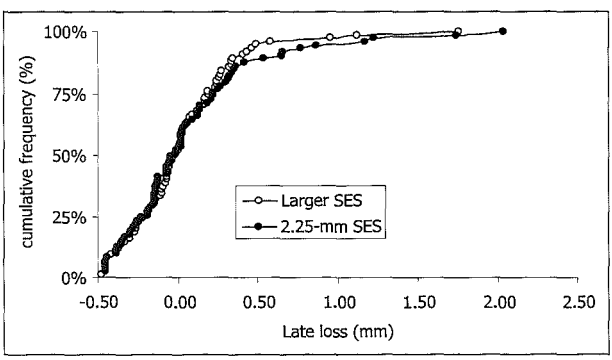


**FIGURE 1. Cumulative frequency of late lumen loss in lesions treated with 2.25-mm SESs and lesions treated with larger stents (≥2.5 mm).**

with the larger SES were used as a reference point for comparison with lesions treated with 2.25-mm SESs.

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

Major adverse cardiac events were defined as death, nonfatal myocardial infarction, or target lesion revascularization. Myocardial infarction was diagnosed by an increase in the creatine kinase level to more than twice the normal limit with an increased MB fraction. Target lesion revascularization was defined as any reintervention to treat a stenosis within the stent or in the 5-mm distal or proximal segments adjacent to the stent. All patients were considered eligible for 6-month angiographic follow-up. Binary angiographic restenosis was defined by diameter stenosis of ≥50% at follow-up angiography. Late lumen loss was calculated by the difference between the minimal luminal diameter after stenting and at follow-up.

Continuous variables were presented as mean ± SD and compared using the Student *t* test. Categorical variables were presented as counts and percentages and compared with the Fishers exact test. All statistical tests were 2-tailed. A p value <0.05 was considered significant.

Baseline clinical characteristics are listed in Table 1. Angiographic findings of lesions treated with the 2.25-mm SES and lesions treated with larger diameter stents in other vessel segments are listed in Table 2. Lesions treated with the 2.25-mm SES were more frequently located at secondary branches, at nonproximal segments, and at ostial lesions and had significantly smaller reference diameters (1.88 ± 0.34 vs 2.52 ± 0.57 mm, p <0.01). Angiographic follow-up (7.1 ± 1.3 months) was available for 62 patients (70% of eligible patients) and 151 lesions. Late lumen loss was similar in both lesion groups (0.07 ± 0.48 mm for 2.25-mm SES vs 0.03 ± 0.38 mm for larger SES, p = 0.5) as illustrated in Figure 1. Binary restenosis was identified in 8 lesions (10.7%) treated with 2.25-mm SESs and in 3 lesions (3.9%) treated with larger SESs (p = 0.1). Of the 8 restenotic lesions in 2.25-mm SESs, 3 (38%) occurred in stents implanted at the vessel ostium. Similarly, of the 3 restenotic lesions treated with larger the SES, 1 (33%) was ostial. Restenosis rates for nonostial lesions were 6.7% in the 2.25-mm SES group (n = 45 lesions with angiographic follow-up) and 3.0% in the larger SES group (n = 66 lesions) (p = 0.4). All restenoses occurred within the stent.

Follow-up clinical information was complete for 90 patients (99%) at an average of 346 ± 92 days (Table 1). There were 2 in-hospital deaths (both patients were admitted with myocardial infarction and cardiogenic shock). Nonfatal ST-elevation myocardial

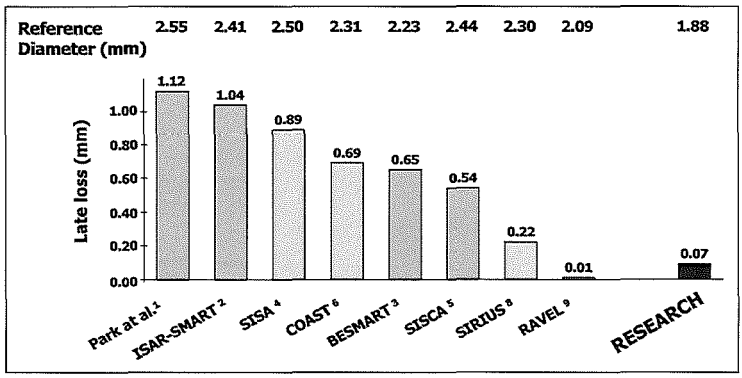


**FIGURE 2. Reference diameter and late lumen loss in the SIRIUS and RAVEL trials (lowest vessel size range) and in the RESEARCH registry (2.25-mm SES) and in the stent arm of 6 randomized trials comparing stent implantation with balloon angioplasty for small vessels. BESMART = BEstent in Small Arteries Trial; COAST = heparin-COAted Stents in small coronary arteries trial; SISA = Stent In Small Arteries Trial; SISCA = Stenting In Small Coronary Arteries trial.**

infarction was diagnosed in 1 patient (increased creatine phosphokinase 2.8 times the upper normal limit) and occurred on the same day of the index procedure because of thrombotic occlusion of a 2.25-mm SES implanted in the distal left anterior descending artery. A distal edge dissection was seen on intravascular ultrasound examination and was treated with implantation of another 2.25-mm SES that overlapped the previous stent. This patient was asymptomatic after 7 months and had a widely patent SES at angiographic evaluation. There were no other cases of stent thrombosis or myocardial infarction. Target lesion revascularization was performed in another 4 patients to treat restenosis occurring after 2.25-mm SES implantation (overall target lesion revascularization rate 5.5%), and the major adverse cardiac event rate was 7.7%.

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

Small vessel size has been shown to be an important independent predictor of restenosis after percutaneous intervention.[11] Currently, the best interventional approach for patients with small coronary vessels is unclear, although a number of strategies have been tested in several randomized trials.[1–6] In the present study, implantation of 2.25-mm SES strikingly inhibited neointimal proliferation in vessels with an average reference diameter of 1.88 mm, which is consistently smaller than the vessel size (range 2.23 to 2.55 mm) in all randomized studies published to date (Figure 2).[1–6] Although SESs were implanted in very small vessels in our study, the late lumen loss (0.07 mm) was clearly smaller than that seen after conventional stenting in previous series (1.12 to 0.54 mm).[1–6] Moreover, the late lumen loss observed after 2.25-mm SES implantation was similar to the late loss in previous trials with larger SESs, even when considering only vessels in the lowest tertile of vessel size included in these studies (Figure 2).[8,9]

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

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

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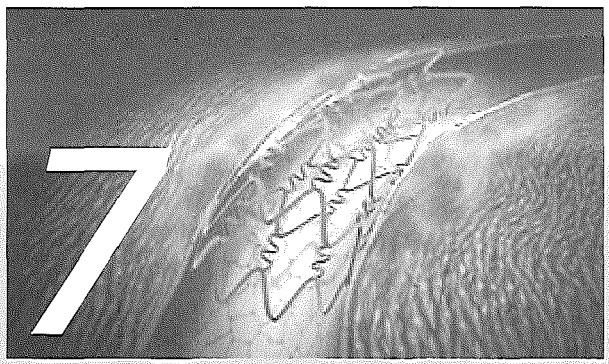

# Effectiveness of Sirolimus-Eluting Stent Implantation for Treatment of Left Main Coronary Artery Disease

Chourmouzios A Arampatzis
Pedro A Lemos
Kengo Tanabe
Angela Hoye
Muzaffer Degertekin
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Georgios Sianos
Pieter C Smits
Wim van der Giessen
Pim de Feyter
Ron van Domburg
Patrick W Serruys

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Erratum in Am J Cardiol. 2003;
92(12):1497

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

Chourmouzios A. Arampatzis, MD; Pedro A. Lemos, MD; Kengo Tanabe, MD; Angela Hoye, MB, CHB
Muzzafer Degertekin, MD; Francesco Saia, MD; Chi-hang Lee, MBBS, MRCP; Arno Ruiter, RN
Eugene McFadden, MD; George Sianos, MD; Pieter C. Smits, MD, PhD; Willem J. van der Giessen, MD, PhD
Pim de Feijter, MD, PhD; Ron van Domburg, PhD; Patrick W. Serruys, MD, PhD

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

*Am J Cardiol* 2003;92:327–329

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

•••

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

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

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

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

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

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

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

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

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

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

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

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

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

•••

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

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

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

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

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

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


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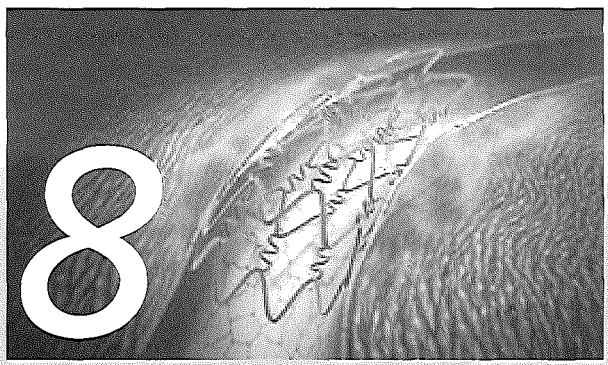

# Elective Sirolimus-Eluting Stent Implantation for Treatment of Left Main Coronary Disease-6 Month Angiographic Follow-up and One Year Clinical Outcome

Chourmouzios A Arampatzis
Pedro A Lemos
Angela Hoye
Francesco Saia
Kengo Tanabe
Pieter C Smits
Wim van der Giessen
Eugene McFadden
Pim de Feyter
Patrick W Serruys

Catheter Cardio Interventions, in press

## SYNOPSIS

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

## INTRODUCTION

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

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

## MATERIALS AND METHODS

### *Patient population and study design*

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

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

### *Follow-up and Clinical Endpoints*

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

We evaluated the incidence of death, myocardial infarction, or any repeat vessel revascularization, either surgical or percutaneous. Target lesion revascularization

(TLR) was defined as either surgical or percutaneous reintervention driven by significant (>50%) luminal narrowing either within the stent or the 5mm borders proximal and distal to the stent, and was undertaken in the presence of either anginal symptoms or objective evidence of ischemia. All patients had a successful procedure as characterized by Thrombolysis in Myocardial Infarction (TIMI) flow 3 and residual in-lesion stenosis≤30%. In addition, the patients were invited to have a follow-up angiographic evaluation at 6-months. The binary restenosis rate, was defined as >50% diameter stenosis occurring in the segment inside the SES or within the 5-mm proximal or distal edges.

*Statistics*

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

## RESULTS

*Baseline characteristics*

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

*Clinical and angiographic follow-up*

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

Complete clinical follow-up information was available for all patients. Mean duration of follow-up was 11.8±1.5 (range 10-15) months and is summarized in table 2. There were no cases of acute, subacute or late thrombosis, or death. One patient required TLR, for proximal edge restenosis. This patient was a diabetic male, with LM ostial stenosis protected by a patent LIMA (patient#12). The stenosis was very heavily calcified as indicated by the fact that the cutting balloon ruptured, and was stented with a 3X18mm and 3X8mm SES. Post dilatation was done with a 4.0mm balloon and the post-procedure diameter stenosis was 43%. At follow-up, intracoronary ultrasound revealed an under expanded stent at the proximal edge, due to 360° calcium located at the ostium.

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

## DISCUSSION

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

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

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

## STUDY LIMITATIONS

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

## ACKNOWLEDGEMENTS

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

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

*** "crush" is defined when the stent of the side branch is firstly deployed being almost in parallel position with the stent in the parent vessel. The second stent is situated in the parent vessel ensuring complete coverage of the ostium of the side branch. The stent in the parent vessell is then deployed, thereby by crushing the proximal part of the stent in the side branch. If necessary, optimization of the result is done by kissing balloon inflations.**

**UA=unstable angina ; SA=stable angina ; SI=silent ischemia ; CS=current smoker ; DM=diabetes mellitus ; HT=hypertension, HC=hypercholesterolemia.**

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

| N=17 | In-hospital events | Late outcome |
|---|---|---|
| Deaths, % | 0 | 0 |
| Non-Q myocardial infarction, % | 1(6%) | 0 |
| Reintervention | | |
| Percutaneous revascularization | 0 | 1 |
| Coronary bypass | 0 | 0 |
| Overall incidence of MACE* | 1(6%) | 1(6%) |

*MACE=major adverse cardiac events

**Table 3. Quantitative Coronary Angiography at index procedure and follow-up***

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

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

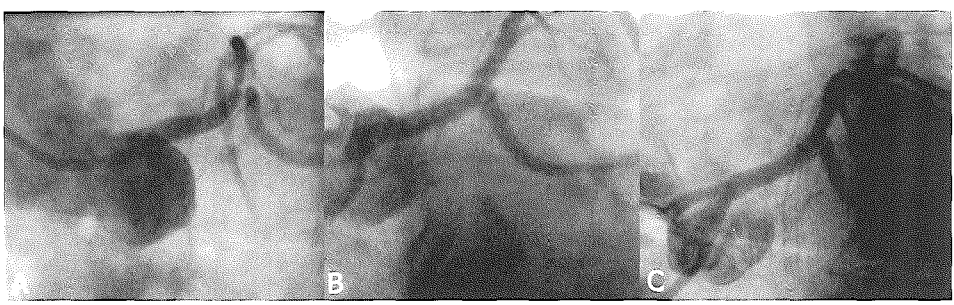

**Figure 1.**
Unprotected LM stenosis involving the distal bifurcation (A). T-stenting with a 3X8mm cypher™ in the circumflex and a 3X18mm in the left anterior descending artery (B). Six-month follow-up angiography with no restenosis(C).

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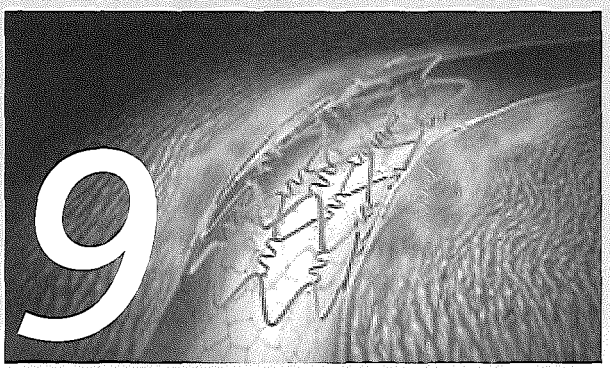

# Iatrogenic Left Main Dissection with Massive Pericoronary Hematoma Treated with 140mm Sirolimus-Eluting Stents

Chourmouzios A Arampatzis
Pieter C Smits
Jurgen M.R. Ligthart
Gio Maatrijk
Patrick W Serruys
Pim de Feyter

Catheter Cardio Interventions, submitted

Coronary angiography is the gold standard method for cardiac coronary imaging. While diagnostic angiograms are performed every day with a finite, small risk on complications, the most unpleasant and sometimes fatal complication remains left main stem dissection. We present a patient with a left main stem dissection followed by massive pericoronary hematoma and reconstructed with a total length of 140mm sirolimus eluting stents.

A 50-year-old woman, current smoker underwent diagnostic coronary catheterization for suspected coronary artery disease. During angiography a left main stem dissection occurred. "Milking" of the left anterior descending (LAD) artery was visible in diastole, caused by compression of the true lumen (Figure 1). The patient was hemodynamically stable with a normal electrocardiogram, and she was transferred to our institution. Intravascular ultrasound (IVUS system: Boston Scientific Galaxy□, IVUS catheter: Boston Scientific Atlantis□ 3F 40Mhz. Motorized pullback 0.5mm/sec) demonstrated a massive hematoma compressing the LAD, which extended from the left main to the distal LAD segment (Figure 2). Emergent bypass surgery was ruled out and a percutaneous approach was preferred. Sirolimus-drug eluting stents were implanted to 'seal' the dissected vessel. The total length of the implanted stents was 140mm [2.25X8mm, 2.75X33(three times) and 3.0X33mm respectively] (Figure 3). Care was taken to 'seal' the entry point of the dissection in the left main stem with SES (Figure 4). The procedure and recovery were uneventful. The patient underwent follow-up angiography 3 and 6 months later (Figure 5). Intravascular ultrasound showed minimal focal neointimal hyperplasia in the mid-LAD, and incomplete absorption of the hematoma (Figure 6).

The treatment approach for dissections involving the left main stem was emergent by-pass surgery,and although stenting has recently offered an alternative solution(1-3), the risk of (sub) acute thrombosis and restenosis causes great concern for the operator. Therefore, surgical treatment is the preferred option. Sirolimus-eluting stents have been increasingly reported with outstanding acute and late results (4,5). We have recently reported that the use of the sirolimus- eluting stent in the left main stem can be safely performed and the efficacy in the long term was promising (6,7).

It largely remains unknown what the best treatment approach is for a dissection. Some advocate to "seal"only the entry point of the dissection; while others, in particular when the lumen is endangered, advocate to stent the entire length of the dissected segment. However, in this case the IVUS findings (Figure 2) were so impressive, showing the whole length of the LAD compressed by the pericoronary dissecting hematoma that we decided to implant a total length of 140mm sirolimus-eluting stents overlapping to minimize the occurrence of restenosis. At 3- and 6-month angiographic follow-up the vessel remained patent without in stent restenosis. At 412 days follow-up the patient was still symptom free.

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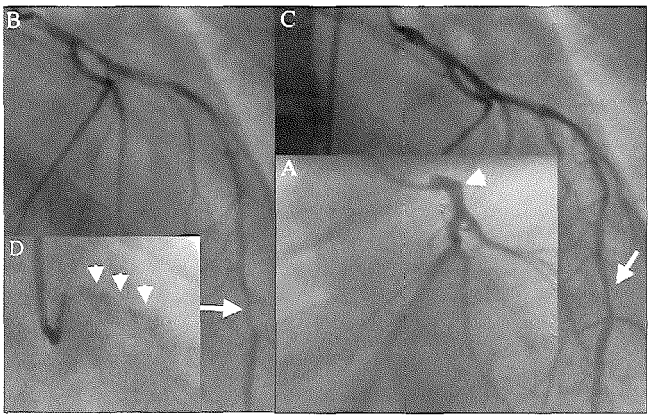



**Figure 1.**
Diagnostic angiogram. The tip of the catheter is protruding the wall of the left main stem (A, arrowhead). Contrast staining in the left main segment, extending into the LAD indicates the dissected area (D, arrowheads). During diastole 'milking' of the LAD is visible (B,arrow), which disappears during systole (C, arrow).

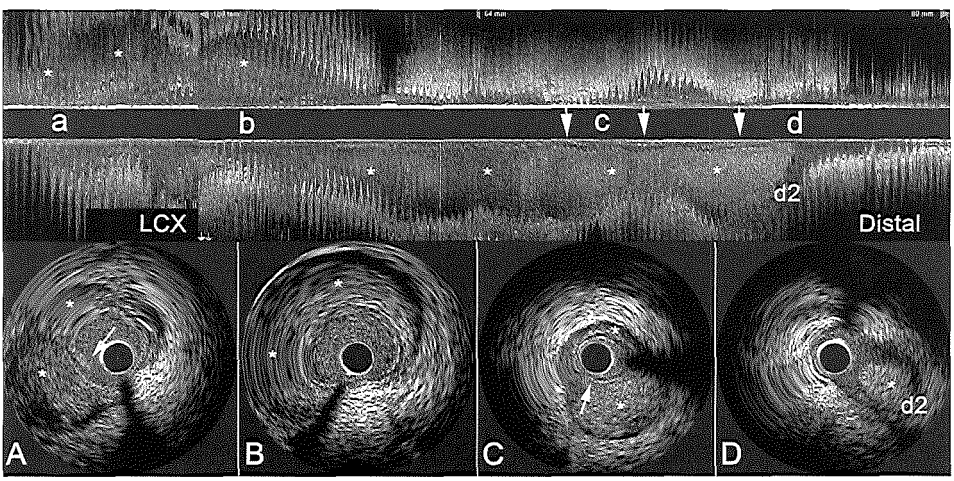



**Figure 2.**
IVUS investigation: The top panel shows a longitudinal reconstruction from the IVUS acquisition in the LAD-left main segment. Cross sections A-D correspond with a-d locations in the longitudinal view. LCx indicates the circumflex artery, d2 indicates the second diagonal branch. In the longitudinal view a massive hematoma is visible compressing the coronary artery (stars). The lumen is severely compromised at c and d by the dissecting hematoma (arrows). At cross section D, the hematoma (star) is visible protruding in the d2. At cross section C, the intima/ media dissected wall is visible (arrow) compressed over 360° by the hematoma (stars). At cross section A, the entry point of the dissection is visible in the left main segment (arrow).

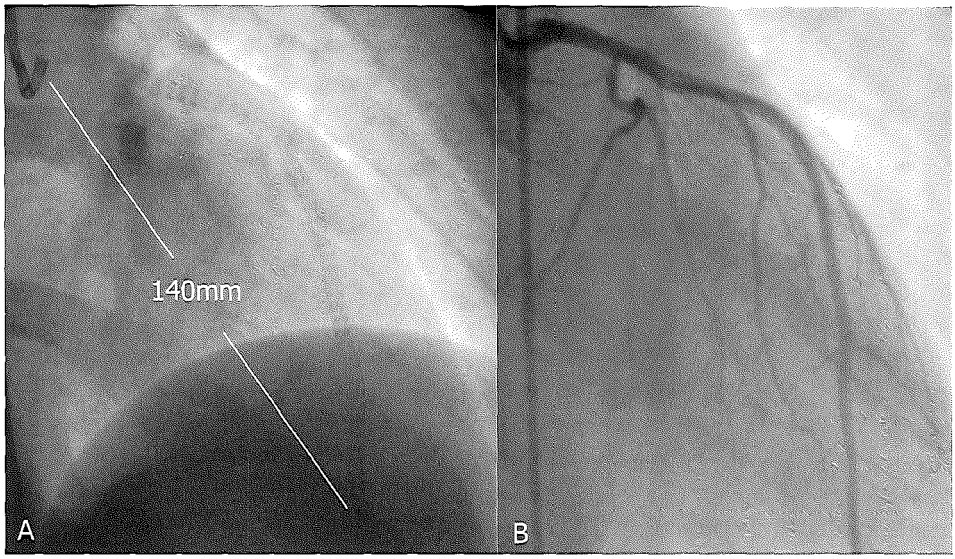



**Figure 3.**
A total of 140mm of overlapping SES implanted (A). Final angiographic result (B).

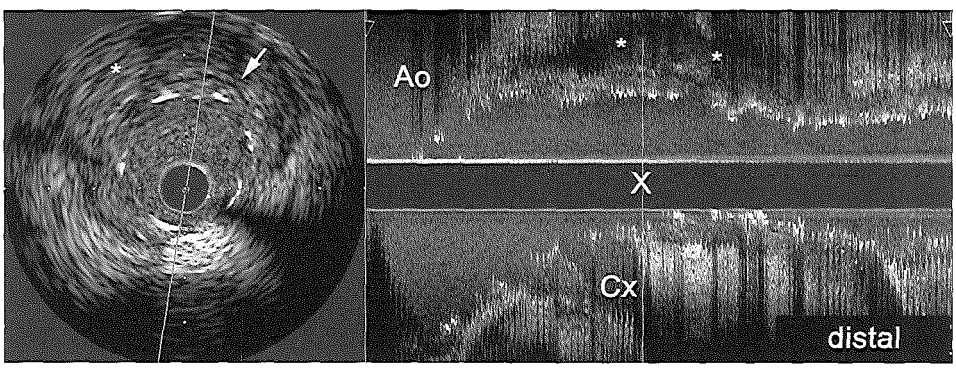



**Figure 4.**
IVUS investigation: The right panel shows a longitudinal view of the proximal LAD and the left main segment, after the sirolimus-eluting stent implantation. Ao indicates the aorta, Cx the circumflex artery and X indicates the level of the cross sectional image in the left panel, which shows the entry point of the dissection in the left main stem. (arrow). Stars indicate the hematoma compressed by the stent struts.

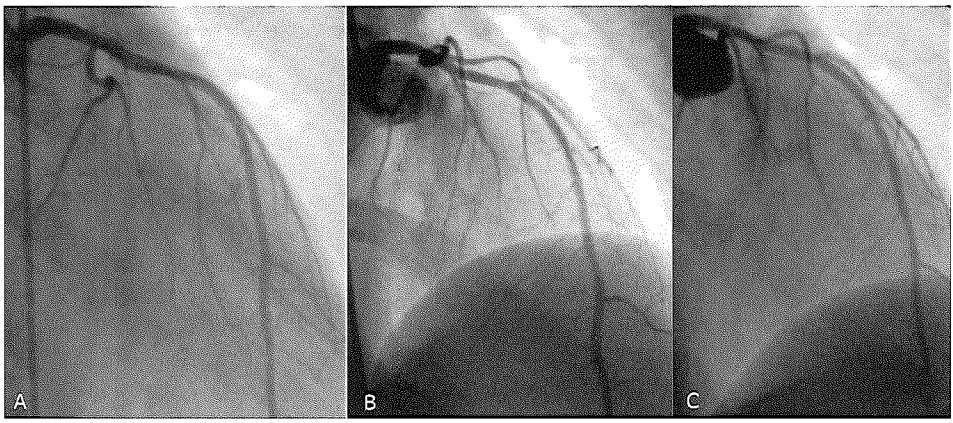



**Figure 5.**
Angiographic illustration of the index procedure (A), three-months (B), and six months follow-up (C), indicating absence of restenosis.

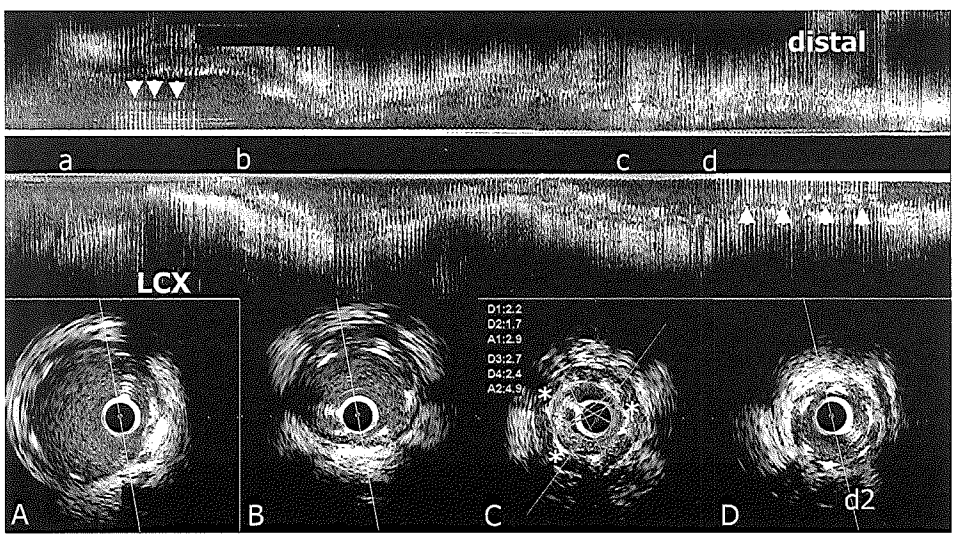
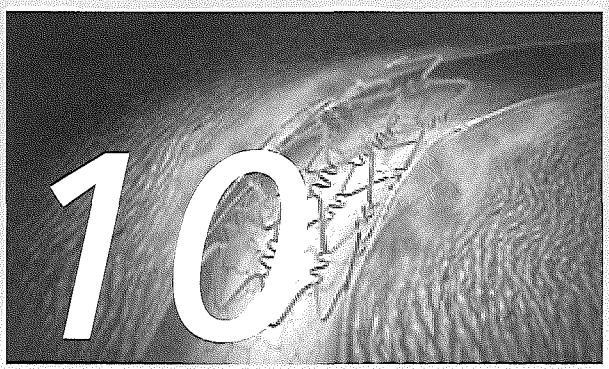



**Figure 6.**
IVUS system: Six-months follow-up. The top panel shows a longitudinal reconstruction in the LAD-left main segment. Cross sections A-D correspond with a-d locations in the longitudinal view. Cx and d2 indicate the left circumflex and the second diagonal. At the longitudinal view the hematoma is suppressed behind the struts in the total stented length. Minimal neointimal hyperplasia is visible (arrow). Arrowheads indicate artifact caused by the guidewire. At cross section C between 6 and 11 o'clock presence of neointimal hyperplasia without restenosis (38% diameter stenosis, 4.9mm$^2$ stent area, 2.0mm$^2$ neointimal area). The stars indicate the suppressed hematoma in between the struts and the vessel wall.

# 2




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

Chourmouzios A Arampatzis
Angela Hoye
Pedro A Lemos
Francesco Saia
Kengo Tanabe
Muzaffer Degertekin
Georgios Sianos
Pieter C Smits
Wim van der Giessen
Eugene McFadden
Ron van Domburg
Pim de Feyter
Patrick W Serruys

Catheter Cardio Interventions, in press

## SYNOPSIS

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

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

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

## INTRODUCTION

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

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

## METHODS

### *Study design and patient population*

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

### *Procedural characteristics, definitions and follow-up*

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

lesion complexity had a total of 6 months clopidogrel [multiple SES implantation (>3 stents), total stent length>36mm,chronic total occlusion, and bifurcations](6).

We evaluated the incidence of MACE defined as death, myocardial infarction (MI), or any repeat vessel revascularization. Myocardial infarction was documented by a rise in the creatine kinase level of more than twice the upper limit with an increased creatine kinase-MB. Cardiac markers were measured serially for all patients maintained in our institution. Among those discharged to their community hospitals, cardiac markers were collected only if a post-procedural MI was suspected. Consequently, enzymatic assessment was not available for all patients, but for those whom the likelihood of post-procedure MI was high. Target lesion revascularization (TLR) was defined as either surgical or percutaneous reintervention driven by significant (>50%) luminal narrowing either within the stent or the 5mm borders proximal and distal to the stent. Target vessel revascularization was defined as reintervention in the treated vessel outside of the target lesion. In-hospital outcome information was retrieved by means of an electronic clinical database for patients maintained in our hospital after the procedure and by review of the hospital records for those discharged to secondary hospitals. After discharge, recording of all repeat interventions (surgical and percutaneous) and re-hospitalizations was performed prospectively in a dedicated database. Living patients were evaluated at our outpatient clinic department, by telephone interviews, or by mail contact.

## STATISTICAL ANALYSIS

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

## RESULTS

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

One patient died in-hospital following a complicated procedure with emergent bypass surgery due to left main stem dissection. Additionally, there was one post-

procedure non-Q wave myocardial infarction [peaked creatine kinase 567U/I (MB fraction: 62U/I)]. Clinical follow-up was available for all but 2 patients (98%). Clinical outcomes at 30 days and 9-months are presented in table 2. Follow-up at 9 months was available for 100% of the patients and the cumulative incidence of MACE was 10%.The average follow-up was 360 ± 59 days (range 297 to 472 days). There were no cases of acute or subacute thrombosis (angiographically documented stent thrombosis requiring repeat intervention). No further patients died or had MI. Overall 8 patients (8%) required subsequent revascularization. Among these, 4 patients (4%) had TLR. Two patients, originally treated for chronic total occlusion, had focal in-stent restenosis in the overlapping segment of two SES. The third had an underexpanded stent at the ostium of the RCA (which was heavily calcified) and had additional cutting balloon dilatation. The fourth patient had a TLR due to restenosis at the proximal edge of the SES. A further 4 patients (4%) had percutaneous reintervention in an untreated segment due to progression of atherosclerosis. The survival rate free of events at one year was 85.6% (Figure 1).

## DISCUSSION

In the present study, we report a low incidence of adverse events in patients treated with SES in a scenario of multivessel stenting, involving the LAD. This reduction is related to the reduced rates of repeat revascularizations presented in this study, predominantly to the reduction of target lesion reintervention. To our knowledge this is the first study reporting a freedom from revascularization of 92% at one year in patients with multivessel stenting. Although the utilization of stents in the ARTS, ERACI II and SOS trials was very high, freedom from revascularization was 79%, 83.2% and 79% respectively(1,9,10). The event-free survival rate reported in the ARTS trial within the stent group was 73.8%. The 85.6% survival rate reported in this study warrants further evaluation. The absence of death or myocardial infarction during the follow-up period is noteworthy. The majority of the patients (87%) were treated with dual anti-thrombotic therapy (aspirin combined with clopidogrel) for six months. Moreover, statins as adjunctive medication were widely used (89%). We hypothesize that this aggressive treatment in combination with the use of drug-eluting stent might be related with this observation.

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

interventional cardiology has been tremendous. The domination of bypass surgery for multivessel disease was based on the historical results comparing angioplasty versus bypass surgery reported in the 1980s and 1990s. The future management of patients with multivessel disease needs to take into account the current evidence.

## LIMITATIONS

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

## CONCLUSIONS

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

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

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

* According to the American College of Cardiology/ American Heart Association classification
LAD=left anterior descending, MI=myocardial infarction, LCx=left circumflex, RCA=right coronary artery

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

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

* non-Q wave myocardial infarction [peaked creatine kinase 567U/l (MB fraction: 62U/l)].
†Angiographically documented SES thrombosis requiring reintervention

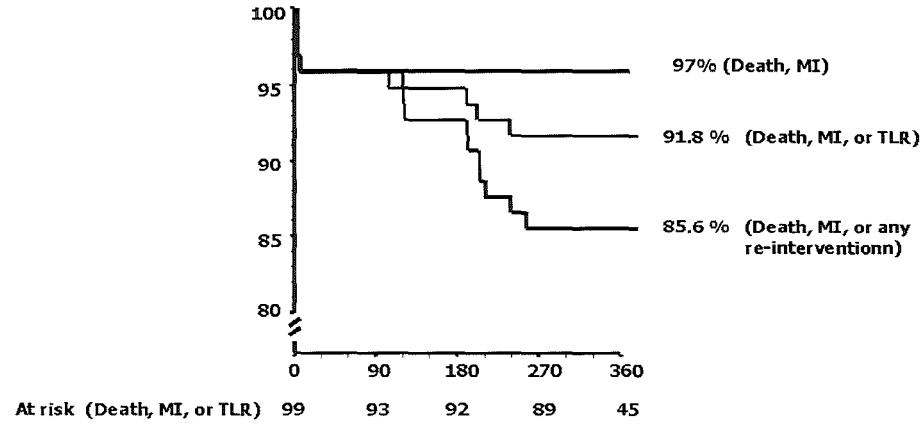
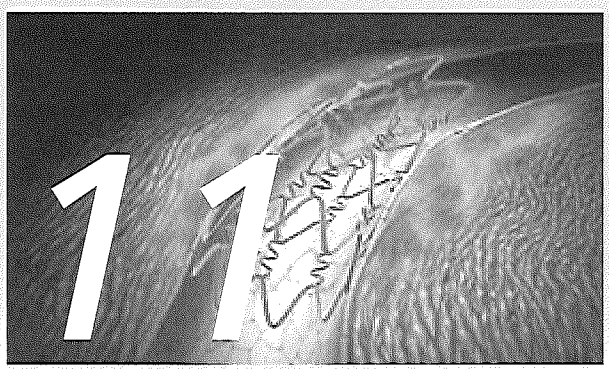



**Figure 1.**
Event-free survival curves of 99 patients treated with SES for multivessel disease and LAD involvement.

# 2



# The Impact of the Introduction of Drug-Eluting Stents on the Clinical Practice of Surgical and Percutaneous Treatment of Coronary Artery Disease

Ron van Domburg
Pedro A Lemos
Tommy Liu
Chourmouzios A Arampatzis
Lex A van Herwerden
Johanna Takkenberg
Pieter C Smits
Joost Daemen
Angeliek C Venema
Patrick W Serruys
Ad JJC Bogers

BMJ, submitted

## ABSTRACT

**Context** Sirolimus-eluting stents (SES) have recently been shown to reduce restenosis in selected patients. The impact of this new stent on the use of coronary artery bypass surgery (CABG) or percutaneous intervention (PCI) in clinical practice is yet unknown.

**Objective** To evaluate the impact of SES on the clinical practice of CABG and PCI in a series of unselected consecutive patients.

**Design, Setting, and Patients** Since April 16th, 2002, a policy of SES implantation for all procedures in all suitable PCI candidates has been instituted in our hospital. From that date, until October 15th, 2002, 798 consecutive patients were referred to PCI and 275 to CABG (SES group). For comparison, a control group was composed of all interventions (806 PCI and 314 CABG) performed during the preceding 6-months (October 16th 2001 to April 15th 2002; pre-SES). Patients who are referred to our institution for coronary revascularization are routinely discussed by a team consisting of thoracic surgeons and interventional cardiologists, who conjointly select the optimal treatment.

**Main Outcome Measure** The occurrence of major adverse cardiac events at 1 year.

**Results** In the SES-era a significant shift was noted to towards more anatomical complex lesions in the PCI group such as more multivessel stenting (28% vs 24%; $p<0.05$), more bifurcation stenting (18% vs 7%; $p<0.0001$) and the use of more stents (1.9 vs 1.5; $p<0.05$). In the elective PCI patients a shift was noted towards more 3-vessel disease (pre-SES:16% vs SES:23%; $p=0.02$). Furthermore, we observed a shift in the CABG group towards more impaired LV function (pre-SES: 34% vs SES: 41%; $p=0.02$) and towards more 3-vessel disease (pre-SES: 67% vs SES: 75%; $p=0.03$). After 1 year of follow-up mortality and the occurrence of myocardial infarction were similar in pre-SES and SES periods. Overall, the cumulative major adverse cardiac event percentages at one year after coronary revascularization (PCI and CABG combined) decreased from 16.8% to 13.8% ($p=0.03$). This was especially due to the use of the sirolimus-eluting stent: the cumulative major adverse cardiac event percentages in the pure SES group and the pre-SES bare metal stent group at 12 months were 15.6% and 19.8%, respectively ($p<0.01$).

**Conclusions** The introduction of the sirolimus-eluting stent has certainly had an impact on the treatment strategy of CAD. Increased use of these stents, allows treatment of anatomically more complex lesions by angioplasty, and results in decreased restenosis rates.

Although both coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI) relieve symptoms of angina in patients with severe ischemia, the most appropriate treatment remains a matter of debate for most of the patients. An important element of the ongoing discussion is the occurrence of restenosis after PCI, the main limitation to this treatmnet strategy. Sirolimus-eluting stent (SES) implantation has recently been demonstrated to markedly reduce the incidence of restenosis and repeat revascularization in selected patients.[1-3] The sirolimus-eluting stent was introduced in our hospital in April 2002. [4,5] The impact of this treatment on the overall clinical management of revascularization is yet unknown. The aim of this study was to investigate the impact of the drug-eluting stent in clinical practice. Therefore, we evaluated all PCI and CABG procedures during the first 6 months of SES use, and in the 6 months preceding the introduction of SES in our clinic.

## METHODS

### *Study design and patient selection*

Since April 16th, 2002 a policy of SES implantation (Cypher; Johnson & Johnson-Cordis unit, Cordis Europe NV, Roden, the Netherlands) for all procedures in all suitable PCI candidates has been instituted in our hospital. [4] All patients with coronary artery disease, both de novo and restenotic lesions, referred for CABG or PCI are routinely discussed in a team consisting of cardio-thoracic surgeons and interventional cardiologists, where the optimal treatment is chosen. As a result, until October 15th, 2002, 798 consecutive patients were referred to PCI (of whom 563 patients received only SES) and 275 to CABG (SES group). For comparison, a control group was composed of all interventions (806 PCI, of whom 718 with a bare stent, and 314 CABG) performed over the same period immediately prior to April 16th, 2002 (pre-SES group). No patients were excluded. The primary end point was the occurrence of major adverse cardiac events (MACE) at 1 year defined as death, post-discharge nonfatal myocardial infarction or all coronary revascularizations regardless of the site of restenosis. Peri-procedural myocardial infarction was only on indication measured in the CABG group. This differed from the PCI group, in which systematic measurement was done. Therefore, all peri-procedural myocardial infarctions were not included in the analyses. Post-discharge myocardial infarction was diagnosed by discretion of the treating physician.

### *Follow-up*

In-hospital outcome information was obtained from an electronic clinical database for patients maintained in our hospital 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 rehospitalizations were collected. Survival status at 6 months and 1 year was assessed by written inquiries to the municipal civil registries at 6 months and at 1 year. In 40% of the PCI patients (acute myocardial infarction [AMI], left main stenting, bifurcation stenting and chronic total occlusions) a scheduled angiographic control was performed at 6 months follow-up. Questionnaires were sent at six months and one year to all living patients, requesting

the occurrence of clinical events. General practitioners and peripheral hospitals were directly approached whenever necessary for additional information. For patients who moved abroad, an effort was made to contact the local civil registries of their new residencies by Internet and e-mail. Of five patients who moved abroad, we were unable to retrieve survival status and the follow-up was censored at the date of last patient contact. Follow-up was complete for all other patients (99.6%).

*Statistical analysis*

Continuous variables were presented as mean ± standard deviation (SD) and were compared using Student's unpaired t-test. Categorical variables were presented as counts and percentages and compared with Fisher's exact test. The cumulative incidence of adverse cardiac events was estimated according to the Kaplan-Meier method. Among patient subgroups the log-rank test was used to compare survival curves. The clinical profile (demographic and procedural details) was recorded during the index procedure. Preselected variables were treated diabetes (NIDDM or IDDM), treated hypertension, treated hypercholesterolemia, smoking habits, family history, previous coronary interventions, prior myocardial infarction, extent of vessel disease and qualitative LV function (normal if >50%, moderate or reduced if between 50% and 35%, and poor if <35%).

In the PCI group a subanalysis was performed according to patients who would have been eligible for inclusion in the drug-eluting stent randomized controlled trials (RCT) such as the SIRIUS study.[3] The following criteria were used for exclusion from RCTs: a primary PCI for acute myocardial infarction (AMI), age older than 80 years, left main stenting, small vessels (≤ 2.5mm), long stented length (>36mm), restenotic lesions, bifurcation stenting and stenting of the saphenous vein graft.

## RESULTS

The CABG patients were 2 years older than the PCI patients (64 years vs 62 years) and more males underwent CABG than PCI (83% vs 70%) (Table 1). The CABG group consisted of more patients with impaired LV function than the PCI group (38% vs 16%). Only a small minority of the patients undergoing CABG had single vessel disease (6%) and more than half of the SES patients had multivessel disease (54%). Left main disease was rare in the PCI group (4%) and was present in 15% of the CABG group. A shift was observed in the CABG group towards more 3-vessel disease (pre-SES: 67% vs SES: 75%; p=0.03) and towards more impaired LV function (pre-SES: 34% vs SES: 41%; p=0.02). No such shift was observed in the total PCI group. However, in those PCI patients who underwent an elective intervention we also noteda shift towards more 3-vessel disease (pre-SES: 16% vs SES: 23%; p=0.02). All other clinical characteristics were similar in CABG and PCI except for more prior myocardial infarction in the pre-SES PCI group as compared with the SES PCI group (40% vs 34%). In the PCI group 17% of the patients underwent primary coronary angioplasty for acute myocardial infarction.

The angiographic and procedural characteristics are shown in Table 2. In 79% of the PCI group solely sirolimus-eluting stents were implanted (pure-SES group). In

the remaining (21%), another type of balloon (31%) or bare stent (69%) was utilized due to unavailability of an appropriate, especially larger size stent. In the CABG group vein grafts without arterial grafts were used in only 5%. In 87% of the CABG group the LAD was grafted, mostly by using the left internal mammaria artery and the mean number of distal anastomoses was 3.5. In the PCI group, SES patients had more bifurcation stenting (18% vs 7%; p<0.0001), more multivessel stenting (28% vs 24%; p<0.05) and more stents used (1.9 vs 1.5; p<0.05) compared to the pre-SES PCI group. The total length of stents implanted per patient increased from 29 mm to 39 mm (p<0.05) and stent usage increased from 87% to 96%. Unexpectedly, the use of periprocedural glycoprotein IIb/IIIa inhibitors during PCI decreased from 28% to 15% (p<0.0001).

*30-days outcome*

After CABG, the incidence of major adverse cardiac events in the first 30 days was similar between the pre-SES and SES periods (Table 3). Early mortality rate was 1.0% (n=6) and early re-CABG was necessary in 0.6% of the patients (n=3). Early recanalization with PCI post-CABG was performed in 1.3% of the patients (n=8).

After PCI, 29 patients (1.8%) died before discharge (24 patients presented with AMI of whom 14 with cardiogenic shock). Early coronary bypass surgery in the pre-SES period was done in 1.6% (rescue in 1.0%) and 0.9% (all rescue) in the SES period and in the first 30 days repeat target vessel angioplasty rates decreased (pre-SES: 2.7%, SES: 1.1%). In two patients (0.5%) an early rescue CABG was needed and 4 patients (0.9%, 2 patients rescue) underwent a rescue rePCI in the first 30 days. Of the 39 PCI patients (16 AMI) who underwent an early rePCI within 30 days, the majority (67%) was planned prior as staged procedures.

*One-year outcome*

At 12 months the rate of major adverse cardiac events after revascularization (PCI and CABG combined) decreased from 16.8% to 13.8% (p=0.03) (Figure 1). This was due to the introduction of the sirolimus-eluting stent: the cumulative major adverse cardiac event percentages in the pre-SES bare metal stent group and the pure SES group at 12 months were 19.8% and 15.6%, respectively (p=0.03) (Figure 2). The cumulative survival free from major adverse cardiac event percentages after CABG in the pre-SES and SES period also showed a slight decrease (pre-SES: 7.4% and SES: 5.9%; p=NS).

*One year outcome according to eligibility for randomized controlled clinical trials (RCT)*

More than 70% of our patients (n=1157) would not have been included for inclusion in the controlled clinical trials. However, also in this patient population a benefit of SES was observed of less major adverse cardiac events (pres-SES: 20.2%, SES: 14.4%; p=0.02) (Figure 3).

## DISCUSSION

We investigated the impact of the sirolimus-eluting stent on the clinical management of all candidates for revascularization in a large consecutive single center series. To the best of our knowledge, this is the first study that addresses that topic. Compared to the pre-sirolimus-eluting stent era more multivessel dilatations and more bifurcation stenting were done, more stents were implanted per patient and in almost all angioplasty procedures, a stent was implanted. An increasing number of patients will be treated with drug-eluting stents and although the problem of restenosis after stenting is not solved yet, it has reduced significantly in our clinical practice. This all, will have an impact on both coronary angioplasty and coronary artery bypass surgery. In the CABG population we already observed a shift towards treatment of more three-vessel disease and more patients with an impaired LV function. In addition, in those patients who underwent elective PCI, a shift was noted towards more three-vessel disease in the SES group versus the pre-SES group.

In this study, all patients were included who were referred to our institution for either coronary bypass surgery or stenting without any exclusion. Nevertheless, patients indicated with acute myocardial infarction are no candidates for primary bypass surgery, but only for primary angioplasty, whereas patients with left main disease or those with extensive complex lesions will primary be sent to surgery. However, after exclusion of these patients the findings remained unchanged.

This study was not a randomized trial but rather an observational registry of real life clinical practice because the choice of the best treatment was completely left to the clinician's decision. We estimate that around 70% of our PCI population would not have been enrolled in the RAVEL or SIRIUS trials.[2,3] However, the results of our study and of other observational studies have been shown to be complementary to randomized controlled trials.[6,7] This study shows that in real life, patients with de novo lesions indeed benefit from SES utilisation. Also most patients with de novo lesions who would not be candidates for randomized controlled trials had benefited from the use of SES. For patients with complex in-stent restenosis, sirolimus-eluting stent implantation was associated with similar outcomes compared with brachytherapy.[8] In addition, the relative benefit of SES in other subsets with ISR remains to be proven. In our opinion, coronary artery bypass surgery can no longer be compared with coronary angioplasty. The ARTS study was the latest randomized trial in a highly selected patient population comparing both modalities.[9] ARTS showed a 13% absolute reduction in the need for revascularizations in the bypass surgery arm as compared with the stent arm. Clinical practice is running ahead of randomized trials and ongoing randomized trials are easily outdated. As todate, our study shows that clinical practice is changing: interventional cardiologists are more daring to stent more complex lesions and only patients such as those with left main disease and patients with complex lesions such as diffuse coronary narrowing, small arteries, total occluded vessels and perhaps in restenotic lesions still undergo bypass surgery. The majority of the patients with triple vessel disease will continue to undergo coronary bypass surgery. Instead of being competitive, CABG and stenting will grow to be complementary to each other.

## CONCLUSIONS

The significant reduction of coronary reinterventions after sirolimus-eluting stent implantation will certainly have an impact on the invasive treatment of coronary artery disease. More complex lesions will be referred to PCI with sirolimus eluting stents allowing optimized treatment and improved patient outcome.

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**Table 1. Baseline characteristics of 589 patients undergoing CABG and 1604 patients undergoing PCI (%).**

| | CABG | | | PCI | | |
|---|---|---|---|---|---|---|
| | pre-SES | SES | P-value | Pre-SES | SES | P-value |
| Number of patients | 314 | 275 | | 806 | 798 | |
| Age, years | 64 | 64 | ns | 61 | 62 | ns |
| range years | 38-85 | 38-86 | ns | 30-86 | 27-90 | ns |
| Male % | 83 | 83 | ns | 72 | 70 | ns |
| Diabetes % | 23 | 24 | ns | 16 | 17 | ns |
| Hypertension % | 45 | 48 | ns | 38 | 40 | ns |
| Dyslipidemia % | 62 | 66 | ns | 56 | 54 | ns |
| Family history % | 16 | 27 | <0.001 | 27 | 29 | ns |
| Previous CABG % | 13 | 12 | ns | 12 | 12 | ns |
| Previous PCI % | 14 | 20 | 0.05 | 27 | 26 | ns |
| Previous MI % | 48 | 46 | ns | 40 | 34 | 0.03 |
| Unstable angina* | 8 | 7 | ns | 3 | 3 | ns |
| AMI | 0 | 0 | ns | 16 | 18 | ns |
| Triple-vessel disease % | 67 | 75 | 0.03 | 20 | 20 | ns |
| In stable angina | | | | 16 | 23 | 0.02 |
| In AMI | | | | 25 | 18 | 0.1 |
| Left main disease | 20 | 17 | | 4 | 4 | ns |
| LV function % | | | 0.02 | | | ns |
| Normal | 66 | 59 | | 83 | 86 | |
| Reduced/Moderate | 29 | 39 | | 14 | 11 | |
| Poor | 5 | 2 | | 3 | 3 | |

* Unstable angina = requiring intravenous medication.

AMI = Acute Myocardial Infarction, CABG = Coronary Artery Bypass Graft; PCI = Percutaneous Coronary Intervention; MI = myocardial infarction; SES = Sirolimus-eluting stent; CCS = Canadian Cardiovascular Society class; ns = not significant

**Table 2. Procedural characteristics of 589 patients undergoing CABG and 1604 patients undergoing PCI (%).**

| | Pre-SES | post-SES | P-value |
|---|---|---|---|
| *CABG* | | | |
| Number of patients | 314 | 275 | |
| Treated vessel % | | | ns |
| RCA | 86 | 86 | |
| LAD | 88 | 91 | |
| LCX | 84 | 85 | |
| LM | 20 | 17 | |
| Grafts % | | | ns |
| Venous only | 6 | 6 | |
| Arterial only | 11 | 8 | |
| Venous and arterial Grafts % | 83 | 87 | ns |
| LIMA | 93 | 94 | |
| RIMA | 15 | 5 | |
| Vein | 88 | 93 | |
| Number of distal anastomoses | 3.4 | 3.5 | ns |
| *PCI* | | | |
| Number of patients | 806 | 798 | |
| Treated vessel % | | | ns |
| RCA | 38 | 37 | |
| LAD | 54 | 57 | |
| LCX | 34 | 34 | |
| LM | 4 | 4 | |
| Pure SES stent % | 0 | 79% | |
| Bifurcation stenting % | 7 | 18 | p<0.0001 |
| Multivessel stenting % | 24 | 28 | p=0.03 |
| Stent use % | 87 | 96 | p<0.001 |
| Number of implanted stents per patient | 1.5 | 1.9 | p=0.03 |
| Total stented length (mm) | 29 | 39 | p=0.01 |
| Brachy therapy % | 5 | 2 | p=0.02 |
| Glycoprotein IIbIIIa inhibitors % | 28 | 15 | p<0.0001 |

SES = Sirolimus Eluting Stent; LIMA = Left Internal Mammarian Artery;RIMA = Right Internal Mammarian Artery; PCI = Percutaneous Coronary intervention; RCA = Right Coronary Artery; LAD = Left Anterior Descending; LCX = Left CircumFlexus; LM = Left Main;

**Table 3. 30-days outcome of 589 patients undergoing CABG and 1604 patients undergoing PCI (%).**

| | CABG | | PCI | |
|---|---|---|---|---|
| | pre-SES | SES | Pre-SES | SES |
| *30-days* | | | | |
| Number of patients | 314 | 275 | 806 | 798 |
| Death % | 0.9 | 1.1 | 1.6 | 1.9 |
| (re-)CABG % | 0.9 | 0.3 | 1.6 | 0.9 |
| Rescue | 0.6 | 0.0 | 1.0 | 0.9 |
| (re-)PCI % | 1.5 | 1.1 | 3.5 | 1.1 |
| Rescue | 0.0 | 0.0 | 0.5 | 0.2 |
| Staged procedure | | | | |

CABG = Coronary Artery Bypass Graft; SES = Sirolimus Eluting Stent;
MI = Myocardial Infarction; PCI = Percutaneous Coronary Intervention; Rescue = same day.

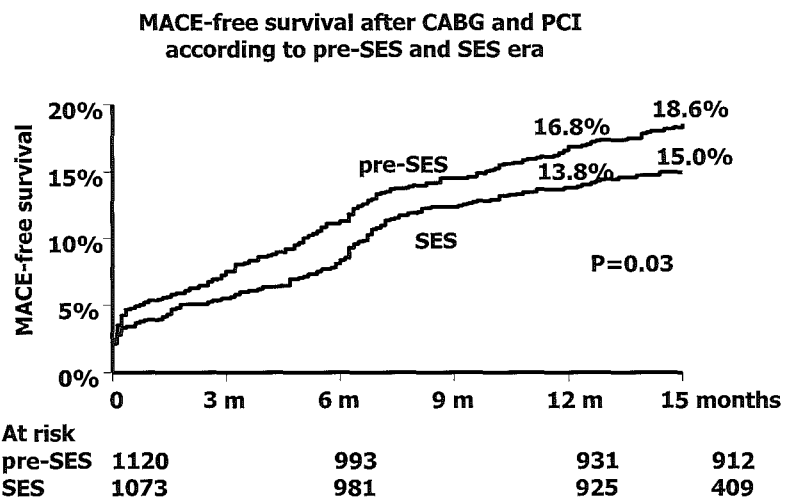


**Figure 1.**
MACE-free survival (death, post-discharge myocardial infarction, revascularization) after revascularization (CABG and PCI combined) according to the pre-SES and SES era

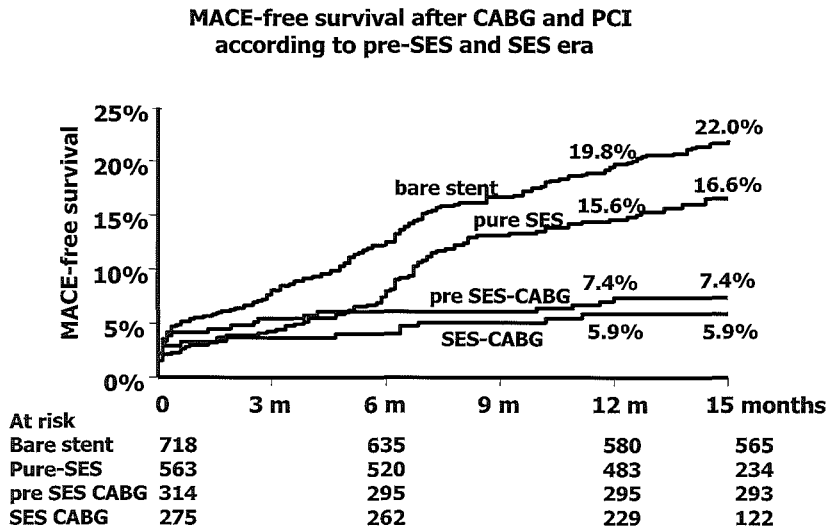


**Figure 2.**

MACE-free survival (death, post-discharge myocardial infarction, revascularization) CABG and PCI according to the bare-stent (implantation of a bare metal stent in the pre-SES period), pure-stent (only sirolimus-eluting stent(s) implanted without bare metal stents), pre-SES CABG and SES CABG.

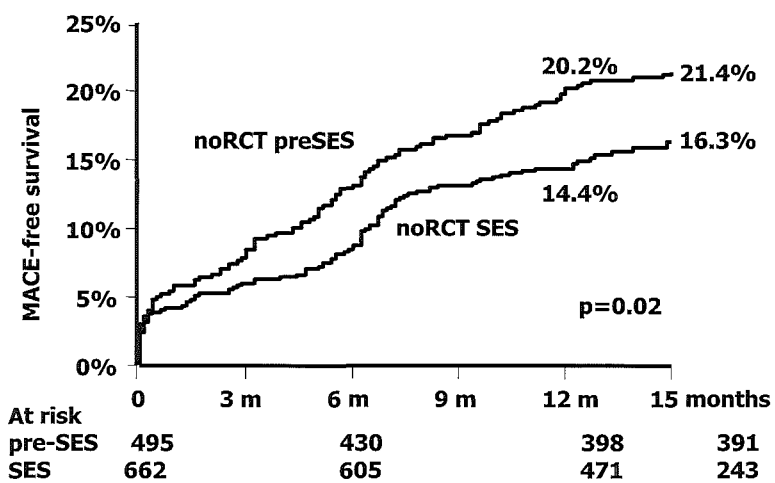


**Figure 3.**

MACE-free survival (death, post-discharge myocardial infarction, revascularization) after PCI according to patients who would not have been eligible for inclusion in randomized controlled trials (RCT) in the pre-SES and SES era.

3

# Detection of a Coronary Plaque: A Treatment Dilemma

Chourmouzios A Arampatzis
Jurgen M.R. Ligthart
Johannes A Schaar
Koen Nieman
Patrick W Serruys
Pim de Feyter

Circulation 2003;108:e34-35

# Images in Cardiovascular Medicine

## Detection of a Vulnerable Coronary Plaque
### A Treatment Dilemma

Chourmouzios A. Arampatzis, MD; Jurgen M.R. Ligthart, RT; Johannes A. Schaar, MD; Koen Nieman, MD; Patrick W. Serruys, MD, PhD; Pim J. de Feyter, MD, PhD

A 34-year-old man who experienced a 30-minute episode of chest pain at rest was admitted to the coronary care unit after becoming symptom free. His ECG was normal. A few hours later, he suffered a 5-minute period of recurrent chest pain with transient ST-segment elevation (Figure 1). The level of creatine phosphokinase reached its peak at 800 IU (upper limit=199 IU), and the maximum troponin T level was 1.85 μg/L. Noninvasive coronary imaging with a 16-slice spiral computed tomography scanner (MSCT) (Sensation 16, Siemens AG; Forchheim, Germany) suggested a nonobstructive lesion in the mid-left anterior descending artery (LAD) (Figure 2), which was confirmed with coronary angiography. Coronary spasm was excluded by methergin provocation test, which only showed general vasoconstriction (31% reduction of reference diameter) but no focal spasm. Intravascular ultrasound (IVUS) (CVIS Atlantis 40-MHz 3F catheter, Boston Scientific, TOMTEC ECG-gated acquisition system) demonstrated a local plaque with vessel remodeling in the mid-LAD. The plaque was covered by a thin layer of speckling, which was different from the plaque and blood speckles, suggesting clot formation (Figure 3B). A small rupture was visible at the proximal shoulder of the plaque (Figure 3A), which was better delineated with a 4D reconstruction image (Movie I). Coronary flow reserve was 4.3, indicating a non–flow-limiting plaque. IVUS palpography demonstrated a strain pattern, which strongly suggested the presence of a vulnerable plaque (Figure 4A and 4B; Movie II). Given the clinical presentation and ultrasound findings, and despite the non–flow-limiting obstruction, we decided after considerable deliberation to implant a drug-eluting stent in the diseased part of the mid-LAD. The procedure and recovery after stent implantation were uneventful.

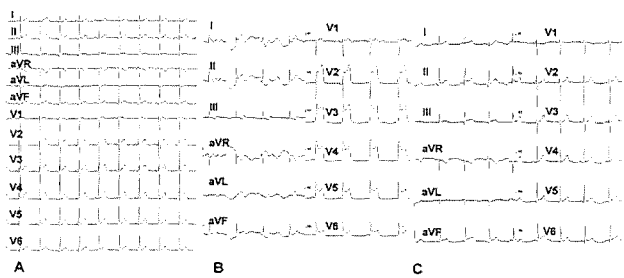


**Figure 1.** ECG. Normal sinus heart rhythm. A, Early repolarization in leads II, III, aVF, V5, and V6. B, Transient ST elevation in leads I, aVL, and V2 through V6 associated with 5 minutes of chest pain. C, ECG changes restored when patient was free of pain.

From the Catheterisation Laboratory (C.A.A., J.M.R.L., J.A.S., K.N., P.W.S., P.J.d.F.) and the Radiology Department (K.N., P.J.d.F), Thoraxcenter, Rotterdam, the Netherlands.

**Movies I and II are available in the online-only Data Supplement at http://www.circulationaha.org.**

Correspondence to Pim J. de Feyter, Catheterisation Laboratory, Thoraxcenter BD 410, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. E-mail defeyter@card.azr.nl

The editor of Images in Cardiovascular Medicine is Hugh A. McAllister, Jr, MD, Chief, Department of Pathology, St Luke's Episcopal Hospital and Texas Heart Institute, and Clinical Professor of Pathology, University of Texas Medical School and Baylor College of Medicine.

*Circulation* encourages readers to submit cardiovascular images to the *Circulation* Editorial Office, St Luke's Episcopal Hospital/Texas Heart Institute, 6720 Bertner Ave, MC1-267, Houston, TX 77030.

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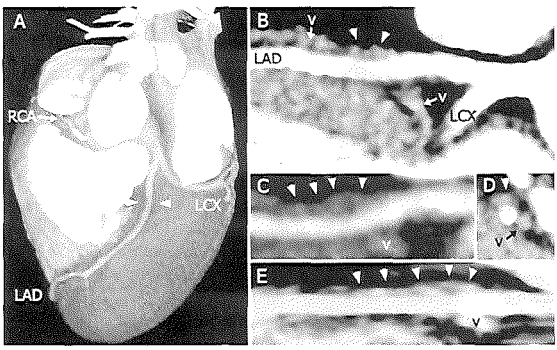



**Figure 2.** Multislice spiral CT coronary angiogram. A, Volume-rendered reconstruction demonstrates nonsignificant stenosis of the mid-LAD (arrowhead). Maximum plaque diameter was 2.8 mm; minimal lumen area, 5 $mm^2$ (2.6×1.8 mm); and reference lumen area, 8 to 9 $mm^2$ (3.4×2.7 mm). Longitudinal plaque size is 13 mm. The multiplanar, cross-sectional images show slight narrowing of the LAD (B). The attenuation value of the plaque was measured as 80 Hounsfield units, suggesting a mixed plaque composition without calcification (C and D, arrowheads). The entire segment can be shown in a single plane by means of vessel tracking (E, arrowhead). The great cardiac vein can be differentiated from the plaque by the higher and homogeneous attenuation of the venous lumen (v). RCA indicates right coronary artery; LCX, left circumflex artery.

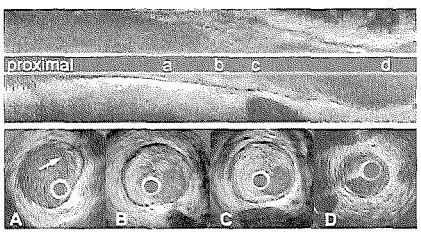



**Figure 3.** IVUS system: Boston Scientific Galaxy. IVUS catheter: Boston Scientific Atlantis 3F 40 MHz. Motorized pullback 0.5 mm/s. Images digitally stored. Top panel shows a longitudinal reconstruction from the IVUS acquisition in the mid-LAD. The lowercase characters a through d indicate the locations of the cross sections A through D. At b and c in the longitudinal view, a soft plaque with different densities is visible. Cross section D shows a normal 3-layered aspect of the LAD distal from the lesion. Cross sections B and C show an eccentric soft plaque between the 6 o'clock and 2 o'clock positions, with thrombus present at the 12 o'clock position. Cross section A shows a small eccentric plaque from the 12 o'clock to the 4 o'clock position, with a "broken" cap (arrow) indicating a former plaque rupture.

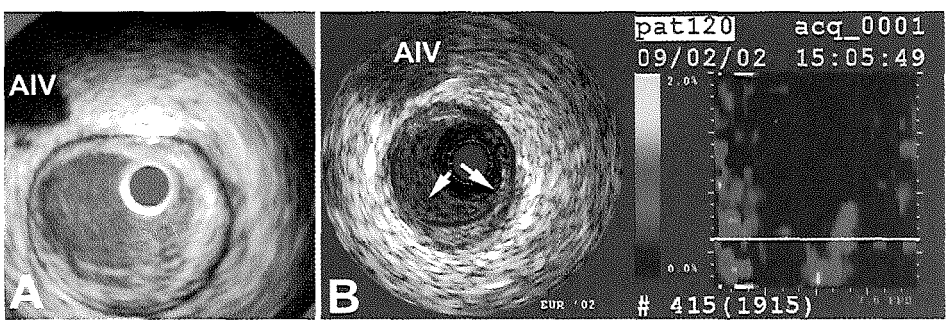
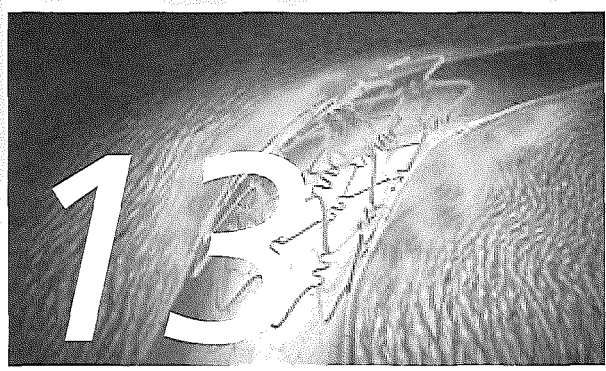



**Figure 4.** Palpograms were calculated using Jomed InVision Gold, a Jomed 20-MHz Avanar catheter, and a dedicated workstation for radio-frequency analysis. Palpography delivers strain information for the plaque surface. The right side of panel B represents the longitudinal view of the palpogram (top: distal LAD; bottom: proximal LAD). In the middle of panel B, a scale ranging from 0% (blue) to 2% (yellow) characterizes the strain pattern. The strain images are color coded; blue indicates stiff (low-strain) material, and red indicates softer (higher-strain) material. In the cross section shown on the left side of panel B, which is in a position identical to that in the IVUS image in panel A (40 MHz), an eccentric soft plaque is visible with shoulders of high strain (arrows) on either side of the otherwise stable cap. Between the 10 o'clock and 12 o'clock positions, the palpogram appears to show an area of high strain; however, this is caused by the nearby cardiac vein (AIV). The white line indicates the position of the cross section across the longitudinal map. Adjacent cross sections show the continuity of the soft caps forming a halo.

# 3



## Sirolimus-Eluting Stent Implantation for Lesions with <50% Diameter Stenosis: Implications for Plaque Stabilization

Angela Hoye
Pedro A Lemos
Chourmouzios A Arampatzis
Francesco Saia
Kengo Tanabe
Muzaffer Degertekin
Joost Daemen
Pieter C Smits
Eugene McFadden
Georgios Sianos
Pim de Feyter
Wim van der Giessen
Sjoerd H Hofma
Ron van Domburg
Patrick W Serruys

Am J Cardiol, accepted

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

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

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

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

The diagnostic approach to evaluate the clinical significance of the lesions utilizing invasive and / or non-invasive investigations, and the decision to proceed to stent implantation, was left at the operator's discretion. Patients were maintained on long-term aspirin medication, together with clopidogrel which was given for a minimum of 3 months. The protocol of the Registry was approved by the local ethics committee and is in accordance with the principles of Good Clinical Practice for Trials of Medicinal Products in the European Community and the Declaration of Helsinki. Written informed consent was obtained from every patient.

Coronary angiograms were obtained in multiple projections after intracoronary nitrate administration. Quantitative analyses were performed with the Cardiovascular Angiography Analysis System II (CAAS II; Pie Medical, Maastricht, The Netherlands) using validated edge-detection techniques. The empty tip of the angiographic

catheter was utilized for image calibration. Lesion measurements were performed in the "worst" view with the end diastolic frame selected for analysis.

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

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

The mean age of the patients was 54 ± 9 years, and 17 (85%) were men. Risk factors were diabetes mellitus in 1 patient (5%), hypercholesterolemia in 12 (60%), current smoking in 8 (40%), hypertension in 7 (35%). There was a history of previous acute myocardial infarction in 5 (25%), and prior coronary angioplasty in 6 (30%), no patient had undergone coronary artery bypass surgery. Of the 20 patients, 7 (35%) were treated for at least one additional severely stenotic lesion (>50% diameter stenosis) during the same procedure. Clinical presentation was stable angina pectoris in 12 (60%) and unstable angina pectoris in the remaining 8 (40%). The 23 lesions were treated with implantation of 26 SESs, with direct stent implantation in 21 lesions (91%). Glycoprotein IIb/IIIa inhibitor therapy was used in 4 patients (20%). The decision to treat was based on a good history of stable angina pectoris in 5 patients (25%), a positive thallium scan in 3 patients (15%), presentation with an acute coronary syndrome (with ECG changes and / or troponin elevation) thought to relate to the target lesion in 4 patients (20%), IVUS examination documenting a minimum lumen area $<4.0mm^2$ in 4 patients (20%), a fractional flow reserve ≤0.75 in 3 patients (15%), and a positive methergine test in 1 patient (5%).

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

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

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

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

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

Evaluation of lesion severity by intracoronary measurements has been advocated to discriminate between patients who should receive invasive treatment from those in whom further treatment should be deferred.[11-17] Accordingly, the rate of subsequent events and need for target lesion revascularization has been shown to be low (4.4% at one year) if IVUS examination demonstrates a minimum lumen area of ≥4.0mm$^2$.[11] In addition, patients with an abnormal fractional flow reserve (<0.75) have been reported to present a higher risk for future complications than those with normal measurements.[15,16] In our series, stent implantation was undertaken in 7 patients (35%) following either IVUS examination showing a minimum lumen area <4.0 mm$^2$, and/or a fractional flow reserve of ≤0.75. However, such historical algorithms were produced when angioplasty was carried out with bare metal stents, and rely heavily on the prohibitively high incidence of adverse events following an eventual percutaneous treatment, which has been found to be around 17% at 1 year.[7,15] Even after following these algorithms, patients with "normal" findings at lesion assessment, who have been considered to be at "low risk" if left untreated, at one

year, the rate of adverse events may still be as high as 11%.[12] Our results suggest that by altering the risk / benefit ratio of stent implantation versus deferred invasive therapy, the introduction of drug-eluting stents into clinical practice may potentially change the current treatment algorithms for patients with mild to moderate lesions. In addition, if the propensity to accelerated plaque progression or vulnerability to plaque rupture or erosion could be better evaluated, this might enable localization of areas of coronary artery plaque which could benefit most from stabilization with stent implantation. Although the present study did not specifically address this issue, this may broaden the applicability of percutaneous coronary intervention with drug-eluting stent implantation.

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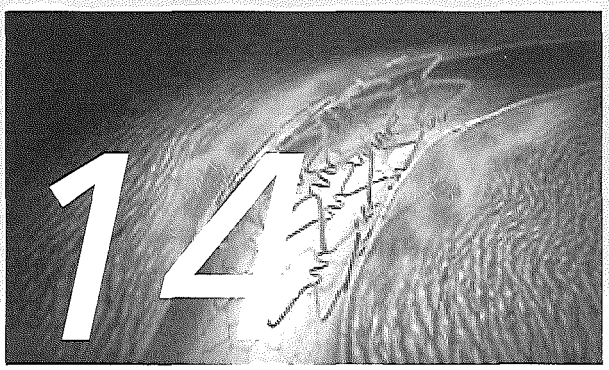


# Summary and Conclusions

The use of percutaneous therapy for 'complex' coronary atherosclerosis has been tempered by an increased risk of complications during the procedure and by a relatively greater risk of restenosis. Commonly the patients are treated surgically.

In Chapter 2, we were able to demonstrate that the presence of diabetes is associated with an almost two-fold increase in the risk of adverse events over that observed in patients without diabetes following successful percutaneous treatment of coronary artery disease. In contrast, patients with diabetes treated with fluvastatin had a risk of adverse events that was not significantly different from that in patients without diabetes. Adjunctive medication is of great importance in order to optimise outcome in this high-risk population; prolonged therapy with fluvastatin appears to retard the progression of atherosclerosis and reduces the incidence of long-term adverse complications.

Renal impairment is an important predictor of complications after percutaneous coronary intervention. The use of the sirolimus-eluting stent in patients with renal impairment is associated with reduced reintervention rates, but this benefit is not associated with a reduction in mortality

(Chapter 3).

Patients with a history of bypass surgery have higher rates of adverse events when percutaneous intervention is undertaken for recurrence of symptoms. The use of the sirolimus-eluting stent is associated with a 72% risk reduction in the rate of adverse events at one year compared to that observed with conventional bare stents, which was predominantly attributed to the reduction of subsequent revascularization (Chapter 4).

Percutaneous treatment of very long coronary segments has thus far displayed unfavourable results. In Chapter 5, when sirolimus-eluting stents are implanted in such complex coronary lesions, there is a marked improvement in angiographic parameters used to measure neointimal hyperplasia, such as in-stent late loss, and a low binary restenosis rate. Small vessel size is an independent predictor of restenosis after percutaneous intervention. We demonstrated that the use of sirolimus-eluting stents in such lesions is safe, effective and associated with the lowest late lumen loss reported to date (Chapter 6).

The ultimate challenge for the interventional cardiologist remains the treatment of the left main coronary artery. We reported the initial experience on patients who received sirolimus-eluting stent in the left main stem. There were no deaths after discharge (Chapters 7,9). In addition, we reported the first series of consecutive patients who underwent elective sirolimus stent implantation for left main stenosis. There was a very low incidence of adverse events at one-year, with a low late lumen loss and a low binary restenosis rate (Chapter 8).

In Chapter 10, our results suggest that sirolimus-eluting stent implantation in patients with multivessel disease improves the event-free survival rate, predominantly due to a reduction in the rate of repeat intervention. The use of the sirolimus-eluting stent is not a panacea, but the impact on the restenosis rates is of great clinical importance, particularly in these complex populations treated in real life scenarios. The enrolment period in the ARTS II trial has been completed, and the results will further shed light on the impact of eluting stent implantation for multivessel stenoses.

We explored the implications of this strategy on patient management in our institution. In the drug eluting-stent era, more multivessel dilatations were undertaken, more bifurcations were treated, and more stents were implanted per patient. On the other hand, patients who underwent surgical revascularization in the DES era had more marked impaired of left ventricular function, and the majority had three-vessel disease. It is noteworthy that the combined rate of adverse events in both the stent and the surgical populations decreased, mainly due to a reduction in restenosis rates. Importantly, we witnessed a shift in both the revascularization strategies towards treatment of more complex patients in each revascularization approach (Chapter 11).

In Chapter 12, we evaluated a patient with a vulnerable plaque and based on the findings took the decision to treat a non-flow limiting lesion with a sirolimus-eluting stent. Afterwards, we were able to demonstrate the safety of this strategy in a small consecutive series of patients (Chapter 13). By increasing the accuracy of the non-invasive and invasive diagnostic modalities for plaque characterization, we hope to investigate in depth the mechanisms of plaque rupture that may lead to an acute coronary event. At this point, our strategy is to accumulate data, in an observational setting, that may provide clues to direct future research. Collaboration between clinicians and basic scientists is essential in this setting and further studies are needed to evaluate the impact of eluting-stent implantation on plaque stabilization, of selected lesions, and its potential in the prevention of future coronary events.

We investigated the impact of new technology in patients presenting with complex coronary atherosclerosis. Our findings corroborate the outstanding performance of the sirolimus-eluting stent presented thus far in the large randomized trials. We conclude that the introduction of new technology with drug-eluting stents into real life clinical scenarios is associated with improved outcomes, which will affect contemporary percutaneous strategies mainly with a shift of patients treated with percutaneous coronary intervention rather than bypass.

# SAMENVATTING EN CONCLUSIES

Complexe vormen van coronaire atheromatose waren tot vrij recent een indicatie voor coronaire bypass chirurgie, omwille van een vrij hoog risico op complicaties tijdens de procedure en de relatief gezien hogere kans op restenose met de andere behandelingsoptie, namelijk PCI.

In hoofdstuk 2 wordt aangetoond dat bij diabetes patienten die een succesvolle PCI procedure ondergaan de kans op een cardiovasculair event dubbel zo hoog is als bij niet-diabetici. Mits behandeling met fluvastatine wordt dergelijk risico evenwel vergelijkbaar als bij de patientengroep zonder diabetes. Adjuvante medicamenteuse therapie met een statine is bijgevolg aangewezen in deze hoog-risico populatie: behandeling met fluvastatine lijkt de progressie van atheromatose af te remmen en vermindert de incidentie van nieuwe cardiovasculaire events.

Nierinsufficientie is een belangrijke risicofactor voor complicaties na PCI. Het gebruik van de SES reduceert de noodzaak tot nieuwe coronaire interventies, doch beinvloedt de mortaliteit niet (hoofdstuk 3).

Patienten met een voorgeschiedenis van CABG hebben een hoger risico op cardiovasculaire events ingeval van PCI voor recidief klachten. In vergelijking met de 'gewone'stent verlaagt de SES dit risico op 1 jaar tijd met 72%, voornamelijk als gevolg van een afname van het aantal nieuwe revascularisatieprocedures (hoofdstuk 4).

De behandeling van lange coronaire lesies via percutane weg leverde tot vrij recent geen goede resultaten op. Het gebruik van de SES in deze groep verbetert de angiografische outcome aanzienlijk, namelijk minder neointima hyperplasie en een geringe kans op restenose (hoofdstuk 5). Coronaire arteries met een kleine diameter vormen een risicofactor voor restenose. Ook in deze subgroep zijn de resultaten met SES gunstig (hoofdstuk 6).

De ultieme uitdaging voor de interventiecardioloog is de behandeling van de linker hoofdstam. De initiele klinische resultaten bij patienten behandeld met een SES voor deze indicatie zijn uitstekend: geen mortaliteit na ontslag uit het ziekenhuis (hoofdstuk 7 en 9). De resultaten in een vervolgstudie zijn eveneens beloftevol: een zeer laag risico op cardiovasculaire events na 1 jaar en een geringe kans op restenose (hoofdstuk 8).

De resultaten in hoofdstuk 10 suggereren dat het gebruik van een SES bij meervats coronair lijden het aantal cardiovasculaire events reduceert, vooral door een afname van het aantal nieuwe coronaire interventies. De belangrijke afname van restenose met de SES is van enorm klinisch belang in deze patientgroep, die nog altijd bij voorkeur chirurgisch wordt behandeld. De resultaten van de ARTS II studie, waarvan de inclusieperiode recent werd beeindigd, zullen het gebruik van de DES bij patienten met meervats coronair lijden beter duiden.

De resultaten van deze strategie die nu in het Erasmus MC wordt toegepast, namelijk om patienten met meervats coronair lijden meer en meer percutaan te behandelen, worden in hoofdstuk 11 besproken. Sinds de introductie van de DES is er een toename van het aantal percutane interventies voor meervats coronair lijden en bifurcatielesies en neemt ook het aantal geimplanteerde stents per patient toe. Binnen de groep patienten die heelkundig worden gerevasculariseerd bemerken we ook een verschuiving: het aandeel van de patienten met een slechte linker ventrikelfunctie en meervats coronair lijden neemt namelijk toe. Voor beide groepen samen blijkt dat het aantal cardiovasculaire events afneemt, voornamelijk door een afname van het aantal

patienten met restenose. Eveneens worden met beide revascularisatiemethodes meer en meer patienten met complexe coronaire pathologie behandeld.

De mogelijke diagnostische aanpak en behandeling met een SES van een patient met een vulnerabele plaque wordt in hoofdstuk 12 besproken. In een kleine serie van opeenvolgende patienten blijkt deze strategie in ieder geval veilig te zijn (hoofdstuk 13). Een toename in de accuraatheid van invasieve en niet-invasieve beeldvormingstechnieken ter karakterisatie van de atheromateuse plaque, zal hopelijk bijdragen tot een beter inzicht in de mechanismen die leiden tot ruptuur van een coronaire plaque en als gevolg hiervan aanleiding geven tot een acuut coronair syndroom. Op dit moment worden in ons centrum op een observationele manier gegevens verzameld, die hopelijk kunnen bijdragen tot nieuwe denkpistes. Een nauwe samenwerking tussen clinicus en personen die zich bezig houden met fundamenteel wetenschappelijk onderzoek is hierbij noodzakelijk. Bijkomende studies zijn noodzakelijk om na te gaan of de DES een rol heeft in de stabilisatie van de vulnerabele plaque en op die manier het natuurlijk beloop van een acuut coronair syndroom kan beinvloeden.

De impact van de technologische vooruitgang op de percutane behandeling van patienten met complexe vormen van coronaire atheromatose werd in deze thesis onderzocht. Onze bevindingen ondersteunen de uitstekende resultaten die werden geboekt met de SES in gerandomiseerde studies. Het feit dat deze gunstige resultaten min of meer kunnen worden gereproduceerd in de dagdagelijkse praktijk, die per definitie niet de restricties vertoont van de gerandomiseerde studie, is een belangrijke bevinding, aangezien dit zal bijdragen tot een verdere verschuiving van het aantal revascularisatieprocedures ten voordele van PCI.

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Muzaffer Degertekin, despite Paul's efforts to create a war in Rotterdam in between us, we became very good friends. I will never forget our productive discussions having always 2 conclusions: the Turkish, and the Greek one. Kengo Tanabe, Ronald Lee, and Evelyn Regar, the fellows before us made a smooth transition and taught us the pathways of devoted research. Your successors in Z-bulding Gaston Rodriguez, and Jiro Aoki have the difficult task to replace you, but *leally* they are doing incredible fine. Andrew Ong, from down under, your enthusiasm for research shines in Bd 416. I was astonished with your capability of knowing Rotterdam's streets better than a taxi-driver.

I was very lucky to have in my last days Carlos van Mieghem as a roommate. Carlos, one of my strongest (and believe me sweetest) memories will be IBIS 5.....I

still have files on my laptop. We never said goodbye, definitely for a reason. My last advice for you: Want to make your computer go really fast? Throw it out of the window. During my first year in Rotterdam I shared the apartment with a Greek friend and colleague of mine Manos Bountioukos. Manos, I will never forget us sitting for endless hours in front of our laptops and sharing our anxieties and concerns with Mr. Jack Daniels.

I thank Prof. Piek, Prof. van Belle, Prof. van der Steen, Prof. Pattynama, and Prof. Louridas for their honorable presence in the thesis' committee.

I would like to express my deepest appreciation for Lena and Alexandros for looking after my family while I was away. At this point I would like to express my gratitude to my parents for tolerating me while being their "revolutionary" son since my birth and supporting me with all their strength to pursuit everything that I wanted. Μητέρα, δεν θα ξεχάσω ποτέ την αγάπη σου και την αγωνία σου για μένα. Πατέρα, σ' ευχαριστώ για την υποστήριξή σου όλα αυτά τα χρόνια. Ποτέ μου δεν πίστευα όταν έφυγα, ότι εκτός από αφοσιωμένος σύζυγος θα ήσουνα και ο καλύτερος ιατρός για την μητέρα.

It's not easy to try to put into some lines in a page, my feelings for my wife, Vicky. Thank you very much for sharing my dreams, my hopes, and my needs all these years. Your devotion and support were the fuel in my engine to leave you in the best moment of our life; the most difficult part for me in Rotterdam was being away from you, and our newborn son Alexandros.

## CURRICULUM VITAE

**Name**
Chourmouzios A. Arampatzis
**Gender**
Male
**Date and place of birth**
March 21, 1969
Serres, Greece

**Education and training**

| | |
|---|---|
| 1983-1986 | 1st High school, Xanthi, Summa cum Laude |
| 1986-1992 | Aristotelian University of Thessaloniki, School of Medicine and Science |
| 1993-1995 | Military doctor |
| 1995-1996 | Rural doctor, Kali, Municipality of Pella |
| 1996-1998 | Saint Paul, First General Hospital, Thessaloniki, Internal Medicine trainee |
| 1998-2002 | George Papanikolaou, General Hospital, Thessaloniki, Cardiology trainee |
| 2000-2002 | Aristotelian University of Thessaloniki, Medical Informatics, Master of Science in Medical Research and Technology, Summa cum Laude |
| 2002- | Thorax Centre, Rotterdam, Clinical Fellow of Interventional Cardiology |

**Teaching and Research experience**

| | |
|---|---|
| 1996-1998 | Clinical Investigator for Cardiovascular Disorders in Sleep Apnea Syndrome, Saint Paul, First General Hospital, Thessaloniki |
| 2000-2002 | Research in Information Technology, and Medical Applications, Aristotelian University of Thessaloniki |

**Topics of interest**
IT medical applications
Vulnerable Plaque
Cell Transplantation
Endothelial Progenitor Cells Stent Technology
**Memberships and registrations**
KNMG-full registration
BIG register
Hellenic National Society of Cardiologists

## PUBLICATIONS

*Original Reports (peer reviewed articles)*

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patients with multivessel disease involving proximal left anterior descending lesions- A subanalysis of the ARTS trial. Am J Cardiol accepted.

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## ASSESSMENT REPORTS

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3. Ong ATL, Lemos PA, Hoye A, **Arampatzis CA**, Saia F, Aoki J, van Mieghem C, Hofma SH, Smits PC, van der Giessen WJ, Sianos G, McFadden E, de Feyter P, Serruys PW. Safety and feasibility of paclitaxel-eluting stents in the treatment of ST-elevation acute myocardial infarction. In: American College of Cardiology-53rd Annual Scientific Session, 2004, New Orleans, USA.
4. Ong ATL, Lemos PA, Hoye A, **Arampatzis CA**, Saia F, Aoki J, van Mieghem C, Hofma SH, Smits PC, van der Giessen WJ, Sianos G, McFadden E, de Feyter P, Serruys PW. Comperative incidence of angiographically proven early stent thrombosis in unselected sirolimus- and paclitaxel-eluting stent populations. In: American College of Cardiology-53rd Annual Scientific Session, 2004, New Orleans, USA.

5. Saia F, Lemos PA, Hoye A, Sianos G, **Arampatzis CA**, van der Giessen WJ, Smits PC, van Domburg RT, de Feyter P, Serruys PW. Similar clinical outcomes for sirolimus-eluting stent implantation and coronary brachytherapy for the treatment of in-stent restenosis. In: American College of Cardiology-53rd Annual Scientific Session, 2004, New Orleans, USA.
6. Lemos PA, Saia F, **Arampatzis CA**, Hoye A, Tanabe K, Degertekin M, Sianos G, Smits PC, van der Giessen WJ, de Feyter P, McFadden E, Hofma S, van Domburg RT, Serruys PW. Unrestricted Utilization of Sirolimus-Eluting Stent Implantation in the "Real World" Reduces Events Compared with Previous Strategies Using Conventional Bare Stents – A Study of 1200 Consecutive Patients from the RESEARCH registry. Circulation 2003; 108 (17 [Suppl]): IV-532
7. Saia F, Lemos PA, Lee CH, **Arampatzis CA**, Hoye A, Tanabe K, Degertekin M, Smits PC, Sianos G, van der Giessen WJ, McFadden E, Hofma S, de Feyter P, van Domburg RT, Serruys PW. Comparison between sirolimus-eluting stents and conventional interventional strategies for patients with acute myocardial infarction – Results from the RESEARCH registry. Circulation 2003; 108 (17 [Suppl]): IV-409
8. **CA. Arampatzis**, D. Goedheart, P.W.Serruys, P. J de Feyter. Fluvastatin reduces the impact of diabetes on long term outcome after coronary intervention. A LIPS substudy. In: European society of cardiology congress 2003, Vienna, Austria.
9. Tanabe K, **Arampatzis CA**, Hoye A, Lemos PA, Sianos G, van der Giessen WJ, van Domburg RT, Serruys PW. Sirolimus-eluting stents for the treatment of bifurcation lesions. In: European society of cardiology congress 2003, Vienna, Austria.
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