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Twenty-four months clinical outcomes of sirolimus-eluting stents for the treatment of small coronary arteries: the long-term SES-SMART clinical study

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Aims It has been demonstrated that, in comparison with bare-metal stents (BMS), sirolimus-eluting stents (SES) reduce restenosis after the percutaneus revascularization of small coronary arteries, but the long-term clinical outcomes of this treatment have not yet been investigated.

Methods and results The long-term SES-SMART clinical study was a multicentre, prospective, randomized, single-blind study of 257 patients receiving a SES or BMS in a small coronary artery, who were evaluated at discharge, 30 days, 8 and 24 months after stenting. The clinical endpoint of the study was a 24 months composite of major adverse cardiac and cerebrovascular events, which included death, non-fatal myocardial infarction, ischaemia-driven target lesion revascularization (TLR), and cerebrovascular accident. The 24 months follow-up was completed by 254 patients (98.8%). The use of SES was associated with a significantly lower incidence of the clinical endpoint (12.6% vs. 33.1%; HR 0.30, 95% CI: 0.17–0.55; $P < 0.0001$), which was not only due to a reduction in TLR (7.9% vs. 29.9%; HR 0.30, 95% CI: 0.16–0.59; $P < 0.0001$), but also to a reduction in myocardial infarction (1.6% vs. 10.2%; HR 0.09, 95% CI: 0.01–0.66; $P = 0.018$).

Conclusion In comparison with BMS, the use of SES in the percutaneous revascularization of small coronary arteries is associated with improved clinical outcomes after 2 years follow-up.

Keywords Stents • Sirolimus • Small coronary arteries • Revascularization • Myocardial infarction

Introduction

Drug-eluting stents (DES) have proved to be effective in reducing angiographic restenosis after percutaneous coronary interventions.[1,2] However, their clinical benefit at late follow-up has not yet been completely established, and their long-term safety has actually been questioned.[3–5] Although late follow-up results from randomized trials have confirmed a persistent reduction in target lesion revascularization (TLR) without any difference in the incidence of death or myocardial infarction,[6,7] a few

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pathological studies,[8,9] a sizeable number of case reports,[10,11] and data from meta-analyses and registries[4,5,12] have all raised concerns about the long-term safety of DES, possibly related to an increased risk of late stent thrombosis.

The Sirolimus-Eluting vs. Uncoated Stents for Prevention of Restenosis in Small Coronary Arteries (SES-SMART) angiographic trial was the first randomized prospective trial, showing that the use of sirolimus-eluting stents (SES) is associated with a reduction in restenosis in patients undergoing percutaneous coronary revascularization of small coronary arteries.[13] The aim of the long-term SES-SMART clinical study was to compare the 24 months efficacy and safety of SES and bare-metal stents (BMS) in this setting.

Methods

Study population

The study design and major inclusion and exclusion criteria of the SES-SMART trial have been previously reported in detail.[13] It was a multicentre, prospective, randomized trial designed to determine whether the use of an SES (Cypher balloon-expandable stent, Cordis, Miami Lakes, FL, USA) for the treatment of small coronary arteries is associated with a reduction in angiographic restenosis after 8 months follow-up in comparison with an identically structured BMS (Bx Sonic balloon-expandable stent, Cordis). The study population included patients with non-ST-segment elevation acute coronary syndrome, stable angina pectoris or silent myocardial ischaemia who had a *de novo* lesion located in a small-diameter native coronary artery (reference vessel diameter at online QCA 2.25–2.75 mm) that was amenable to percutaneous coronary intervention and could be completely covered by a single stent (maximum length 33 mm). Only approved indications for the use of SES were allowed, and so the following clinical and angiographic conditions were excluded per protocol: recent ST-segment elevation myocardial infarction (within the previous 15 days), calcified or thrombus-containing lesions, planned direct stenting, unprotected left-main, ostial or bifurcation lesion locations, total occlusions, and excessive vessel tortuosity. The other exclusion criteria were a left ventricular ejection fraction of less than 30%, severe renal dysfunction, and known allergies to aspirin, clopidogrel, ticlopidine, heparin, stainless steel, contrast agents, or sirolimus.

Study protocol

The long-term SES-SMART clinical study involved clinical evaluations prospectively scheduled at the time of hospital discharge, 30 days (±7 days), 8 months (±2 weeks), and 24 months (±1 month) after the index procedure. At each time point, the patients were evaluated in terms of their vital status and the occurrence of the following adverse events: myocardial infarction (Q wave and non-Q wave), cerebrovascular accident, and the need for re-hospitalization, re-angiography or repeated revascularization procedures (repeated coronary angioplasty or coronary artery bypass grafting). Stent thrombosis was also prospectively assessed at each visit. A 12-lead electrocardiogram was recorded and compared with those obtained before and immediately after the index procedure, in order to identify any new appearance of Q waves. Complete information was also collected concerning medication regimens, especially the duration of antiplatelet therapy, which included aspirin (100 mg/day) indefinitely and clopidogrel (75 mg/day) for at least 2 months. All clinical events were assessed by an independent Clinical Events Committee unaware of the treatment assignment. The study protocols of both the angiographic and the clinical study were approved by the Ethics Committee of each participating centre, and all of the patients gave their written informed consent.

Study endpoints

The clinical endpoint of the study was the composite of major adverse cardiac and cerebrovascular events (MACCE) after 24 months follow-up. The MACCE were defined as all-cause death, non-fatal myocardial infarction (Q wave and non-Q wave), cerebrovascular accident, emergency or elective coronary artery bypass surgery, and emergency or elective repeat coronary angioplasty of the target lesion. Q wave myocardial infarction was defined as the occurrence of prolonged chest pain with an increase in the creatine-kinase MB fraction (to more than three times the upper limit of normal within the first 24 h of the index procedure, or to more than twice the upper limit if occurring later) and the development of new abnormal Q waves. Non-Q wave myocardial infarction required only the first two characteristics. Target lesion revascularization was defined as emergency or elective coronary artery bypass surgery, or emergency or elective repeat coronary angioplasty because of restenosis in association with angina or objective evidence of myocardial ischaemia. Cerebrovascular accident was defined as the sudden onset of vertigo, numbness, aphasia, or dysarthria, persisting for more than 24 h.

The individual components of the clinical endpoint and stent thrombosis were also evaluated. Stent thrombosis was defined as evidence of thrombus within the stented segment at the time of coronary angiography performed because of documented myocardial ischaemia.

Statistical methods

The data were analysed on the basis of the intention-to-treat principle using SAS software (version 6.12) and a significance level of 0.05; all of the tests were two-tailed. Categorical variables were described as percentages and compared using the χ^2 test. The binary study endpoints were analysed using Fishers' exact test. The hazard risks and their 95% confidence intervals were also calculated. Kaplan–Meier estimates were generated, and events were compared using the log-rank test.

Results

A total of 257 patients were enrolled in the SES-SMART angiographic trial by 20 Italian centres: 129 were randomized to receive an SES and 128 a BMS. There were no between-group differences in their baseline clinical and angiographic characteristics (*Table 1*) or procedural results, which have been previously reported.[13] The primary endpoint of the 8 months angiographic study was the binary rate of in-segment restenosis, which occurred in 53.1% of the patients receiving a BMS but in only 9.8% of those receiving an SES and was consistent with an 82% relative risk reduction. The 8 months secondary endpoints were in-segment minimal lumen diameter, late luminal loss, and the late loss index; all of these parameters significantly improved in the SES group ($P < 0.001$ for all).[13]

The 24 months follow-up of the long-term SES-SMART clinical study was completed by 254 of 257 randomized patients (98.8%): 127 of the 129 (98.4%) assigned to receive an SES and 127 of 128 (99.2%) assigned to receive a BMS. Three patients were lost to follow-up: one between the 30 days and 8 months visit, and two between the 8 and 24 months visit.

Table 1 Patients' baseline clinical and angiographic characteristics

Variable	All patients ($n = 257$)	Sirolimus-eluting stent ($n = 129$)	Bare-metal stent ($n = 128$)	*P*-value
Demographics				
Mean age, years (SD)	63.6 (11.27)	63.2 (11.5)	63.7 (10.9)	0.68
Males, no. (%)	184 (71.6)	99 (76.7)	85 (66.4)	0.07
Risk factors, no. (%)				
Diabetes mellitus	64 (24.9)	25 (19.4)	39 (29.7)	0.06
Hypertension	165 (64.7)	84 (65.1)	81 (64.3	0.85
Hyperlipidaemia	162 (63)	79 (61.2)	83 (64.8)	0.54
Current smoking	42 (16.3)	24 (18.6)	18 (14.1)	0.32
History, no. (%)				
Acute coronary syndromes without ST-segment elevation	109 (42.3)	63 (48.8))	46 (35.8)	
Chronic stable angina pectoris	119 (46.4)	56 (43.4)	63 (49.6)	0.06
Silent myocardial ischaemia	29 (11.3)	10 (8.0)	19 (14.6)	
Previous myocardial infarction	74 (28.8)	38 (29.5)	36 (28.1)	0.81
Previous PCI	55 (21.5)	26 (20.3)	29 (22.7)	0.65
Previous CABG	21 (8.2)	13 (10.2)	8 (6.3)	0.26
Diseased vessels, no. (%)				
1	90 (35.2)	47 (36.4)	43 (33.9)	
2	93 (36.3)	46 (35.7)	47 (37.3)	0.91
3	73 (28.4)	36 (27.9)	37 (29.1)	
Target artery, no. (%)				
Left anterior descending	71 (27.5)	41 (31.5)	30 (23.6)	
Diagonal branch	23 (9.2)	13 (10.3)	10 (7.9)	
Left circumflex	77 (29.9)	32 (24.4)	45 (35.4)	0.32
Obtuse marginal branch	45 (17.7)	23 (18.6)	22 (17.3)	
Right coronary artery	40 (15.7)	20 (15.7)	20 (15.8)	
Type of lesion (ACC/AHA), no. (%)				
A	63 (24.6)	30 (23.3)	33 (25.8)	
B1	120 (46.7)	60 (46.5)	60 (46.9)	
B2	52 (24.5)	31 (24.2)	32 (25.0)	0.48
C	11 (4.3)	8 (6.2)	3 (2.3)	
Mean lesion characteristics, mm (SD)				
Reference vessel diameter	2.20 (0.28)	2.22 (0.29)	2.17 (0.26)	0.15
Lesion length	11.84 (6.15)	13.01 (6.53)	10.66 (5.51)	0.002

PCI, percutaneous coronary intervention; CABG, coronary artery bypass surgery; ACC, American College of Cardiology; AHA, American Heart Association.

During the 24 months of the study, MACCE were observed in 16 patients randomized to receive an SES and 42 randomized to receive a BMS (12.6% vs. 33.1%; hazard risk 0.30, 95% CI: 0.17–0.55; $P < 0.0001$). As a consequence, the rate of survival free from the composite clinical endpoint was significantly higher in the patients treated with an SES (87.6% vs. 67.2%; $P < 0.0001$) (*Figure 1*).

Six deaths occurred during the 24 months follow-up period: one in the SES group and five in the BMS group (0.8% vs. 3.9%; hazard risk 0.17, 95% CI 0.02–0.38; $P = 0.097$), including one non-cardiac death in the SES group (due to malignancy) and four in the BMS group (due to malignancy in two cases, pneumonia in one, and following a stroke in one); the other death in the BMS group was sudden and therefore considered to be due to a cardiac cause.

The incidence of myocardial infarction was significantly lower in the patients treated with SES (1.6% vs. 10.2%; hazard risk 0.09, 95% CI 0.01–0.66; $P = 0.018$), as was that of TLR (7.9% vs. 29.9%; hazard risk 0.30, 95% CI 0.16–0.59; $P \leq 0.0001$).

Thirty-four patients in the BMS group underwent TLR during the follow-up period: the revascularization was driven by myocardial ischaemia (stable angina or acute coronary syndrome) in 23 cases (67.6%) and occurred at different times after the index procedure; in the remaining 11 patients (32.3%), it was a consequence of restenosis revealed by the 8 months protocol angiogram in the

absence of symptoms. Of the nine patients in the SES group who underwent TLR, six (66.6%) had angina at the time of re-angiography and three (33.3%) were asymptomatic. Among the revascularized patients as a whole, only one from the BMS group (who had undergone early re-angiography and TLR three months after the index procedure because of effort angina) developed a periprocedural myocardial infarction. No other procedure-related events occurred in the patients undergoing TLR, including myocardial infarction and death during the follow-up period. The rate of survival free of myocardial infarction was significantly higher in the patients treated with an SES (98.2% vs. 94.5%; $P < 0.0001$) (*Figure 2*).

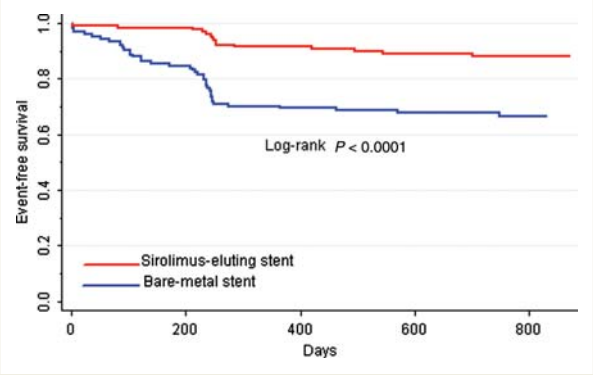

Figure 1 Kaplan–Meier curve showing survival free from the composite clinical endpoint after 24 months.

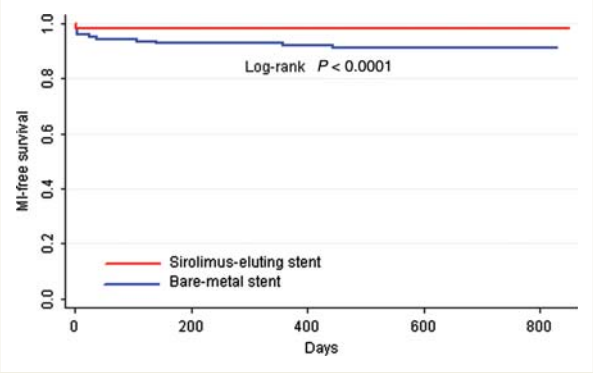

Figure 2 Kaplan–Meier curve showing survival free from myocardial infarction after 24 months (MI, myocardial infarction).

There was no difference between the two study groups in terms of the incidence of cerebrovascular accidents (2.4% vs. 2.4%; hazard risk 0.48, 95% CI 0.09–2.62; $P = 0.395$).

The combination of death and myocardial infarction was significantly reduced in the SES group (2.4% vs. 12.6%; hazard risk 0.13, 95% CI 0.03–0.59; $P = 0.008$).

Five stent thromboses occurred during the 24 months follow-up period: one in the SES group and four in the BMS group (0.8% vs. 3.1%; relative risk 0.25, 95% CI 0.20–2.32; $P = 0.36$). All were subacute and occurred within 5 days of stent implantation; they were all angiographically documented and therefore classified as definite stent thrombosis on the basis of the ARC criteria. One possible stent thrombosis was reported in the BMS group as a consequence of an unexplained sudden death occurring 11 months after the index procedure. No probable or possible cases of stent thrombosis occurred in the SES group. *Table 2* shows the clinical outcomes of the study in detail, and *Table 3* shows the distributions of the individual components of the endpoint and stent thromboses at discharge and after 8 and 24 months.

There were relatively few adverse events in both groups during the last 16 months of the study. It is particularly worth noting that MACCE were more than halved in the SES group and showed a trend towards a lower incidence in comparison with the BMS group (3.9% vs. 8.7%; hazard risk 0.45, 95% CI 0.16–1.29; $P = 0.138$).

Table 4 shows medical therapy, including antiplatelet treatment, at the time of hospital discharge, after 30 days and after 8 and 24 months. There was no difference between the two groups at any of these time points.

Table 2 Clinical outcomes after 24 months

Variable	Sirolimus-eluting stent ($n = 127$)	Bare-metal stent ($n = 127$)	HR (95% CI)	*P*-value
All MACCE[a]	16 (12.6%)	42 (33.1%)	0.30 (0.17–0.55)	<0.0001
Death	1 (0.8%)	5 (3.9%)	0.17 (0.02–0.38)	0.097
Myocardial infarction	2 (1.6%)	13 (10.2%)	0.09 (0.01–0.66)	0.018
Q wave	0	3 (2.3%)	—	—
Non-Q wave	2 (1.6%)	10 (7.9%)		
Target lesion revascularization	11 (7.9%)	38 (29.9%)	0.30 (0.16–0.59)	<0.0001
Surgical revascularization	0	4 (3.2%)	—	—
Percutaneous revascularization	11 (7.9%)	34 (28.6%)	—	—
Cerebrovascular accident	3 (2.4%)	3 (2.4%)	0.48 (0.09–2.62)	0.395
Death and myocardial infarction	3 (2.4%)	16 (12.6%)	0.13 (0.03–0.59	0.008
Stent thrombosis	1 (0.8%)	4 (3.1%)	0.24 (0.03–2.14)	0.201

[a]Major adverse cardiac and cerebrovascular events included death, non-fatal myocardial infarction, ischaemia-driven target lesion revascularization, and cerebrovascular accident.

Table 3 Distribution of clinical events during different follow-up intervals

Variable	Sirolimus-eluting stent ($n = 129$)	Bare-metal stent ($n = 128$)
Before hospital discharge		
Death	0	0
Cardiac death	0	0
Myocardial infarction	2 (1.6%)	3 (2.3%)
Non-Q wave	2 (1.6%)	3 (2.3%)
Q wave	0	0
Target lesion revascularization	0	0
Cerebrovascular accident	0	0
Stent thrombosis	1 (0.8%)	1 (0.8%)
Variable	Sirolimus-eluting stent ($n = 128$)	Bare-metal stent ($n = 128$)
From hospital discharge to 8 months		
Death	0	2 (1.6%)
Cardiac death	0	0
Myocardial infarction	0	7 (5.5%)
Non-Q wave	0	5 (3.9%)
Q wave	0	2 (1.6%)
Target lesion revascularization	9 (7.0%)	33 (25.8%)
Surgical revascularization	0	3 (2.4%)
Percutaneous revascularization	9 (7.0%)	30 (23.4%)
Cerebrovascular accident	1 (0.8%)1)	1 (0.8%)
Stent thrombosis	0	3 (2.4%)
Variable	Sirolimus-eluting stent ($n = 127$)	Bare-metal stent ($n = 125$)
From 8 to 24 months		
Death	1 (0.8%)	3 (2.4%)
Cardiac death	0	1 (0.8%)
Myocardial infarction	0	3 (2.4%)
Non-Q wave	0	1 (0.8%)
Q wave	0	2 (1.6%)
Target lesion revascularization	2 (1.6%)	5 (4.0%)
Surgical revascularization	0	1 (0.8%)
Percutaneous revascularization	2 (1.6%)	4 (3.2%)
Cerebrovascular accident	2 (1.6%)	2 (1.6%)
Stent thrombosis	0	0

Table 4 Percentage of patients receiving medical therapy at different follow-up times

	Discharge		30 Days		8 Months		24 Months	
	SES	BMS	SES	BMS	SES	BMS	SES	BMS
Aspirin	98.4	98.4	94.3	94.4	90.1	87.3	85.7	88.1
Clopidogrel	65.1	59.3	53.4	57.1	8.4	7.0	4.6	6.3
Ticlopidine	34.1	40.6	32.0	29.1	11.5	11.9	6.9	6.3
Beta-blockers	82.9	81.2	81.4	78.3	73.3	77.8	70.3	75.4
ACE-inhibitors	55.8	56.3	55.0	56.2	50.4	54.6	46.5	50.2
Statins	71.3	70.3	71.3	70.3	68.7	67.4	68.0	68.2

SES, sirolimus-eluting stent; BMS, bare-metal stent. None of the *P*-values was statistically significant.

Discussion

The most important finding of the study is that the use of SES for the percutaneous revascularization of small coronary arteries is associated with a reduction in the 24 months incidence of the composite endpoint of death, myocardial infarction, clinically driven TLR, and cerebrovascular accident in comparison with BMS. This reduction was mainly due to the lower incidence of myocardial infarction and clinically driven TLR. The reduced need for TLR was expected with SES, but not the lower incidence of myocardial infarction.

Data from *post hoc* analyses,[3] meta-analyses[4,5] and registries[12] have suggested an increased risk of adverse ischaemic events at long-term follow-up possibly related to stent thrombosis in patients treated with DES (hence the recent aphorism 'trading restenosis for thrombosis'). More recent results from meta-analyses of randomized trials[14,15] and registries[16,17] have shown that the use of DES rather than BMS is not associated with different outcomes in terms of 'hard' endpoints, including death or myocardial infarction, but it is still unclear why the reduction in restenosis and the need for repeat revascularization associated with DES does not translate into a reduction in the incidence of myocardial infarction. One possible reason, at least in the general population, could be the balance between the increased risk of late thrombotic events with DES and the increased risk of adverse events related to repeated revascularization procedures with BMS.

However, the idea that the reduced incidence of angiographic restenosis does not translate into a clear long-term clinical benefit and that thrombosis may be the price that has to be paid for it, does not seem to apply to our results, because we found that the use of SES to treat small coronary arteries improved both angiographic and clinical outcomes. The reduced incidence of myocardial infarction observed in our study is in line with the findings of a recent retrospective analysis of the BASKET trial, which showed that the 'small vessel' variable is an independent predictor of a reduction in the composite endpoint of death and myocardial infarction after 18 months follow-up in patients treated with DES.[18] Similarly, data from a large meta-analysis have shown that SES are associated with a lower incidence of myocardial infarction than BMS.[19] These results may not apply to larger vessels because no difference in the incidence of death or myocardial infarction has been found in unselected populations.[14–17] Although stent thrombosis was not a study endpoint, it is also worth noting that there was no difference in the incidence of stent thrombosis between the patients receiving a SES and those receiving a BMS and that there was only one case of possible late stent thrombosis.

Another important finding of the present study is that the 8 months reduction in adverse events obtained with the use of SES persisted during the second part of the follow-up. There were no signs of reduced efficacy or late catch-up, but there was a trend towards a further reduction in the need for revascularization. Moreover, there were very few adverse events (including death and myocardial infarction) after 8 months in the SES group, thus showing that SES has a favourable long-term safety profile at least up to 24 months. Similarly, a low adverse event rate at long-term follow-up in patients treated with SES has also been reported in a sub-analysis of the Sirtax trial.[20]

It is not known why the implantation of an SES in small coronary arteries seems to reduce the incidence of myocardial infarction during long-term follow-up, but one possible explanation is the prevention of restenosis itself. By reducing the need for repeat revascularization, DES may prevent periprocedural myocardial infarction, and this could be particularly relevant in the case of small vessels, which are at high risk of restenosis. However, this explanation does not apply to our cases because only one myocardial infarction occurred as a consequence of repeat revascularization. Another possible explanation is that the restenotic process in small coronary arteries is more likely to lead to a total occlusion, because a narrow diameter cannot accommodate even minimal degrees of neointimal hyperplasia without becoming occluded. It is tempting to speculate that DES may prevent coronary occlusion (and ultimately myocardial infarction) by reducing neointimal hyperplasia, but the biological mechanism by which their use in small coronary arteries seems to reduce the occurrence of myocardial infarction has not been clearly identified, and only speculative hypotheses can be made. However, although our observation needs to be confirmed by larger and specifically designed studies, evidence from subgroup analyses of larger trials (including the long-term data from the BASKET study) seems to support it.[21]

Study limitations

This was a single-blind study as the clinicians were not blinded to the assigned treatment; however, the risk of a selection bias was minimized by its randomized design. Furthermore, the study has limited statistical power for rare events such as death or stent thrombosis because the sample size was calculated on the basis of the primary angiographic endpoint.

Conclusions

The SES-SMART angiographic and long-term clinical studies provide evidence that using SES to revascularize small coronary arteries is safe and highly effective in reducing angiographic restenosis and MACCE after 24 months follow-up.

The improvement in clinical outcomes is not only related to the reduction in ischaemia-driven TLR, but also to the lower incidence of myocardial infarction. These findings support the use of SES for the percutaneus revascularization of small coronary arteries.

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Conflict of interest: none declared.

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