Published by Elsevier Inc.

ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2004.01.045

Significant Reduction in Restenosis After the Use of Sirolimus-Eluting Stents in the Treatment of Chronic Total Occlusions

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OBJECTIVES The aim of this study was to assess sirolimus-eluting stent (SES) implantation for the treatment of chronic total coronary occlusions (CTO).

BACKGROUND Long-term results after percutaneous coronary intervention (PCI) in the treatment of CTOs is hindered by a significant rate of restenosis and reocclusion. In the treatment of relatively simple nonocclusive lesions, SESs have shown dramatically reduced restenosis rates compared with bare metal stents (BMS), but whether these results are more widely applicable is unknown.

METHODS From April 2002, all patients at our institution were treated with SES as the device of choice during PCI. During the first six months, 563 patients were treated solely with SES, with treatment of a de novo CTO in 56 (9.9%). This CTO cohort was compared with a similar group of patients (n = 28) treated in the preceding six-month period with BMS.

RESULTS At one year, the cumulative survival-free of major adverse cardiac events was 96.4% in the SES group versus 82.8% in the BMS group, $p < 0.05$. At six-month follow-up, 33 (59%) patients in the SES group underwent angiography with a binary restenosis rate (>50% diameter stenosis) of 9.1% and in-stent late loss of 0.13 ± 0.46 mm. One patient (3.0%) at follow-up was found to have reoccluded the target vessel.

CONCLUSIONS The use of SESs in the treatment of chronic total coronary occlusions is associated with a reduction in the rate of major adverse cardiac events and restenosis compared with BMS. (J Am Coll Cardiol 2004;43:1954–8) © 2004 by the American College of Cardiology Foundation

Chronic total occlusions (CTO) are common, and found in approximately one-third of patients with significant coronary disease who undergo angiography (1,2). Percutaneous intervention (PCI) of CTOs accounts for 10% to 15% of all angioplasties; however, after successful recanalization, there is an increased rate of subsequent restenosis and reocclusion compared with nonocclusive stenoses (3,4). Although several randomized trials demonstrated the efficacy of stent implantation over balloon-only angioplasty, even with stents there remains a significant rate of both restenosis (32% to 55%) and reocclusion (8% to 12%) (5–9).

In the treatment of relatively simple lesions, sirolimus-eluting stents (SES) markedly reduce the restenosis rate, with continued benefit documented up to two years follow-up (10,11). Whether these results can be extrapolated to more complex lesions such as CTOs has yet to be determined. We sought to evaluate the effectiveness of the SES in a consecutive series of patients with at least one de novo CTO compared with a similar series treated with bare metal stents (BMS).

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Manuscript received October 29, 2003; revised manuscript received January 15, 2004, accepted January 19, 2004.

METHODS

Patient population. Commencing in April 2002, all PCI at our institution was done solely with SESs, irrespective of clinical presentation or lesion morphology; these patients comprise the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital registry (RESEARCH) registry (further details of the methodology are described elsewhere) (12,13). Those deemed at an increased risk of restenosis (including the CTO population) were considered for six-month angiographic follow-up. Sirolimus-eluting stents were available in lengths between 8 mm and 33 mm, and diameters 2.25 mm to 3.0 mm. In the first six months, 563 patients were treated, including 56 (9.9%) with successful revascularization of at least one CTO. These patients make up the present study cohort; all received six months dual antiplatelet therapy with clopidogrel in addition to aspirin. As predetermined by the RESEARCH protocol, this study cohort of patients were compared with all those treated for a CTO in the preceding six months with BMS, identified from the departments' dedicated database. Both groups were treated by the same operators utilizing standard techniques, the only difference being the type of stent. The protocol was approved by the local ethics committee and is in accordance with the principles of Good Clinical Practice

Abbreviations and Acronyms

BMS	= bare metal stent
CTO	= chronic total occlusion
MACE	= major adverse cardiac events
PCI	= percutaneous coronary intervention
RESEARCH	= Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital registry
SES	= sirolimus-eluting stent
TVR	= target vessel revascularization

for Trials of Medicinal Products in the European Community and the Declaration of Helsinki. All patients signed a written informed consent

CTO definition. Chronic occlusion was defined as an occlusion on angiography with no antegrade filling of the distal vessel other than via collaterals. All patients included had a native vessel occlusion estimated to be at least one month's duration (9) based on either a history of sudden chest pain, a previous acute myocardial infarction in the same target vessel territory, or the time between the diagnosis made on coronary angiography and PCI.

Length of occlusion. The length of occlusion was measured by quantitative coronary angiography either utilizing antegrade filling via collaterals, or assessment of the retrograde collateral filling. This was achieved by catheterizing both the left and right coronary arteries, and making a simultaneous injection to delineate the distance between the site of occlusion and the most proximal part of the vessel filled retrogradely.

Follow-up. Patients were followed up prospectively and evaluated for survival-free of major adverse cardiac events (MACE) using questionnaires and telephone enquiries; MACE was predefined as: 1) death; 2) nonfatal myocardial infarction; or 3) repeat target vessel revascularization (TVR). The diagnosis of acute myocardial infarction required an elevation of creatine kinase to twice the upper limit of normal, together with a rise in creatine kinase-MB fraction. Target vessel revascularization was defined as either surgical or percutaneous reintervention driven by significant (>50%) luminal narrowing within the treated vessel, and was undertaken in the presence of either anginal symptoms or objective evidence of ischemia.

Angiographic analysis. Quantitative analysis in those SES patients with follow-up angiography was undertaken in three coronary segments: in-stent (encompassing the entire length of stented segment), and the 5-mm proximal and distal edge segments either side of the in-stent segment. The target lesion comprised the in-stent plus the proximal and distal edge segments. Binary restenosis was defined as >50% diameter stenosis within the target lesion. Late lumen loss was calculated from the difference in minimal lumen diameter between postprocedure and follow-up.

Statistical analysis. Discrete variables are presented as percentages and compared with Fisher exact test. Continuous variables are expressed as mean ± SD and compared with Student *t* test. Survival-free of adverse events was calculated according to the Kaplan-Meier method. The log-rank test was used to compare MACE-free survival between the two groups. All tests were two-tailed, and a p value of <0.05 was considered statistically significant.

RESULTS

The baseline patient and lesion characteristics of the two groups are presented in Tables 1 and 2. One patient in the BMS group underwent successful recanalization and stent implantation in two CTOs, thereby making a total of 29 lesions in this group. Mean length of occlusion could be determined in 45 (80.4%) of the SES group and 17 (58.6%) of the BMS group. There was no significant difference between the groups with respect to the postprocedural quantitative angiography; however, the mean diameter of stent utilized was greater in the BMS cohort.

There were no in-hospital MACE. Clinical follow-up data was obtained in 100% of both groups. There were no deaths in either group; one non–Q-wave acute myocardial infarction occurred related to subacute stent thrombosis 11 days after SES implantation. This was successfully recanalized percutaneously; intravascular ultrasound suggested underexpansion of the SES (2.5 × 33 mm), and the patient was treated with abciximab and balloon dilation of the previously implanted stent. At one year, the cumulative survival-free of MACE was 96.4% in the SES group compared with 82.8% in the BMS group, $p < 0.05$ (Fig. 1). One patient in each group had a reocclusion (1.8% SES group vs. 3.6% BMS group, p = NS).

At six months, 33 (58.9%) patients in the SES group underwent follow-up angiography (none in the BMS group) (Table 3). The binary restenosis rate was 9.1%: one occlusion, one stenosis at the ostium of a side branch after

Table 1. Baseline Patient Demographics

	Bare Stents n = 28	SES n = 56	p Value
Mean age (yrs)	59.8 ± 11.1	60.2 ± 10.0	0.9
Male gender (%)	85.7	71.4	0.2
Current smoker (%)	35.7	26.8	0.5
Diabetes mellitus (%)	7.1	14.3	0.4
Hypertension (%)	39.3	39.3	1.0
Hypercholesterolemia (%)	57.1	55.4	1.0
Previous myocardial infarction (%)	46.4	55.4	0.6
Previous PCI (%)	21.4	12.5	0.3
Previous CABG (%)	0	0	–
Glycoprotein IIb/IIIa inhibitor usage (%)	25.0	21.4	1.0
Presence of multivessel disease (%)	60.7	46.3	0.3
PCI in at least one additional (nonoccluded) major epicardial vessel during the index procedure (%)	28.6	42.6	0.2

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; SES = sirolimus-eluting stents.

Table 2. Baseline Procedural Characteristics

	Bare Stents n = 29	SES n = 56	p Value
Target vessel			0.06
LAD (%)	27.6	51.8	
LCX (%)	27.6	25.0	
RCA (%)	44.8	23.2	
Mean length of occlusion (mm, range)	12.7 (2.4–31.8)	11.3 (4.0–32.1)	0.5
Bifurcation stenting (%)	17.9	14.3	1.0
Mean number of stents in the target vessel	1.8	2.0	1.0
Mean nominal diameter of stent in the main vessel (mm)	3.03 ± 0.56	2.75 ± 0.26	< 0.001
Mean length of stent in the main vessel (mm)	23.31 ± 9.34	23.89 ± 9.21	0.7
Mean total length of overlapping stents in the main vessel (mm, range)	41.8 (18–112)	45.2 (8–117)	0.7
Postprocedure vessel reference diameter (mm)	2.37 ± 0.50	2.35 ± 0.46	0.9
QCA data			
Minimal lumen diameter (mm)	2.18 ± 0.49	2.06 ± 0.48	0.3
Diameter stenosis (%)	10.4	11.6	0.6

LAD = left anterior descending artery; LCX = circumflex artery; QCA = quantitative coronary angiography; RCA = right coronary artery; SES = sirolimus-eluting stents.

T-stenting, and the third at the distal outflow of the SES (this is the same patient with the subacute thrombosis, and restenosis occurred at the site of balloon dilation during the second procedure). The patient with occlusion had undergone bifurcation T-stenting after successful recanalization of a heavily calcified left anterior descending artery. At follow-up, the artery had reoccluded, and there was new akinesis of the left ventricular anterior wall. This patient with occlusion was managed with medical therapy; the other two patients with restenosis underwent percutaneous revascularization.

DISCUSSION

Previous studies have demonstrated the importance of revascularization of CTOs, with improvement in anginal symptoms, exercise capacity, and left ventricular function (14–16). In addition, successful recanalization reduces the subsequent need for bypass surgery and, importantly, long-term evaluation has shown a 10-year survival advantage of 73.5% after successful PCI compared with 65.1% in those with unsuccessful PCI (4,17).

To our knowledge, this is the first report regarding the efficacy of SES in CTOs, a subset of patients previously excluded from other protocols and, importantly, at increased risk of developing restenosis after conventional stent implantation (3). Of the patients who underwent follow-up angiography, both the in-stent and proximal 5-mm segments analyzed showed an encouraging late loss of 0.13 ± 0.46 mm and 0.10 ± 0.80 mm, respectively. The distal 5 mm actually showed an overall benefit, with enlargement of the vessel (late loss, −0.06 ± 0.54 mm).

In addition to the angiographic data, the clinical follow-up is very encouraging. Importantly, there were no significant differences in baseline demographics between the SES and BMS groups, and all procedures were carried out in the same center by the same operators. There was an episode of subacute thrombosis in the SES group, but there appears to be an underlying mechanical cause with underexpansion of the stent documented on intravascular ultrasound. The restenosis rate for BMS is known to be inversely

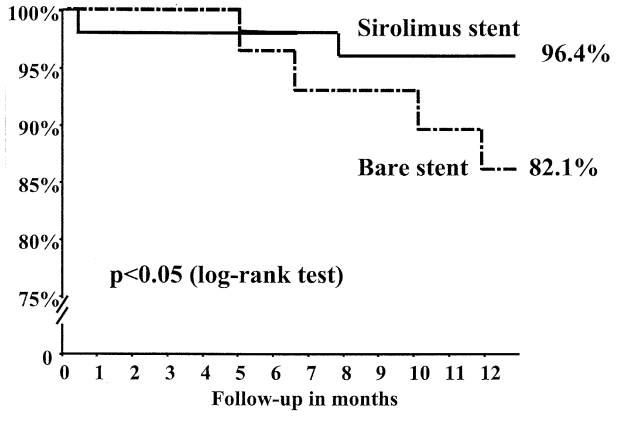

Figure 1. Kaplan-Meier curves for survival-free of death, acute myocardial infarction, or target vessel revascularization.

Table 3. Postprocedural and Six-Month Follow-Up Quantitive Angiographic Data for the Sirolimus-Eluting Stent (Patient Number n = 33)

	Proximal 5 mm	In-Stent	Distal 5 mm
Postprocedure			
Mean diameter (mm)	2.82 ± 0.66	2.58 ± 0.55	2.10 ± 0.64
Minimal lumen diameter (mm)	2.43 ± 0.51	2.04 ± 0.45	1.75 ± 0.53
% Diameter stenosis	14.1	12.9	21.8
Six-month follow-up			
Mean diameter (mm)	3.02 ± 0.53	2.46 ± 0.81	2.12 ± 0.83
Minimal lumen diameter (mm)	2.33 ± 0.90	1.91 ± 0.68	1.81 ± 0.75
% Diameter stenosis	20.1	21.9	18.2
Late lumen loss (mm)	0.10 ± 0.80	0.13 ± 0.46	−0.06 ± 0.54

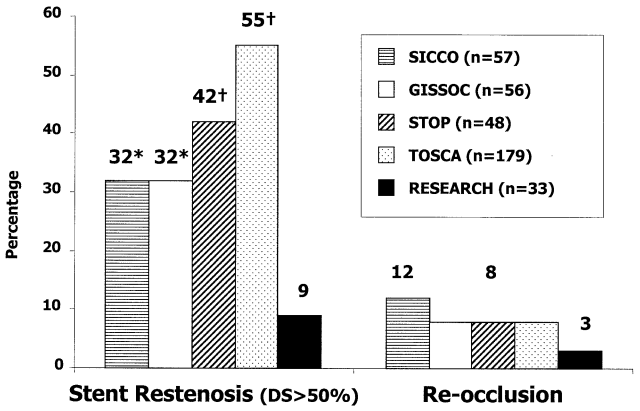

Figure 2. The percentage binary restenosis rate (>50% diameter stenosis) and reocclusion rate of Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital registry (RESEARCH) compared with published data from the patients treated with stent implantation in the randomized trials Stenting in Chronic Coronary Occlusion (SICCO) (5), Gruppo Italiano di Studio sullo Stent nelle Occlusioni Coronariche (GISSOC) (6), Stents in Total Occlusion for Restenosis Prevention (STOP) (7), and the Total Occlusion Study of Canada (TOSCA) (8). DS = diameter stenosis. *$p < 0.05$ compared with the results of RESEARCH; †$p < 0.01$ compared with the results of RESEARCH.

related to the postprocedural minimal lumen diameter and the number of stents utilized (18). In the current study, although the mean diameter of stent used was significantly greater in the BMS cohort (related to a maximum available SES diameter of 3.0 mm) with free utilization of postdilation, the postprocedural minimal lumen diameter was not significantly different between the two groups. The majority of events related to TVR, with, at one year, a significantly higher rate of survival free of MACE of 96.4% in the SES group versus 82.8% in the BMS group.

Four major randomized trials have demonstrated the efficacy of stent implantation over balloon-only angioplasty in the treatment of CTOs, reducing the six-month restenosis rate from 68% to 74%, to 32% to 55% (5–8). Compared with this historical data, our study suggests that the SES confers a marked further advantage with a significantly lower binary restenosis rate of 9.1% ($p < 0.05$) (Fig. 2). In addition, we had only one patient (3.0%) with vessel reocclusion, compared with rates of between 8% to 12% in the same published trials utilizing BMS. A recent study of the clinical results of 376 patients discharged from hospital without an adverse event after successful intervention of a CTO showed, at one-year follow-up, a MACE rate of 12.2% (19); our results are, therefore, quite remarkable, with a MACE-free survival rate of 96.4%.

Study limitations. This study evaluated only a small cohort of patients, and angiographic follow-up was not obtained in all, so additional patients with silent reocclusion cannot be excluded. However, those who did not undergo repeat angiography were all symptomatically well at follow-up. In addition, despite the discrepancy in follow-up angiography rates between the two groups, which might have biased the results towards more revascularization in the SES group, the MACE rate remained statistically significant with a beneficial effect in favor of the SES. The study was not randomized, and used a retrospective comparitive population; however, the same operators and interventional techniques were utilized.

Conclusions. The use of SESs in the treatment of complex patients with CTOs is associated with a reduction in the rate of MACE and restenosis compared with BMS.

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