Sirolimus-Eluting vs Uncoated Stents for Prevention of Restenosis in Small Coronary Arteries: A Randomized Trial

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Sirolimus-Eluting vs Uncoated Stents for Prevention of Restenosis in Small Coronary Arteries

A Randomized Trial

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Context Percutaneous coronary revascularization of small vessels is associated with a high restenosis rate. Sirolimus-eluting stents reduce restenosis in simple and previously untreated lesions of large coronary arteries, but their outcomes in small vessels have not been adequately investigated.

Objective To determine whether sirolimus-eluting stents are associated with a reduced 8-month rate of angiographic restenosis in comparison with an uncoated stent.

Design, Setting, and Patients This was a randomized, multicenter, single-blind, prospective trial performed with 257 patients undergoing percutaneous coronary revascularization for ischemic heart disease, and who had a previously untreated atherosclerotic lesion located in a small segment with a diameter of 2.75 mm or less, in 20 Italian centers between August 2002 and December 2003.

Intervention Patients were randomly assigned to receive a sirolimus-eluting stent (129 patients) or an uncoated stent having an identical architecture and radiographic appearance (128 patients).

Main Outcome Measures The primary end point was the 8-month binary in-segment restenosis rate; secondary end points included procedural success and the 8-month rate of major adverse cardiac and cerebrovascular events.

Results The mean (SD) reference diameter of the treated segment was 2.2 (0.28) mm; the lesion length, 11.84 (6.15) mm. After 8 months, the binary in-segment restenosis rate was 53.1% (60/113) in the patients receiving an uncoated stent and 9.8% (12/123) in those receiving a sirolimus-eluting stent (relative risk [RR], 0.18; 95% confidence interval [CI], 0.10-0.32; $P<.001$). Fewer patients randomized to sirolimus-eluting stents experienced major adverse cardiac events (12/129 [9.3%] vs 40/128 [31.3%]; RR, 0.30; 95% CI, 0.15-0.55; $P<.001$) mainly because of a reduction in target lesion revascularization (9/129 [7%] vs 27/128 [21.1%]; RR, 0.33; 95% CI, 0.14-0.70; $P=.002$) and myocardial infarction (2/129 [1.6%] vs 10/129 [7.8%]; RR, 0.20; 95% CI, 0.01-0.93; $P=.04$).

Conclusion The use of sirolimus-eluting stents to treat atherosclerotic lesions in small coronary arteries reduces restenosis and may also reduce major adverse cardiac events.

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Atherosclerotic lesions of small coronary arteries are frequently found in patients undergoing revascularization.[1-5] However, the revascularization of small coronary arteries is a problem for bypass surgery because it is technically difficult and associated with a high failure and mortality rate[6,7] and for percutaneous coronary revascularization because it is associated with high rates of acute complications and restenosis after standard balloon angioplasty[1-3] and stent implantation.[4,5]

It has been shown that sirolimus-eluting stents reduce angiographic restenosis and improve the rate of event-free survival in patients who have coronary artery disease and are at low risk of restenosis.[8] More recent reports

For editorial comment see p 2777.

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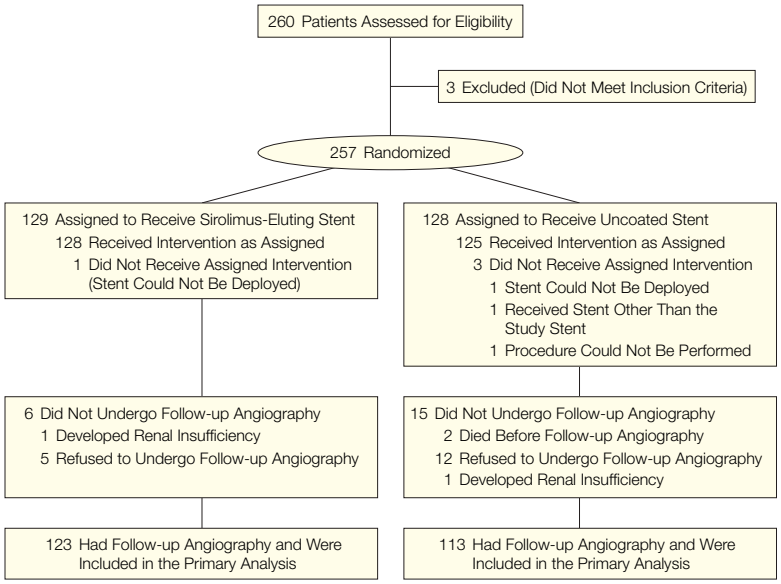
Figure 1. Trial Profile



have also shown the efficacy of drug-eluting stents under more challenging conditions such as long and complex lesions, and post hoc analyses of trial subpopulations suggest that drug-eluting stents may also effectively prevent restenosis in small vessels.[9-11]

This randomized, multicenter, prospective trial was designed to test the hypothesis that the implantation of a sirolimus-eluting stent in small coronary arteries is associated with a reduced 8-month rate of angiographic restenosis in comparison with the implantation of an uncoated stent having an identical architecture.

METHODS

Patients

Eligible patients had to be aged 18 years or older, with a documented diagnosis of acute coronary syndrome (without persistent ST-segment elevation), stable angina pectoris, or silent myocardial ischemia as shown by exercise stress test. Additional eligibility criteria were the presence of a single, previously untreated 50% to 99% target lesion in a native coronary artery 2.75 mm in diameter or less, which could be completely covered by a single stent (maximum length, 33 mm). The patients could have had single-vessel or multivessel disease but, in the latter case, had to have the nonrandomized lesion located in other coronary vessels.

Major exclusion criteria were recent ST-segment elevation acute coronary syndrome (within the previous 15 days), severe calcifications or thrombus-containing lesions, a left ventricular ejection fraction less than 30%, and known allergies to aspirin, clopidogrel, ticlopidine, heparin, stainless steel, contrast agents, or sirolimus. The study protocol was approved by the ethics committee of each participating center, and all patients gave written informed consent.

Randomization and Interventions

Online quantitative coronary angiography confirming vessel diameter and lesion-length enrollment criteria was performed before randomization. An automated telephone randomization system was used to assign the patients to treatment with a sirolimus-eluting stent (Cypher balloon-expandable stent; Cordis, Miami Lakes, Fla) or an uncoated stent of identical architecture and radiographic appearance (Bx Sonic balloon-expandable stent; Cordis), in a 1:1 ratio according to a centralized list. The randomization list was generated for a completely randomized design, ie, without blocks or stratification factors, using the SAS PLAN (SAS Institute Inc, Cary, NC) procedure. The investigators had to digitize patient date of birth, site number, vessel size, and stent length by means of an interactive voice recording system to obtain the assigned treatment. Data were confirmed by fax, which was included in the case report form.

Diameters of both types of stents were 2.25, 2.50, and 2.75 mm, and lengths were 8, 13, 18, 23, 28, and 33 mm. The 2 types of stents were visually and angiographically indistinguishable. The lesions were treated by using standard interventional techniques, including mandatory balloon dilatation before stent placement.

Before the index procedure, all patients received oral aspirin once daily and clopidogrel (a loading dose of 300 mg at least 2 hours before the procedure). Patients who had been pretreated with ticlopidine (250 mg twice a day) or clopidogrel (75 mg once daily) for at least 72 hours did not receive a clopidogrel loading dose. During the procedure, heparin was given as a bolus at 70 U/kg, with additional boluses to maintain an activated clotting time of more than 250 seconds. The use of glycoprotein IIb/IIIa inhibitors was encouraged but left to the discretion of the attending physician. Heparin administration was discontinued immediately after the procedure.

A 12-lead electrocardiogram was obtained before the procedure, immediately afterward, and 24 hours later or at discharge if earlier. Cardiac enzymes creatine kinase (CK) and CK-MB were evaluated twice within 8 to 16 and 18 to 24 hours of the procedure or at hospital discharge if earlier. Discharged patients received a regimen of aspirin (100 mg once daily indefinitely) and clopidogrel (75 mg once daily for at least 2 months). All patients were clinically followed up after 1 and 8 months by the trial coordinator at each site. Follow-up coronary angiography was performed after a mean (SD) of 8 (0.5) months.

Quantitative Coronary Angiography

Coronary angiograms obtained at baseline, on completion of the stenting procedure, and after 8 months were analyzed with a computer-based algorithm developed by MEDIS (version 5.1) (MEDIS, Medical Imaging System, Leiden, the Netherlands). The projection that best showed the stenosis in its tightest view was used for all angiograms; all details of the angiographic procedure were recorded in the case report forms. For standardization, each angiogram sequence was preceded by an intracoronary injection of 200 µg of nitroglycerin. Quantitative angiographic analyses were performed by 1 experienced cardiologist who was blinded to the patient's identity, type of stent used, outcome, and film sequence. The minimal luminal diameter (MLD) and the nearest normal reference diameter (RVD) were measured in millimeters by using the catheter as a scaling factor. Percentage of stenosis was calculated as 100 (1 – MLD/RVD). Binary restenosis was defined as a stenosis of more than 50% of the MLD in the target lesion at angiographic follow-up. Acute gain was defined as the difference between the MLD after stent implantation and baseline MLD. Late luminal loss was defined as the difference between the MLD at the end of the stenting procedure and that measured during follow-up. The late loss index was defined as late loss divided by acute gain. Quantitative angiographic measurements of the target lesion were obtained in the "in-stent" zone (including only the stent segment) and in the "in-segment" zone (including the stented segment and the 5-mm margins proximal and distal to the stent); intraobserver and interobserver variabilities of the quantitative assessments have been previously reported.[12]

Outcomes

The primary end point of the study was the 8-month angiographic binary in-segment restenosis rate. Secondary end points were procedural success, 8-month in-segment MLD, late luminal loss, late loss index, and major adverse cardiac and cerebrovascular events. Procedural success was defined as the achievement of a residual in-stent stenosis of less than 30% associated with thrombolysis in myocardial infarction 3 flow, in the absence of a dissection of more than D1, a grade according to the National Heart, Lung, and Blood Institute classification, without the occurrence of death, myocardial infarction, or repeated target lesion revascularization during hospitalization. Major adverse cardiac and cerebrovascular events were defined as cardiac death, myocardial infarction (Q wave and non–Q wave), cerebrovascular accident, emergency or elective coronary artery bypass grafting, or emergency or elective repeated percutaneous transluminal coronary intervention of the target lesion. All deaths were considered cardiac unless an unequivocal noncardiac cause could be established. Q-wave myocardial infarction was defined as the occurrence of prolonged chest pain with an increase in the CK-MB fraction of more than 3 times the upper normal limit and the develop-

Table 1. Clinical and Angiographic Characteristics of the Patients

	All Patients (n = 257)	Sirolimus Stent Group (n = 129)	Uncoated Stent Group (n = 128)	*P* Value
Demographics, No. (%)				
Age, mean (SD), y	63.6 (11.27)	63.2 (11.5)	63.7 (10.9)	.68
Male sex, No. (%)	184 (71.6)	99 (76.7)	85 (66.4)	.07
Risk factors, No. (%)				
Diabetes mellitus	64 (24.9)	25 (19.4)	39 (29.7)	.06
Hypertension	165 (64.7)	84 (65.1)	81 (64.3)	.85
Hyperlipidemia*	162 (63)	79 (61.2)	83 (64.8)	.54
Current smoking	42 (16.3)	24 (18.6)	18 (14.1)	.32
History, No. (%)				
Acute coronary syndromes without ST-segment elevation	109 (42.3)	63 (48.8)	46 (35.8)	.06
Chronic stable angina pectoris	119 (46.4)	56 (43.4)	63 (49.6)	
Silent myocardial ischemia	29 (11.3)	10 (8.0)	19 (14.6)	
Previous myocardial infarction	74 (28.8)	38 (29.5)	36 (28.1)	.81
Previous percutaneous coronary intervention	55 (21.5)	26 (20.3)	29 (22.7)	.65
Previous coronary artery bypass surgery	21 (8.2)	13 (10.2)	8 (6.3)	.26
Diseased vessels				
1	90 (35.2)	47 (36.4)	43 (33.9)	.91
2	93 (36.3)	46 (35.7)	47 (37.3)	
3	73 (28.4)	36 (27.9)	37 (29.1)	
Target artery, No. (%)				
Left anterior descending coronary artery	71 (27.5)	41 (31.5)	30 (23.6)	.32
Diagonal coronary artery	23 (9.2)	13 (10.3)	10 (7.9)	
Left circumflex coronary artery	77 (29.9)	32 (24.4)	45 (35.4)	
Obtuse marginal coronary artery	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 class), No. (%)				
A	63 (24.6)	30 (23.3)	33 (25.8)	.48
B1	120 (46.7)	60 (46.5)	60 (46.9)	
B2	52 (24.5)	31 (24.2)	32 (25.0)	
C	11 (4.3)	8 (6.2)	3 (2.3)	
Diameter of reference vessel, mean (SD), mm				
Interpolated	2.20 (0.28)	2.22 (0.29)	2.17 (0.26)	.15
Lesion length	11.84 (6.15)	13.01 (6.53)	10.66 (5.51)	.002

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association.
*Hyperlipidemia was defined as a low-density lipoprotein cholesterol level above 130 mg/dL (3.7 mmol/L).

ment of new abnormal Q waves: non–Q-wave myocardial infarction was defined as the absence of the latter. Target lesion revascularization was defined as repeated emergency or elective percutaneous transluminal coronary intervention or emergency or elective coronary artery bypass grafting performed because of restenosis of the target lesion in association with angina, objective evidence of myocardial ischemia, or both. A cerebrovascular accident was defined as the sudden onset of vertigo, numbness, aphasia, or dysarthria persisting for more than 24 hours.

Stent thrombosis was defined as an angiographic thrombus within the stented vessel at a clinically driven angiographic restudy for documented myocardial ischemia.

All major adverse cardiac and cerebrovascular events and stent thrombosis were determined for the in-hospital period, from hospital discharge up to 8 months, and cumulatively for all of the 8-month follow-up period; they were assessed by an independent clinical events committee unaware of treatment assignment.

Statistical Methods

On the basis of the available data concerning the restenosis rate in small arteries, it was calculated that the sample size required to demonstrate a 66% reduction in restenosis (from 30% to 10%) by means of a 2-sided test with an α error of .05 and a β error of .10 was 103 patients per group. To compensate for unsuccessful interventions and losses to follow-up, the sample size was increased by 25% to 128 patients per group.

The continuous variables were compared between groups by using the *t* test. Categorical variables were compared using the χ^2 test. The binary study end points were analyzed using the Fisher exact test; the relative risks or odds ratios and their 95% confidence intervals (CIs) are also reported. All of the statistical analyses were performed using SAS software (version 6.12; SAS Institute) on the basis of the intention-to-treat principle, ie, the primary analysis included all of the patients randomized to 1 of the 2 treatments and for whom follow-up coronary angiography was available, regardless of treatment actually received. Because of some imbalances in baseline characteristics, the main study results were confirmed by means of stratified analyses and by multivariable logistic regression analysis. Differences were considered statistically significant at $P<.05$ (2 tailed).

RESULTS

The trial profile is shown in FIGURE 1.

Between August 2002 and February 2003, 260 patients were enrolled in 20 Italian centers. Three patients were not randomized because of the discovery of exclusion criteria that became apparent only after enrollment. The final patient cohort therefore included 257 patients: 129 in the sirolimus-eluting stent group and 128 in the uncoated stent group.

Characteristics of the patients, lesions, and procedures are reported in TABLES 1 and 2. The groups were generally well matched in terms of patient and lesion characteristics; however, the patients treated with sirolimus-eluting stents had longer target lesions and therefore received longer stents. Procedural success rates were excel-

Table 2. Characteristics of the Procedures

	All Patients (n = 257)	Sirolimus Stent Group (n = 129)	Uncoated Stent Group (n = 128)	*P* Value
Pharmacological intervention, No. (%)				
Pretreatment with thienopyridines	167 (65.1)	78 (61.8)	88 (68.5)	.25
Clopidogrel loading dose	90 (34.9)	49 (38.2)	40 (31.5)	.25
Glycoprotein IIb/IIIa antagonists	19 (7.4)	11 (8.5)	8 (6.3)	.48
Balloon predilatation, mean (SD)				
Diameter, mm	2.13 (0.26)	2.12 (0.26)	2.14 (0.27)	.52
Length, mm	17.26[4]	17.63 (3.96)	16.88 (4.02)	.13
Balloon-artery ratio	0.98 (0.15)	0.97 (0.15)	1.00 (0.16)	.09
Stent implantation, mean (SD)				
Diameter, mm	2.48 (0.17)	2.50 (0.18)	2.47 (0.16)	.14
Length, mm	15.87 (5.13)	16.99 (5.71)	14.73 (4.2)	<.001
Stent length/lesion length ratio	1.58 (0.64)	1.55 (0.64)	1.61 (0.64)	.45
Maximal inflation pressure, atm	13.53 (2.26)	13.38 (2.08)	13.67 (2.43)	.39

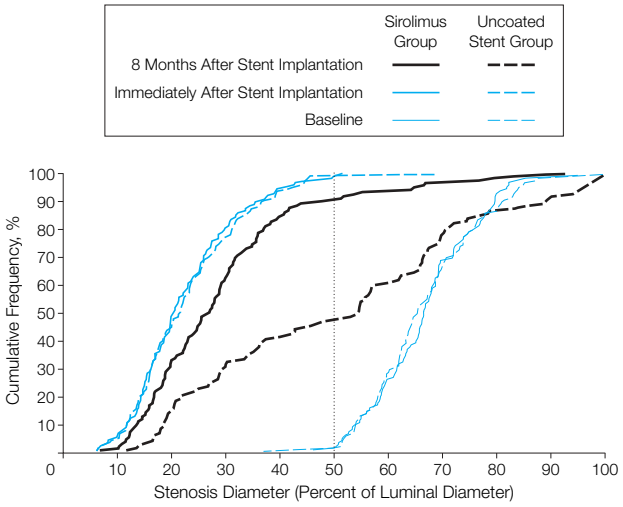
Table 3. Results of Quantitative Coronary Angiography

	In-Segment Zone			In-Stent Zone		
Variable	Sirolimus Stent	Uncoated Stent	*P* Value	Sirolimus Stent	Uncoated Stent	*P* Value
Binary restenosis, No. (%)	12 (9.8)	60 (53.1)	<.001	6 (4.9)	55 (49.1)	<.001
Minimal luminal diameter, mean (SD), mm						
Before procedure	0.73 (0.23)	0.71 (0.23)	.48	0.73 (0.23)	0.71 (0.23)	.48
After procedure	1.84 (0.36)	1.79 (0.34)	.21	2.16 (0.24)	2.14 (0.24)	.39
After 8 mo	1.70 (0.48)	1.09 (0.6)	<.001	2.01 (0.43)	1.20 (0.64)	<.001
Stenosis, luminal diameter, mean (SD), %						
Before procedure	66.88 (9.52)	66.83 (10.35)	.96	66.88 (9.52)	66.83 (10.35)	.96
After procedure	22.39 (9.62)	22.93 (10.32)	.66	11.33 (6.53)	10.53 (5.6)	.29
After 8 mo	29.26 (15.84)	50.78 (25.83)	<.001	17.22 (14.79)	46.49 (27.73)	<.001
Late luminal loss, mean (SD), mm	0.16 (0.46)	0.69 (0.61)	<.001	0.16 (0.38)	0.9 (0.62)	<.001
Loss index, mean (SD)	0.11 (0.5)	0.68 (0.68)	<.001	0.11 (0.29)	0.68 (0.49)	<.001

lent (>95%) and similar in both groups. The patients in both groups had small vessels, with a mean reference diameter of only 2.2 (SD, 0.28) mm.

Minimal luminal diameter and percentage of stenosis diameter at baseline and after stent implantation were similar in the 2 groups (TABLE 3). Follow-up angiographic data were available for 123 patients treated with sirolimus-eluting stents (95.3%) and 113 of those receiving uncoated stents (88.3%). After 8 months, the MLD, percentage of the stenosis diameter, late luminal loss, and the late loss index in the in-segment and in-stent zones improved more in the sirolimus-eluting stent group ($P<.001$ for all comparisons). The frequency of binary in-segment restenosis was 9.8% in the patients receiving sirolimus-eluting stents and 53.1% in those receiving uncoated stents (relative risk, 0.18; 95% CI, 0.10-0.32; $P<.001$); the frequency of binary in-stent restenosis was 4.9% and 49.1%, respectively (relative risk, 0.10; 95% CI, 0.04-0.22; $P<.001$). Cumulative frequency curves of in-segment percentage of the diameter of stenosis at baseline, after stent implantation, and at 8 months of follow-up are shown in FIGURE 2. In stratified analyses, the re-

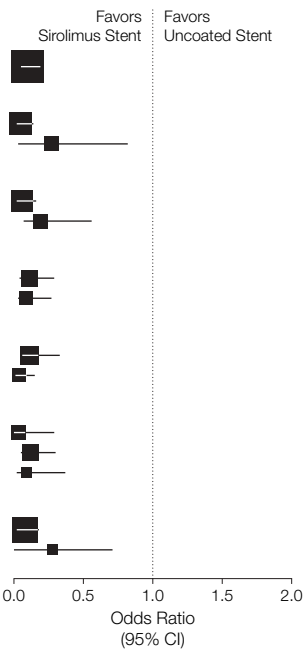
Figure 2. Cumulative Frequency of Stenosis



The cumulative frequency of the percentage of stenosis diameter at baseline, immediately after stent implantation, and after 8 months for patients receiving a sirolimus-eluting stent (solid lines) or an uncoated stent (dashed lines). Dotted line indicates threshold for restenosis.

Figure 3. Rates of Binary In-Segment Restenosis, Odds Ratios After 8 Months in the Patient Subgroups

Group	No. of Patients	Binary In-Segment Restenosis: Sirolimus Stent, No./Total, %	Binary In-Segment Restenosis: Uncoated Stent, No./Total, %	Odds Ratio (95% CI)
All	236	12/123 (9.8)	60/113 (53.1)	0.10 (0.05-0.19)
Sex				
Men	168	6/94 (6.4)	41/74 (55.4)	0.05 (0.02-0.14)
Women	68	6/29 (20.7)	19/39 (48.7)	0.27 (0.03-0.82)
Diabetes				
No	167	5/95 (5.3)	34/72 (47.2)	0.06 (0.02-0.17)
Yes	69	7/28 (25)	26/41 (63.4)	0.19 (0.07-0.56)
Clinical Presentation				
Chronic Stable Angina or Silent Ischemia	136	6/65 (9.2)	34/71 (47.9)	0.11 (0.04-0.29)
Acute Coronary Syndrome Without ST Elevation	100	6/58 (10.3)	26/42 (61.9)	0.06 (0.02-0.20)
Target Lesion in LAD Coronary Artery				
No	149	9/71 (11.3)	37/78 (47.4)	0.14 (0.06-0.33)
Yes	87	4/52 (7.7)	23/35 (65.7)	0.04 (0.01-0.15)
Stent Diameter, mm				
2.25	61	1/28 (3.6)	17/33 (51.5)	0.03 (0.00-0.29)
2.50	128	7/65 (10.8)	32/63 (50.8)	0.12 (0.05-0.30)
2.75	46	4/29 (13.8)	11/17 (64.7)	0.09 (0.02-0.37)
Stent Length, mm				
8, 13, 18	203	7/97 (7.2)	53/106 (50.0)	0.08 (0.03-0.18)
23, 28, 33	33	5/26 (19.2)	7/7 (100.0)	0.28 (0.00-0.71)*



CI indicates confidence interval; LAD, left anterior descending. The size of the data markers is proportional to the number of patients.
*Median unbiased exact odds ratio.

duction of risk of restenosis with the sirolimus-eluting stent in comparison with the uncoated stent was independent of sex, diabetes mellitus status, clinical presentation (acute coronary syndrome vs chronic stable angina or silent myocardial ischemia), epicardial vessel location, stent diameter, and stent length (FIGURE 3). Similarly, in a multivariable logistic regression model, treatment with a sirolimus-eluting stent was associated with a markedly lower rate of restenosis (adjusted odds ratio, 0.11; 95% CI, 0.05-0.24; $P<.001$).

The major in-hospital, out-of-hospital, and cumulative 8-month adverse cardiac and cerebrovascular event rates are listed in TABLE 4. There were 2 deaths in the uncoated stent group (one caused by pneumonia and the other by stroke followed by pneumonia) and none in the sirolimus stent group. The cumulative frequency of myocardial infarction was lower in the sirolimus stent group (relative risk, 0.20; 95% CI, 0.01-0.93; $P=.04$). Target lesion revascularization was performed less frequently in the patients receiving sirolimus-eluting stents (relative risk, 0.33; 95% CI, 0.14-0.70; $P=.002$). Major adverse cardiac and cerebrovascular events were less frequently observed in the sirolimus stent group (relative risk, 0.30; 95% CI, 0.15-0.55; $P<.001$). Stent thrombosis was infrequent and occurred in 2 patients during hospital stay, 1 in the sirolimus stent group and 1 in the uncoated stent group; out-of-hospital stent thrombosis occurred in 3 of the patients receiving the uncoated stents and in none of the sirolimus stent group (relative risk, 0.26; 95% CI, 0.1-2.3). One of the non–Q-wave myocardial infarctions that occurred during hospitalization in the sirolimus stent group was clearly unrelated to the target lesion, as was the related stent thrombosis.

COMMENT

Percutaneous coronary revascularization by means of balloon angioplasty has a lower primary success rate and a higher restenosis rate in small coronary arteries than in large vessels.[1-3] Restenosis in small coronary arteries may be as high as 50%, as an inverse relationship between vessel size and angiographic restenosis has reported.[4,5] Stenting has become the major means of percutaneous coronary revascularization because it has been demonstrated to be superior to balloon angioplasty in preventing restenosis of new focal lesions in large coronary arteries,[13,14] but conflicting results have been reported about efficacy in small vessels.[15-20] Potential explanations for the lack of efficacy of coronary angioplasty with or without stent implantation in preventing restenosis in small vessels may be related to characteristics of patients harboring atherosclerotic small-vessel lesions, ie, women, diabetic patients, the elderly, and patients with peripheral vascular disease, all of whom are associated with a higher risk of restenosis.[21,22] Another possible explanation may be related to the narrow diameter of the vessels, which cannot accommodate even minimal neointimal hyperplasia after angioplasty or stent deployment without becoming restenotic.

Given their ability to deliver prolonged and sufficient intramural drug concentrations to target coronary segments, drug-eluting stents are able to dramatically reduce neointimal hyperplasia,[23,24] and this specific mechanism may be particularly useful in reducing restenosis in small coronary arteries.

The results of the present study demonstrate that the implantation of a sirolimus-eluting stent to treat atherosclerotic lesions of small coronary arteries is safe, effective, and associated with a lower incidence of angiographic restenosis in comparison with an uncoated stent. Because the 2 stents had an identical architecture, the only difference between them was the release of sirolimus, which reduced the rate of angiographic restenosis from 53.1% to 9.8%, with a relative risk reduction of 82%. The high restenosis rate observed in the uncoated stent group may partially account for the high absolute and relative risk reduction; however, this rate

Table 4. Major Adverse Cardiac and Cerebrovascular Events in and Outside Hospital and Cumulatively During the 8 Months of Follow-up

	No. (%)						
	In-Hospital		From Discharge to 8 mo		Cumulative		
Variable	Sirolimus Stent (n = 129)	Uncoated Stent (n = 128)	Sirolimus Stent (n = 129)	Uncoated Stent (n = 128)	Sirolimus Stent (n = 129)	Uncoated Stent (n = 128)	*P* Value*
Death	0	0	0	2 (1.6)	0	2 (1.6)	.24
Myocardial infarction	2 (1.6)	3 (2.3)	0	7 (5.5)	2 (1.6)	10 (7.8)	.04
Q wave	0	0	0	2 (1.6)	0	2 (1.6)	.24
Non–Q wave	2 (1.6)	3 (2.3)	0	5 (3.9)	2 (1.6)	8 (6.3)	.06
Target lesion revascularization	0	0	9 (7)	27 (21.1)	9 (7)	27 (21.1)	.002
Surgical revascularization	0	0	0	2 (1.6)	0	2 (1.6)	.24
Percutaneous revascularization	0	0	9 (7)	25 (19.5)	9 (7)	25 (19.5)	.005
Cerebrovascular accident	0	0	1 (0.8)	1 (0.8)	1 (0.8)	1 (0.8)	>.99
Any major adverse cardiac or cerebrovascular event	2 (1.6)	3 (2.3)	10 (7.8)	37 (28.9)	12 (9.3)	40 (31.3)	<.001
Stent thrombosis	1 (0.8)	1 (0.8)	0	3 (2.4)	1 (0.8)	4 (3.1)	.21

**P* values refer to cumulative events from index procedure to 8 months of follow-up.

of restenosis is not all that surprising, given the high-risk population and high-risk lesions treated. Nevertheless, the 9.8% restenosis rate in the sirolimus-eluting stent group is also remarkably low. Previous post hoc analyses of the effect of overlapping sirolimus-eluting stents in small vessels revealed less satisfactory results (18.4% of restenosis in vessels with an average diameter of 2.32 mm).[9] The use of adequately sized single stents that were almost 60% longer than the lesion may explain the remarkably low restenosis rate.

Not only was there a reduction in the risk of angiographic restenosis but also a lower rate of major adverse cardiovascular events, mainly because of the decreased incidence of ischemia-driven target-lesion revascularization and myocardial infarction. Why the implantation of a sirolimus-eluting stent may prevent the development of myocardial infarction remains unclear and needs to be confirmed. The beneficial effects of the sirolimus-eluting stent were achieved without any increase in complications, including stent thrombosis, which is a feared event, particularly in patients receiving stents in small vessels.

This was a single-blind, randomized trial, and therefore the cardiologists performing the procedure knew whether the patients were receiving a drug-eluting or an uncoated stent. However, the risk of a selection bias was minimized by the completely randomized design. Furthermore, because patients and the angiographic core laboratory personnel were blinded to the assigned treatment, symptom reporting and the angiographic results should not have been influenced by the open-label design.

Another possible limitation is related to the comparator bare-metal stent used. A different comparator with thinner struts might have led to a lower incidence of restenosis in the uncoated stent group. However, our purpose was to compare 2 angiographically indistinguishable stents with the same architecture to verify the effect of the eluting drug.

Despite these limitations, we found that in a highly challenging condition, namely, revascularization of small coronary arteries in patients with stable angina pectoris or acute coronary syndrome without ST-segment elevation, the use of sirolimus-eluting stents likely represents an advance in the prevention of angiographic restenosis and the short-term recurrence of adverse cardiac events. To establish their long-term efficacy and cost-effectiveness in the treatment of small coronary arteries, extended follow-up is required.

Author Contributions: Dr Ardissinio had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Independent Statistical Analysis: Drs Ardissino and Cavallini and the contract research organization (CRO) Mediolanum Cardiovascular Research had direct access to the raw data. The statistical analysis was performed by Erminio Bonizzoni, who is an academic statistician at the University of Milan. For this project he worked with Fabio Bravi (another independent statistician) as consultants for Mediolanum Cardiovascular Research. The statistical analyses were made independently of the sponsor, which had no access to the data. However, another academic statistician, Silavano Milani, not employed by the sponsor and without any relationship with the CRO, repeated the statistical analyses and provided written confirmation that the results are correct.
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> Probably . . . the larger part of the labour of an author in composing his work is critical labour; the labour of sifting, combining, constructing, expunging, correcting, testing: this frightful toil is as much critical as creative.
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> —T. S. Eliot (1888-1965)