Universiteit
Leiden
The Netherlands

Optimization of care for ST-elevation myocardial infarction

Velders, M.A.

Citation
Velders, M. A. (2014, January 23). *Optimization of care for ST-elevation myocardial infarction*. Retrieved from https://hdl.handle.net/1887/23056

Version:	Corrected Publisher's Version
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/23056

Note: To cite this publication please use the final published version (if applicable).

Cover Page

Universiteit Leiden

The handle http://hdl.handle.net/1887/23056 holds various files of this Leiden University dissertation

Author: Velders, Matthijs A.
Title: Optimization of care for ST-elevation myocardial infarction
Issue Date: 2014-01-23

CHAPTER 7

Second-generation everolimus-eluting stents vs 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

J Am Coll Cardiol 2012;60:381-7.

S.H. Hofma,
J. Brouwer,
M.A. Velders,
A.W.J. van 't Hof,
P.C. Smits,
M. Queré,
C.J. de Vries,
A.J. van Boven.

Abstract

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 to combine the 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, EES or SES, in the XAMI trial (Xience vs Cypher in AMI). Primary endpoint was major adverse cardiac events (MACE) at 1 year consisting of cardiac death, non-fatal AMI or any target vessel revascularization (TVR). The study was powered for non-inferiority of EES. Secondary endpoints contain ST rates and MACE rate up to 3 years.

Results: The MACE rate was 4.0% for EES and 7.7% for SES, absolute difference -3.7% [95% CI: - 8.28;-0.03], p = 0.048, RR 0.52, [95% CI: 0.27;1,00]. One year cardiac mortality was low at 1.5% (EES) vs 2.7% (SES) (p=0.36) and one year incidence of definite and/or probable ST 1.2% (EES) vs 2.7% (SES) (p=0.21).

Conclusions: In this all-comer randomized multi-center AMI trial, second generation EES was non-inferior to SES and superiority for MACE was suggested. ST rate in EES at one 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.

Introduction

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 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 stenting has previously been reported.[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 show efficacy and safety.[9-12]

Newer anti-proliferative drugs and more biocompatible polymers have shown promise in reducing further the rate of (late) stent thrombosis in stable patients.[13,14] However, no randomized data is available on the efficacy and safety of newer generation DES in AMI patients.

In our center, Cypher (Cordis, Bridgewater, New Jersey), the sirolimus-eluting Cypher 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 multi-center randomized trial was designed to compare both stents in AMI patients (XAMI : Xience vs Cypher in AMI).

Methods

Study design and patient population

Between February 2008 and December 2009 consecutive patients presenting with ST-elevation myocardial infarction (STEMI) treated with primary PCI and fulfilling the inclusion criteria were included in three large interventional centres in the Netherlands. To be included, patients had to have ST-elevation myocardial infarction and be eligible for primary PCI. Patients with Non-ST elevation myocardial infarction (NSTEMI) with 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 sealed envelope, directly after diagnostic angiography and assessment of feasibility for stenting. Operators were not blinded to the allocated stent. An independent Data Safety Monitoring Board (DSMB) evaluated the study safety after 30 day inclusion of 300 patients, blinded to the allocated stent type. At one year, all events were evaluated and adjudicated by an independent Clinical Event Committee (CEC), again blinded to treatment assignment.

Procedure

All patients were pretreated with i.v. aspirin, heparin 5000 IE bolus and received clopidogrel with a loading dose of preferably 600 mg. Interventions were performed according to local practice in three high volume centres by high volume operators. GP IIb/IIIa receptor blocker use, thrombus aspiration and balloon predilatation were left up to the operator. Aspirin was recommended for life and clopidogrel for a minimum of one year. The study has a planned follow-up of 3 years.

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, non-fatal re-infarction or any target vessel revascularization (TVR). The secondary endpoints were (sub)-acute stent thrombosis (SAT) at 30 days and late stent thrombosis (LST) at 1, 2 and 3 year, MACE at 30 days and 2 and 3 years and all-cause mortality at 1, 2 and 3 year. Reinfarction was defined by recurrent symptoms and/or new electrocardiographic changes, with re-elevation of the creatine kinase (CK) of > 1.5 times the previous value with elevation of CK-MB, 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 CK was required for the diagnosis of AMI after bypass surgery. TVR was defined as any repeat percutaneous intervention or by-pass grafting of the target vessel and Target Lesion Revascularization (TLR) as any repeat percutaneous intervention or by-pass grafting of the target lesion or the 5 mm proximal or distal to the initial stent. Definite and probable stent thrombosis was defined according to the Academic Research Consortium criteria (ARC).[15]

Statistical analysis

Data collection, handling and statistical analyses were performed by an independent Core Lab, 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 non-inferiority margin and a 95% confidence interval. We calculated that a sample size of 600

patients (2:1 randomisation) would give a power of 80% (Farrington and Manning method). This sample size took into account an expected one year MACE rate of 8% and a non-inferiority margin of 6%, and a two 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 both intention-to-treat and per-protocol analyses. The intention-to-treat population included all patients who were randomized. These results are reported in this paper. The per-protocol population included all patients who fulfilled the inclusion and exclusion criteria and in which the randomized stent was placed. A second per-protocol analysis also excluded the included NSTEMI patients in the trial to check consistency of the trial results in true STEMI patients. Data are reported as percentages for discrete variables. Continuous variables are reported as mean with standard deviation or median with 25th and 75th percentiles. Categorical variables were compared with the chi-square test or Fisher's exact test. Continuous variables were compared with 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 tested using the log rank test.

Results

Patients and baseline characteristics

A total of 625 consecutive patients with AMI were included in three 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 is present 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 minutes in this study. At diagnosis, the ambulance personnel immediately administer both high dose acetylsalicylic acid and heparin intravenously and in some regions clopidogrel orally.

Procedure

Angiographic and procedural characteristics are shown in table 2. More than 50% of patients had TIMI 0 flow 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 all parameters except

Table 1. Baseline Characteristics of the Patients

	EES (n= 404)	SES (n = 221)	p-value
Male gender - no. (%)	295 (73.0)	167 (75.1)	0.57
Age (mean) – yr ± SD	61.2 ± 11.3	62.0 ± 11.4	0.39
Killip class I - no. (%)	377 (93.3)	206 (92.8)	0.79
STEMI - no. (%)	387 (95.8)	213 (96.4)	0.72
NSTEMI - no. (%)	17 (4.2)	8 (3.6)	0.72
History			
Previous Q wave MI - no. (%)	6 (1.5)	7 (3.2)	0.24
Previous non Q wave MI - no. (%)	17 (4.2)	7 (3.2)	0.52
Previous PCI - no. (%)	17 (4.2)	6 (2.8)	0.34
Previous CABG - no. (%)	1 (0.2)	4 1.8)	0.06
Previous stroke - no. (%)	10 (2.5)	12 (5.4)	0.06
Risk factors			
Smoking - no. (%)	220 (54.5)	122 (55.2)	0.86
Diabetes Mellitus - no. (%)	36 (8.9)	25 (11.3)	0.33
Hypertension - no. (%)	119 (29.5)	66 (29.9)	0.92
Family history - no. (%)	172 (42.6)	99 (44.8)	0.59
Renal failure - no. (%)	4 (1.0)	4 (1.8)	0.46
Time (median in minutes)			
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
Infact size (peak in U/l; mean ± SD)			
CPK	1831 ± 1816	1923 ± 1994	0.93
CPK-MB	205 ± 180	216 ± 219	0.96
Pre hospital 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 2b/3a blocker iv - (%)	5.2	6.8	0.41
Access site (%)			0.27
Radial	52.0	56.6	
Femoral	48	43.4	
IABP (%)	1.5	1.4	1.00

CABG:Coronary artery bypass grafting; CPK:Creatinin phosphokinase; EES: Everolimus-eluting stent; GP:Glycoprotein; MI:Myocardial infarction; NSTEMI:Non-ST-elevation myocardial infarction; PCI:Percutaneous coronary intervention; SES: Sirolimus-eluting stent; STEMI: ST-elevation myocardial infarction.

Table 2. Angiographic and Procedural Characteristics

	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	
Extend of coronary artery disease (%)			0.54
One vessel	54.2	49.8	
Two vessels	32.7	36.7	
Three vessels	13.1	13.6	
Clopidogrel 300 mg loading (%)	3.2	2.3	0.62
Clopidogrel 600 mg loading (%)	96.0	97.2	0.46
Overall GP2b/3a 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 0-2 (%)	5.0	6.3	0.47
Total stent length target segment (mm)	25.1 ± 13.5	27.9 ± 17.0	0.09
Max 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
Number of stents per patient	1.3 ± 0.6	1.4 ± 0.7	0.45

GP:Glycoprotein; IABP:Intra-aortic balloon pump; TIMI:Thrombolysis in myocardial infarction.

Table 3. Medication at discharge

	EES (n= 404)*	SES (n=221)*	p-value
ASA	98.5	98.2	0.75
Clopidogrel	98.5	98.6	1.00
Beta blocker	83.7	81.9	0.57
Ace inhibitor	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
Spironolacton	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. ASA: acetylsalicylic acid; AT: Angiotensin.

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 consisted entirely of cardiac mortality. Acute stent thrombosis was seen in 1 patient of each group and definite and/or probable stent thrombosis at 30 day was low at 1.3%. Subacute stent thrombosis was higher with SES though 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, non-fatal MI or any TVR at 1 year was 4.0 % for EES and 7.7% for SES. The non-inferiority criterion for EES was met with an absolute difference of -3.7% (95% CI: -8.28; -0.03). MACE rate was significantly reduced for EES with a p-value of 0.048 and a relative risk (RR) of 0.52 (95% CI: 0.27; 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 was not statistically significant.

Table 4. Clinical results at 30 days and one year follow-up

	Total	EES	SES	p-
	(n=624) *	(n=403)	(n=221)	value
30 day follow-up - no. (%)				
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
Non fatal 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
Sub acute	6 (1.0)	2 (0.5)	4 (1.8)	0.19
One Year follow-up- no. (%)	(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
Non fatal 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 is excluded, withdrawal informed consent. †: In total by 1 year two patients excluded because of withdrawal of consent ‡: MACE is primary endpoint: Cardiac Death, Non fatal MI, any TVR §:Non-inferiority criterion was met, absolute difference -3.7% (95% CI: -8.28; -0.03); p value: 0.048 with RR 0.52 (95% CI: 0.27; 1.00).

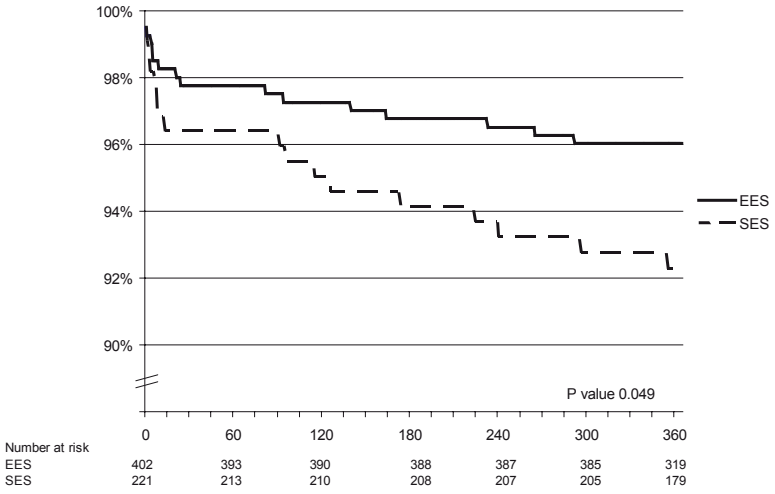

Figure 1. Kaplan-Meier estimates of MACE-free survival at one year of infarct patients randomized to EES and SES.

The overall one 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 day 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 ASA or with oral anticoagulants. 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) vs 7.8% (SES), p= 0.01; RR 0.43 (95% CI: 0.21; 0.86). Per protocol analysis, excluding the 4% NSTEMI patients which were included in the trial, also revealed a clear benefit of the EES with a MACE rate of 3.5 % vs 7.6 % for SES, p= 0.027, RR 0.46 (95 % CI: 0.22; 0.93).

Discussion

In this randomized trial, the first generation drug-eluting stent, the SES Cypher stent was compared with the second generation EES Xience V stent in patients with AMI. The results show very low MACE rates and low percentages of stent thrombosis at one 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 one year 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. This is 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 like the large HORIZONS-AMI trial[12] and the PASSION trial,[16] and higher risk than the Typhoon trial,[10] in which sirolimus-eluting stents were compared to BMS in AMI patients. In this study, mortality was low and quite 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 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 over 50 % of cases impacts 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 thrombus aspiration was used in only 11 % of patients. Using these contemporary interventional techniques, DES was associated with a low re-intervention rate at 1 year. Overall TLR 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 TYPHOON and HORIZONS-AMI, 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 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 preclude comparison of our event rates with other STEMI trials. Per protocol analysis, excluding the 4% NSTEMI patients, confirmed this hypothesis, showing a clear benefit for EES in MACE rate at 1 year, with a p-value of 0.027.

Stent Thrombosis

The event rate was accompanied by a low rate of definite and/or probable stent thrombosis. The rate for sirolimus-eluting stent was 2.7 % and for everolimus-eluting stent even only 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 bare metal stent thrombosis rate (definite or probable) was 3.4 %. Pre-randomization 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. The difference in stent thrombosis rates at 30 days was mainly responsible for the difference at one year. Though the influence of procedural and patient characteristics cannot be excluded, it has been suggested that the newer polymer coatings used in second generation DES, like 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 as their highly thrombotic lesions are more prone to stent thrombosis. Despite this, randomized trials and large risk-adjusted retrospective studies have shown superiority of first generation DES over bare metal stents (BMS) up to several years 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. 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 endotheliali-

zation 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 20-30 % of AMI patients were presented. Very few additional stent thromboses were seen between one and two year in the EES stent arms,[27-29] as well as in a (not separately randomized) subgroup analysis of AMI patients.[30] The XAMI trial will conduct a follow-up up to 3 years to investigate the incidence of very late ST.

Study Limitations

Despite the fact that this was an all-comer trial and infarct enzymes 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 general total AMI population, but patient characteristics were very comparable to most other reported clinical AMI trials comparing DES and BMS as discussed previously. The lesions in the SES group were more calcified and despite comparable peak enzymes in both groups, medication at discharge shows a higher percentage of diuretics 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 non-inferiority of the EES for MACE. The trial was not powered for superiority, but at one 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 one year, longer follow-up may answer this question in the coming years. The trial is not powered to detect significant differences in adverse events like 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 three years and continuing trends towards 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. This would also not be ethical as each stent type has its own typical behaviour and handling. Despite the higher profile of the sirolimus-eluting stent, only once the operator had to cross over from the SES to EES to cross the lesion. Four times the EES was crossed over to a non-study stent. However, analysis of MACE was performed on “intention to treat” basis and performed by a blinded independent CEC.

Conclusions

In this contemporary all-comer randomized multi-center AMI trial, low MACE rates were seen at 1 year with the use of DES in primary PCI in AMI. Although not pow-

ered for superiority, the second generation everolimus-eluting DES displayed a significantly lower MACE rate than the first generation sirolimus-eluting stent, at least proving non-inferiority and even suggesting superiority. Stent thrombosis rate in EES was very low, but long-term follow-up and larger scale studies will have to show whether the reported continuing stent thrombosis rates beyond one year as shown in first generation DES will also be improved in EES.

Acknowledgements

Prof H. Boersma PhD, Thoraxcenter, Erasmus University Rotterdam, The Netherlands, is especially appreciated as chairman of the DSMB and for his statistical advise. Data collection, handling and statistical analyses were performed by an independent Core Lab, Diagram b.v., Zwolle, The Netherlands, with special thanks to ms Evelien Kolkman, MSc.

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;356:1009–1019.
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;369:667–678.
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;27:166-170;Epub 2005 Oct 25.
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;55:810-814.
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: 201–09.
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;106:148-154.
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;151:1260-64.

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. Editorial, 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: 1241–47.

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. COMPARE-AMI: Everolimus-eluting and paclitaxel-eluting stents for treatment of ST-elevation myocardial infarction: Two-year clinical outcome. Paper presented at: Transcatheter Cardiovascular Therapeutics; September, 2010; Washington, DC.

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. London, 27July 2000. http://www.tga.gov.au/pdf/euguide/ewp048299en.pdf