Very Long Sirolimus-Eluting Stent Implantation for De Novo Coronary Lesions

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Long-length stenting has a poor outcome when bare metal stents are used. The safety and efficacy of the sirolimus-eluting stent (SES) in long lesions has not been evaluated. Therefore, the aim of the present study was to evaluate the clinical and angiographic outcomes of SES implantation over a very long coronary artery segment. Since April 2002, all patients treated percutaneously at our institution received a SES as the device of choice as part of the Rapamycin Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. During the RESEARCH registry, stents were available in lengths of 8, 18, and 33 mm. The present report includes a predefined study population consisting of patients treated with >36-mm-long stented segments. Patients had a combination of ≥2 overlapping stents at a minimum length of 41 mm (i.e., one 33-mm SES overlapping an 8-mm SES) to treat native de novo coronary lesions. The incidence of major cardiac adverse events (death, nonfatal myocardial infarction, and target lesion revascularization) was evaluated. The study group comprised 96 consecutive patients (102 lesions). Clinical follow-up was available for all patients at a mean of 320 days (range 265 to 442). In all, 20% of long-stented lesions were chronic total occlusions, and mean stented length per lesion was 61.2 ± 21.4 mm (range 41 to 134). Angiographic follow-up at 6 months was obtained in 67 patients (71%). Binary restenosis rate was 11.9% and in-stent late loss was 0.13 ± 0.47 mm. At long-term follow-up (mean 320 days), there were 2 deaths (2.1%), and the overall incidence of major cardiac events was 8.3%. Thus, SES implantation appears safe and effective for de novo coronary lesions requiring multiple stent placement over a very long vessel segment. ©2004 by Excerpta Medica, Inc.

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Treatment of complex coronary artery stenosis with a long segment of bare metal stent is associated with high restenosis rates and poorer clinical outcome.[1–7] Therefore, in contrast to shorter lesions, stent placement for diffusely diseased coronary segments is frequently avoided. The efficacy of the sirolimus-eluting stent (SES) implantation has been recently evaluated in the context of 2 large randomized trials. The RAndomized study with the sirolimus-eluting Bx VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions (RAVEL) trial[8] included only single lesions covered by an 18-mm-long stent and had a zero restenosis rate. In the US Multicenter, Randomized, Double-Blind Study of the SIRolImUS-eluting Bx velocity balloon expandable stent (SIRIUS) trial,[9] relatively long stent placement was allowed (maximum of 2 overlapping 18-mm-long SESs) and the restenosis rate was 9.2%. The efficacy of a SES implanted over a total coronary length >36 mm has not been tested to date. In the present study, we sought to evaluate the outcomes of patients receiving overlapping stents implanted over a length >36 mm to treat native de novo coronary lesions.

METHODS

Since April 16, 2002, it has been our policy to use the SES (Cypher, Cordis Europa NV, Roden, The Netherlands) as the device of choice for every percutaneous coronary intervention performed at our institution as part of the Rapamycin Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. Further details of the methods have been previously described.[10]

Study group and stent implantation: During the RESEARCH registry enrollement, SESs were available at lengths of 8, 18, and 33 mm. The present report includes a predefined study group composed of pa-

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TABLE 1 Baseline Patient Demographics and Procedural Data

	Patients with Longer Stented Segment (n = 96, 102 lesions)
Age (yrs)	64 ± 12
Men	62%
Diabetes	18%
Current smoking	26%
Hypercholesterolemia	57%
Hypertension	45%
Previous myocardial infarction	32%
Previous balloon angioplasty	19%
Target vessel	
Left anterior descending artery	47%
Left circumflex artery	9%
Right coronary artery	44%
Chronic total occlusion	20%
Direct stenting	53%
Multivessel disease	52.1%
Primary percutaneous coronary intervention	8%
Glycoprotein IIb/IIIa inhibitor use	31%
Mean no. of sirolimus-eluting stents per lesion	2.66 ± 0.9 (range 2–6)
Mean length of sirolimus-eluting stent per lesion (mm)	61.2 ± 21.4 (range 41–134)
Mean diameter of Sirolimus-eluting stent (mm)	2.82 ± 0.24

tients treated with stented segments >36 mm long. Therefore, because of the availability of stent lengths, all included patients had a combination of at least 2 overlapping stents at a minimum length of 41 mm (i.e., one 33-mm SES overlapping an 8-mm SES). Patients receiving a SES to treat in-stent restenotic lesions were excluded from the present analysis. Also, lesions with angiographically visible gaps between stents were not included in this study. During 6 months of enrollment, 96 consecutive patients (102 lesions) fulfilled the above criteria and formed the present study group. The stented length was based on the cumulative length of the patient's adjacent stents. All procedures were performed according to standard interventional techniques, except with the use of the SES as the device of choice. However, the final interventional strategy was entirely left at the discretion of the operator (angiographic success defined as <30% residual diameter stenosis by visual assessment in the presence of Thrombolysis In Myocardial Infarction (TIMI-3) trial anterograde flow). All patients received lifelong aspirin and clopidogrel 75 mg/day for 6 months. Glycoprotein IIb/IIIa inhibitors were given at the discretion of the physician. The hospital ethics committee approved the study protocol and written informed consent was obtained from all patients.

Definitions and follow-up: All patients were evaluated for the occurrence of major cardiac adverse events, defined as death, myocardial infarction, target lesion revascularization, and target vessel revascularization. In-hospital outcome information was retrieved by means of an electronic clinical database for patients maintained in our hospital after the procedure and by review of the hospital records for those discharged to secondary hospitals. After discharge, recordings of all repeat interventions (surgical and percutaneous) and rehospitalizations were prospectively collected in a dedicated database. Follow-up information was obtained by regular outpatient evaluation, by phone contact, or by mail. Myocardial infarction was documented by an increase in the creatine kinase level of more than twice the upper limit, with an increased creatine kinase-MB. Cardiac markers were measured serially for all patients maintained in our institution. Among those discharged to their community hospitals, cardiac markers were collected only if a postprocedural myocardial infarction was suspected. Consequently, enzymatic assessment was not available for all patients, but for those whom the likelihood of postprocedure myocardial infarction was high.[10] Target vessel revascularization was defined as either surgical or percutaneous reintervention driven by significant (>50%) luminal narrowing either within the stent or within the 5-mm borders proximal and distal to the stent, and was undertaken in the presence of either anginal symptoms or objective evidence of ischemia. All living patients at 6 months were considered eligible for angiographic follow-up. Binary restenosis was defined as diameter stenosis >50% within the stent or in the 5-mm segments proximal or distal to the stent. Late loss was defined as the difference between the minimal luminal diameter immediately after the procedure and at follow-up.

Statistical analysis: Discrete variables are presented as counts and percentages. Continuous variables are presented as mean ± SD and compared by Student's *t* test.

RESULTS

Baseline and procedural characteristics of the 96 patients (102 lesions) are listed in Table 1. Approximately half of lesions were located in the left anterior descending coronary artery (47%) or in the right coronary artery (44%). The mean number of stents per lesion was 2.66 ± 0.9 (range 2 to 6 stents), and the average stented length was 61.2 ± 21.4 mm. The angiographic success rate was 97%. Follow-up coronary angiography was performed in 67 patients (71% of eligible cases) (Table 2). Binary restenosis (diameter stenosis >50%) was identified in 8 lesions (11.9%). Among the 8 lesions (8 patients) with binary restenosis, 5 occurred within the stent, 1 in the proximal segment, and 2 in the distal 5-mm adjacent vessel segment. All post-SES restenoses were focal and <10 mm in length. Among these 8 patients, 4 were asymptomatic and did not undergo repeat revascularization. Complete clinical follow-up was available for all patients at an average of 320 ± 67.4 days (range 265 to 442) and is summarized in Table 3.

Two patients died. One patient died during the in-hospital period after emergent bypass surgery for a procedure related to left main stem dissection caused by the guiding catheter. The second patient was admitted in cardiogenic shock due to postinfarction un-

TABLE 2 Quantitative Coronary Angiography Analysis After Procedure and Data at Six-month Follow-up (n = 67)

Postprocedure	Proximal 5 mm	In-stent	Distal 5 mm
Vessel reference diameter (mm)	3.17 ± 0.55	2.68 ± 0.51	2.45 ± 0.51
Minimal lumen diameter (mm)	2.76 ± 0.54	2.17 ± 0.47	1.94 ± 0.53
% diameter stenosis	12	18	20
6-mo follow-up			
Vessel reference diameter (mm)	3.30 ± 0.61	2.82 ± 0.59	2.63 ± 0.62
Minimal lumen diameter (mm)	2.74 ± 0.58	2.04 ± 0.64	2.12 ± 0.60
% diameter stenosis	17	27	19
Late lumen loss (mm)	0.02 ± 0.52	0.13 ± 0.47	−0.16 ± 0.47

TABLE 3 Major Adverse Cardiac Events (n = 96) at 320 Days of Follow-up

Death	2 (2.1%)
Nonfatal myocardial infarction	1 (1.0%)*
Target vessel revascularization	6 (6.2%)
Target lesion revascularization	4 (4.2%)
CABG	2 (2.1%)†
Any major adverse cardiac event	8 (8.3%)

*Non–Q-wave myocardial infarction peak creatine kinase 567IU (MB fraction 62IU).
†One of 2 patients who underwent emergency coronary artery bypass graft surgery for left main stem dissection died in the hospital.
CABG = coronary artery bypass graft surgery.

stable angina. He had 3-vessel disease, but the treatment was restricted to the culprit lesion. In total, six 2.25-mm diameter SESs were implanted in the left anterior artery/diagonal bifurcation. The patient died suddenly 43 days after the procedure. Although there is no clear evidence, subacute stent thrombosis cannot be ruled out in this case. Nonfatal myocardial infarction occurred in 1 patient. He developed a no-reflow phenomenon after stent placement, which was resolved after intracoronary adenosine and nitropruside infusion. At 6 months follow-up angiography, the patient was asymptomatic with a patent long-stented segment.

Two patients underwent emergent bypass surgery for left main dissection. One patient died in the hospital as previously mentioned, and the other had been successfully treated for left main dissection, but developed cardiac tamponade after the procedure and underwent surgical pericardial drainage, during which he received a venous graft to the first obtuse marginal branch.

In all, 4 patients were successfully treated with repeat percutaneous coronary intervention electively for focal restenotic lesions. Overall, major adverse cardiac event-free survival was 91.7% at 320-day follow-up.

DISCUSSION

We report that the use of long length of SES implantation for de novo coronary lesions is associated with a low rate of major adverse cardiac events, mainly because of a reduced incidence of target lesion revascularization. In particular, SES demonstrated effective suppression of neointimal hyperplasia with a late lumen loss of 0.13 mm, which is substantially lower than that of major published studies with bare metal stents for long segments, ranging from 0.79 to 1.41 mm.[1,3–5] Accordingly, the restenosis rate observed after SES was strikingly lower. Importantly, the average stented length in our study was at least 10 mm longer than in previous series with bare metal stents.

Longer stented segment length using bare metal stents is an independent predictor of restenosis and adverse events.[1] Long stenting is frequently associated with prolonged intracoronary manipulation due to multiple and overlapping stent placement, which may lead to injury to the vessel wall integrity. Moreover, the greater metal density may be potentially associated with a higher degree of local vascular injury, which altogether may increase the risk of cardiac events and restenosis. The incidence of late complications has been reported to be directly proportional to the total length of stents implanted. Previously, Schalij et al[6] reported a 25% incidence of major adverse events for patients treated with bare metal stents at a mean stented length of 45 mm. In the Additional Value of NIR Stents for Treatment of Long Coronary Lesions (ADVANCE)[3] Study, the reported major adverse cardiac event rate was 23%. The present results are reassuring, because the relatively low incidence of adverse events (8.3%) presented in our series occurred in association with a markedly long length of the implanted SES (61 mm on average).

Among 5 patients (7.4%) with in-stent restenosis, only 1 focal in-stent restenosis was seen in the overlapped stented segment. Furthermore, consistent with previous reports regarding the angiographic pattern of restenosis of SES,[11] all our restenoses were focal and therefore easy to treat with repeat percutaneous coronary intervention. Because all patients with angiographically visible gaps between stents were excluded from the present analysis, incomplete lesion coverage was not identified as a possible mechanism of restenosis in any case.

There have been concerns that the risk for thrombosis may increase after implantation of the long length of the stent. In the present study, no documented thrombotic stent occlusion was observed, although we cannot rule out stent thrombosis in the patient who died suddenly 43 days after the index procedure. There is no consensus for the period of clopidogrel prescription after SES implantation, espe-

cially after treatment of complex lesions. Although no late thrombotic events were diagnosed after discontinuation of clopidogrel in our series (i.e., after 6 months), additional studies are warranted to further evaluate the best antiplatelet scheme for these patients.

Several limitations are noteworthy because of the small cohort of patients without a direct comparative control group. Angiographic follow-up could not be obtained in all patients. Nonetheless, not consenting to angiographic follow-up was not considered as an exclusion criterion for the RESEARCH study, which enrolled all unselected, consecutive patients treated in daily practice with percutaneous interventions. Obviously, this scenario differs substantially from that of randomized trials and limits the compliance to angiographic restudy. However, all eligible patients for whom angiographic re-evaluation was not obtained remained event free throughout the follow-up period. Postprocedure cardiac markers were not collective routinely for all patients (available for 46 of 96 patients [46%] in the study group). This was justified by the fact that high-grade enzymatic elevations (those with proved prognostic impact) rarely occur undetected in asymptomatic patients.

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