

CLINICAL RESEARCH

Interventional Cardiology

Long-Term Outcome in Patients Treated With Sirolimus-Eluting Stents in Complex Coronary Artery Lesions

3-Year Results of the SCANDSTENT (Stenting Coronary Arteries in Non-Stress/Benestent Disease) Trial

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- Objectives** Our purpose was to evaluate the long-term use of sirolimus-eluting stents (SES) and bare-metal stents (BMS) in patients with complex coronary artery lesions.
- Background** Although the use of SES has proved to be effective in patients with simple coronary artery lesions, there are limited data of the long-term outcome of patients with complex coronary artery lesions.
- Methods** We randomly assigned 322 patients with total coronary occlusions or lesions located in bifurcations, ostial, or angulated segments of the coronary arteries to have SES or BMS implanted.
- Results** At 3 years, major adverse cardiac events had occurred in 20 patients (12%) in the SES group and in 59 patients (38%) in the BMS group ($p < 0.001$). Four versus 2 patients suffered a cardiac death ($p = \text{NS}$), and 5 versus 1 died of a noncardiac disease ($p = \text{NS}$) in the SES versus the BMS group. Six patients in the SES group versus 15 patients in the BMS group suffered a myocardial infarction ($p < 0.05$) during the 3-year observation period, and target lesion revascularization was performed in 8 patients (4.9%) versus 53 patients (33.8%), respectively ($p < 0.001$); of these, 4 in the SES versus 7 in the BMS group were performed between 1 and 3 years after the index treatment ($p = \text{NS}$). According to revised definitions, stent thrombosis occurred in 5 patients (3.1%) in the SES group and in 7 patients (4.4%) in the BMS group ($p = \text{NS}$); very late stent thrombosis was observed in 4 versus 1 patient.
- Conclusions** A continued benefit was observed up to 3 years after implantation of SES in patients with complex coronary artery lesions. The rate of late adverse events was similar in the 2 groups, and stent thromboses occurred rarely after 1 year. (Sirolimus Eluting Stents in Complex Coronary Lesions [SCANDSTENT]; [NCT00151658](https://clinicaltrials.gov/ct2/show/study/NCT00151658)) (J Am Coll Cardiol 2008;51:2011-6) © 2008 by the American College of Cardiology Foundation

Drug-eluting stents (DES) reduce the rate of both angiographic and clinical restenosis in simple coronary artery lesions (1-3), whereas the experience of their use in complex lesions is limited (4,5). Patients with total coronary occlusions and lesions located in bifurcations, ostial regions, or angulations have been consequently excluded from most previous trials, and recommendations for DES have there-

fore been limited to on-label use in rather simple coronary artery lesions (6).

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Late adverse events recently have been indicated to occur more frequently in patients who have DES implanted compared with those who have received bare-metal stents (BMS) (7-10). Long-term follow up of different categories of patients and lesions is therefore warranted. The authors of the SCANDSTENT (Stenting Coronary Arteries in Non-Stress/Benestent Disease) trial reported improved short-term clinical and angiographic outcomes after im-

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Abbreviations and Acronyms

BMS = bare-metal stent(s)
DES = drug-eluting stents
MACE = major adverse cardiac events
MI = myocardial infarction
PCI = percutaneous coronary intervention
SES = sirolimus-eluting stent(s)
TLR = target lesion revascularization

plantation of 1 or more sirolimus-eluting stents (SES) compared with BMS in patients with complex coronary artery lesions (11), and a recent report focused upon the short-term clinical course after changing from dual- to mono-antiplatelet therapy (12). The present study was undertaken to reveal the long-term clinical outcome after SES versus BMS implantation in SCANDSTENT patients with complex coronary lesions, with special attention given to events occurring 1 to 3 years

after the index treatment, during which a vast majority of the patients were on antithrombotic monotherapy.

Methods

Study design. The trial was conducted at 4 Danish centers with invasive cardiology. The objective of this study was to compare the 3-year clinical outcome in patients participating in the SCANDSTENT trial who had been randomized to have either an SES or BMS implanted in their complex coronary artery lesions. Criteria for inclusion and exclusion of patients have been described elsewhere (11). In brief, patients with symptomatic coronary artery disease and at least 1 complex lesion in a native coronary vessel were included provided they had at least 1 total or subtotal occlusion, a bifurcation lesion with a side branch of significant size, a lesion located in an ostium, or a lesion located in a tortuous segment of a coronary artery. No restrictions were applied with regard to vessel size or lesion length. Exclusion criteria were myocardial infarction (MI) <3 days before the procedure or lesions in unprotected left main stems or in bypass grafts. The protocol was approved by the local ethics committees, and all patients consented to participate in writing.

Study procedures. After pre-dilation of the lesions, patients were randomized by computerized assignment stratified with regard to gender and the presence of diabetes. The Bx Velocity balloon-expandable stent (Cordis/Johnson & Johnson, Miami Lakes, Florida) or the Cypher balloon-expandable stent (Cordis/Johnson & Johnson) was implanted in the lesions under high pressure (>12 atms). Long lesions and dissections were treated with supplementary stents of the same type as the one(s) implanted in the index lesion. Bifurcations were treated as previously described (13). Stenting of the side branch in bifurcations was performed at the discretion of the operator attempting to keep the side branch open. Heparin was administered to maintain the activated clotting time at >250 s during the procedure, and all patients were treated with clopidogrel for at least 1 year after the procedure and aspirin indefinitely.

Glycoprotein receptor antagonists were used at the discretion of the operator. In patients who underwent percutaneous coronary intervention (PCI) again or a nontarget lesion PCI in the follow-up period, clopidogrel was continued for 12 months after the last stent implantation.

Follow-up. Reangiography was performed in connection with recurrent symptoms and in any case at 6 months, and all patients were followed clinically for 3 years after stent implantation. In case of rehospitalization of the patients, the course was carefully monitored by the study coordinator to identify any target vessel involvement.

Study end points and definitions. The primary end point of the original trial was an angiographic reduction in the minimal lumen diameter of the target lesion (11). The focus of this study was the occurrence of major adverse cardiac events (MACE) and stent thrombosis within 3 years after stent implantation. Major adverse cardiac events were defined as death from any cause, MI, and target lesion revascularization (TLR). An MI was defined as the development of new Q waves lasting ≥ 0.4 s in at least 2 contiguous leads and/or an increase in blood concentrations of creatine kinase (total) ≥ 2 times the upper normal limit with a concomitant increase in creatine kinase-myocardial band blood concentration. Target lesion revascularization was defined as repeat revascularization, PCI within 5 mm proximally or distally to the stent or coronary bypass surgery of the target vessel, including side branches of bifurcations in the presence of myocardial ischemia, or a >70% target lesion diameter stenosis (regardless of symptoms). A target vessel revascularization included both TLR and repeat revascularization in the target vessel remote of the target lesion. A stent thrombosis was considered definite in the case of an acute coronary syndrome with angiographically visible signs of a contrast filling defect or occlusion of the target lesion according to definitions suggested by the Academic Research Consortium (10). Probable stent thromboses included any unexplained death within 30 days or a target vessel MI (without angiographic documentation). A possible stent thrombosis was present in case of any unexplained death later than 30 days after stent implantation. Early stent thrombosis occurred within 1 month, late stent thrombosis from 1 to 12 months, and very late stent thrombosis after 1 year.

Statistical analysis. The original study was powered to detect a significant increase in the target lesion minimal lumen diameter in the SES compared with the BMS group. In addition, the inclusion of 300 patients was sufficient to detect a 40% reduction in MACE in the 2 groups with a power of 80% and a type 1 error of 0.05. Differences in categorical variables were analyzed with the use of the Fisher exact test, and continuous variables were analyzed with the Student *t* test for unpaired samples. The Kaplan-Meier method was used to create survival estimates, and the log-rank test was used to test differences in these estimates. Univariate odds ratio and 95% confidence intervals for categorical values were calculated using 2×2 tables. All

Table 1 Demographic Data of the Patients

	SES (n = 163)	BMS (n = 159)	p Value
Age (yrs)	62.9 (9.2)	62.5 (9.4)	0.94
Male gender (%)	74	79	0.30
Diabetes (%)	18	18	0.90
Hypertension (%)	46	38	0.21
Hyperlipidemia (%)	81	84	0.46
Previous myocardial infarction (%)	54	50	0.58
Unstable angina (%)	25	26	0.70
Multivessel disease (%)	43	45	0.29
Coronary artery, LAD/CX/RCA (%)	45/25/30	53/23/24	0.31
Lesion length (mm)	18.8 (13.0)	17.2 (11.1)	0.43

Numbers are mean values with SD in parentheses.
 BMS = bare-metal stent; CX = circumflex artery; LAD = left anterior descending artery; RCA = right coronary artery; SES = sirolimus-eluting stent.

analyses were performed with the use of the SPSS statistical package version 15 (SPSS Inc., Chicago, Illinois). All p values were 2-sided.

Results

Of the 322 patients included in the trial, 3 patients were excluded from the analyses because of technical problems as previously described (11). All events, even those occurring after TLR, were imputed to the original treatment group, according to the intention-to-treat principle.

MACE. The patients were well matched with regard to clinical characteristics (Table 1). Within 3 years, 9 patients in the SES group and 3 patients in the BMS group died (p = 0.06), of which 4 were cardiac deaths (1 probable and 3 possible stent thromboses) in the SES group versus 2 cardiac deaths (1 definite stent thrombosis and 1 due to progressive heart failure) in the BMS group. Five deaths in the SES group were noncardiac (3 the result of cancer of the liver, prostate, and colon; 1 the result of pneumonia; and 1 the result of rupture of an aortic aneurysm) versus 1 in the BMS group (the result of pneumonia).

During the 3-year follow-up period, MI was observed in 6 patients in the SES group versus 15 patients in the BMS group (p = 0.04). In 6 cases in the BMS group versus 1 case in the SES group, the MI was related to a stent thrombosis (definite or probable).

Target lesion revascularization was performed in 8 (4.9%) of the patients with a SES versus 53 (33.8%) of those with a BMS (p < 0.001) (Fig. 1). Restenosis in the SES group was treated with balloon angioplasty in 4 cases, with a new drug-eluting stent in 3 cases, and with coronary artery bypass surgery in 1 case. Restenosis in the BMS group was treated with a drug-eluting stent in 36 cases (SES in 83%), with balloon angioplasty in 10 cases, and with coronary artery bypass surgery in 2 cases, whereas 1 patient received another BMS and 1 patient no treatment. Four cases of TLR in the SES group and 7 in the BMS group were

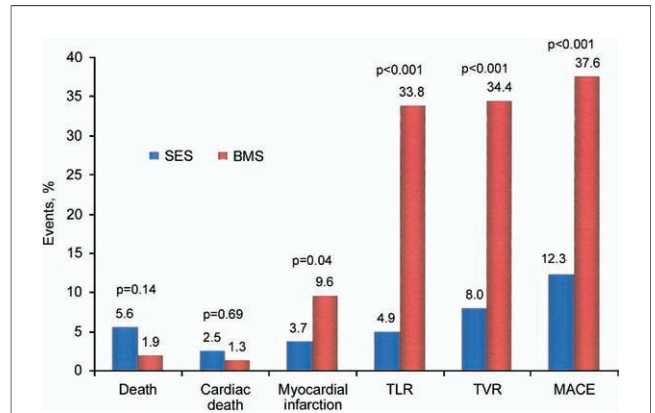


Figure 1 MACE Within 3 Years After Stent Implantation

Frequency of major adverse cardiac events (MACE) (i.e., death, myocardial infarction, and target lesion revascularization [TLR]), occurring 3 years after implantation of sirolimus-eluting stents (SES) and bare-metal stents (BMS). TVR = target vessel revascularization.

performed between 1 and 3 years after the index treatment. Of 29 patients who suffered a late event, 3 of 14 patients in the SES group (21%) versus 10 of 15 patients in the BMS group (67%) had had a previous event (p = 0.03).

During the 3-year period after stent implantation, MACE occurred in 20 patients (12.3%) in the SES group and in 59 patients (37.6%) in the BMS group (p < 0.001); therefore, the initial clinical improvement of SES compared with BMS implantation was continued during the whole observation period (Fig. 2).

Subgroup analysis. The results of the subgroup analysis demonstrated a long-term benefit of SES versus BMS implantation in all subsets of patients (Fig. 3). None of the

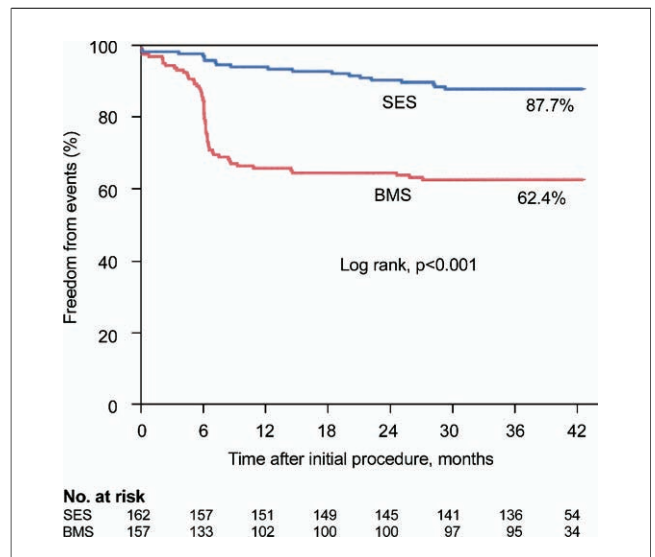


Figure 2 Kaplan-Meier Estimates of Survival Free From MACE

Abbreviations as in Figure 1.

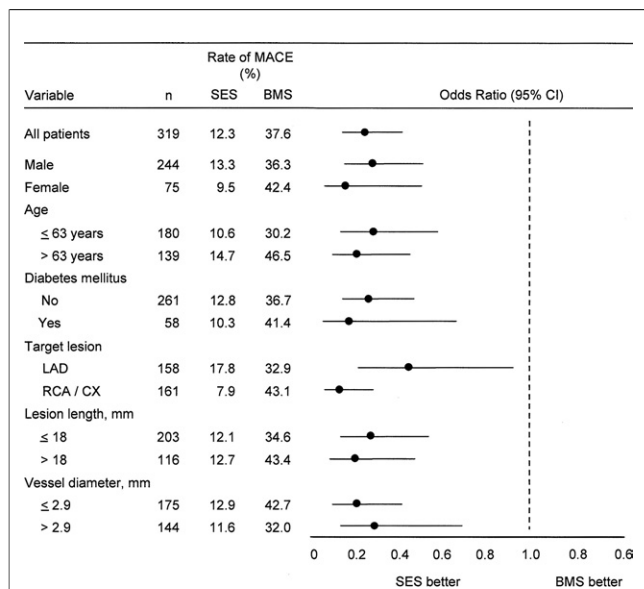


Figure 3 Subgroup Analysis for the 3-Year Rate of MACE

Odds ratios for the occurrence of MACE in the SES and BMS groups. CI = confidence intervals; CX = circumflex artery; LAD = left anterior descending artery; RCA = right coronary artery; other abbreviations as in Figure 1.

diabetic patients in the SES group had TLR performed during the 3-year period, and only 3 diabetics (10.3%) suffered MACE. Although some of the subgroups of lesion types were too small to show a significant difference, the same trend toward a lower rate of MACE in the SES versus the BMS group was observed in all types of complex lesions (Table 2).

Stent thrombosis. According to revised definitions, stent thrombosis occurred in 12 patients totally: 7 were classified as definite, 2 as probable, and 3 as possible stent thromboses (Table 3). At the time of stent thrombosis, 4 of 5 patients in the SES group were on single antiplatelet therapy, whereas 6 of 7 patients in the BMS group were on dual antiplatelet therapy. Of the definite stent thromboses, 6 occurred in a BMS, and very late stent thrombosis occurred in 4 patients (2.5%) in the SES group and 1 (0.6%) in the BMS group. With the exception of 1 patient who developed clopidogrel allergy, all patients who suffered a definite or a probable stent thrombosis were on clopidogrel treatment at the time of stent thrombosis.

Discussion

In this randomized study involving patients with complex coronary artery lesions, implantation of SES resulted in an improved clinical outcome after 3 years in comparison with that associated with the implantation of BMS. Implantation of SES markedly reduced the frequency of both TLR and MACE compared with BMS in our patients, and even from 1 to 3 years, both the occurrence of MI and TLR were significantly lower in the SES group. Thus, the clinical benefit of SES implantation reported after 6 months, with regard to reducing neointimal growth in the stent and thereby lowering the need for repeat revascularization, continued beyond the point when more than 95% of the patients had discontinued their dual antiplatelet therapy, without increasing the risk of late adverse events. These findings contribute to closing some of the gaps between approved indications for the use of DES and their real-world applications (14).

Death and MI. There seemed to be a trend toward an increase in death from any cause in the SES group compared with the BMS group in a 3-year follow-up of the RAVEL (Randomized Comparison of a Sirolimus-Eluting Stent With a Standard Stent for Coronary Revascularization) trial that included patients with simple coronary artery lesions, mainly because of a slight overweighting of noncardiac deaths occurring in the SES group (15). Although the present study was not powered to address hard end points, a similar unexplained trend toward greater all-cause mortality in the SES group urges a continued close monitoring of the clinical course of these patients. On the other hand, large-scale pooled analyses of randomized trials that compared long-term outcomes after implantation of drug-eluting stents versus BMS in a large variety of coronary artery lesions did not reveal any difference in either cardiac or noncardiac mortality (16–18). In addition, it is hard to explain a connection between the stent type and 3 deaths due to cancer, 1 due to pneumonia, and 1 due to aortic rupture in the SES group versus 1 death due to pneumonia in the BMS group.

We found a greater rate of MI in the BMS group that at least, to some extent, can be explained by an excess rate of definite stent thrombosis in the target lesion. On the other hand, we are unable to rule out that a MI might have occurred in connection with some of the cases of sudden death in the SES group. That MI occurs at similar frequen-

Table 2 MACE in Different Types of Lesions

	SES (n = 162)	BMS (n = 157)	p Value
Occlusions (n = 115), n (%)	4 (6.8)	23 (41.1)	<0.001
Bifurcations (n = 107), n (%)	11 (19.3)	19 (36.5)	0.054
Ostial lesions (n = 72), n (%)	4 (11.4)	14 (36.8)	0.014
Angulation (n = 25), n (%)	1 (8.3)	3 (23.1)	0.59
Total	20 (12.3)	59 (37.1)	<0.001

Abbreviations as in Table 1.

Table 3 Stent Thrombosis

	SES (n = 162)			BMS (n = 157)		
	Definite (%)	Probable (%)	Possible (%)	Definite (%)	Probable (%)	Possible (%)
Early	0	1 (0.6)	0	3 (1.9)	0	0
Late	0	0	0	3 (1.9)*	0	0
Very late	1 (0.6)	0	3 (1.9)	0	1 (0.6%)	0
Total	1 (0.6)	1 (0.6)	3 (1.9)	6 (3.8)	1 (0.6%)	0

*In 1 patient after target lesion revascularization.
 Abbreviations as in Table 1.

cies in patients treated with drug-eluting and BMS has been demonstrated in large-scale pooled analyses of the long-term outcome in patients included in randomized trials (16–20).

Antiplatelet therapy. Only few of the previous trials have focused on patients with lesions such as bifurcations, total occlusions, and ostial and angulated lesions (21,22); therefore, long-term experience is limited to patients with relatively simple coronary lesions (15,23,24). A comparison of our data with the 3-year clinical outcome of patients with very simple coronary lesions reveals a similar MACE rate in both patients treated with SES and BMS (15). On the other hand, it must be taken into consideration that all of our patients were treated with clopidogrel for 12 months after the index stent implantation as opposed to only 2 months in the RAVEL trial. In addition, as the result of a greater rate of multivessel disease, 10% of the SCANDSTENT patients were treated with PCI, including stent implantation, in a nontarget lesion after the first 12-month period and thus received dual antiplatelet therapy for an even longer period.

Stent thrombosis. Implantation of DES not only decreases neointimal hyperplasia but may induce pathological changes involving a process of delayed healing of the coronary artery wall not observed in association with the implantation of BMS (25). It was not until recently, however, that reports raised concerns about the use of DES because of a risk of late stent thrombosis and MI, especially in patients with complex disease or complex coronary artery lesions (7,9,26). Our patients all had complex coronary lesions and, thus, their clinical outcome contributes to the long-term experience with DES in patients with “off-label” lesions. Our study did not reveal any difference in the occurrence of stent thrombosis in the 2 groups but was, on the other hand, not powered to detect such a difference.

Late events and events after TLR. Almost 10% of the SCANDSTENT patients suffered an event between 1 and 3 years. In the SES group, a late event was considerably more likely to be a first event, whereas late events were second events in a majority of the BMS patients. Thus, previous events do not protect against events occurring later in the clinical course after BMS implantation in complex lesions.

As stressed by Mauri et al. (19), events occurring after TLR were previously censored according to protocol designs. Such events are as clinically relevant as those occur-

ring before TLR, and special attention should be paid to stent thromboses occurring after TLR (10). On the other hand, treatment of in-stent restenoses in BMS with brachytherapy or implantation of DES makes the interpretation of the long-term outcome of the initial treatment of these patients even more difficult.

Subgroup analyses. Subgroup analyses revealed a substantial effect in favor of SES implantation in all demographic subgroups of patients with complex coronary artery lesions, including those with diabetes. Thus, no signs of limited long-term effects of SES implantation in patients with this disease could be recorded, a finding that concurs with that of Sabaté et al. (27). In addition, the same tendency of treatment effect was found in all types of lesions.

Study limitations. The investigators initiated the study and were thus restrained from using identically appearing manufactured stents. In addition, we chose to inform the patients of the stent type they were allocated to. Thus, we have to take inherent methodologic limitations into consideration when interpreting the clinical outcomes. On the other hand, the primary end point of the original study was angiographic, and clinical end points were all adjudicated by a blinded clinical events committee. In addition, the study is strengthened by the fact that the manufacturer of the stents was not involved in any part of the process, including preparation of the protocol or case record form, monitoring, interpretation of the study results, or elaboration of the manuscript.

Conclusions

Sirolimus-eluting stent implantation, compared with BMS, improves the clinical outcome of patients and can be used safely in patients with a variety of complex lesions without any increase in delayed restenosis or excess rate of adverse events, including stent thrombosis, up to 3 years after stent implantation, although careful monitoring of some of the events is still necessary.

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