JACC: CARDIOVASCULAR INTERVENTIONS VOL. 2, NO. 6, 2009

ISSN 1936-8798/09/$36.00
PUBLISHED BY ELSEVIER INC. DOI: 10.1016/j.jcin.2009.03.013

CLINICAL RESEARCH

Impact of Target Lesion and Nontarget Lesion Cardiac Events on 5-Year Clinical Outcomes After Sirolimus-Eluting or Bare-Metal Stenting

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Objectives We sought to compare patient-oriented outcomes related to target vessel or nontarget vessel events for sirolimus-eluting stents (SES) versus bare-metal stents.

Background SES significantly reduce restenosis but the influence of reduced restenosis on overall patient-oriented outcome has not been reported.

Methods The study population included 1,057 patients randomized in the SIRIUS (Sirolimus-Eluting Stent in De Novo Native Coronary Lesions) study and followed clinically for 5 years. The primary end point was a composite of all-cause mortality, any myocardial infarction, or any repeat revascularization. In secondary analyses, myocardial infarction and repeat revascularization events attributed to the target vessel or a nontarget vessel were compared by stent type.

Results Patients with an SES were more likely to be free from the primary composite end point at 5 years (60.4% vs. 47.8%, $p < 0.001$) chiefly due to a sustained reduction in target lesion revascularization for SES (cumulative incidence: 12.5% vs. 28.8%, $p < 0.001$). There was no difference in the cumulative incidence of myocardial infarction or revascularization attributed to remote segments of the target vessel. Events attributed to the nontarget vessel were frequent and not different for SES versus bare-metal stents (25.7% vs. 25.8%).

Conclusions The benefit of SES over bare-metal stents for reduced target lesion revascularization is maintained for 5 years. Remote coronary segments of the target vessel and nontarget vessel remain an important cause of future adverse events despite sustained restenosis benefit. (J Am Coll Cardiol Intv 2009;2:498–503) © 2009 by the American College of Cardiology Foundation

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Manuscript received February 26, 2009, accepted March 4, 2009.

Drug-eluting stents (DES) have been shown to significantly reduce restenosis compared with bare-metal stents (BMS) (1–3). Despite the benefit in restenosis, there remains a concern for a small, but clinically significant increased risk for late and very late stent thrombosis (4). This balance in events of restenosis and stent thrombosis related to the target lesion has contributed to an overall risk for death or myocardial infarction (MI) that is not different between BMS and DES (5). Although the influence of safety and effectiveness outcomes related to the target lesion is important for assessment of the biologic effect of the device, a patient-oriented composite that includes all-cause mortality, any MI, and any revascularization, has been suggested as a more important measure of device influence on clinical outcome (6,7). We have reported previously that during 5-year follow-up of BMS clinical trial patients, outcomes after the first year are determined mostly by events attributable to disease progression unrelated to the target lesion (8). It has been questioned if restenosis itself may have an impact on these distant outcomes, due to increased surveillance for recurrent symptoms or adverse effects of repeat revascularization procedures. Furthermore, it has also been suggested that sirolimus-eluting stents (SES) may result in adverse events related to endothelial dysfunction remote from the stented coronary segments (9,10).

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We hypothesized that the events related to disease progression would be frequent but similar in BMS and SES patients. We sought to evaluate the affect of disease progression at sites remote from the target lesion on patient-oriented outcome for SES and BMS during 5-year follow-up of the SIRIUS (Sirolimus-Eluting Stent in De Novo Native Coronary Lesions) trial.

Methods

Study design. The study population included patients randomized in the SIRIUS study. The design of SIRIUS has been previously reported (1). After approval of the device by the U.S. Food and Drug Administration, study patients were to be followed for 5 years. Treatment assignment remained masked during the follow-up. Patients were queried by telephone interview, and in the case of potential clinical events, source medical documents were retrieved and reviewed.

For this study, all rehospitalizations and suspected clinical end points were reviewed and adjudicated according to the criteria recommended by the Academic Research Consortium for the patient-oriented composite, defined as all-cause mortality, any MI, and any repeat revascularization (6). Events were classified further according to attribution to a specific coronary segment based on the CASS (Coronary Artery Surgery Study) trial classification or to a coronary vessel if the specific segment could not be determined. Independent central core laboratory analyses were available for electrocardiography and coronary angiography at baseline and for suspected clinical events.

End point definitions and classification. The primary end point was the patient-oriented composite. Deaths were further categorized as cardiac unless a clear noncardiac cause was identified. Deaths could generally not be assigned to a specific coronary segment or vessel and were included as both target vessel and nontarget vessel events. Academic Research Consortium and Global Task Force recommendations (6,11) were used to define MI. Periprocedural MI was defined as creatine kinase-myocardial band >3 times the upper reference limit if after percutaneous coronary intervention or creatine kinase-myocardial band >5 times the upper reference limit after coronary artery bypass surgery, and spontaneous MI was defined as any signs or symptoms of acute myocardial ischemia with troponin or creatine kinase-myocardial band above the upper reference limit. Myocardial infarction was attributed to a CASS segment according to angiography if available or a specific vessel territory based on serial electrocardiograms at baseline and the time of the event. Repeat revascularization procedures were attributed to 1 or more CASS segments based on review of coronary angiography by the core laboratory. The target lesion was defined as the CASS segment containing the originally stented lesion. The target vessel was defined as the target lesion or any other CASS segment within the same epicardial vessel or 1 of its side branches. Segments of the target vessel not including the target lesion were termed target vessel remote segments. A nontarget vessel was defined as either of the epicardial coronary arteries not including the target lesion. For MI and repeat revascularization, events were attributed to the target vessel unless there was clear evidence of nontarget vessel involvement.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
MI = myocardial infarction
SES = sirolimus-eluting stent(s)
TLR = target lesion revascularization

Secondary end points included a target vessel composite, defined as any cardiac death, MI involving the target vessel territory, or target vessel revascularization, and a nontarget vessel composite, defined as any cardiac death, MI clearly attributable to a nontarget vessel, or nontarget vessel revascularization

Statistical analysis. The comparison of baseline characteristics between patients experiencing the primary end point and those who remained free of an end point event was performed using chi-square or Fisher exact test for dichotomous outcomes and Student *t* or Wilcoxon rank sum test for continuous outcomes. Event-free survival was estimated

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Table 1. Baseline Patient Characteristics

	No Primary End Point (n = 583)	Primary End Point (n = 474)	p Value
Sirolimus-eluting stent, %	56.3	43.2	<0.001
Age, mean ± SD, yrs	62.50 ± 11.08	61.92 ± 11.05	0.399
Male, %	69.8	72.8	0.306
Prior myocardial infarction, %	26.0	36.0	<0.001
Diabetes, %	23.2	30.2	0.011
Hypertension, %	67.0	68.6	0.596
Coronary artery bypass surgery, %	7.7	11.6	0.035
Hyperlipidemia, %	73.2	74.2	0.725
Left ventricular ejection fraction, mean ± SD, n	56 ± 10	56 ± 10	0.965

by Kaplan-Meier method and the comparison of survival curves between groups was performed using the log-rank test. Cox proportional hazards regression was used to evaluate for the association of baseline variables with the primary end point after confirmation of proportional hazard assumptions.

Results

Study patients and follow-up compliance. Of 1,058 patients enrolled in the SIRIUS trial, 1 patient with stenting involving a vein graft was excluded from this analysis. Complete 5-year follow-up for the mortality end point was available for 456 of 533 (86%) DES and 446 of 524 (85%) BMS patients. The mean follow-up duration was 1,689 ± 339 days for DES and 1,704 ± 296 days for BMS groups.

Clinical outcomes. Patients who experienced the primary end point were less likely to receive a SES and had a higher frequency of diabetes, prior MI, or prior bypass surgery (Table 1). The cumulative incidences for the primary end point and each of the components are shown in Table 2, and freedom from the primary end point over the 5-year follow-up is shown in Figure 1A. At 1 year, there was a significantly lower risk for the primary end point for the SES group and this difference was maintained at 5 years. This difference was driven by reduced target lesion revascularization (TLR) without a difference in target vessel revascularization remote from the target lesion, death, MI, or nontarget vessel revascularization throughout the 5-year follow-up. The survival curves for the secondary end point of target vessel outcome also demonstrated a significant difference by 1 year and were then also essentially parallel (Fig. 1B). The survival curves for the secondary end point of nontarget vessel outcomes overlapped throughout, demonstrating an annual hazard rate of approximately 5% to 6% per year for each stent type (Fig. 1C).

Table 2. 5-Year Outcomes of SES Versus BMS

	SES (n = 533)		BMS (n = 524)		
Event	n	Cumulative Incidence*	n	Cumulative Incidence*	p Value†
Patient-oriented composite	205	39.6	269	52.8	<0.001
Death, all causes	44	8.5	44	8.7	0.967
Cardiac death	20	4.0	19	3.7	0.889
Noncardiac death	24	4.5	25	5.0	0.858
Myocardial infarction	65	12.5	71	13.8	0.521
Target vessel	47	8.5	59	11.3	0.197
Nontarget vessel	18	3.6	12	2.5	0.284
Revascularization	165	32.3	230	45.0	<0.001
Target lesion	64	12.5	148	28.8	<0.001
Target vessel remote	59	11.7	78	15.0	0.069
Nontarget vessel	113	22.3	115	22.9	0.801

*Cumulative incidence (%) based on Kaplan-Meier estimate. †Comparison by log-rank.
BMS = bare-metal stent(s); SES = sirolimus-eluting stent(s).

The relative annual hazard rates for TLR, remote target vessel MI or revascularization, and nontarget vessel MI or revascularization are depicted for BMS and SES in Figure 2.

Predictors of the primary end point. The independent predictors of the primary end point are shown in Table 3. Assignment to SES remained as a significant protective factor for the patient-oriented composite end point during 5-year follow-up. Diabetes was a significant predictor, but the interaction of diabetes and stent type was not.

Discussion

During 5 years of clinical follow-up, patients randomized to receive a SES at the time of the index procedure were significantly less likely to suffer the patient-oriented composite outcome. This benefit proved to be entirely due to a reduction in TLR that was present after 1 year and sustained thereafter. All-cause mortality, cardiac mortality, and MI were all similar for the SES and BMS groups. A large proportion of events were attributed to a nontarget vessel, with over 25% of patients in each group sustaining a nontarget vessel event.

A patient-oriented composite has been proposed as the best reflection of overall benefit or harm when comparing alternative treatments such as DES versus BMS (6,7). Previous studies that have focused only on target lesion or

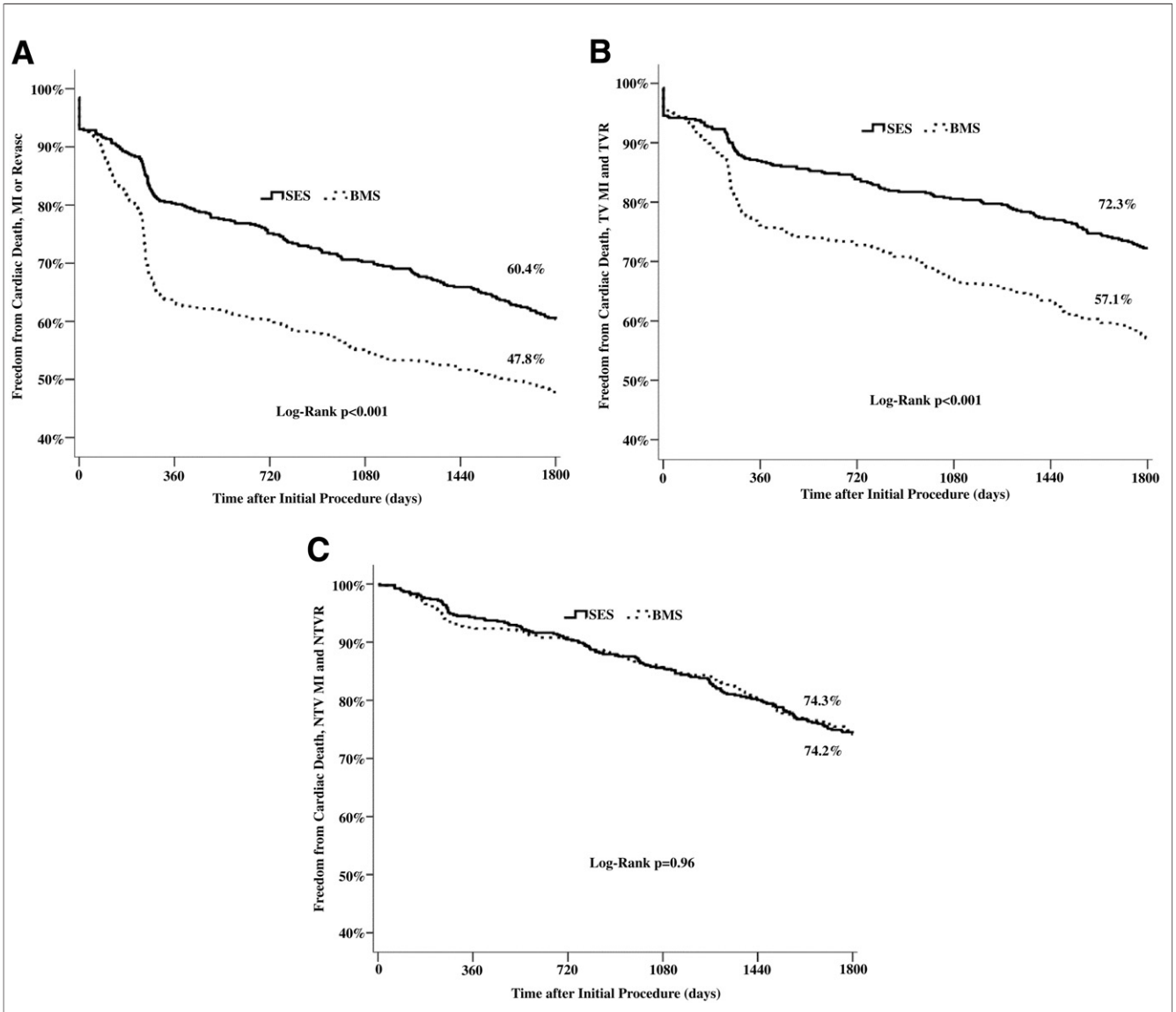

Figure 1. Kaplan Meier 5-Year Event-Free Survival Comparing SES Versus BMS

(A) Patient-oriented composite of all-cause mortality, any myocardial infarction (MI), or any repeat revascularization. **(B)** Freedom from cardiac death, MI involving target vessel territory (TV MI), or target vessel revascularization (TVR). **(C)** Freedom from cardiac death, MI involving nontarget vessel territory (NTV MI) or nontarget vessel revascularization (NTVR). **Solid lines** indicate sirolimus-eluting stents (SES) and **dashed lines** indicate bare-metal stents (BMS).

target vessel events fail to assess whether a reduction in restenosis has a significant impact on overall outcome, which is influenced not only by the balance of safety and effectiveness of the restenosis preventive therapy itself but also progression of disease at other sites. The large and sustained reduction in TLR for SES in the SIRIUS trial confirms previous reports (12–14) and was sufficient to result in a significant improvement in the patient-oriented composite.

Whereas the patient-oriented composite is a better measure of net risk and benefit, it is still limited by combining events of unequal severity, such as death and revascularization. In that regard, it is important to note that our study confirms a prior report of a pooled analysis of 4-year outcomes by Stone et al. (5) that showed no significant difference between SES and BMS in all-cause mortality, cardiac mortality, or MI.

There has been concern that SES may result in increased risk for events remote from the target lesion due to reports of endothelial dysfunction at distant sites (9). Progression of disease requiring repeat revascularization in segments of the target vessel remote from the target lesion actually tended to be lower for SES than BMS, possibly reflecting imperfect assessment of restenosis, but not indicative of more rampant

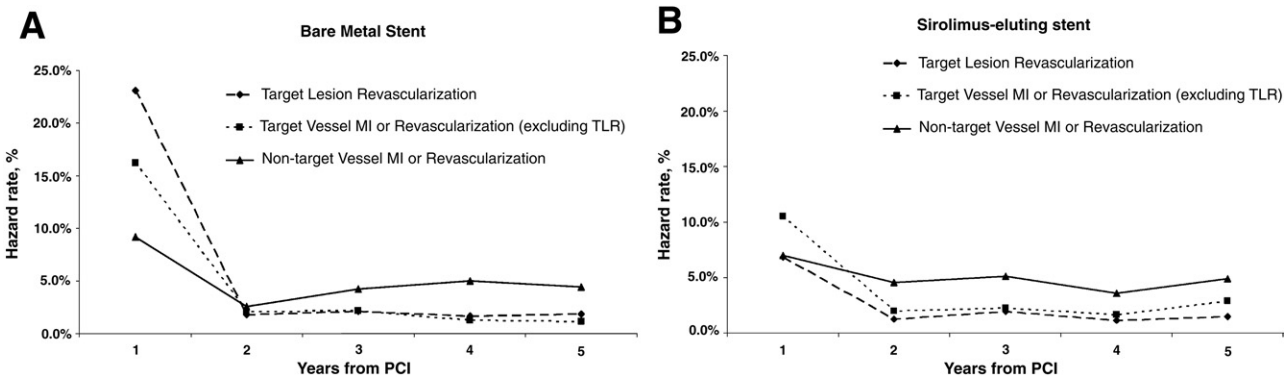

Figure 2. Annual Hazards of TLR, Target Vessel Events Excluding TLR, and Nontarget Vessel Events

(A) Bare-metal stent cohort. **(B)** Sirolimus-eluting stent cohort. MI = myocardial Infarction; PCI = percutaneous coronary intervention; TLR = target lesion revascularization.

disease progression at sites distal or proximal from the SES stent. Myocardial infarction attributed to the target vessel was also not different between SES and BMS. The result of these findings was a significant benefit for SES in overall events attributed to the target vessel.

Although a sustained reduction in TLR resulting in a net benefit in patient outcome for SES is encouraging, the impact of disease progression in nontarget vessels on the patient-oriented composite in both SES and BMS patients remains a concern. It has been reported previously that disease progression, rather than restenosis, after BMS is the most important cause of subsequent events (8,15). Indeed in the current study, events attributed to the nontarget vessel were the most frequent cause of adverse outcome in the SES group during the 5-year follow-up period. This is similar to a previous report among diabetic patients, in which over 50% of repeat revascularization procedures in SES patients during 2-year follow-up did not involve the target lesion (16). The annual hazard for target vessel remote and nontarget vessel events was similar among the SES and BMS patients and to prior reports from BMS studies. It has been suggested that restenosis itself may have contributed to the high rates of target vessel and nontarget vessel events in these earlier BMS studies, due to recurrent ischemia and ongoing surveillance. The similar risk for these events in the SES and BMS groups, despite clear differences in restenosis events, suggests the occurrence or prevention of restenosis had no major impact.

Table 3. Predictors of the Primary End Point Based on Cox Proportional Hazard Model

Variable	Hazard Ratio	95% Confidence Interval	p Value
Sirolimus-eluting stent	0.66	0.55–0.79	<0.001
History of myocardial infarction	1.36	1.13–1.65	0.002
History of diabetes	1.29	1.06–1.57	0.012
Prior coronary artery bypass graft surgery	1.44	1.08–1.92	0.012
Pre-procedure reference vessel diameter, mm	0.77	0.63–0.94	0.001
Pre-procedure lesion length, mm	1.03	1.01–1.04	<0.001

Our study is the first to report results from a randomized, double-blinded controlled trial regarding progression of coronary disease in coronary segments remote from the target lesion. There are important implications of these findings for future development and clinical application of DES. As applied in the SIRIUS trial, the benefit of SES was limited to a reduction in TLR that was most marked during the first year. The ongoing risks of events unrelated to restenosis reduced the relative benefit of this protection from >50% after 1 year to <25% at 5 years. Disease progression may result in lesser benefit for a DES strategy when the primary end point is determined by clinical outcomes other than restenosis. On the other hand, improvements in DES technology that maintain or increase the restenosis benefit while reducing the safety risk to a level significantly below the inherent risk associated with progression of subclinical coronary artery disease may provide for a pre-emptive therapeutic strategy that can markedly reduce overall coronary events. Whether these lesions can be identified prospectively by measures of plaque vulnerability or accelerated progression and whether local or regional therapy will offer any advantage over systemic medical therapy will require randomized trial evaluation (17). Finally, the findings of our study have implications for the validity of attributing late unexplained events to stent thrombosis or other stent-related complications.

Study limitations. Our study has several limitations. Because routine biomarker assays were not mandated during repeat hospitalizations or subsequent revascularization, it is likely that spontaneous MI may have been underestimated.

We also did not record medication use during the follow-up period, so the impact of longer term clopidogrel therapy beyond the protocol-mandated 3 months or of statins on late events cannot be assessed. Finally, our results are restricted to a clinical trial population undergoing coronary stenting according to a specified protocol. Given the generally accepted low risk of these patients, the findings of a high risk for disease progression may have even greater relevance. Moreover, because the protocol specified routine angiographic follow-up with its documented inherent bias, we cannot exclude an exaggeration of the impact of TLR relative to nontarget vessel events.

Conclusions

SES were associated with a marked reduction in a patient-oriented composite outcome as defined by the Academic Research Consortium, including all-cause mortality, any MI, or any repeat revascularization, during the 5 years after stenting. This benefit was due to a significant reduction in TLR during the first year that was sustained for 5 years. Events attributed to the remote segments of the target vessel and nontarget vessels occurred frequently and were nearly identical between SES and BMS. Remote coronary segments remain an important cause of future adverse events and limit the relative benefit of DES during longer term follow-up.

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Key Words: stent ■ restenosis ■ atherosclerosis.