

Differential outcomes after sirolimus-eluting stent implantation: comparing on-label versus off-label patients in the 'real world'

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Background Randomized controlled trials indicate that sirolimus-eluting stents (SES) reduce the rates of restenosis and need for subsequent revascularization procedures, but patients enrolled in randomized trials represent a highly selected population. This study examined the performance of SES in a 'real world' setting by comparing the outcomes of trial-eligible versus ineligible patients undergoing percutaneous coronary intervention.

Methods From the US commercial introduction of SES in April 2003 until December 2003, all patients that received an SES at our institution were followed in a prospective registry ($n=838$). For the purpose of this analysis, the registry population was divided into two groups based on the inclusion and exclusion criteria of the stenosis in a native coronary artery (SIRIUS) trial. The primary endpoint of the study was the rate of target lesion revascularization (TLR) at follow-up. Secondary endpoints included major adverse cardiac events (MACE) such as cardiac death, myocardial infarction, and target vessel revascularization. Clinical follow-up was complete for 92% of patients with a median duration of 14.2 months.

Results Overall, 296 patients (35.3%) met entry criteria for the SIRIUS trial and thus comprised the SIRIUS eligible group. Patients in the SIRIUS ineligible group ($n=542$) were more likely to have chronic kidney disease and earlier bypass surgery and had longer mean stent length. At 1 year, TLR occurred in 3.0% of the SIRIUS eligible population and in 9.2% of the SIRIUS ineligible group

($P=0.001$). The secondary endpoint of cumulative MACE occurred in 6.6% of the SIRIUS eligible versus in 17.7% of the SIRIUS ineligible population ($P<0.001$). Two patients (0.4%) in the SIRIUS ineligible group had a late stent thrombosis on days 39 and 99, respectively, versus none in the SIRIUS eligible group.

Conclusion Among 'real world' patients treated with SES, the incidence of TLR and MACE at 1 year was substantially greater among SIRIUS ineligible patients compared with SIRIUS eligible patients. These findings confirm that pivotal clinical trials of drug-eluting stents tend to enroll low-risk patients and that the estimated rates of TLR and MACE derived from such trials may not reflect subsequent outcomes with unrestricted clinical use. *Coron Artery Dis* 19:111–115 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Recent randomized trials have demonstrated that the use of sirolimus-eluting stents (SES; Cypher, Cordis Corporation, Miami Lakes, Florida, USA) during percutaneous coronary interventions (PCI) can dramatically reduce the incidence of angiographic and clinical restenosis compared with conventional bare metal stent designs [1–4]. All of these studies have, however, been conducted among carefully selected patient populations with relatively straightforward lesions. Indeed, the SES versus Standard Stents in Patients with Stenosis in a Native Coronary Artery (SIRIUS) trial excluded many patients

that are commonly treated with PCI in current practice including patients with complex, multiple, bifurcation, ostial and unprotected left main lesions as well as recent or ongoing myocardial infarction (MI) and depressed ejection fractions [2]. Consequently, the SIRIUS trial and similar pivotal trials may not accurately depict the impact of SES implantation in 'real world' patients.

Data from the European research registry demonstrated that SES implantation is safe and effective in decreasing both target lesion revascularization (TLR) and major adverse cardiac events (MACE) at 1-year compared with

bare metal stents (BMS) in a broad patient population [5]. More recently, investigators from the Registro Regionale Angioplastiche (REAL) registry reported reduced rates of MACE and TLR with SES compared with BMS use among patients with high-risk clinical and angiographic characteristics [6].

Although SES seem to be effective in the reduction of TLR compared with BMS, to date no studies have formally compared the results of SES in patients with lower risk characteristics versus those patients with higher risk features. The aim of the current study was to examine the 1-year clinical outcomes after SES implantation among an unselected 'real world' patient population and to directly compare the outcomes between SIRIUS eligible and SIRIUS ineligible patients. We hypothesized that patients who were excluded from the SIRIUS trial would represent a high-risk cohort with demonstrably worse long-term outcomes than their trial-eligible counterparts.

Methods

Study design and patient population

This study was based on a registry comprising 838 consecutive patients that underwent implantation of one or more SES (Cypher, Cordis Corporation) at the Beth Israel Deaconess Medical Center between 24 April 2003 and 31 December 2003. All patients provided written informed consent and the study was approved by the institutional review board. During this period, SESs were used preferentially in our catheterization laboratory, and 71% of the population undergoing PCI received at least one SES. The main reason for not using an SES during this interval was the unavailability of the appropriate stent size or length. In addition, while there were no explicit restrictions on SES use based on clinical or angiographic characteristics, during this period, most operators chose a BMS for those patients presenting with a ST-segment elevation MI. All other patients received an SES when deemed clinically appropriate by the primary operator. Thirty-day outcomes from this registry experience have been reported previously [7].

To compare the efficacy of SES implantation in lower risk versus higher risk patients, this initial study population was subsequently divided into two groups at the time of data analysis: (1) those patients meeting entry criteria for the SIRIUS trial ('SIRIUS eligible' group) and (2) those patients who would have been excluded from the SIRIUS trial ('SIRIUS ineligible' group). As previously described, SIRIUS-enrolled patients with evidence of myocardial ischemia and a single *de novo* target lesion that measured 15–30 mm in length (by visual estimate) and was located within a native coronary artery [2]. Exclusion criteria included the following: MI within the previous 48 h; left-ventricular ejection fraction less than 25%; a target lesion

within the vessel ostium, bifurcation lesions, unprotected left main stenosis, target lesion with angiographic thrombus or severe calcification, and multilesion or multivessel PCI procedures.

Procedural and medical therapy

All patients undergoing PCI were premedicated with 325 mg aspirin. Antithrombotic regimens included either intravenous heparin or bivalirudin, and glycoprotein IIB/IIIA inhibitors were used selectively at the discretion of the treating physicians. A loading dose of clopidogrel (300–600 mg) was given in the catheterization laboratory, and clopidogrel (75 mg daily) was recommended for 3–12 months.

Data collection and study endpoints

Baseline clinical, angiographic, and procedural data were collected from all patients, and telephone follow-up was obtained at a minimum of 9 months following the index procedure. Vital status was determined by direct communication with the patient, a family member, the referring physician, or by searching the Social Security Death Index. Noncardiac death was defined as death by a clearly documented noncardiac cause. All other deaths were considered cardiac. All hospital admissions during the follow-up period were reviewed by two independent observers for evidence of MI or revascularization procedures.

During follow-up, coronary angiography was performed as clinically indicated by symptoms or by evidence of myocardial ischemia. Clinically driven repeat revascularization was defined as any intervention motivated by a significant luminal stenosis (> 50% diameter stenosis) in the presence of anginal symptoms or proven myocardial ischemia in the target vessel territory by noninvasive testing. Late stent thrombosis was defined as recurrent ischemia in the territory of the target vessel with evidence of thrombus in the target vessel during coronary angiography occurring more than 30 days after the index procedure. The primary study endpoint was the rate of TLR defined as any clinically driven repeat revascularization procedure (PCI or bypass surgery) performed to treat a significant luminal stenosis within the stent or within a 5 mm segment proximal or distal to the stent. Secondary endpoints included MACE: a composite of target vessel revascularization (TVR), nonfatal MI, or cardiac death. TVR was defined as a repeat intervention owing to a luminal stenosis within the same epicardial vessel or its branches. Nonfatal MI was defined as anginal symptoms with an elevation of creatine kinase-MB more than three times the upper limit of normal.

Statistical analysis

Continuous variables are described as mean \pm SD and were compared using unpaired *t*-tests. Categorical

variables are described as counts, and percentages and were compared by means of the Fisher exact test. The cumulative incidence of adverse events was estimated according to the Kaplan–Meier method and compared by the log-rank statistic. Results were considered statistically significant at $P < 0.05$. All statistical analyses were performed using Stata version 8.2 (Stata Corp., College Station, Texas, USA).

Results

Baseline clinical and angiographic characteristics

Baseline clinical and angiographic data are presented in Table 1. Overall, 296 (35.3%) of patients were SIRIUS eligible, whereas the remaining 542 (64.7%) were SIRIUS ineligible. Among SIRIUS ineligible patients, 5.8% underwent treatment for a ST-segment elevation MI, and 1.9% were found to be in cardiogenic shock at the time of presentation. Patients who were SIRIUS ineligible were more likely to have chronic renal insufficiency and to have undergone previous bypass surgery. SIRIUS ineligible patients had lower mean ejection fractions than SIRIUS eligible patients as well. Other baseline characteristics were similar between the two groups.

Angiographic characteristics and procedural factors are summarized in Table 2. By definition, only SIRIUS ineligible patients underwent multivessel PCI (31 vs. 0%). The number of implanted stents per lesion and mean total stent length per lesion was greater for SIRIUS-ineligible versus SIRIUS-eligible patients.

Clinical outcomes

During index hospitalization, SIRIUS ineligible patients demonstrated a trend toward higher rates of periprocedural MI (3.5 vs 1.4%, $P = 0.08$). In addition, 8 (1.5%) patients from the SIRIUS ineligible group underwent

Table 1 Baseline characteristics of the study population

	SIRIUS eligible (n=296)	SIRIUS ineligible (n=542)	P-value
Age, years	65.6 ± 12	65.9 ± 12.2	0.38
Age over 80 years	11.5%	11.8%	0.82
Previous MI	33.7%	36.8%	0.38
Female sex	28.7%	30.4%	0.56
Previous CABG	17.0%	23.0%	0.05
Chronic renal insufficiency ^a	5.1%	12.7%	<0.001
Current cigarette smoking	16.3%	11%	0.03
Dyslipidemia ^b	85.4%	84.3%	0.69
Diabetes mellitus	32.0%	37.9%	0.09
Arterial hypertension	79.3%	85.6%	0.02
LV ejection fraction	54.5 ± 8.8	50.8 ± 12	<0.001
ST-Elevation MI Presentation	0.0%	5.8%	<0.001
Cardiogenic Shock Presentation	0.0%	1.9%	0.03

Presented in percent and mean ± SD. CABG, coronary artery bypass grafting; LV, left ventricular; MI, myocardial infarction, SIRIUS, stenosis in a native coronary artery trial.

^aDefined as serum creatinine ≥ 2.0 mg/dl or on renal replacement therapy.

^bDefined as total cholesterol >200 mg/dl or on lipid-lowering therapy.

Table 2 Angiographic and procedural data (per lesion)

	SIRIUS eligible (296 lesions)	SIRIUS ineligible (726 lesions)	P-value
Total stent length, (mm)	18.9 ± 5.0	24.5 ± 14.5	<0.001
Number of stents implanted	1.0 ± 0.1	1.2 ± 0.6	<0.001
Nominal stent diameter, (mm)	2.9 ± 0.4	2.8 ± 0.6	0.88
Maximal inflation pressure, (atm.)	14.9 ± 3.1	15.2 ± 3.6	0.99
Pre-dilation, (%)	80.9%	79.7%	0.68
Post-dilation, (%)	66.4%	60.8%	0.09
Lesion location			0.35
LMCA	0.0%	3.2%	
LAD	32.1%	37.3%	
LCX	30.7%	22.9%	
RCA	37.2%	28.5%	
SVG	0.0%	8.1%	
Glycoprotein IIb/IIIa inhibitor	78.4%	75.6%	0.36
Bivalirudin	4.7%	7.2%	0.16

Presented in mean ± SD and percent. LAD, left anterior descending; LCX, left circumflex; LMCA, left main coronary artery; RCA, right coronary artery; SIRIUS, stenosis in a native coronary artery trial; SVG, saphenous vein graft.

Table 3 1-year clinical outcomes

	Overall population (%)	SIRIUS eligible (%)	SIRIUS ineligible (%)	P-value*
Cardiac Death	2.3	0.7	3.2	0.03
Non-Cardiac Death	1.7	1.0	2.1	0.40
ST-elevation MI	1.4	0.4	2.1	0.07
NonST-elevation MI	3.1	0.4	4.8	<0.001
TLR	6.8	3.0	9.2	<0.001
TVR	8.9	5.6	12.2	<0.001
NonTVR	8.0	6.6	9.5	0.19
Late stent thrombosis	0.2	0.0	0.4	0.27
MACE (any)	15.2	6.6	17.7	<0.001

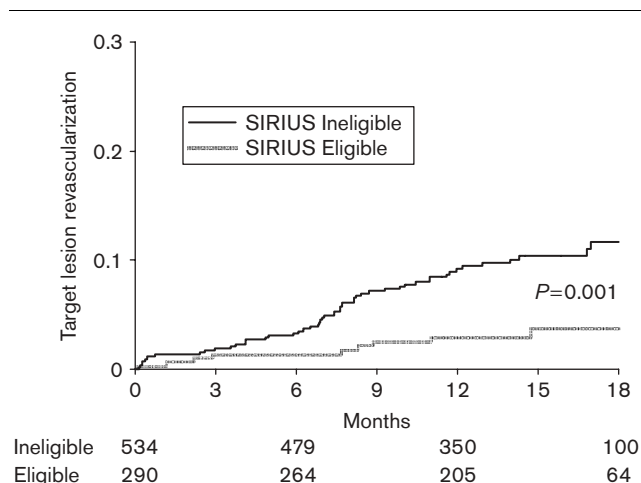
*For comparison of SIRIUS eligible versus SIRIUS ineligible group.

One-year event rates based on Kaplan-Meier estimates; MACE, major adverse cardiac events; MI, myocardial infarction; SIRIUS, stenosis in a native coronary artery trial; TLR, target lesion revascularization; TVR, target vessel revascularization.

urgent coronary artery bypass graft versus none in the SIRIUS eligible group.

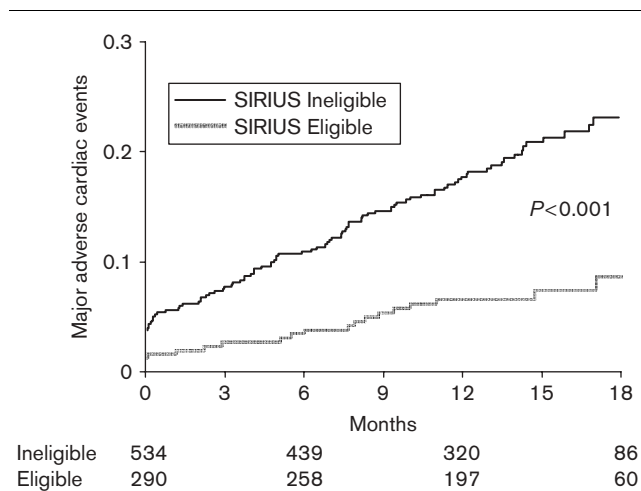
Clinical follow-up was available for 92% of patients in the total study population with a median follow-up period of 14.2 months (with similar follow-up between the two groups). Compared with SIRIUS eligible patients, 12-month clinical outcomes were consistently and uniformly worse for the SIRIUS ineligible group (Table 3). In particular, the primary endpoint of TLR was significantly higher for the SIRIUS-ineligible cohort (9.2 vs 3.0%, $P < 0.001$; Fig. 1). Similarly, rates of TVR, late MI (excluding periprocedural events), and cardiac death were all higher between the SIRIUS ineligible group compared with the SIRIUS eligible group. The overall incidence of MACE at one year was 17.7% among SIRIUS ineligible patients compared with 6.6% among the SIRIUS eligible cohort ($P < 0.001$; Fig. 2). Two patients (0.4%) in the SIRIUS ineligible group had a late stent thrombosis on days 39 and 99, respectively (one of those patients also had a subacute stent thrombosis).

Fig. 1



Cumulative risk of clinically-driven target lesion revascularization in patients treated with sirolimus-eluting stents based on stenosis in a native coronary artery trial eligibility.

Fig. 2



Cumulative risk of major adverse events (cardiac death, myocardial infarction or target-vessel revascularization) in patients treated with sirolimus-eluting stents based on stenosis in a native coronary artery trial eligibility.

Discussion

This study compared the effectiveness of unrestricted SES implantation among trial-eligible versus trial-ineligible patients, based on the entry and exclusion criteria described in the SIRIUS trial [2]. As expected, higher risk, SIRIUS ineligible patients experienced significantly increased rates of TLR and MACE at 1 year when compared with lower-risk, SIRIUS eligible patients. Despite the diffusion of SES use outside of the limits

of clinical trial eligibility, the rates of revascularization observed in this registry were still relatively favorable – even for the trial-ineligible group.

The major objective of this US registry was to evaluate the effectiveness of SES implantation in an unselected patient population outside the realm of controlled clinical trials. We used the entry and exclusion criteria from the SIRIUS trial to divide our population because of the pivotal role that this study has played in demonstrating the feasibility of SES implantation for the treatment of coronary stenosis. Moreover, this trial still serves as the sole basis for the Food and Drug Administration-approved ‘on label’ use of SES in the United States. The results from our study provide further evidence that SES implantation is effective in the treatment of ‘real world’ patients. In fact, the 1-year incidence of TLR in our SIRIUS eligible population was lower than the 4.9% rate reported in the clinical trial, itself [2]. Meanwhile, the incidence of TLR in the SIRIUS ineligible population was still less than previously reported revascularization rates with the utilization of BMS [8].

This study also demonstrates one of the key explanations for the discrepancy between the outcomes observed in controlled clinical trials and ‘real world’ patients. Given the extensive inclusion and exclusion criteria in most clinical trials, it is sometimes difficult to interpret the results in the context of standard clinical care. Registries that include all patients can therefore be of great value in illuminating outcomes in broader patient populations. Our study clearly demonstrates that clinical outcomes are significantly more favorable for patients that would have been eligible for inclusion in a clinical trial as opposed to patients that would have been excluded. These findings suggest that clinicians should be aware of the specific eligibility criteria for drug-eluting stent trials and that extrapolation of trial results to the broader patient populations encountered in standard practice should be performed with caution.

The study population in this registry is comparable in size to the recently reported Italian REAL registry, which prospectively evaluated SES implantation in a ‘real world’ population of 872 patients, subsequently divided into two groups based upon prespecified clinical and anatomical risk factors [6]. The rates of TLR in our SIRIUS eligible and ineligible patients were higher than those reported in the low and high-risk (2.7 and 3.4%, respectively) subgroups from the REAL registry, but the rates of MACE were similar among the two study populations. Whereas data from the REAL registry suggest that the benefits of SES implantation may be accentuated in higher versus lower risk patient populations, our study also suggests a more cautious interpretation.

Indeed, whether SESs provide meaningful benefits in terms of TLR reduction to trial-ineligible patients cannot be addressed directly by our study. Nonetheless, it is encouraging to note that even in the trial-ineligible group, rates of TLR are lower than previously reported for unselected BMS [8]. The higher TLR and TVR rates in this study as compared with the European registries may be owing to differences in patient populations or operator technique. A recent study evaluated the differences between PCI outcomes in Europe versus the United States for patients enrolled in the prevention of restenosis with tranilast and its outcomes trial PRESTO [9]. Interestingly, angiographic restenosis and ischemia-driven TVR rates were significantly higher among patients treated in the United States.

This study has several limitations. First, long-term clinical follow-up was available for only 92% of the initial study population. Second, given the nature of a registry study, we cannot completely exclude a selection bias. Although all consecutive patients with SES were included, the decision to implant a SES was at the discretion of the treating physicians. Whereas the most common reason not to use a SES was the unavailability of the appropriate stent size or length, other unmeasured factors may have influenced this decision.

In conclusion, this study demonstrates a significantly increased incidence of 1-year TLR and MACE for higher versus lower risk 'real world' patients undergoing SES implantation. These findings illustrate that clinical trials testing novel devices typically enroll a low-risk population

and thus trial outcomes should be interpreted in the context of the studied population rather than extrapolated to broader and higher risk patient subgroups.

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