Effectiveness of the sirolimus-eluting stent in the treatment of patients with a prior history of coronary artery bypass graft surgery

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Objective **Percutaneous coronary intervention in patients with a history of previous coronary artery bypass grafting (CABG) is associated with an increased rate of subsequent adverse events compared to those without prior CABG. We evaluated the impact of utilizing the sirolimus-eluting stent (SES) in this high-risk population.**

Methods **Since April 2002, SES implantation was utilized as the default strategy for all percutaneous procedures in our hospital. Consecutive patients with a history of previous CABG and *de novo* lesions ($n=47$) treated exclusively with SES, were compared to 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 3.0 mm). 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%, hazard ratio 0.37 (95% confidence interval 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 1 year. *Coron Artery Dis* 15:171–175 © 2004 Lippincott Williams & Wilkins.**

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Conflicts of interest: none

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Introduction

More than 300 000 people undergo coronary artery bypass graft (CABG) surgery every year in the USA alone, yet CABG is not a definitive therapy and patients continue to have considerable cardiovascular morbidity and mortality. Recurrence of ischaemia and angina relates to either progression of native vessel atherosclerosis, or failure of the bypass grafts themselves. Indeed, angiographic studies have shown that by 10–12 years, 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 that were not grafted [3,4]. In the large Coronary Artery Surgery Study (CASS) of more than 9500 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 percutaneous coronary intervention (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 is, in itself, is associated with a high

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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).

Materials and study population

From April 2002, all percutaneous coronary interventions at our centre were 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. The SESs were available in lengths between 8 and 33 mm, and diameters of between 2.25 and 3.0 mm. All patients were treated with long-term aspirin therapy and received a loading dose of 300 mg clopidogrel followed by a daily dose of 75 mg 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). Major adverse cardiac events were 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 re-intervention 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's *t*-test. The 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 two 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 sub-acute 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, one patient treated with SES (2.1%) required TVR for restenosis of a stent within a saphenous vein graft (SVG), giving an overall TVR rate within this population of 6.3% (one out of the 16 survivors). This compares with 15 patients (22.7%) treated with BMS who required TVR. Of these 15 patients, nine underwent TVR for in-stent restenosis within a native vessel. The remaining six underwent TVR

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
Hypercholesterolaemia (%)	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.

(one re-do CABG) for restenosis within a SVG giving an overall TVR rate within this population of 25.0% (six out of the 24 survivors). The Kaplan–Meier curves for the cumulative incidence of major adverse cardiac events are presented in Figure 1.

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 3 years, the overall survival of patients with previous CABG and medically refractory angina was similar whether treated with either PCI or repeated CABG [21]. Moreover, when given the choice of PCI or a repeat CABG, the majority of patients preferred the former option. The investigators concluded that PCI may be the preferred revascularization strategy.

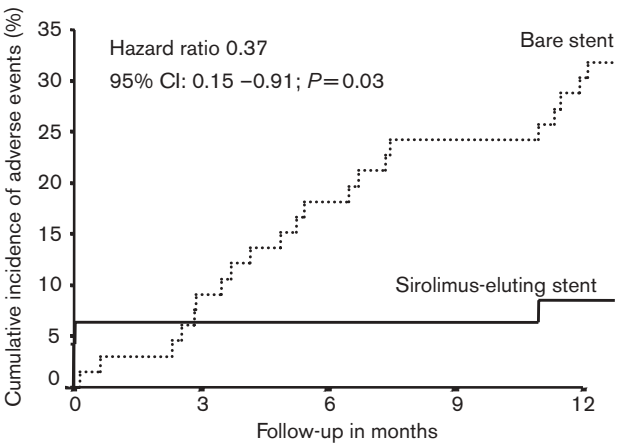
In the present study, 40.9% in the bare stent group, and 36.2% of the SES group underwent intervention within at least one bypass graft. Compared to native vessels, percutaneous revascularization of diseased saphenous vein grafts is hampered by an increased rate of adverse events thereby contributing to the worse outcome of post-CABG patients. Procedural complications may relate to distal embolization 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 target lesion revascularisation was 73% in the stented

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.

Fig. 1



Kaplan–Meier curves for the cumulative incidence of major adverse events at 1 year, for patients with a history of previous coronary artery bypass surgery treated with sirolimus-eluting stent implantation versus bare stent implantation.

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 revascularisation (%)	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; CI, confidence interval.

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 in-stent 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. However, 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 prevalence 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 centre 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 3.0 mm [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 comparative 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 1 year, in a high-risk population with a history of previous coronary artery bypass graft surgery.

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