

Long-term follow-up of second-generation everolimus-eluting stents versus first-generation sirolimus-eluting stents in acute myocardial infarction: three-year results of the XAMI trial

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KEYWORDS

- drug-eluting stent
- primary PCI
- STEMI

Abstract

Aims: Evaluation of the long-term safety and efficacy of second-generation everolimus-eluting stents (EES) versus first-generation sirolimus-eluting stents (SES) in acute myocardial infarction (AMI) patients.

Methods and results: Six hundred and twenty-five patients were randomised (2:1) to EES or SES in the multicentre XAMI (XienceV stent vs. Cypher stent in Primary PCI for Acute Myocardial Infarction) trial. The primary endpoint was cardiac death, non-fatal AMI or any target vessel revascularisation (TVR) at one year, with a planned follow-up of three years. At three-year follow-up, the primary endpoint was 8.0% for EES and 10.5% for SES (p=0.30). Cardiac death was low and comparable in both groups (EES: 2.5% versus SES: 2.7%; p=0.86), as was definite/probable stent thrombosis (EES: 2.3% versus SES 3.2%; p=0.60).

Conclusions: The event rate at three years in this all-comer, randomised, multicentre AMI trial was low, including stent thrombosis, with no significant difference between first- and second-generation DES. Registration of trial: <http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1123> Candidate number: 2869; NTR number: NTR1123

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Introduction

Despite the proven efficacy and safety of drug-eluting stents (DES) in the treatment of coronary artery disease, increased very late stent thrombosis (VLST) rate is still a major concern, especially in first-generation DES. Second-generation DES with more biocompatible coatings and newer antiproliferative drugs have shown increased efficacy and reduced risk of VLST comparable to bare metal stents (BMS) in stable patients.

The XAMI (XienceV stent vs. Cypher stent in Primary PCI for Acute Myocardial Infarction) trial was designed to evaluate the efficacy and safety of the second-generation XIENCE V (Abbott Vascular, Santa Clara, CA, USA) everolimus-eluting stent (EES) compared to the first-generation sirolimus-eluting CYPHER stent (SES) (Cordis Corporation, Bridgewater, NJ, USA) in acute myocardial infarction (AMI) patients undergoing primary angioplasty.

The primary endpoint of cardiac death, non-fatal AMI or any target vessel revascularisation (TVR) at one year confirmed non-inferiority of the EES and suggested superiority with a low stent thrombosis rate in both stents¹. We report here the three-year follow-up of this trial.

Methods

STUDY DESIGN AND PATIENT POPULATION

The design of the XAMI trial has been reported previously¹. Six hundred and twenty-five patients with AMI were randomised (2:1) to receive EES or SES in this all-comer, multicentre, non-inferiority trial.

RANDOMISATION, PROCEDURE, STUDY ENDPOINTS

Randomisation, procedure, endpoints and definitions have been described previously¹. The primary endpoint was major adverse cardiac events (MACE) at 12 months, consisting of cardiac death, non-fatal reinfarction or any target vessel revascularisation (TVR). The secondary endpoints were stent thrombosis, MACE and all-cause mortality at 30 days, one, two and three years.

STATISTICAL ANALYSIS

Data collection, handling and statistical analyses were performed by an independent core lab (Diagram B.V., Zwolle, The Netherlands). Outcome data are reported on an intention-to-treat basis. Sample size calculations and statistics were reported previously¹.

Results

PATIENTS AND BASELINE CHARACTERISTICS

Baseline characteristics have been shown previously¹. Several characteristics indicative of the strength of the trial were: a short first medical contact to balloon time (75 minutes), over 50% of patients treated by radial access, and thrombectomy in over 60% of patients.

OUTCOME AT THREE-YEAR FOLLOW-UP

MACE rates are shown in **Table 1** and **Figure 1**. MACE at three years was 8.0% for EES and 10.5% for SES ($p=0.30$). None of the individual endpoints was significantly different, neither was target

Table 1. Events between one and three years and total number of events at three-year follow-up.

	Total	EES	SES	p-value
1-3 year FU, no. (%)	(n=620)	(n=400)	(n=220)	
MACE	22 (3.5)	16 (4.0)	6 (2.7)	0.50
Death	12 (1.9)	7 (1.8)	5 (2.3)	0.76
Cardiac death	4 (0.6)	4 (1.0)	0 (0.0)	0.30
Non-fatal MI	12 (1.9)	8 (2.0)	4 (1.8)	1.00
TVR	11 (1.8)	7 (1.8)	4 (1.8)	1.00
TLR	7 (1.1)	5 (1.3)	2 (0.9)	1.00
Very late stent thrombosis (definite, probable)	5 (0.8)	4 (1.0)	1 (0.5)	0.66
Three-year follow-up, no. (%)	(n=620)	(n=400)	(n=220)	
MACE	55 (8.9)	32 (8.0)	23 (10.5)	0.30
Death	27 (4.4)	15 (3.8)	12 (5.5)	0.32
Cardiac death	16 (2.6)	10 (2.5)	6 (2.7)	0.86
Non-fatal MI	17 (2.7)	10 (2.5)	7 (3.2)	0.62
TVR	30 (4.8)	17 (4.3)	13 (5.9)	0.36
TLR	14 (2.3)	10 (2.5)	4 (1.8)	0.78
Stent thrombosis (definite, probable)	16 (2.6)	9 (2.3)	7 (3.2)	0.60

MACE: major adverse cardiac events (cardiac death, non-fatal myocardial infarction or any target vessel revascularisation); TLR: target lesion revascularisation

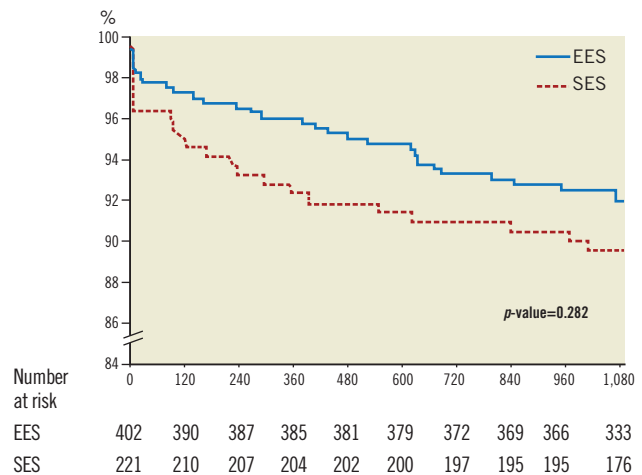


Figure 1. Kaplan-Meier estimate of MACE-free survival up to three years. EES: everolimus-eluting stent; MACE: major adverse cardiac events (cardiac death, non-fatal myocardial infarction or target vessel revascularisation); SES: sirolimus-eluting stent

lesion revascularisation (TLR) nor stent thrombosis (**Table 1**, **Figure 2**).

The overall cardiac death rate was low at 2.6%, as was TLR at 2.3% after three years. Beyond one year, five cases of definite stent thrombosis (four EES patients [1.0%] and one SES patient [0.5%]) were seen and there was no probable stent thrombosis. All these patients were still alive at latest follow-up. Dual antiplatelet therapy was used in 4% of patients at two years and <0.5% at three-year follow-up without significant differences between groups. With three withdrawals of informed consent and two patients lost to follow-up, the follow-up at three years was 99.2%.

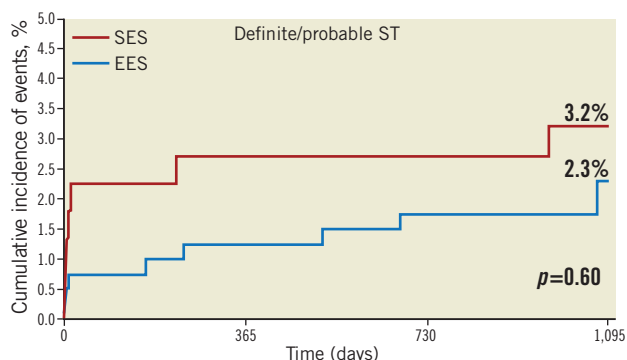


Figure 2. Stent thrombosis rate up to three years for both stent types. EES: everolimus-eluting stent; SES: sirolimus-eluting stent; ST: stent thrombosis

Discussion

The most important finding of this long-term follow-up of the XAMI trial is a low cardiac event rate and no significant difference in MACE or any individual endpoint.

LOW EVENT RATES

The low event rates may have contributed to not demonstrating a significant difference between both stents after three years, next to the rather small sample size. These low event rates may be influenced by a “symptom-to-balloon” time up to 60 minutes shorter than other AMI trials^{2,3}, only 7% of patients in Killip class >1, and a high percentage of thrombectomy and radial access. Long-term follow-up is mainly available from studies comparing first-generation SES or paclitaxel-eluting stents (PES) with bare metal stents in STEMI.

In a recent network meta-analysis of 22 trials including 12,453 randomised STEMI patients treated with BMS, first- or second-generation DES⁴, it was shown that first-generation SES performed significantly better than PES and BMS, with a significant reduction in cardiac death/MI and TVR. For EES, the data beyond one year are still very limited. Palmerini et al⁴ only report EES data up to two years of subgroup analyses of all-comer trials, showing no significant differences between SES and EES. The only dedicated randomised study is the RACES-MI trial⁵, randomising 500 patients to EES or SES, showing no significant difference in cardiac death, MI or TVR at three years.

VERY LATE STENT THROMBOSIS

VLST rates were low for both stent types. EES showed 1.0% VLST between one and three years. The HORIZONS-AMI trial reported a 0.9% VLST rate for BMS between one and three years². This comparable risk of VLST in second-generation DES and BMS was also reported in the SCAAR registry⁶. However, the increased risk of VLST in older DES in SCAAR, also seen for SES in the RACES-MI trial⁵, could not be found in the XAMI trial, despite comparable trial size to RACES-MI. Higher GP IIb/IIIa inhibitor and thrombectomy use in XAMI may have decreased remnant thrombus, possibly reducing early and late stent malapposition.

This might play a role in VLST and could be more important in thick strut stents like SES.

LIMITATIONS

The limitations of the XAMI trial have been discussed previously¹. The trial was powered for non-inferiority of MACE at one year. At one year, MACE rate curves diverged in favour of EES and statistical analysis pointed to superiority for EES; however, this significant difference was lost at three-year follow-up. This may also be partly due to the lower than expected event rate, decreasing the power of the study. The incidence of the primary endpoint was still 25% lower in EES than in SES, and it cannot be excluded that a much larger trial would have shown persistent superior results for EES at three years.

Conclusions

The XAMI trial is among the first to report the long-term outcome of a second-generation compared to a first-generation DES in AMI patients. The event rate was low for both DES up to three years, including VLST, without differences between both generations of DES in this trial.

Impact on daily practice

The XAMI trial showed very reassuring low event rates after primary PCI using DES, but the significantly lower MACE rate in EES at one-year follow-up was not sustained at three years. The fear of increased very late stent thrombosis has limited the use of DES in myocardial infarction patients in recent years. The long-term outcomes of this and other trials show that the use of second-generation DES, like EES in AMI patients, is highly effective and safe up to at least three years of follow-up.

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Conflict of interest statement

P. Smits has received speaker's fees from Abbott Vascular and institutional research grants from Abbott Vascular, Boston Scientific, St. Jude and Terumo. A. van 't Hof has received speaker's fees from MSD and Iroko Cardio, and is on the advisory board of AstraZeneca, The Medicines Company, Daiichi Sankyo and Lilly. The other authors have no conflicts of interest to declare.

References

1. Hofma SH, Brouwer J, Velders MA, van 't Hof AW, Smits PC, Queré M, de Vries CJ, van Boven AJ. 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. *J Am Coll Cardiol.* 2012;60:381-7.

2. Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Kornowski R, Hartmann F, Gersh BJ, Pocock SJ, Dangas G, Chiu Wong S, Fahy M, Parise H, Mehran R; HORIZONS-AMI Trial Investigators. Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): final 3-year results from a multicentre, randomised controlled trial. *Lancet*. 2011;377:2193-204.
3. Räber L, Kelbæk H, Ostojic M, Baumbach A, Heg D, Tüller D, von Birgelen C, Roffi M, Moschovitis A, Khattab AA, Wenaweser P, Bonvini R, Pedrazzini G, Kornowski R, Weber K, Trelle S, Lüscher TF, Taniwaki M, Matter CM, Meier B, Jüni P, Windecker S; COMFORTABLE AMI Trial Investigators. Effect of biolimus-eluting stents with biodegradable polymer vs bare-metal stents on cardiovascular events among patients with acute myocardial infarction: the COMFORTABLE AMI randomized trial. *JAMA*. 2012;308:777-87.
4. Palmerini T, Biondi-Zoccai G, Della Riva D, Mariani A, Sabaté M, Valgimigli M, Frati G, Kedhi E, Smits PC, Kaiser C, Genereux P, Galatius S, Kirtane AJ, Stone GW. Clinical outcomes with drug-eluting and bare metal stents in patients with ST-segment elevation myocardial infarction: evidence from a comprehensive network meta-analysis. *J Am Coll Cardiol*. 2013;62:496-504.
5. Di Lorenzo E, Sauro R, Varricchio A, Capasso M, Lanzillo T, Manganelli F, Carbone G, Lanni F, Pagliuca MR, Stanco G, Rosato G, Suryapranata H, de Luca G. Randomized comparison of everolimus-eluting stents and sirolimus-eluting stents in patients with ST elevation myocardial infarction: RACES-MI trial. *JACC Cardiovasc Interv*. 2014;7:849-56.
6. Sarno G, Lagerqvist B, Nilsson J, Frobert O, Hambræus K, Varenhorst C, Jensen UJ, Tödt T, Göteborg M, James SK. Stent thrombosis in new-generation drug-eluting stents in patients with STEMI undergoing primary PCI: a report from SCAAR. *J Am Coll Cardiol*. 2014;64:16-24.