Journal of the American College of Cardiology Vol. 60, No. 5, 2012

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.01.073

Second-Generation Everolimus-Eluting Stents Versus First-Generation Sirolimus-Eluting Stents in Acute Myocardial Infarction

1-Year Results of the Randomized XAMI (XienceV Stent vs. Cypher Stent in Primary PCI for Acute Myocardial Infarction) Trial

Sjoerd H. Hofma, MD, PhD,* Jan Brouwer, MD, PhD,* Matthijs A. Velders, MD,* Arnoud W. J. van't Hof, MD, PhD,† Pieter C. Smits, MD, PhD,‡ Michel Queré, MD,* Cornelis Jan de Vries, MD,* Adrianus J. van Boven, MD, PhD*

Leeuwarden, Zwolle, and Rotterdam, the Netherlands

Objectives The goal of this study was to compare the efficacy and safety of second-generation everolimus-eluting stents (EES) with first-generation sirolimus-eluting stents (SES) in primary percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI).

Background Drug-eluting stents (DES) in AMI are still feared for possible late and very late stent thrombosis (ST). Newer-generation DES, with more hemocompatible polymers and improved healing, may show promise regarding increased efficacy of DES with improved safety. However, no randomized trials in AMI are available.

Methods A total of 625 patients with AMI were randomized (2:1) to receive EES or SES in the XAMI (XienceV Stent vs Cypher Stent in Primary PCI for Acute Myocardial Infarction) trial. Primary endpoint was major adverse cardiac events (MACE) at 1 year consisting of cardiac death, nonfatal AMI, or any target vessel revascularization. The study was powered for noninferiority of EES. Secondary endpoints comprised ST rates and MACE rate up to 3 years.

Results The MACE rate was 4.0% for EES and 7.7% for SES; the absolute difference was −3.7% (95% confidence interval: −8.28 to −0.03; p = 0.048) and relative risk was 0.52 (95% confidence interval: 0.27 to 1.00). One-year cardiac mortality was low at 1.5% for EES versus 2.7% for SES (p = 0.36), and 1-year incidence of definite and/or probable ST was 1.2% for EES versus 2.7% for SES (p = 0.21).

Conclusions In this all-comer, randomized, multicenter AMI trial, second-generation EES was noninferior to SES, and superiority for MACE was suggested. ST rate in EES at 1-year was low, but long-term follow-up and larger studies will have to show whether very late ST rates will also be improved in newer DES. (XienceV Stent vs Cypher Stent in Primary PCI for Acute Myocardial Infarction [XAMI]; NTR1123) (J Am Coll Cardiol 2012;60:381–7) © 2012 by the American College of Cardiology Foundation

The efficacy and safety of drug-eluting stents (DES) in the treatment of coronary artery disease is well established. Restenosis rates have dramatically decreased for both on-label and off-label indications (1–3). Despite these results, the concern for increased (late) stent thrombosis is still present (3–5). This finding may be due to delayed vascular healing after DES implantation (6,7), probably as a result of drug and/or polymer reaction. Late coronary endothelial dysfunction after DES implantation has been reported previously (8). Because acute myocardial infarction (AMI) presents the highest possible thrombotic coronary lesions, DES implantation during primary percutaneous coronary intervention (PCI) for AMI is still not advocated by many interventional cardiologists. However, even in this challenging population, the use of DES has increased over the last few years, and several randomized studies and large cohort studies have reported efficacy and safety (9–12).

Newer antiproliferative drugs and more biocompatible polymers have shown promise in reducing further the rate of (late) stent thrombosis in patients in stable condition

From the *Medical Center Leeuwarden, Leeuwarden, the Netherlands; †Isala Clinics, Zwolle, the Netherlands; and the ‡Maasstad Hospital Rotterdam, the Netherlands. Dr. Hofma was the primary investigator of the study; Drs. Van't Hof and Smits were the local primary investigators at their institution. The Cardiology Research Foundation of the Medical Center Leeuwarden received an unrestricted research grant from Abbott Vascular. Dr. Smits has received speaker and travel fees from Abbott Vascular; and is a consultant for Blue Medical. Dr. van't Hof has received speaker fees from Merck Sharp & Dohme and IrokoCardio; and is on the advisory board of AstraZeneca, The Medicines Company, Daiichi Sankyo, and Lilly. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received November 2, 2011; revised manuscript received January 19, 2012, accepted January 23, 2012.

Abbreviations and Acronyms

AMI = acute myocardial infarction
BMS = bare-metal stent(s)
CI = confidence interval
DES = drug-eluting stent(s)
EES = everolimus-eluting stent
MACE = major adverse cardiac event(s)
NSTEMI = non–ST-segment elevation myocardial infarction
PCI = percutaneous coronary intervention
SES = sirolimus-eluting stent(s)
STEMI = ST-segment elevation myocardial infarction
TVR = target vessel revascularization

(13,14). However, no randomized data are available on the efficacy and safety of newer-generation DES in AMI patients.

In our center, Cypher (Cordis, Bridgewater, New Jersey), the sirolimus-eluting stent (SES), has been the default stent since 2004 in PCI for all indications, including acute coronary syndromes. With the emergence of a second-generation "limus" DES stent (Xience V [Abbott Vascular, Santa Clara, California], an everolimus-eluting stent [EES]), a multicenter randomized trial was designed to compare both stents in AMI patients (XAMI [XienceV Stent vs Cypher Stent in Primary PCI for Acute Myocardial Infarction]).

Methods

Study design and patient population. Between February 2008 and December 2009, consecutive patients presenting with ST-segment elevation myocardial infarction (STEMI) treated with primary PCI and fulfilling the inclusion criteria where included in three large interventional centers in the Netherlands. To be included, patients had to have STEMI and be eligible for primary PCI. Patients with non–ST-segment elevation myocardial infarction (NSTEMI) with an emergency indication for PCI at admission were also allowed.

Exclusion criteria were as follows: stent thrombosis of previous stent or chronic total occlusion as target lesion; known allergy or intolerance to sirolimus, everolimus, aspirin, or clopidogrel; intubated patient after extensive resuscitation or shock patients for whom no informed consent could be obtained; estimated life expectancy <1 year; or stent size required to treat lesion >3.5 mm (maximum diameter of SES).

The study was approved by the institutional ethics committee at each participating center, and written informed consent was obtained from all patients.

Randomization and blinding. Patients were randomized 2:1 to EES or SES by using a sealed envelope technique, directly after diagnostic angiography and assessment of feasibility for stenting. Operators were not blinded to the allocated stent. An independent Data Safety Monitoring Board evaluated the study safety after 30-day inclusion of 300 patients, blinded to the allocated stent type. At 1 year, all events were evaluated and adjudicated by an independent clinical event committee, again blinded to treatment assignment.

Procedure. All patients were pretreated with intravenous aspirin and heparin 5,000 IE bolus, and they received clopidogrel with a loading dose of preferably 600 mg. Interventions were performed according to local practice in three high-volume centers by high-volume operators.

Glycoprotein IIb/IIIa receptor blocker use, thrombus aspiration, and balloon pre-dilation were left up to the operator. Aspirin was recommended for life, and clopidogrel for a minimum of 1 year.

The study has a 3-year planned follow-up.

Study endpoints and definitions. The primary endpoint was major adverse cardiac events (MACE) at 12 months consisting of any event during follow-up in hierarchical order: cardiac death, nonfatal reinfarction, or any target vessel revascularization (TVR).

The secondary endpoints were (sub) acute stent thrombosis at 30 days and late stent thrombosis at 1, 2, and 3 years, MACE at 30 days and 2 and 3 years, and all-cause mortality at 1, 2, and 3 years.

Reinfarction was defined according to recurrent symptoms and/or new electrocardiographic changes, with re-elevation of the creatine kinase concentrations >1.5 times the previous value with elevation of creatine kinase-myocardial band, if within 48 h, or >3 times the upper normal limit if after 48 h from the index AMI. More than 5 times the upper limit of normal creatine kinase was required for the diagnosis of AMI after bypass surgery.

TVR was defined as any repeat percutaneous intervention or bypass grafting of the target vessel, and target lesion revascularization as any repeat percutaneous intervention or bypass grafting of the target lesion or 5 mm proximal or distal to the initial stent.

Definite and probable stent thrombosis was defined according to the Academic Research Consortium criteria (15).

Statistical analysis. Data collection, handling, and statistical analyses were performed by an independent core laboratory (Diagram B.V., Zwolle, the Netherlands).

This trial was based on the notion that the performance of EES would not be inferior to SES in relation to the primary outcome, MACE at 1 year, with the use of a pre-specified noninferiority margin and a 95% confidence interval (CI).

We calculated that a sample size of 600 patients (2:1 randomization) would provide a power of 80% (Farrington and Manning method). This sample size took into account an expected 1-year MACE rate of 8% and a noninferiority margin of 6%, and a 2-sided risk of 0.05. Sample size was increased to 625 patients (after the pilot phase without any unblinding of data) to compensate for a small pilot phase of 80 patients, randomized 1:1, to maintain adequate power of the trial.

Study outcomes were assessed by using both intention-to-treat and per-protocol analyses. The intention-to-treat population included all patients who were randomized to treatment. These results are reported in this paper. The per-protocol population included all patients who fulfilled

the inclusion and exclusion criteria and in whom the randomly chosen stent was placed. A second per-protocol analysis also excluded the NSTEMI patients in the trial to confirm consistency of the trial results in true STEMI patients.

Data are reported as percentages for discrete variables. Continuous variables are reported as mean ± SD or median with 25th and 75th percentiles. Categorical variables were compared by using the chi-square test or Fisher exact test. Continuous variables were compared by using the nonparametric Mann-Whitney *U* test. Kaplan-Meier survival estimates were used to compare time to the first occurrence of MACE with pair-wise differences assessed by using the log-rank test.

Results

Patients and baseline characteristics. A total of 625 consecutive patients with AMI were included in 3 large referral interventional clinics in the Netherlands. Four percent of patients were included with NSTEMI, treated with emergency PCI at presentation. All other patients presented with STEMI. Baseline characteristics are shown in Table 1. Seven percent of patients presented with Killip class >1. Diabetes was present in 10% of patients. In the Netherlands, a dedicated infrastructure exists to directly refer AMI patients to the catheterization suite of an interventional center without any interference of a local hospital, general practitioner, or even the emergency department. First medical contact is typically at the patient's home, and median time from this first contact to balloon inflation was only 75 min in this study. At diagnosis, the ambulance personnel immediately administer both high-dose aspirin and heparin intravenously; in some regions, clopidogrel is also given orally.

Procedure. Angiographic and procedural characteristics are shown in Table 2. More than 50% of patients had Thrombolysis In Myocardial Infarction flow grade 0 at presentation and single-vessel disease. Compared with previous AMI studies, a high percentage of radial access of >50% was used. High-dose clopidogrel loading was administered in most patients; there was also a high percentage of glycoprotein IIb/IIIa receptor blocker use and thrombus aspiration catheter use. No significant differences were seen in any of the parameters except for more heavy calcification in the SES group. Medication at discharge is shown in Table 3.

30-day outcome. One patient was excluded because of withdrawal of informed consent. Results can be seen in Table 4. Mortality was low, and all deaths were cardiac related. Acute stent thrombosis was seen in 1 patient in each group, and definite and/or probable stent thrombosis at 30 days was low (1.3%). Subacute stent thrombosis was higher with SES, although it was not statistically significant.

1-year outcome. At 1 year, 1 additional patient withdrew informed consent and was excluded. This withdrawal resulted in a clinical follow-up at 1 year of 99.7%. One-year results are listed in Table 4. The primary endpoint of MACE, consisting of cardiac death, nonfatal MI, or any TVR at 1 year, was 4.0% for EES and 7.7% for SES. The noninferiority criterion for EES was met with an absolute difference of −3.7% (95% CI: −8.28 to −0.03). MACE rate was significantly reduced for EES with a p value of 0.048 and a relative risk of 0.52 (95% CI: 0.27 to 1.00). Diverging of the MACE-free survival curves can be seen in Figure 1. The cardiac death rate was 1.9% for the total group. Individual endpoints of all-cause mortality, cardiac death, AMI, and TVR all showed a consistently slightly higher event rate in the SES group, but this finding was not statistically significant.

The overall 1-year definite and/or probable stent thrombosis rate was 1.8%. The difference between EES (1.2%) and SES (2.7%) could be attributed to an early difference at 30 days. Late stent thrombosis rate beyond 30 days and up to 1 year was identical and 0.5% in each group. At 1 year, 94% of patients were still using clopidogrel, together with

Table 1 Baseline Characteristics of the Patients

Characteristic	EES (n = 404)	SES (n = 221)	p Value
Male	295 (73.0)	167 (75.1)	0.57
Age (yrs)	61.2 ± 11.3	62.0 ± 11.4	0.39
Killip class I	377 (93.3)	206 (92.8)	0.79
STEMI	387 (95.8)	213 (96.4)	0.72
NSTEMI	17 (4.2)	8 (3.6)	0.72
History			
Previous Q-wave MI	6 (1.5)	7 (3.2)	0.24
Previous non–Q-wave MI	17 (4.2)	7 (3.2)	0.52
Previous PCI	17 (4.2)	6 (2.8)	0.34
Previous CABG	1 (0.2)	4 (1.8)	0.06
Previous stroke	10 (2.5)	12 (5.4)	0.06
Risk factors			
Smoking	220 (54.5)	122 (55.2)	0.86
Diabetes mellitus	36 (8.9)	25 (11.3)	0.33
Hypertension	119 (29.5)	66 (29.9)	0.92
Family history	172 (42.6)	99 (44.8)	0.59
Renal failure	4 (1.0)	4 (1.8)	0.46
Time (min)			
Symptoms to first medical contact	94 (60–180)	97.5 (60–186)	0.92
First medical contact to balloon	75 (60–103)	75 (61–100)	0.58
Infarct size (peak in U/l)			
CK	1,831 ± 1,816	1,923 ± 1,994	0.93
CK-MB	205 ± 180	216 ± 219	0.96
Prehospital anticoagulation/ antithrombotics			
Aspirin	85.3	83.1	0.47
Unfractionated heparin	74.6	71.7	0.43
Clopidogrel loading	37.3	34.2	0.45
GP IIb/IIIa blocker intravenously	5.2	6.8	0.41

Values are n (%), mean ± SD, median (range), or %.

CABG = coronary artery bypass graft; CK = creatine kinase; EES = everolimus-eluting stent(s); GP = glycoprotein; MB = myocardial band; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; SES = sirolimus-eluting stent(s); STEMI = ST-segment elevation myocardial infarction.

JACC Vol. 60, No. 5, 2012
July 31, 2012:381–7

Table 2 Angiographic and Procedural Characteristics

Characteristic	EES (n = 404)	SES (n = 221)	p Value
Target vessel			0.43
RCA	42.3	36.7	
LAD	38.6	43.0	
RCX	18.8	19.5	
Left main	0	0.5	
Graft	0.2	0.5	
Lesion type			0.44
A	1.2	0	
B1	31.4	32.6	
B2	34.7	34.9	
C	32.7	32.6	
Heavy calcification	5.7	11.0	0.02
Severe tortuosity	11.2	9.5	0.52
Ostial lesion	3.5	5.4	0.24
Bifurcation	11.4	15.8	0.12
Visible thrombus	85.1	86.4	0.67
TIMI flow			0.74
0	54.5	57.2	
1	6.7	5.0	
2	17.8	15.8	
3	21.0	22.1	
Extent of coronary artery disease			0.54
1-vessel	54.2	49.8	
2-vessel	32.7	36.7	
3-vessel	13.1	13.6	
Access site			0.27
Radial	52.0	56.6	
Femoral	48.0	43.4	
Periprocedural antithrombotics			
Clopidogrel, 300 mg loading	3.2	2.3	0.62
Clopidogrel, 600 mg loading	96.0	97.2	0.46
Overall GP IIb/IIIa blocker	74.5	77.8	0.36
Thrombus aspiration	61.9	63.8	0.64
Stent placement	99.5	99.5	1.00
TIMI flow grade 0 to 2	5.0	6.3	0.47
IABP	1.5	1.4	1.00
Total stent length, target segment (mm)	25.1 ± 13.5	27.9 ± 17.0	0.09
Maximum stent diameter, target segment (mm)	3.1 ± 0.4	3.1 ± 0.4	0.54
Additional treatment/other vessel than target	5.2	5.9	0.72
No. of stents/patient	1.3 ± 0.6	1.4 ± 0.7	0.45

Values are % or mean ± SD.

IABP = intra-aortic balloon pump; LAD = left anterior descending; RCA = right coronary artery; RCX = right circumflex artery; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

aspirin or with oral anticoagulant agents. No significant difference between both groups was seen (data not shown).

Additional per-protocol analysis, including NSTEMI patients, confirmed robustness of the outcome of the primary endpoint, with a MACE rate of 3.3% (EES) versus 7.8% (SES) (p = 0.01; relative risk: 0.43 [95% CI: 0.21 to 0.86]).

According to the protocol analysis, excluding the NSTEMI patients (4% of the population) who were included in the trial also revealed a clear benefit of the EES, with a MACE rate of 3.5 % versus 7.6 % for SES (p = 0.027; relative risk: 0.46 [95% CI: 0.22 to 0.93]).

Table 3 Medication at Discharge

Medication	EES (%) (n = 404)*	SES (%) (n = 221)*	p Value
Aspirin	98.5	98.2	0.75
Clopidogrel	98.5	98.6	1.00
Beta-blocker	83.7	81.9	0.57
ACE-I	45.8	47.1	0.76
AT II blocker	5.2	5.9	0.72
Statin	90.6	90.0	0.82
Diuretics	8.9	14.5	0.03
Insulin	3.5	3.6	0.92
Oral antidiabetic	5.7	6.8	0.58
Calcium antagonist	4.0	5.9	0.28
Anticoagulation	2.5	6.8	0.01
Nitrate	4.5	2.3	0.16
Spironolactone	2.2	5.4	0.03
Digoxin	0	0.5	0.35

*In case of in-hospital mortality, medication was checked at time of death.

ACE-I = angiotensin-converting enzyme inhibitor; AT = angiotensin; other abbreviations as in Table 1.

Discussion

In this randomized trial, the first-generation DES, the SES Cypher, was compared with the second-generation EES Xience V in patients with AMI. The results show very low MACE rates and low percentages of stent thrombosis at 1

Table 4 Clinical Results at 30 Days and 1 Year of Follow-Up

Outcome	Total	EES	SES	p Value
30-day follow-up	(n = 624)*	(n = 403)	(n = 221)	
Death	10 (1.6)	4 (1.0)	6 (2.7)	0.18
Cardiac death	10 (1.6)	4 (1.0)	6 (2.7)	0.18
Nonfatal MI	1 (0.2)	0	1 (0.5)	0.35
TVR	7 (1.1)	5 (1.2)	2 (0.9)	1.00
TLR	2 (0.3)	1 (0.2)	1 (0.5)	1.00
Stent thrombosis (definite, probable)	8 (1.3)	3 (0.7)	5 (2.3)	0.14
Acute	2 (0.3)	1 (0.2)	1 (0.5)	1.00
Subacute	6 (1.0)	2 (0.5)	4 (1.8)	0.19
1-year follow-up	(n = 623)†	(n = 402)	(n = 221)	
MACE‡	33 (5.3)	16 (4.0)	17 (7.7)§	0.048
Death	15 (2.4)	8 (2.0)	7 (3.2)	0.36
Cardiac death	12 (1.9)	6 (1.5)	6 (2.7)	0.36
Nonfatal MI	5 (0.8)	2 (0.5)	3 (1.4)	0.35
TVR	19 (3.0)	10 (2.5)	9 (4.1)	0.27
TLR	7 (1.1)	5 (1.2)	2 (0.9)	1.00
Stent thrombosis (definite, probable)	11 (1.8)	5 (1.2)	6 (2.7)	0.21
Late (30–365 days)	3 (0.5)	2 (0.5)	1 (0.5)	1.00

*One patient was excluded (withdrawal of informed consent). †In total, by 1 year, 2 patients were excluded because of withdrawal of consent. ‡Primary endpoint: cardiac death, nonfatal myocardial infarction (MI), or any target vessel revascularization (TVR). §Noninferiority criterion was met; absolute difference of −3.7% (95% confidence interval: −8.28 to −0.03; p = 0.048) with a relative risk of 0.52 (95% confidence interval: 0.27 to 1.00).

TLR = target lesion revascularization; other abbreviations as in Table 1.

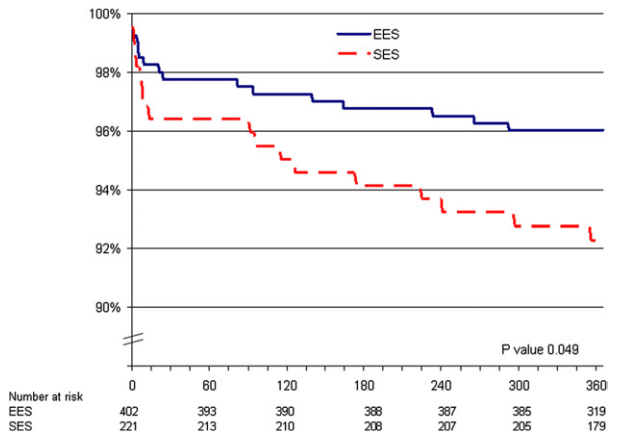

Figure 1 **MACE-Free Survival at 1 Year**

Kaplan-Meier estimates of major adverse cardiac event (MACE)-free survival at 1 year in infarct patients randomized to receive everolimus-eluting stents (EES **[blue line]**) or sirolimus-eluting stents (SES **[red dashed line]**).

year in these very thrombotic lesions. Superiority of the EES was shown for the primary endpoint, and MACE-free survival curves are still diverging at 1 year of follow-up. Robustness of outcome was confirmed with additional per-protocol analysis.

Study population. The current study represents a medium mortality risk, all-comer AMI population, illustrated by the mean peak infarction enzyme levels and comparable to other trials (12,16). Diabetes was present in only 10% of patients, which is almost identical to findings from several other Dutch AMI trials (16,17). Patient characteristics were comparable to other AMI trials such as the large HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial (12) and the PASSION Paclitaxel-Eluting Stent versus Conventional Stent in Myocardial Infarction with ST-Segment Elevation trial (16), and higher risk than the Typhoon trial (Trial to Assess the Use of the CYPHer Sirolimus-Eluting Coronary Stent in Acute Myocardial Infarction Treated With BallOON Angioplasty) (10), in which SES were compared with bare-metal stent (BMS) in patients with AMI. In this study, mortality was low and similar to our study, but extensive exclusion criteria made this a low mortality risk population.

Event rates. All-cause mortality and cardiac mortality rates at 1 year were very low in both arms of our study. This finding may also reflect the progress over the last few years in patient treatment. Pre-medication with aspirin and heparin at the patient's home and direct referral to interventional centers leading to a short " first contact to balloon" times will undoubtedly have an effect on final infarct size and mortality. The use of radial access in >50% of cases affects the risk of bleeding and the morbidity and mortality related to bleeding complications (18,19). The benefit of thrombus aspiration was demonstrated in the TAPAS study (17). Thrombus aspiration was used in almost 63% of cases in the XAMI trial. For comparison, in the HORIZONS-AMI study (12), thrombus aspiration was used in only 11% of patients. Using these contemporary interventional techniques, DES was associated with a low reintervention rate at 1 year. Overall target lesion revascularization rate in this trial was only 1.1% at 1 year. In-stent restenosis, as seen in BMS in 20% to 23% of patients in the TYPHOON and HORIZONS-AMI studies, may not be benign (20), and reintervention for in-stent restenosis is also associated with complication risks.

The entire cohort of patients in our trial was not treated for STEMI. The inclusion criteria allowed NSTEMI patients to be randomized to treatment under strict conditions of indication for emergency PCI at presentation. The pathophysiology of these very unstable lesions will barely differ and frequently also reflect a totally thrombotic occluded vessel in NSTEMI. In our trial, only 4% of patients with NSTEMI were included and will not prevent comparison of our event rates with other STEMI trials. Per-protocol analysis, excluding these NSTEMI patients confirmed this hypothesis, showing a clear benefit for EES in MACE rate at 1 year ($p = 0.027$).

Stent thrombosis. The event rate was accompanied by a low rate of definite and/or probable stent thrombosis. The rate for SES was 2.7%, and for EES it was 1.2%. In comparison, rates were 3.1% for paclitaxel-eluting stents in the largest randomized AMI trial with DES so far, the HORIZONS-AMI. In that trial, the BMS thrombosis rate (definite or probable) was 3.4%. Pre-randomization with heparin and a 600-mg clopidogrel loading dose were independent predictors of reduced acute and subacute stent thrombosis in HORIZONS-AMI, respectively (21). In the XAMI trial, a very high percentage of patients received both agents.

The difference in stent thrombosis rates at 30 days was mainly responsible for the difference at 1 year. Although the influence of procedural and patient characteristics cannot be excluded, it has been suggested that the newer polymer coatings used in second-generation DES, such as the EES, may have anti-inflammatory properties and may be partly responsible for reduction in early stent thrombosis.

Emerging data on delayed healing (6,7) and late endothelial dysfunction after stenting with SES (8,22), possibly involved in (very late) stent thrombosis, has hampered the use of DES, especially in patients with acute coronary syndromes because their highly thrombotic lesions are more prone to stent thrombosis. Despite this finding, randomized trials and large risk-adjusted retrospective studies have shown superiority of first-generation DES over BMS up to several years of follow-up (23,24). Next to a significant decrease in re-interventions, some studies also indicate decreased mortality (23), although randomized trials have not confirmed this finding.

Despite the promising low percentage of stent thrombosis, long-term follow-up will have to demonstrate safety, as continuing rates of late stent thrombosis have been reported

in first-generation DES during the first few years (5,25). Data on improved vascular healing and endothelialization of second-generation DES (7,26) provide some incentive for the hypothesis that in these newer-generation DES, incremental rates of (very) late stent thrombosis may be ameliorated, even in this highly thrombotic subset of patients. Recently, 2-year follow-up data of large randomized all-comer trials including 20% to 30% of AMI patients were presented. Very few additional stent thromboses were seen between 1 and 2 years in the EES stent arms (27–29), as well as in a subgroup analysis of AMI patients who were not separately randomized (30). The XAMI trial will conduct a follow-up up to 3 years to investigate the incidence of very late stent thromboses.

Study limitations. Despite the fact that this was an all-comer trial and infarct enzyme levels do not reflect a low-risk population, clinically unstable shock patients were less likely to be enrolled, and only 7% of patients were in Killip class >1. The low MACE rate cannot be extended to the total general AMI population, but patient characteristics were comparable to most other reported clinical AMI trials comparing DES and BMS (12,16,17), as discussed previously.

The lesions in the SES group were more calcified, and despite comparable peak enzyme levels in both groups, medication at discharge shows a higher percentage of diuretic and oral anticoagulation use in the SES patients. A small imbalance between groups with lower ejection fraction in the SES group at presentation cannot be excluded, but quantified data on left ventricular function at presentation or follow-up were not collected.

The primary objective of the XAMI trial was to demonstrate noninferiority of the EES for MACE. The trial was not powered for superiority, but at 1-year follow-up, a marginally significant better outcome was seen for EES. According to several statistical papers (31,32), superiority may be claimed in this case, but a definite verdict is questionable. As MACE curves diverge at 1 year, longer follow-up may answer this question in the coming years. The trial was not powered to detect significant differences in adverse events such as stent thrombosis, which has a low incidence. Very large trials are necessary to be adequately powered for these events. However, our trial has a planned follow-up of 3 years, and continuing trends toward differences in incidence of very late stent thrombosis may be seen at longer follow-up.

The cardiologists performing the primary PCI were not blinded to the allocated stent type. Such blinding would not be ethical because each stent type has its own typical behavior and handling. Despite the higher profile (due to thicker stent struts) of the SES, only once did the operator have to cross over from the SES to EES to cross the lesion. Four times the EES was crossed over to a nonstudy stent. However, analysis of MACE was conducted on an intention-to-treat basis and performed by a blinded, independent clinical event committee.

Conclusions

In this contemporary, all-comer, randomized multicenter AMI trial, low MACE rates were seen at 1 year with the use of DES in primary PCI in AMI. Although not powered for superiority, the second-generation EES displayed a significantly lower MACE rate than the first-generation SES, at least proving noninferiority and even suggesting superiority. Stent thrombosis rate in EES was very low, but long-term follow-up and larger-scale studies will be needed to show whether the reported continuing stent thrombosis rates beyond 1 year as shown in first-generation DES will also be improved in EES.

Acknowledgments

The authors especially appreciate the assistance of Prof. H. Boersma PhD, Thoraxcenter, Erasmus University Rotterdam, the Netherlands, as chairman of the Data Safety Monitoring Board and for his statistical advice. Data collection, handling, and statistical analyses were performed by Diagram B.V., with special thanks to Evelien Kolkman, MSc.

Reprint requests and correspondence: Dr. Sjoerd H. Hofma, Cardiology, Medical Center Leeuwarden, Henri Dunantweg 2, 8934 AD Leeuwarden, the Netherlands. E-mail: s.h.hofma@znb.nl.

REFERENCES

1. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221–31.
2. Caixeta A, Leon MB, Lansky AJ, et al. 5-year clinical outcomes after sirolimus-eluting stent implantation. J Am Coll Cardiol 2009;54:894–902.
3. Kastrati A, Mehilli J, Pache J, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007;356:1030–9.
4. Lagerqvist B, James SK, Stenestrand U, Lindback J, Nilsson T, Wallentin L. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. N Engl J Med 2007;356:1009–19.
5. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice. Lancet 2007;369:667–78.
6. Kotani J, Awata M, Nanto S, et al. Incomplete neointimal coverage of sirolimus-eluting stents. Angioscopic findings. J Am Coll Cardiol 2006;47:2108–11.
7. Joner M, Nakazawa G, Finn AV, et al. Endothelial cell recovery between comparator polymer-based drug-eluting stents. J Am Coll Cardiol 2008;52:333–42.
8. Hofma SH, van der Giessen WJ, van Dalen BM, et al. Indication of long-term endothelial dysfunction after sirolimus-eluting stent implantation. Eur Heart J 2006;27:166–70.
9. Lemos PA, Saia, F, Hofma SH, et al. Short- and long-term clinical benefit of sirolimus-eluting stents compared to conventional bare stents for patients with acute myocardial infarction. J Am Coll Cardiol 2004;43:704–8.
10. Spaulding C, Henry P, Teiger E, et al. Sirolimus-eluting versus uncoated stents in acute myocardial infarction. N Engl J Med 2006;355:1093–104.
11. Violini R, Musto C, De Felice F, et al. Maintenance of long-term clinical benefit with sirolimus-eluting stents in patients with ST-elevation myocardial infarction: 3 year results of the SESAMI trial. J Am Coll Cardiol 2010;55:810–14.

12. Stone GW, Lansky AJ, Pocock SJ, et al. Paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction. N Engl J Med 2009;360:1946–59.
13. Kedhi E, Sheik Joesoef K, McFadden E, et al. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. Lancet 2010;375:201–9.
14. Stone GW, Rizvi A, Newman W, et al. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. N Engl J Med 2010;362:1663–74.
15. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
16. Laarman GJ, Suttorp MJ, Dirksen MT, et al. Paclitaxel-eluting versus uncoated stents in primary percutaneous coronary intervention. N Engl J Med 2006;355:1105–13.
17. Vlaar PJ, Svilaas T, van der Horst IC, et al. Cardiac death and re-infarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS): a 1-year follow-up study. Lancet 2008;371:1915–20.
18. Arzamendi D, Quoc H, Tanquay JF, et al. Effect on bleeding, time to revascularization, and one-year clinical outcomes of the radial approach during primary PCI in patients with STEMI. Am J Cardiol 2010;106:148–54.
19. Jolly SS, Yusuf S, Cairns J, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL). Lancet 2011;377:1409–20.
20. Chen MS, John JM, Chew DP, et al. Bare metal stent restenosis is not a benign clinical entity. Am Heart J 2006;151:1260–4.
21. Dangas GD, Caixeta A, Mehran R, et al. Frequency and predictors of stent thrombosis after percutaneous coronary intervention in acute myocardial infarction. Circulation 2011;123:1745–56.
22. Obata J, Kitta Y, Takano H, et al. Sirolimus-eluting stent implantation aggravates endothelial vasomotor dysfunction in the infarct-related coronary artery in patients with acute myocardial infarction. J Am Coll Cardiol 2007;50:1305–9.
23. Mauri L, Silbaugh TS, Garg P, et al. Drug-eluting or bare-metal stents for acute myocardial infarction. N Engl J Med 2008;359:1330–42.
24. Brar SS, Leon MB, Stone GW, et al. Use of drug-eluting stents in acute myocardial infarction: a systematic review and meta-analysis. J Am Coll Cardiol 2009;53:1677–89.
25. Räber L, Windecker S. Primary percutaneous coronary intervention and risk of stent thrombosis. A look beyond the HORIZON. Circulation 2011;123:1709–12.
26. Hamilos MI, Ostojic M, Beleslin B, et al. Differential effects of drug-eluting stents on local endothelium-dependent coronary vasomotion. J Am Coll Cardiol 2008;51:2123–9.
27. Silber S, Windecker S, Vranckx P, et al. Unrestricted randomised use of two new generation drug-eluting coronary stents: 2-year patient-related versus stent-related outcomes from the RESOLUTE All Comers trial. Lancet 2011;377:1241–7.
28. Räber L, Jüni P, Nüesch E, et al. Long-term comparison of everolimus-eluting and sirolimus-eluting stents for coronary revascularization. J Am Coll Cardiol 2011;57:2143–51.
29. Smits PC, Kedhi E, Royaards K, et al. Two year follow-up of a randomized controlled trial of everolimus- and paclitaxel-eluting stents for coronary revascularization in daily practice. J Am Coll Cardiol 2011;58:11–8.
30. Kedhi E, Gomes M, Sheik Joesoef K, et al. Everolimus-eluting stents and paclitaxel-eluting stents in patients presenting with myocardial infarction: insights from the two-year results of the COMPARE prospective randomised controlled trial. EuroIntervention 2012;7:1376–85.
31. Snapinn SM. Non-inferiority trials; commentary. Curr Control Trials Cardiovasc Med 2000;1:19–21.
32. EMEA. Points to consider on switching between superiority and non-inferiority. Available at: http://www.tga.gov.au/pdf/euguide/ewp048299en.pdf. Accessed July 27, 2011.

Key Words: acute myocardial infarction ■ drug-eluting stent ■ percutaneous coronary intervention ■ stent thrombosis.