Effect of Coronary Target Lesion Revascularization on Late Cardiac Events After Insertion of Sirolimus-Eluting or Bare Metal Stents

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Restenosis is associated with acute myocardial infarction (MI) either at presentation or related to complications of target lesion revascularization (TLR). The cumulative late effect of TLR after drug-eluting or bare metal stent placement on cardiac death or MI is uncertain. Of the 1,057 patients with one native coronary lesion randomized to a sirolimus-eluting stent or bare metal stent in the Sirolimus-Eluting Stent in De Novo Native Coronary Lesions (SIRIUS) trial, the 983 who survived free of MI for the first 30 days were evaluated for the primary outcome of cardiac death or MI for 5 years. Patients with events occurring at or after TLR were assigned to TLR group. Cox proportional hazards regression analysis with TLR as a time-dependent variable and adjustment for baseline clinical and demographic covariates was used to assess the independent effect of TLR on the primary outcome. TLR occurred in 160 patients (16.3%) and was an independent predictor of the primary end point (hazard ratio 2.8, 95% confidence interval 1.7 to 4.5). This association was significant for sirolimus-eluting stents and bare metal stents. TLR was also associated with an increased risk of subsequent stent thrombosis and nontarget vessel revascularization. Intracoronary brachytherapy in the TLR group was associated with an increased risk of cardiac death or MI. In conclusion, restenosis requiring TLR was associated with an increased risk of cardiac death or MI occurring at TLR and during the subsequent 5 years. **© 2010 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2010;106:774–779)**

Restenosis requiring repeat percutaneous or surgical revascularization procedures has been the major limitation of balloon angioplasty and bare metal stent (BMS) placement for coronary artery disease. Recent reports have indicated the frequent occurrence of myocardial infarction (MI) at repeat target lesion revascularization (TLR).[1] Drug-eluting stents (DESs) have reduced the frequency of restenosis requiring TLR within the first year, ranging from 3% to 4% for DESs to 11% to 16% for BMSs in pivotal clinical trials.[2,3] In 2006, reports were published of increased late mortality in patients receiving a DES.[4–7] Subsequent patient-level pooled analyses of clinical trial data suggested a small increase in late stent thrombosis >1 year after stenting,[8] but no increase in death or MI for DESs compared to BMSs.[9] A post hoc analysis of pooled paclitaxel versus BMS studies reported equal numbers of deaths in patients who received either a BMS or a paclitaxel DES complicated by either TLR or stent thrombosis.[10] The investigators hypothesized a balance between the small late mortality risk due to stent thrombosis and the accrued benefits of restenosis prevention in a larger number of patients.[10] The direct late clinical effect of restenosis requiring TLR after stent implantation with DESs or BMSs has not been specifically investigated. The aim of the present study was to evaluate the effect of TLR performed for in-stent restenosis after BMS or sirolimus-eluting stent (SES) placement on long-term cardiac outcomes. We hypothesized that TLR would be associated with a significantly in-

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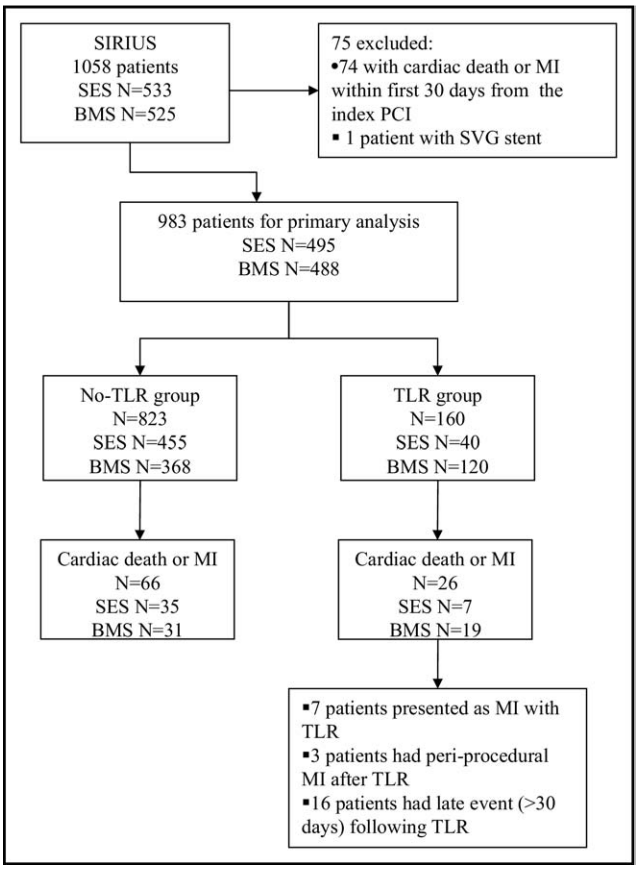

Figure 1. Study population flow chart.

Table 1
Clinical and demographic characteristics

Variable	TLR		p Value
	Yes (n = 160)	No (n = 823)	
Age (years)	61.3 ± 11.2	62.2 ± 11.1	0.33
Men	75.0%	70.7%	0.29
Sirolimus-eluting stent	25.0%	55.3%	< 0.001
Diabetes mellitus	38.1%	24.5%	< 0.001
Hypertension (history or treatment)	68.4%	67.8%	0.93
Hyperlipidemia (history or treatment)	76.6%	73.3%	0.43
Current smoker	19.4%	20.4%	0.68
Renal dialysis	0%	0.6%	1.00
Stroke	7.5%	6.8%	0.74
Heart failure	7.0%	5.0%	0.33
Peripheral arterial disease	12.5%	6.4%	0.01
Previous myocardial infarction	32.1%	28.4%	0.34
Previous percutaneous coronary intervention	26.3%	24.2%	0.62
Previous bypass surgery	12.5%	8.9%	0.18
Ejection fraction (%)	56.9 ± 10.2	55.7 ± 10.1	0.20
No. of narrowed coronary arteries			0.28
1	55.0%	59.8%	
2	28.8%	26.0%	
3	16.3%	14.2%	

Table 2
Angiographic characteristics (per lesion analysis)

Variable	TLR		p Value
	Yes (n = 161)	No (n = 824)	
Coronary lesion location			0.01
Left anterior descending artery	53.8%	41.0%	
Left circumflex	23.8%	24.9%	
Right	22.5%	34.1%	
American College of Cardiology-American Heart Association lesion classification			0.16
A	6.9%	7.4%	
B1	30.0%	37.0%	
B2	37.5%	32.9%	
C	25.6%	22.7%	
Coronary lesion characteristics			
Diameter stenosis (%)	64.8 ± 12.3	65.3 ± 12.3	0.67
Total occlusion	1.3%	2.9%	0.29
Angiographic thrombus	1.3%	1.1%	0.70
Thrombolysis In Myocardial Infarction flow before procedure			0.11
0	0.6%	0.7%	
1	0.6%	2.2%	
2	3.8%	6.2%	
3	95.0%	90.9%	
Vessel diameter (mm)	2.72 ± 0.45	2.82 ± 0.47	0.01
Lesion length (mm)	15.4 ± 7.3	14.1 ± 5.4	0.04

creased risk of subsequent cardiac events, defined as the composite end point of cardiac death or MI.

Methods

The study population included patients randomized in the Sirolimus-Eluting Stent in De Novo Native Coronary Lesions (SIRIUS) study. The design of the SIRIUS trial has been previously reported.[2] After approval of the device by the United States Food and Drug Administration, the study patients were to be followed up for 5 years. The patients were queried by telephone interview, and, in the case of potential clinical events, the source medical documents were retrieved and reviewed. All study end points were adjudicated by an independent committee that remained masked to the treatment assignment.

The TLR group included patients who required clinically driven TLR for presumed restenosis at any point >30 days from the index procedure. The no-TLR group included patients who had remained free of clinically driven TLR throughout the follow-up period. Because TLR was treated as a time-dependent variable, the patients entered into the TLR group at TLR. The exception was that patients who experienced MI ≤7 days before TLR were considered to have MI related to restenosis and were entered into the TLR

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