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DOTTORATO DI RICERCA IN DIAGNOSTICA PER IMMAGINI AVANZATA CON TECNICHE TRIDIMENSIONALI AD INDIRIZZO INTERVENTISTICO

XIX CICLO

LONG TERM CLINICAL OUTCOMES OF SIROLIMUS ELUTING-STENTS FOR THE TREATMENT OF SMALL CORONARY ARTERIES

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Abstract

***Background*:** Sirolimus-eluting stents have proved to be effective in reducing restenosis in comparison with bare-metal stents in a highly challenging condition such as the percutaneous revascularization of small coronary arteries. However, long-term clinical outcomes in such patients treated with a sirolimus-eluting stent have not yet been investigated.

***Methods and Results*:** The long-term SES-SMART clinical study was a randomized, multicenter, single-blind, prospective study of 257 patients treated with a sirolimus-eluting or bare-metal stent of identical structure in a lesion located in a small coronary artery.

Visits were scheduled at discharge, and 30 days, 8 months and 24 months after the index procedure. The primary end-point of the study was a 24-month composite of major adverse cardiac and cerebrovascular events, which included death, non-fatal myocardial infarction, ischemia-driven target lesion revascularization, and cerebrovascular accident. The individual components of the primary end-point and the occurrence of stent thrombosis were also prospectively evaluated. The 24-month follow-up was completed by 254 patients (98.8%).

The use of sirolimus-eluting stents was associated with a significantly lower incidence of the primary end-point (12.6% versus 33.1%, RR 0.38, 95% CI: 0.21-0.65, P=0.0002), not only due to a reduction in ischemia-driven target lesion revascularization (7.9% versus 29.9%, RR 0.29, 95%

CI: 0.14-0.55, P<0.0001), but also to a reduction in myocardial infarction (1.6% versus 10.2%, RR 0.15, 95% CI: 0.0-0.69, P=0.007).

***Conclusions*:** In comparison with bare-metal stents, the use of sirolimus-eluting stents in the percutaneous revascularization of small coronary arteries is associated with improved clinical outcomes after two years' follow-up.

Key words

Coronary artery disease, coronary stents, drugs, percutaneous revascularization, myocardial infarction, acute coronary syndrome.

Drug-eluting stents have proved to be effective in reducing angiographic restenosis after percutaneous coronary interventions[1,2]. However, the clinical benefit of drug-eluting stents at late follow-up has not yet been completely established, and their long-term safety has actually been recently questioned[3,4,5].

Although, late follow-up results from randomized trials have confirmed a persistent reduction in target lesion revascularization with the use of drug-eluting stents without any difference in the incidence of death or myocardial infarction[6,7], a few pathology studies[8,9], a sizeable number of case reports[10,11] and data from metanalyses and registries[4,5,12] have raised concerns about their long-term safety possibly in relation to an increased risk of late stent thrombosis.

The Sirolimus-Eluting versus Uncoated Stents for Prevention of Restenosis in Small Coronary Arteries (SES-SMART) angiographic trial was the first randomized prospective study showing that the use of sirolimus-eluting stents 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-month efficacy and safety of sirolimus-eluting and bare-metal stents in the highly challenging condition of the revascularization of small coronary arteries.

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 prospective, multicenter, randomized trial designed to determine whether the use of a sirolimus-eluting stent (Cypher balloon-expandable stent, *Cordis*, Miami Lakes, FL) for the treatment of small coronary arteries, in comparison with a bare-metal stent of identical structure and radiographic appearance (Bx Sonic balloon-expandable stent, *Cordis,* Miami Lakes, FL), was associated with a reduction in angiographic restenosis after eight months' follow-up.

The study population included patients with non ST-segment elevation acute coronary syndrome, stable angina pectoris or silent myocardial ischemia, with a single *de novo* (50 to 99%) target lesion located in a native coronary artery with a small diameter (2.75 mm or less) amenable to percutaneous coronary intervention, which could be completely covered by a single stent (maximum length 33 mm).

Only approved indications for the use of sirolimus-eluting stents were allowed; therefore, the following clinical and angiographic conditions were excluded as per protocol: recent ST-segment elevation myocardial infarction (within the previous 15 days), calcified or thrombus-containing lesion, planned direct stenting, unprotected left-main coronary artery

disease, ostial or bifurcation lesion location, and excessive vessel tortuosity.

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 hospital discharge, and 30 days (± 7 days), eight months (± 2 weeks) and 24 months (± 1 month) after the index procedure.

At each time point, the patients were evaluated for 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 twelve-lead electrocardiogram was recorded and compared with those obtained before and immediately after the index procedure, in order to identify new appearances of Q-waves. Complete information was also collected about medication regimens, especially the duration of antiplatelet therapy, which included aspirin (100 mg/day) indefinitely and clopidogrel (75 mg/day) for at least two months.

All clinical events were assessed by an independent Clinical Events Committee unaware of the treatment assignment. The study protocols for

both the angiographic and the clinical study were approved by the Ethics Committee of each participating center, and all patients gave their written informed consent.

Study end-points

The primary end-point of the present study was the composite of major adverse cardiac and cerebrovascular events after 24 months' follow-up.

Major adverse cardiac and cerebrovascular events were defined as all-cause death, nonfatal 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 hours of the index procedure or more than twice the upper limit if occurring later than 24 hours), 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, emergency or elective repeat coronary angioplasty performed because of restenosis in association with angina or objective evidence of myocardial ischemia. Cerebrovascular accident was defined as the sudden onset of hemiplegia, vertigo, numbness, aphasia or dysarthria, persisting for more than 24 hours.

The individual components of the primary end-point 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 ischemia.

Statistical methods

The data were analyzed on the basis of the intention-to-treat principle using SAS software. Categorical variables were described as percentages and compared using the χ^2 test. The binary study end-points were analyzed using Fishers' exact test. The relative risks or odd ratios 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 in 20 Italian centers, of whom 129 were randomized to receive a sirolimus-eluting stent and 128 a bare-metal stent. The baseline clinical and angiographic characteristics and the procedural results were not different between the two groups and have been previously reported[13].

The 8-month angiographic results showed binary restenosis in 53.1% of the patients receiving a bare-metal stent and in only 9.8% of those receiving a sirolimus-eluting stent, consistent with an 82% relative risk reduction[13] (Figure 1).

In the long-term SES-SMART clinical study, the 24-month follow-up was

completed by 254 of the 257 randomized patients (98.8 percent): 127/129 (98.4%) assigned to receive a sirolimus-eluting stent and 127/128 (99.2%) assigned to receive a bare-metal stent. Three patients were lost to follow-up: one during the interval between the 30-day and 8-month visit and two between the 8- and 24-month visit.

The 24-month occurrence of major adverse cardiac and cerebrovascular events (the primary end-point of the study) was observed in 16 patients randomized to receive a sirolimus-eluting stent, and 42 patients randomized to a bare-metal stent (12.6% versus 33.1%; relative risk 0.38, 95% CI 0.21-0.65, P=0.0002). A detailed description of the results is given in Table 1.

Six deaths occurred during the 24-month follow-up period, one in the sirolimus-eluting stent group and five in the group of patients treated with a bare-metal stent (0.8% versus 3.9%; relative risk 0.20, 95% CI 0.0-1.71, P=0.21), including one non-cardiac death in the sirolimus-eluting stent group (due to malignancy) and four in the bare-metal stent group (in two patients due to malignancy, in one due to pneumonia and in one following a stroke). In one patient from control group, the death was sudden and therefore considered to be due to cardiac reason.

A statistically significant reduction was observed in the incidence of myocardial infarction in the patients treated with sirolimus-eluting stents (1.6% versus 10.2%, relative risk 0.15, 95% CI 0.0-0.91, P=0.007).

Clinically-driven target-lesion revascularization was also significantly

lower in the patients treated with sirolimus-eluting stents (7.9% versus 29.9%, relative risk 0.29, 95% CI 0.14-0.55, P<0.0001). There was no difference in the incidence of cerebrovascular accident between the two groups (2.4% versus 2.4%; relative risk 1.00, 95% CI 0.13-6.18, P=0.21).

The combination of death and myocardial infarction was significantly reduced in the sirolimus-eluting stent group (2.4% versus 12.6%, relative risk 0.19, 95% CI 0.03-0.66, P=0.004).

Five stent thromboses occurred during the 24-month follow-up period: one in the sirolimus-eluting stent group and four in the bare-metal stent group (0.8% vs 3.1%, relative risk 0.25, 95% CI 0.20-2.32, P=0.36). All of the stent thromboses were subacute and all occurred within five days of stent implantation.

The distributions of the individual components of the primary end-point and stent thromboses at discharge, and after eight and 24 months, are shown in Table 2.

The rate of survival free from the primary end-point was significantly higher in the patients treated with a sirolimus-eluting stent than in those receiving a bare-metal stent (87.6% versus 67.2%, P<0.0001) (Figure 2).

Table 3 shows medical treatments at hospital discharge, and after eight and 24 months.

There was no difference between the two groups at any time point. No clustering of adverse events was observed after the discontinuation of dual antiplatelet therapy.

Discussion

The most important finding of the present study is that the use of sirolimus-eluting stents for the percutaneous revascularization of small coronary arteries is associated with a reduced 24-month incidence of the composite end-point of death, myocardial infarction, clinically-driven target lesion revascularization and cerebrovascular accident in comparison with bare-metal stents. The reduction in the primary composite end-point was mainly due to the lower incidence of myocardial infarction and clinically-driven target-lesion revascularization. The reduction in the need for target-lesion revascularization was expected with sirolimus-eluting stents, but not the lower incidence of myocardial infarction.

Our results are even more surprising in the light of data from *post hoc* analyses[3], metanalyses[4,5] and registries[12] suggesting an increased risk of adverse ischemic events at long-term follow-up possibly related to stent thrombosis in patients treated with drug-eluting stents (hence the recent aphorism *"trading" restenosis with thrombosis*). The concept that the reduction in the incidence of angiographic restenosis does not translate into a 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 sirolimus-eluting stents to treat small coronary arteries improved both angiographic and clinical outcomes.

The reduced incidence of myocardial infarction observed in the present study is in keeping 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 drug-eluting stents[14].

Even though it was not a study end-point, it is also worth nothing that there was no excess of stent thrombosis in our patients receiving sirolimus-eluting stents in comparison with those receiving bare-metal stents, and there was no clustering of events immediately after the discontinuation of dual antiplatelet therapy in either group.

Of note, very few adverse events occurred after the 8 months follow-up period in the study stent group, thus showing the good long-term safety-profile of the sirolimus-eluting stents, at least up to 24-month.

It is not known why the implantation of a sirolimus-eluting stent 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 repeated revascularization, drug-eluting stents may prevent periprocedural myocardial infarction, and this mechanism could be particularly relevant in the case of small vessels in which the risk of restenosis is high. However, this explanation does not apply to our cases because only one myocardial infarction occurred as a consequence of repeated revascularization. Another possible explanation could be 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 drug-eluting stents may prevent coronary occlusion and ultimately myocardial infarction by reducing neointimal hyperplasia.

Conclusions

The SES-SMART angiographic and long-term clinical studies provide evidence that using sirolimus-eluting stents to revascularize small coronary arteries is safe and highly effective in reducing angiographic restenosis and major adverse cardiac and cerebrovascular events after 24-months' follow-up.

The improvement in clinical outcomes is not only related to the reduction in ischemia-driven target lesion revascularization, but also to the lower incidence of myocardial infarction. These findings support the use of sirolimus-eluting stents for the percutaneous revascularization of small coronary arteries.

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Figures & Tables

Figure 1: Cumulative Frequency of Stenosis in the SES-SMART Trial at baseline, immediately after stent implantation, and after 8 months. Dotted line indicates threshold for angiographic restenosis (JAMA, 2004;292:2727-2734)

SES: Sirolimus-Eluting Stent; BMS: Bare-Metal Stent (Uncoated)

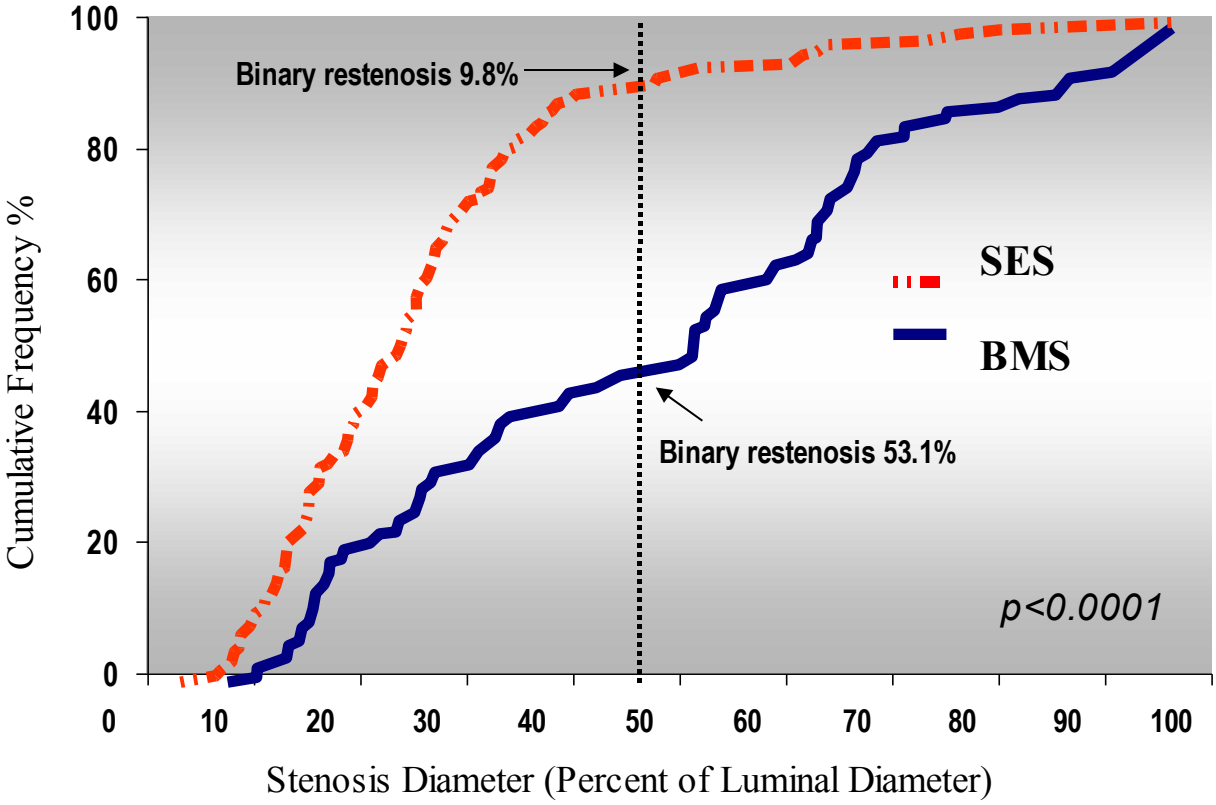

Figure 2: Kaplan-Meier curve showing survival free from primary end-point after 24 months.

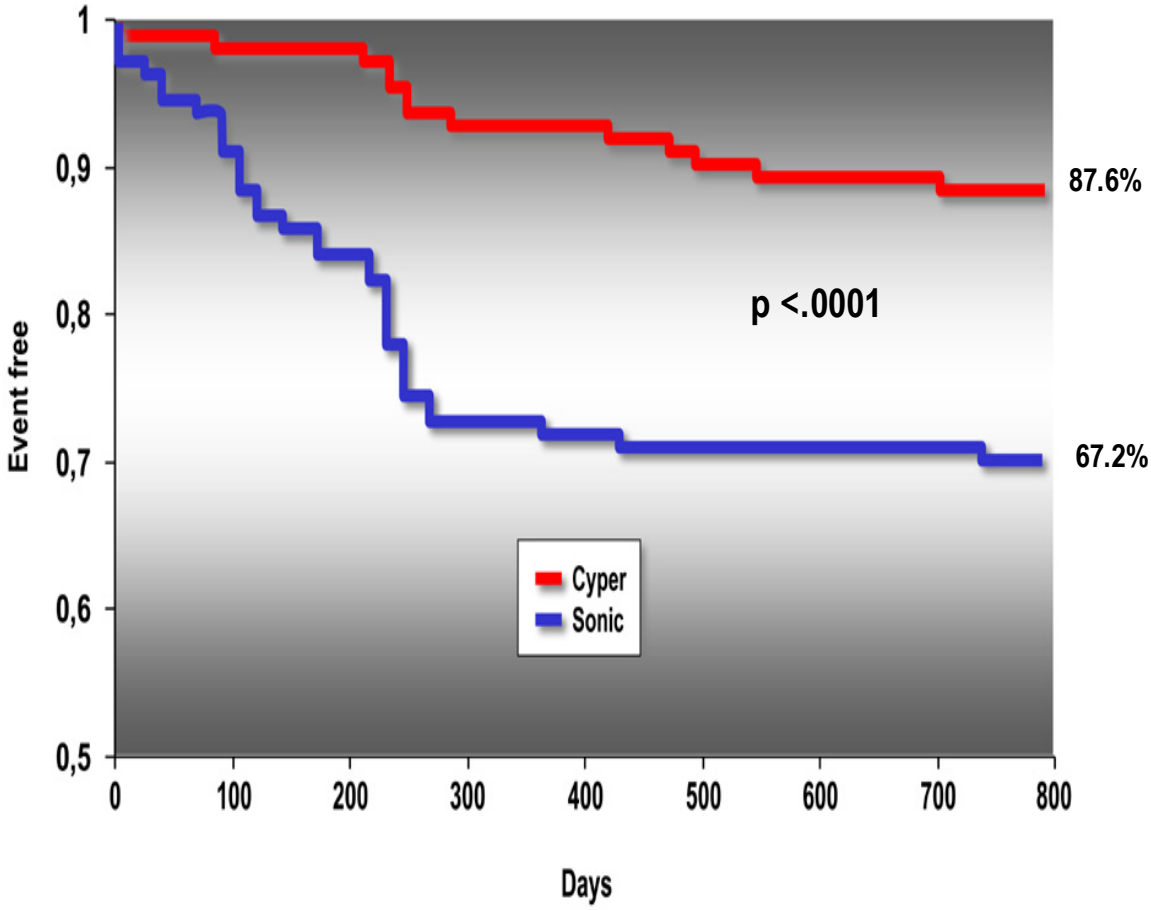

Table 1: Clinical outcomes after 24 months

Variable	Sirolimus-eluting stent (n°=127) n (%)	Uncoated-eluting stent (n°=127) n (%)	RR (95% CI)	p
ALL MACCE*	**16 (12.6)**	**42 (33.1)**	**0.38 (0.21-0.65)**	**.0002**
Death	**1 (0.8)**	**5 (3.9)**	**0.20 (0.0-1.71)**	**.21**
Myocardial infarction	**2 (1.6)**	**13 (10.2)**	**0.15 (0.0-0.69)**	**.007**
- Q-wave	0	3 (2.3)		
- Non-Q wave	2 (1.6)	10 (7.9)		
Target Lesion Revascularization	**11 (7.9)**	**38 (29.9)**	**0.29 (0.14-0.55)**	**< .0001**
- Surgical revascularization	0	4 (3.2)		
- Percutaneous revascularization	11 (7.9)	34 (28.6)		
Cerebrovascular Accident	**3 (2.4)**	**3 (2.3)**	**1.00 (0.13-6.18)**	**.68**
Death and myocardial infarction	**3 (2.4)**	**16 (12.6)**	**0.19 (0.03-0.66)**	**.004**
Stent Thrombosis	**1 (0.8)**	**4 (3.1)**	**0.25 (0.20-2.32)**	**.36**

* Major Adverse Cardiac and Cerebrovascular Events included death, non-fatal myocardial infarction, ischemia-driven target lesion revascularization and cerebrovascular accident.

Table 2: Distribution of clinical events during different follow-up intervals

Before hospital discharge		
Variable	**Sirolimus-eluting stent (n°=129) n (%)**	**Uncoated-eluting stent (n°=128) n (%)**
Death	**0**	**0**
Myocardial infarction	**2 (1.6)**	**3 (2.3)**
- Q-wave	0	0
- Non-Q wave	2 (1.6)	3 (2.3)
Target Lesion Revascularization	**0**	**0**
Cerebrovascular Accident	**0**	**0**
Stent Thrombosis	**1 (0.8)**	**1 (0.8)**
From hospital discharge to 8 months		
Variable	**Sirolimus-eluting stent (n°=128) n (%)**	**Uncoated-eluting stent (n°=128) n (%)**
Death	**0**	**2 (1.6)**
Myocardial infarction	**0**	**7 (5.5)**
- Q-wave	0	2 (1.6)
- Non-Q wave	0	5 (3.9)
Target Lesion Revascularization	**9 (7.0)**	**33 (25.8)**
Cerebrovascular Accident	**1 (0.8)**	**1 (0.8)**
Stent Thrombosis	**0**	**3 (2.4)**
From 8 to 24 months		
Variable	**Sirolimus-eluting stent (n°=127) n (%)**	**Uncoated-eluting stent (n°=127) n (%)**
Death	**1 (0.8)**	**3 (2.4)**
Myocardial infarction	**0**	**3 (2.4)**
- Q-wave	0	2 (1.6)
- Non-Q wave	0	1 (0.8)
Target Lesion Revascularization	**2 (1.6)**	**5 (4.0)**
Cerebrovascular Accident	**2 (1.6)**	**2 (1.6)**
Stent Thrombosis	**0**	**0**

Table 3: Medical treatments at different follow-up times (percentage of patients)

	Discharge		8 months		24 months	
	SES*	BMS†	SES	BMS	SES	BMS
Aspirin	98.4	98.4	90.1	87.3	85.7	88.1
Clopidogrel	65.1	59.3	8.4	7.0	4.6	6.3
Ticlopidine	34.1	40.6	11.5	11.9	6.9	6.3
Beta-blockers	82.9	76.2	73.3	77.8	70.3	75.4
ACE inhibitors	55.8	56.3	50.4	57.9	46.5	50.2
Statins	71.3	68.7	68.7	67.4	68.0	68.2

*SES = sirolimus eluting stent; †BMS = bare-metal stent