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EXPRESS PUBLICATION

Short- and Long-Term Clinical Benefit of Sirolimus-Eluting Stents Compared to Conventional Bare Stents for Patients With Acute Myocardial Infarction

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OBJECTIVES This study investigated the clinical outcomes of patients with ST-segment elevation myocardial infarction (MI) treated with sirolimus-eluting stents (SESs) or with conventional bare stents.

BACKGROUND The clinical impact of SES implantation for patients with ST-segment elevation MI is currently unknown.

METHODS Primary angioplasty was performed with SESs in 186 consecutive patients with acute MI who were compared with 183 patients treated with bare stents. The incidence of death, reinfarction, and repeat revascularization was assessed at 30 and 300 days.

RESULTS Postprocedure vessel patency, enzymatic release, and the incidence of short-term adverse events were similar in both the sirolimus and the bare stents (30-day rate of death, reinfarction, or repeat revascularization: 7.5% vs. 10.4%, respectively; p = 0.4). Stent thrombosis was not diagnosed in any patient in the sirolimus group and occurred in 1.6% of patients treated with bare stents (p = 0.1). At 300 days, treatment with SESs significantly reduced the incidence of combined adverse events (9.4% vs. 17%; hazard ratio [HR] 0.52 [95% confidence interval (CI) 0.30 to 0.92]; p = 0.02), mainly due to a marked reduction in the risk of repeat intervention (1.1% vs. 8.2%; HR 0.21 [95% CI 0.06 to 0.74]; p = 0.01).

CONCLUSIONS Compared to conventional bare stents, the SESs were not associated with an increased risk of stent thrombosis and were effective in reducing the incidence of adverse events at 300 days in unselected patients with ST-segment elevation acute MI referred for primary angioplasty. (J Am Coll Cardiol 2004;43:704–8) © 2004 by the American College of Cardiology Foundation

Routine stent implantation has been advocated for patients with acute myocardial infarction (MI) referred for primary angioplasty, with superior results compared to balloon dilation (1–3). However, the late clinical efficacy is still hampered by the occurrence of in-stent restenosis and the need for repeat intervention.

Sirolimus-eluting stents (SESs) have proven to be effective in reducing late restenosis compared to conventional stenting in elective patients (4–6). We have recently shown in a relatively small consecutive series of cases that SES implantation in patients with acute MI was safe and associated with an extremely low (zero) incidence of angiographic restenosis at six months (7). However, the clinical benefit of SESs in comparison to conventional stent implantation remains currently unknown. Therefore, we evaluated the long-term clinical outcomes of a large series of patients with acute MI treated with primary angioplasty utilizing either SESs or conventional metal stents.

METHODS

Since April 2002, SES implantation (Cypher, Johnson & Johnson-Cordis unit, Cordis Europa NV, Roden, The Netherlands) has been utilized as the strategy of choice for patients treated with percutaneous intervention in our institution (8). Up until January 2003, a total of 186 consecutive patients with ST-segment elevation acute MI have been treated with primary angioplasty utilizing exclusively SESs and were included in the present report. The first 89 patients of the present series were included in an angiographic substudy, of which the results have been reported previously (7). A control group for comparison was composed of 183 consecutive patients with ST-segment elevation acute MI treated with conventional bare stents in the period immediately before the introduction of SESs. The following bare metal stents were used: BX Sonic or BX Velocity in 53% (Cordis, Johnson & Johnson, Warren, New Jersey); Multi-Link Penta in 22% (Guidant Corp., Santa

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Abbreviations and Acronyms

CI = confidence interval
CK = creatine kinase
HR = hazard ratio
MI = myocardial infarction
SES = sirolimus-eluting stent
TIMI = Thrombolysis In Myocardial Infarction

Clara, California); Multi-Link Tetra in 6% (Guidant Corp.); R-Stent in 6% (Orbus Medical Technologies, Fort Lauderdale, Florida), and other stents in 12%. In both study phases, all patients were enrolled regardless of the clinical or anatomical presentation, including patients admitted with cardiogenic shock (defined as persistent systolic blood pressure <90 mm Hg, or the need of vasopressors or intra-aortic balloon pumping required to maintain blood pressure >90 mm Hg with evidence of end-organ failure and elevated left ventricular filling pressures). Therefore, the total study population comprised all 369 consecutive patients with ST-segment elevation acute MI undergoing primary angioplasty with either bare stents or SESs in the two study phases, respectively. Patients with angioplasty after failed thrombolytic therapy were excluded from the present analysis. This study protocol was approved by the local ethics committee, and written informed consent was given by every patient.

The final interventional strategy, as well as the utilization of periprocedural glycoprotein IIb/IIIa inhibitors and antithrombotic medications, was entirely left to the discretion of the operator. Baseline and postprocedure anterograde flow were evaluated off-line according to the Thrombolysis In Myocardial Infarction (TIMI) criteria (9) by cardiologists blinded to both the stent group and to the clinical outcomes. Clopidogrel was recommended for at least one month in the control group. In the SES group, clopidogrel was prescribed for three months, unless one of the following was present (in which case clopidogrel was maintained for at least six months): multiple SES implantation (>3 stents), total stented length >36 mm, bifurcation stenting, and in-stent restenosis.

Patients were prospectively followed for the occurrence of major adverse cardiac events: 1) all-cause death, 2) nonfatal MI, or 3) target vessel revascularization. Reinfarction was diagnosed by recurrent symptoms and/or new electrocardiographic changes in association with re-elevation of the creatine kinase (CK) and CK-MB levels of >1.5 times the previous value, if within 48 h, or >3 times the upper normal limit, if after 48 h from the index infarction (1,7). Target vessel revascularization was defined as a repeat intervention (surgical or percutaneous) driven by any lesion located in the same epicardial vessel treated at the index procedure. Thrombotic stent occlusion was angiographically documented as a complete occlusion (TIMI flow grade 0 or 1) or a flow-limiting thrombus (TIMI flow grade 1 or 2) of a previously successfully treated artery. Routine angiographic follow-up was obtained only for patients treated with SESs enrolled during the first six months; results of this subanalysis have been previously reported (7).

Continuous variables were presented as mean ± standard deviation, and were compared using the Student unpaired *t* test. Categorical variables were presented as counts and percentages and compared with the Fisher exact test. Survival free of adverse events was estimated using the Kaplan-Meier method and differences between curves were evaluated by the log-rank test. Cox proportional hazards survival models were used to assess risk reduction. Multivariate analyses were performed to identify independent predictors of long-term major adverse cardiac events. Baseline and procedural characteristics associated with the incidence of adverse events at univariate analysis (p value for selection ≤0.2) were tested for their multivariate predictive value (tested variables: SES utilization, diabetes, cardiogenic shock, multivessel disease, culprit vessel, pre-procedure TIMI flow, postprocedure TIMI flow, current smoking). The final model was built by backward stepwise variable selection with an entry and exit criteria set at the $p = 0.05$ and $p = 0.1$ levels, respectively.

RESULTS

Baseline characteristics were similar between both study groups, except by an older age and a lower incidence of previous MI in the sirolimus group (Table 1). Procedural characteristics differed between both groups in terms of the utilization of glycoprotein IIb/IIIa inhibitors (sirolimus: 37% vs. bare stents: 56%; $p < 0.01$) and the number of stents implanted (sirolimus: 1.9 ± 1.2 vs. bare stents: 1.7 ± 1.0; $p = 0.03$). As defined by the study protocol, the duration of clopidogrel prescription was longer for patients with sirolimus stents (Table 1).

No significant differences existed in the 30-day outcomes between patients treated with sirolimus or bare stents (Table 2). Stent thrombosis was diagnosed in three patients (1.6%) treated with bare stents and was not detected in the SES group ($p = 0.1$) (Table 2).

At 300 days, no differences were noted between both study groups in the incidence of death and death or reinfarction (Table 2). However, the incidence of 300-day major adverse events was significantly lower in the sirolimus stent group compared to the bare stent group (9.4% vs. 17%, respectively; hazard ratio [HR] 0.52 [95% confidence interval (CI) 0.30 to 0.92]; $p = 0.02$) (Table 2, Fig. 1), mainly due to a marked reduction in the risk of repeat intervention (1.1% vs. 8.2%, respectively; HR 0.21 [95% CI 0.06 to 0.74]; $p = 0.01$). A multivariate analysis was performed to adjust for baseline and procedural imbalances between the study groups (Table 3). Sirolimus-eluting stent utilization was identified as an independent predictor of 300-day death, reinfarction, or repeat revascularization (HR 0.53 [95% CI 0.29 to 0.95]; $p = 0.03$).

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Table 1. Baseline and Procedural Characteristics of Patients Treated With Bare Stents or SES Implantation

	Bare Stents (n = 183)	SES (n = 186)	p Value
Male (%)	79	75	0.4
Age, yrs ± SD	57 ± 12	60 ± 12	0.04
Diabetes (%)	12	11	0.9
Current smoking (%)	47	46	0.8
Previous myocardial infarction (%)	24	14	0.03
Previous angioplasty (%)	9	7	0.4
Previous bypass surgery (%)	3	2	0.3
Coronary disease			0.3
Single-vessel (%)	48	55	
Double-vessel (%)	29	27	
Triple-vessel (%)	24	18	
Cardiogenic shock (%)	10	13	0.3
Time from symptom onset to angioplasty, h ± SD	3.0 ± 2.7	3.2 ± 1.9	0.6
Infarct-related vessel			0.3
Right coronary artery (%)	30	37	
Left anterior descending (%)	57	53	
Left circumflex artery (%)	10	8	
Left main coronary artery (%)	1	2	
Bypass graft (%)	2	—	
TIMI flow baseline			0.7
Grade 0/I (%)	73	73	
Grade II (%)	15	17	
Grade III (%)	13	10	
TIMI flow after angioplasty			0.5
Grade 0/I (%)	4	2	
Grade II (%)	17	15	
Grade III (%)	79	83	
Number of stents ± SD	1.7 ± 1.0	1.9 ± 1.2	0.03
Glycoprotein IIb/IIIa inhibitor (%)	56	37	<0.01
Clopidogrel prescription, months ± SD	2.1 ± 1.5	3.7 ± 2.1	<0.01
Peak CK, IU/l ± SD*	3,957 ± 5,135	3,126 ± 3,126	0.1
Peak CK-MB, IU/l ± SD†	319 ± 230	296 ± 255	0.5

*Upper limit of normal 199 IU/l. †Upper limit of normal 23 IU/l.
CK = creatine kinase; SD = standard deviation; SES = sirolimus-eluting stents; TIMI = Thrombolysis In Myocardial Infarction.

DISCUSSION

The main finding of the present study was that SES implantation was effective in reducing the incidence of adverse events at 300 days in unselected patients with ST-segment elevation acute MI, compared to conventional bare stenting. Furthermore, the risk of subacute thrombosis within the first 30 days did not appear higher compared with bare metal stents. Sirolimus-eluting stents were asso-

Table 2. Kaplan-Meier Estimates of Adverse Events at 30 Days and at 300 Days

	Bare Stents (n = 183)	SES (n = 186)	p Value
30-Day outcomes			
Death (%)	5.5	5.9	1.0
Death or nonfatal reinfarction (%)	7.1	6.5	0.8
Target vessel revascularization (%)	4.4	1.1	0.1
Any event (%)	10.4	7.5	0.4
Stent thrombosis (%)*	1.6	0	0.1
300-Day outcomes			
Death (%)	8.2	8.3	0.8
Death or nonfatal reinfarction (%)	10.4	8.8	0.5
Target vessel revascularization (%)	8.2	1.1	<0.01
Any event (%)	17.0	9.4	0.02

*Angiographically documented stent thrombosis.
SES = sirolimus-eluting stents.

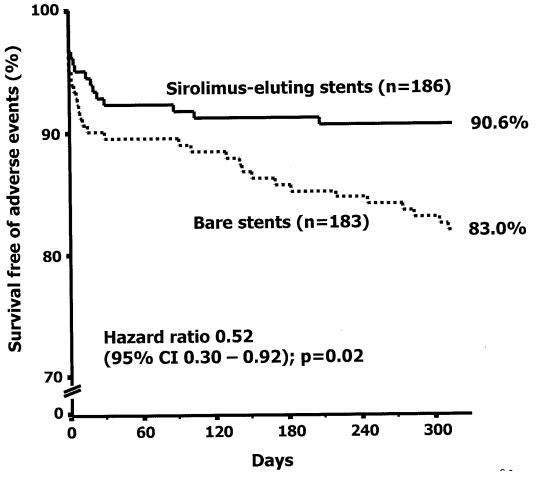

Figure 1. Survival free of reinfarction or target vessel revascularization in the sirolimus-eluting stent and conventional stent groups. CI = confidence interval.

Table 3. Multivariate Predictors of 300-Day Major Adverse Cardiac Events

	Hazard Ratio	95% Confidence Interval	p Value
SES utilization	0.53	0.29–0.95	0.03
Cardiogenic shock	3.31	1.72–6.34	<0.01
Culprit vessel left main coronary	6.05	1.60–22.87	<0.01
Culprit vessel left anterior descending	2.02	1.10–3.71	0.02
Postprocedure TIMI flow grade			<0.01
Grade 0/I (reference)	1.00	—	
Grade II	0.29	0.11–0.76	
Grade III	0.17	0.07–0.40	
Current smoking	0.57	0.31–1.02	0.06

SES = sirolimus-eluting stents; TIMI = Thrombolysis In Myocardial Infarction.

ciated with a relative reduction of 48% in the risk of death, reinfarction, or repeat intervention and a relative reduction of 79% in the risk of repeat intervention at 300 days.

In our series, reperfusion treatment with SESs was associated with similar rates of vessel patency, enzymatic release, and 30-day complications compared to bare stents. The death rate and the incidence of death or reinfarction were similar in both study groups, but somewhat higher than those reported in randomized trials with selected patients (1,2). These findings most probably reflect the unrestrictive inclusion criteria of our series (10), which frequently enrolled patients not included in randomized studies, as, for instance, cardiogenic shock, multivessel disease, and unprotected left main lesions. Importantly, stent thrombosis has not been identified in any patient treated with sirolimus stents and occurred in three controls (1.6%), with no statistical difference between the groups. Although the incidence of stent thrombosis in the bare stent group was at a somewhat higher range, our results in this group were not discrepant from historical series with conventional stents (1,2,11–13).

Coronary stenting for the treatment of acute MI has been limited by the need of late repeat intervention, which has been reported to occur in approximately 9% of cases at six months, ranging from 3.6% to 22.7% (1–3). The incidence of repeat intervention after conventional stenting in our series (8.2%) was in line with these previous figures. Conversely, patients treated with SES implantation clearly had a reduced risk of reintervention at 10 months. Of note, between 30 days and 10 months, no additional patient was referred for repeat revascularization, which is consistent with the lack of angiographic restenosis after sirolimus stent implantation, as previously shown in a subset of patients from the present population (7).

The peri- and postprocedural antiplatelet therapeutic scheme differed between patients treated with either bare or sirolimus stents in our series. Patients in the sirolimus group received fewer glycoprotein IIb/IIIa inhibitors but had a longer clopidogrel prescription time. However, none of these characteristics were identified as independent predictors influencing the outcomes of patients. The impact of clopidogrel and glycoprotein IIb/IIIa inhibitors on the long-term clinical outcomes of patients with ST-segment elevation acute MI remains to be established (2,14,15).

Conclusions. Sirolimus-eluting stent implantation for unselected patients with ST-segment elevation acute MI was associated with similar procedural and 30-day outcomes compared to bare stents, but markedly reduced the risk of major adverse events and repeat intervention at 10 months. By providing effective mechanical reperfusion with similar results to the current therapeutic standard, and decreasing the incidence of late complications, SESs appeared as an attractive approach for patients admitted with acute MI. The promising results of the present study warrant further confirmation in the context of a randomized trial.

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