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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

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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

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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