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Randomised comparison of drug-eluting versus bare-metal stenting in patients with non-ST elevation myocardial infarction

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ABSTRACT

Objective: The superiority of drug-eluting stents (DES) over bare-metal stents (BMS) in patients with ST elevation myocardial infarction (STEMI) is well studied; however, randomised data in patients with non-ST elevation myocardial infarction (NSTEMI) are lacking. The objective of this study was to investigate whether stenting with everolimus-eluting stents (EES) safely reduces restenosis in patients with NSTEMI as compared to BMS.

Methods: ELISA-3 patients were asked to participate in the angiographic substudy and were randomised to DE (Xience V) or BM (Vision) stenting (ELISA-3 group). The primary end point was minimal luminal diameter (MLD) at 9-month follow-up angiography. In addition, 296 patients with NSTEMI who were excluded or did not want to participate in the ELISA-3 trial (RELI group) were randomised to DE or BM stenting and underwent clinical follow-up only (major adverse cardiac events (MACE), stent thrombosis (ST)). A pooled analysis was performed to assess an effect on clinical outcome.

Results: 178 of 540 ELISA-3 patients participated in the angiographic substudy. MLD at 9 months angiography was 2.37±0.63 mm (DES) versus 1.84 ±0.62 mm (BMS), p<0.001. Binary restenosis occurred in 1.9% in the DES group versus 16.7% in the BMS group (RR 0.11, 95% CI 0.02 to 0.84, p=0.007). In the pooled analysis, the incidence of MACE, target vessel revascularisation and ST at 2 years follow-up in the DES versus BMS group was 12.5% versus 16.0% (p=0.28), 4.0% versus 10.4% (p=0.009) and 1.3% versus 3.0% (p=0.34), respectively.

Conclusions: In patients with NSTEMI, use of EES is safe and decreases both angiographic and clinical restenosis as compared to BMS http://www.isrctn.com/search?q=39230163.

Trial registration number: 39230163; Post-results.

KEY QUESTIONS

What is already known about this subject?
▶ The superiority of drug-eluting stents (DES) over bare-metal stents (BMS) in patients with ST elevation myocardial infarction (STEMI) is well studied.

What does this study add?
▶ This trial provides randomised data, showing that also in non-STEMI (NSTEMI), everolimus-eluting stents are safe and decrease restenosis compared to BMS.

How might this impact on clinical practice?
▶ Considering that randomised data on usage of second-generation DES in patients with NSTEMI are scarce, our study provides more evidence that our current clinical practice of treating patients with STEMI with DES is safer and more efficient than treating with BMS.

INTRODUCTION

Percutaneous coronary intervention with bare metal stent implantation is associated with high restenosis rates as compared to the first-generation drug-eluting stents (DES).[1–4] The second-generation everolimus-eluting stent (EES) has shown a strong antiproliferative effect with a non-inferior efficacy profile compared to the first-generation DES but with an improved safety profile. While the effect of DE versus BM stenting in ST elevation myocardial infarction (STEMI) populations has been extensively evaluated, consistently showing that the second-generation DES are as safe as bare-metal stents (BMS) in terms of stent thrombosis while reducing restenosis rates,[5–8] there are no randomised studies comparing DES versus its BMS counterpart in the setting of non-STEMI (NSTEMI). This subset of patients, however, comprises up to 50% of patients included in some stent trials, particularly those with an all-comer design. This evidence has translated into a class I, level of evidence a recommendation in current

clinical guidelines for the use of new-generation DES over BMS.[9]

Montalescot et al[10] demonstrated that patients with STEMI and NSTEMI have similar in hospital and long-term prognoses as well as similar independent correlates of outcome, despite different in-hospital management and despite differences in lesion pathology. In STEMI, the culprit artery is usually occluded by a red thrombus, whereas in NSTEMI the culprit artery is usually patent with a non-occlusive white thrombus. Also, patient characteristics differ; the NSTEMI population is older, has a higher cardiovascular risk profile more often with diabetes and hypertension. Patients with NSTEMI have more extensive coronary artery disease than patients with STEMI and more often a personal history of coronary heart disease.[11]

In this randomised study, we focus on the effects of the use of an EES on the incidence of restenosis and on long-term safety in terms of MACE in this population with NSTEMI, treated with either DES or its bare metal counterpart.

METHODS

In this article, we describe the results of the ELISA-3 angiographic substudy and the ELISA prospective Registry (RELI).

The rationale, design and primary results of ELISA-3 have been previously described.[12]

Briefly, the ELISA-3 trial is a prospective multicentre randomised controlled trial, in which 542 patients, hospitalised with non-ST elevation acute coronary syndrome (NSTE-ACS), were randomised to either an immediate (angiography and revascularisation if appropriate<12 hour) or a delayed invasive strategy (>48 hour after randomisation). This prespecified substudy investigates whether stenting with EES safely decreases the incidence of restenosis, compared to stenting with a BMS with the same stent frame design.

Patients were eligible if they were hospitalised with ischaemic chest pain or dyspnoea at rest, with the last episode occurring 24 hours or less before randomisation, and had at least two of three of the following high-risk characteristics: (1) evidence of extensive myocardial ischaemia on ECG (shown by new cumulative ST depression >5 mm or temporary ST segment elevation in two contiguous leads <30 min), (2) elevated biomarkers (troponin T >0.10 µg/L or myoglobin >150 µg/L) or elevated CKMB fraction (>6% of total CK), (3) age above 65 years. Exclusion criteria were persistent ST segment elevation, symptoms of ongoing myocardial ischaemia despite optimal medical therapy, contraindication for diagnostic angiography, active bleeding, cardiogenic shock, acute posterior infarction and life expectancy <1 year.

During the same study period, patients with NSTEMI who did not want to participate in, or who did not meet the inclusion criteria for, high-risk NSTEMI of the ELISA-3 study, were recruited in the ELISA prospective registry.

Both patients in the ELISA-3 trial and in the ELISA registry, who underwent coronary angiography and were deemed appropriate for percutaneous coronary intervention (PCI) and stenting, underwent randomisation in the catheterisation laboratory to either EE or BM stenting. Patients with multiple lesions in need of more than one stent were treated with the same type of stent for all lesions.

Patients received dual antiplatelet therapy (acetylsalicic acid and clopidogrel) for the duration of 1 year.

Between July 2007 and June 2012, 542 patients were randomised in the ELISA-3 trial. About 344 of these patients were eligible for PCI and 178 of these patients underwent a second randomisation to EES (n=87) and BMS (n=91). In the same period, 296 patients in the ELISA registry group were also randomised (EES n=147, BMS n=149). Patients in the ELISA-3 group were planned to undergo coronary angiography at 9 months, whereas patients in the prospective registry were followed for 2 years for clinical end points without planned follow-up angiography (figure 1).

The trial was conducted in six Dutch hospitals of which one had 24 hour facilities for (primary) PCI and coronary artery bypass graft (CABG) surgery. The study complied with the Declaration of Helsinki, was approved by the ethics committee of Isala, Zwolle, the Netherlands, and all patients gave written informed consent before entering the study or the registry. The study was registered in the ISRCTN Register (ISRCTN39230163).

Randomisation and treatment

Patients were randomised by a closed envelope system to blinded stent designs. Operators were blinded to the device used and the clinical end points were adjudicated by investigators blinded with regard to patients' treatment allocation (flow chart: summary of the study design). Coronary angioplasty was performed according to the local standards of the intervention centre. All patients were treated according to the guidelines. Concomitant medication included a loading dose of aspirin (500 mg orally or intravenously), clopidogrel (600 mg orally) and 5000 IU unfractionated heparin intravenously as soon as possible after diagnosis. Tirofiban (bolus of 25 mg/kg followed by continuous infusion of 0.15 mg/min/kg), nitrates, β-blockers and calcium channel blockers were given at the discretion of the investigator.

Definitions

Procedure time was defined as the time interval between placement of the arterial sheath and removal of the guiding catheter. Clinical procedural success was defined as immediate angiographic success (defined as a diameter stenosis postprocedure of <50% (visual assessment) and TIMI 3 flow) without major in-hospital complication, including death, myocardial infarction (MI), stent thrombosis or emergency coronary artery bypass surgery. MI was defined by the presence of new

Figure 1 Flow diagram of study design. BMS, bare-metal stent; EES, everolimus-eluting stent; MACE, major adverse cardiac events (composite of death, myocardial infarction and target vessel revascularisation); PCI, percutaneous coronary intervention.
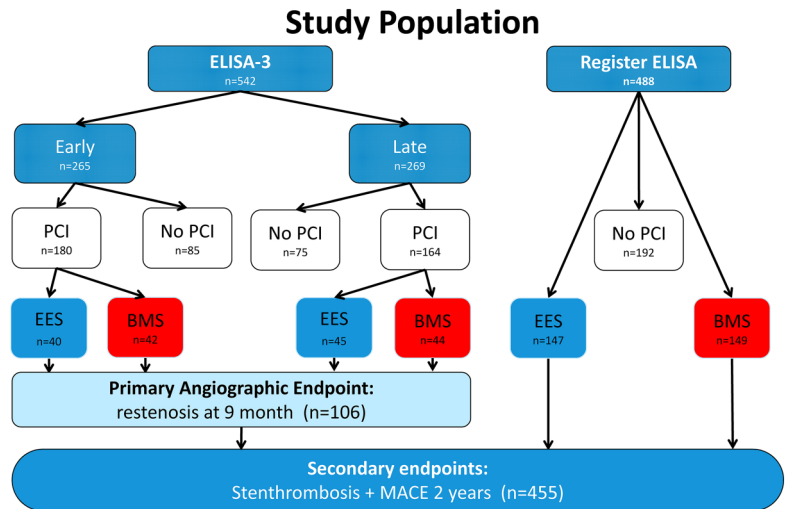
Q waves or creatine kinase level or MB fraction at least twice the upper limit of normal. Lesions were classified according to the definitions recommended by the American College of Cardiology/American Heart Association task force.

Stent thrombosis was defined as complete occlusion of the stented lesion at follow-up angiography or at recurrent angiography performed because of recurrent chest pain and signs of ischaemia.

End points

The primary end point of the ELISA-3 angiographic substudy was the extent of restenosis, expressed by the difference in minimal luminal diameter at 9-month follow-up angiography, as assessed by an independent core laboratory.

We conducted a pooled analysis of the ELISA-3 and the prospective ELISA registry patients, in which the incidence of definite stent thrombosis at 2 years follow-up was the key secondary and safety end point. The incidence of MACE at 2 years follow-up was an exploratory end point in this pooled analysis.

Qualitative and quantitative coronary analysis

Coronary angiograms were performed before angioplasty, immediately after angioplasty and at 9-month follow-up. Standard acquisition procedures were followed for qualitative and quantitative coronary angiography analysis. To improve the accuracy and reproducibility of measurements, intracoronary isosorbide-dinitrate (1–3 mg) was given before the initial and final post-stent placement angiograms. Angiographies were recorded on a CD-ROM. Matched orthogonal views were used for quantitative analysis at each control. Dye-filled guiding catheters were used for magnification calibration. Data collection included assessment of TIMI flow grade, lesion eccentricity, estimation of thrombus load and AHA/ACC classification. An independent laboratory (DIAGRAM, Zwolle, the Netherlands) performed routine quantitative coronary angiography measurements using the Coronary Angiography Analysis System (CAAS II System). Two orthogonal angiographic views with minimised vessel foreshortening were obtained, and the angiogram showing the most severe stenosis was selected for quantitative coronary analysis. Postprocedure and follow-up angiograms, which duplicate the initial orthogonal views, were obtained after the removal of the balloon and guidewire.

Follow-up

Coronary angiography was planned at 9 months in the ELISA-3 angiographic substudy patients. Coronary angiography could be prematurely performed on the basis of clinical indications; it was used as the follow-up angiogram in the case of restenosis or if performed after 4 months. When it was performed within 4 months' time without evidence of restenosis, angiographic control was repeated at 9 months. All major clinical events including death, MI, readmission to hospital for unstable angina pectoris and the need for additional (ischaemia driven) revascularisation of the target vessel were monitored at the time of repeated angiography or by phone at 9 and 24 months for all patients and adjudicated by two independent physicians blinded to randomised treatment.

Statistical analysis

The study is designed to demonstrate superiority of EES based on the assumption that at follow-up angiography minimal luminal diameter (MLD) coated—MLD non-coated >0.20 mm (H0: MLD coated # MLD non-coated —0.20, H1: MLD coated >MLD non-coated—0.20).

Previous studies have shown that it is reasonable to assume that the MLD measurement after angioplasty follows a normal distribution. It is expected that in all groups the mean will be ~1.9 mm and the SD will be ~0.5 mm. Allowing for a type I error of 5% and a dropout rate of 20%, a sample of 280 patients (140 per group) will give 85% power to prove superiority of

Table 1 Characteristics and history (Elisa-3)

	Total	EES	BMS	p Value
Male gender	136/178 (76.4%)	70/87 (80.5%)	66/91 (72.5%)	0.213
Hypertension	91/178 (51.1%)	44/87 (50.6%)	47/91 (51.6%)	0.886
Previous MI	28/178 (15.7%)	14/87 (16.1%)	14/91 (15.4%)	0.897
Previous CABG	22/178 (12.4%)	9/87 (10.3%)	13/91 (14.3%)	0.425
Previous PCI	30/178 (16.9%)	13/87 (14.9%)	17/91 (18.7%)	0.505
Previous stroke	6/178 (3.4%)	1/87 (1.1%)	5/91 (5.5%)	0.211
Previous TIA	8/178 (4.5%)	1/87 (1.1%)	7/91 (7.7%)	0.066
Diabetes Mellitus	34/178 (19.1%)	17/87 (19.5%)	17/91 (18.7%)	0.884
Smoking	53/178 (29.8%)	28/87 (32.2%)	25/91 (27.5%)	0.492
Family history	72/176 (40.9%)	32/85 (37.6%)	40/91 (44.0%)	0.395

BMS, bare-metal stent; CABG, coronary artery bypass graft; EES, everolimus-eluting stent; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack.

Table 2 Characteristics and history by study

	Total	Elisa-3	Elisa registry	p Value
Randomisation everolimus	234/474 (49.4%)	87/178 (48.9%)	147/296 (49.7%)	0.868
Male gender	351/474 (74.1%)	136/178 (76.4%)	215/296 (72.6%)	0.365
Hypertension	226/474 (47.7%)	91/178 (51.1%)	135/296 (45.6%)	0.244
Previous MI	69/473 (14.6%)	28/178 (15.7%)	41/295 (13.9%)	0.584
Previous CABG	47/474 (9.9%)	22/178 (12.4%)	25/296 (8.4%)	0.167
Previous PCI	70/474 (14.8%)	30/178 (16.9%)	40/296 (13.5%)	0.321
Previous stroke	21/474 (4.4%)	6/178 (3.4%)	15/296 (5.1%)	0.385
Previous TIA				
Diabetes Mellitus	85/474 (17.9%)	34/178 (19.1%)	51/296 (17.2%)	0.607
Smoking	167/473 (35.3%)	53/178 (29.8%)	114/295 (38.6%)	0.051
Family history	200/472 (42.4%)	72/176 (40.9%)	128/296 (43.2%)	0.620

CABG, coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention.

coated stenting compared to the use of a non-coated stent.

Data were analysed according to the intention-to-treat analysis. Continuous variables were expressed as means ±SD and were compared between the intervention groups using a Mann-Whitney U test. Categorical data were described by proportions and compared with the χ^2 or Fisher's exact test. Logistic regression was used to calculate the p value of the interaction between the effect of the intervention and the prespecified subgroups on the primary end point. All tests were two-sided and an α of 5% was used. Statistical analysis was performed with SPSS (V.20); SPSS, Chicago, Illinois, USA

MACE survival Kaplan-Meier curves were obtained and compared by means of the log-rank test.

RESULTS
Baseline characteristics
Between July 2007 and June 2012, 178 ELISA-3 patients (87 EES, 91 BMS) and 296 ELISA registry patients (147 EES, 149 BMS) were randomised. Baseline characteristics in the ELISA-3 population were well balanced between the treatment groups (table 1). There was a significant difference in age between ELISA-3 and the

ELISA registry group (68.0±10.9 vs 63.6±12.5 years, p<0.001); other baseline characteristics did not differ between Elisa-3 and the registry group (tables 2 and 3).

Angiographic outcome
Follow-up angiography was performed at 9 months in 124 (70%) of the ELISA-3 patients. Baseline characteristics of patients who declined follow-up angiography were similar to those of patients who had a follow-up angiography. The primary end point, the degree of restenosis (MLD), was significantly different when comparing DES to BMS (2.37±0.63 mm vs 1.84±0.62 mm, p<0.001) (table 4). The incidence of binary restenosis, defined as a diameter stenosis at 9 months follow-up of more than 50%, was 1.9% in the DES group vs 16.7% in the BMS group (RR 0.11, 95% CI (0.02 to 0.84), p=0.01).

Clinical outcome
In the ELISA-3 group, clinical follow-up at 24 months was complete in 173 (97%) patients.

The rate of MACE was 10.7% (EES) versus 14.6% (BMS) p=0.442. Target vessel revascularisation was necessary in 4.8% (EES) versus 11.2% (BMS) p=0.119 and stent thrombosis occurred in 1.2% (EES) versus 3.4% (BMS) p=0.621.

Table 3 Characteristics and history (pooled analysis)

	EES (N=234)	BMS (N=240)	p Value
Age, years (mean±SD)	65.91±11.69	64.63±12.24	0.288
Male gender	176/234 (75.2%)	175/240 (72.9%)	0.627
Hypertension	110/234 (47.0%)	116/240 (48.3%)	0.773
Previous MI	36/233 (15.5%)	33/240 (13.8%)	0.600
Previous CABG	21/234 (9.0%)	26/240 (10.8%)	0.498
Previous PCI	37/234 (15.8%)	33/240 (13.8%)	0.527
Previous stroke	12/234 (5.1%)	9/240 (3.8%)	0.466
Previous TIA	1/87 (1.1%)	7/91 (7.7%)	0.065
Diabetes mellitus	45/234 (19.2%)	40/240 (16.7%)	0.467
Smoking	81/234 (34.6%)	86/239 (36.0%)	0.756
Family history	97/232 (41.8%)	103/240 (42.9%)	0.808
Infarct-related vessel			0.934
RCA	61/232 (26.3%)	68/240 (28.3%)	
LAD	93/232 (40.1%)	89/240 (37.1%)	
CX	61/232 (26.3%)	62/240 (25.8%)	
Graft	15/232 (6.5%)	18/240 (7.5%)	
LM	2/232 (0.9%)	3/240 (1.2%)	
Lesion length			0.239
<10 mm	55/180 (30.6%)	56/182 (30.8%)	
10–20 mm	91/180 (50.6%)	103/182 (56.6%)	
>20 mm	34/180 (18.9%)	23/182 (12.6%)	
Calcification			
Little or none	170/204 (83.3%)	183/213 (85.9%)	
Moderate or heavy	34/204 (16.7%)	30/213 (14.1%)	
Angulation			0.786
None	175/181 (96.7%)	174/183 (95.1%)	
Moderate	6/181 (3.3%)	8/183 (4.4%)	
Severe	0/181 (0.0%)	1/183 (0.5%)	
Modified ACC/AHA lesion type			0.683
A	4/214 (1.9%)	4/219 (1.8%)	
B1	39/214 (18.2%)	33/219 (15.1%)	
B2	127/214 (59.3%)	142/219 (64.8%)	
C	44/214 (20.6%)	40/219 (18.3%)	
Bifurcation			0.299
No side branch involvement	94/182 (51.6%)	86/186 (46.2%)	
Side branch involvement	88/182 (48.4%)	100/186 (53.8%)	
Ostial location	51/178 (28.7%)	57/182 (31.3%)	0.581
Stent placement	225/229 (98.3%)	234/237 98.7%)	0.720
Direct stenting	69/225 (30.7%)	83/234 (35.5%)	0.274
Balloon size (mm)	2.80±0.42	2.80±0.43	0.935
Total number of stents	1.22±0.48	1.18±0.42	0.392
Maximal stent diameter (mm)	3.13±0.41	3.14±0.42	0.878
Total stent length (mm)	22.80±10.34	22.34±8.97	0.717

Values are the number of cases (%) or mean±SD.
ACC/AHA, American College of Cardiology/American Heart Association; BMI, body mass index; CABG, coronary artery bypass graft; CX, left circumflex artery; IRV, infarct-related vessel; LAD, left anterior descending artery; LM, left main artery; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery.

In the registry group, clinical follow-up at 24 months was complete in 282 (95%) patients. The rate of MACE was 13.6% (EES) versus 16.9% (BMS) p=0.437. Target vessel revascularisation was necessary in 3.6% (EES) versus 9.9% (BMS) p=0.035 and stent thrombosis occurred in 1.4% (EES) versus 2.8% (BMS) p=0.684.

The secondary end point, stent thrombosis, in the pooled population (1.3% (DES) versus 3.0% (BMS), p=0.339) did not differ significantly between the groups at 2 years follow-up. Neither did the exploratory end point MACE (12.5% (DES) versus 16.0% (BMS), p=0.284)

(table 3), as also illustrated by the Kaplan-Meier event-free survival curves (figures 2 and 3). DE stenting, however, significantly reduced target vessel revascularisation as compared to BM stenting (4.0% vs 10.4%, p=0.009) (table 5).

DISCUSSION

The main finding of this study was that the use of an everolimus eluting second-generation DES is safe and decreased restenosis, angiographic as well as clinical, in patients with NSTEMI.

Table 4 Angiographic results preprocedural and postprocedural and at 9 months follow-up

	EES (n=85)	BMS (n=87)	p Value
Pre-PCI			
Time from randomisation to PCI (hours)	26.4±40.2	41.7±67.3	0.075
MLD (mm)	0.81±0.42	0.81±0.40	0.928
Diameter stenosis (%)	69.73±15.28	69.00±14.92	0.711
Lesion length (mm)	14.43±6.63	13.39±7.03	0.234
Reference diameter pre-PCI (mm)	2.73±0.52	2.65±0.55	0.304
Post-PCI			
MLD (mm)	2.36±0.57	2.30±0.46	0.163
Diameter stenosis (%)	11.85±16.75	13.06±10.80	0.107
Lesion length (mm)	18.30±7.88	17.58±7.08	0.709
Stent placement	82/84 (97.6%)	87/89 (97.8%)	>0.99
Direct stenting	27/82 (32.9%)	32/87 (36.8%)	0.599
Number of stents	1.26±0.49	1.15±0.39	0.114
Maximal stent diameter (mm)	3.14±0.43	3.13±0.45	0.660
Total stent length (mm)	22.57±10.74	21.47±7.72	0.825
Balloon size (mm)	2.82±0.45	2.69±0.45	0.084
Acute gain (mm)	1.53±0.50	1.50±0.52	0.498
Nine-month follow-up	*EES (n=60)*	*BMS (n=64)*	
Time from randomisation to 9 months follow-up (months)	8.9±1.6	9.2±2.4	0.468
MLD (mm)	2.37±0.63	1.84±0.62	<0.001
Diameter stenosis (%)	11.25±18.03	31.13±18.65	<0.001
Binary restenosis*	1/54 (1.9%)	10/60 (16.7%)	0.007
Late loss (mm)	0.09±0.52	0.52±0.51	<0.001

Values are mean±SD or count/sample size (%).
*diameter stenosis at 9 months follow-up >50%.
Acute gain, MLD after stenting minus MLD at baseline; Late loss, MLD after stenting minus MLD at follow-up; MLD, minimal lumen diameter.
BMS, bare-metal stent; EES, everolimus-eluting stent; PCI, percutaneous coronary intervention.
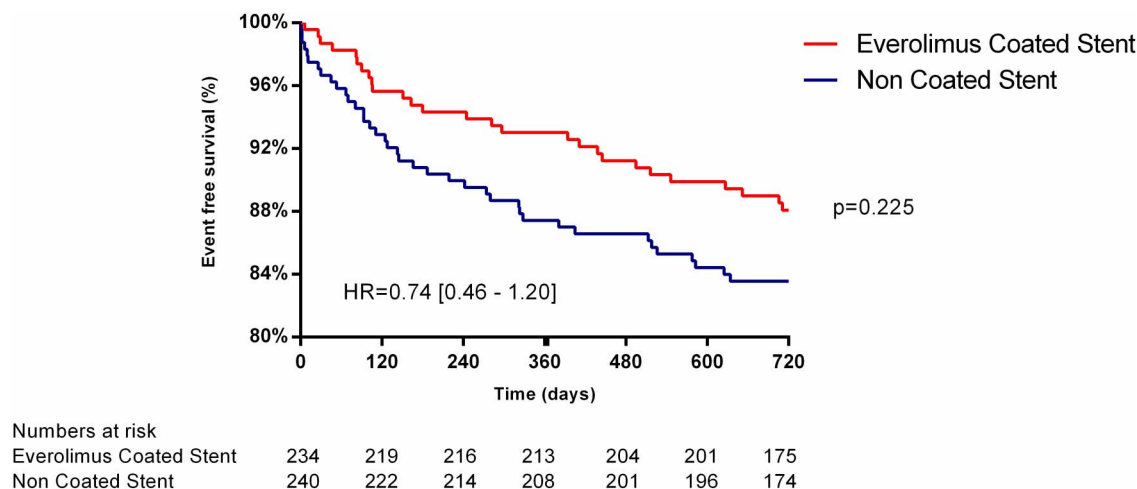

Figure 2 Kaplan-Meier curves showing freedom from MACE up to 720 days after the index procedure in the pooled population. MACE, major adverse cardiac events (composite of death, myocardial infarction and target vessel revascularisation).

In STEMI, Laarman *et al*[7] found no significant benefit associated with the use of first-generation paclitaxel-eluting stents in primary PCI as compared with uncoated stents with the same design. Spaulding *et al*,[13] however, found a significant reduction in the incidence of target-vessel failure at 1 year, using a sirolimus-eluting stent, compared with uncoated stents. Rates of stent thrombosis were similar in the coated and uncoated stent groups in both studies.

In the EXAMINATION trial, an allcomer trial in 1498 patients with STEMI comparing second-generation EES versus BMS, Sabate *et al*[14] showed that the rate of target lesion revascularisation and the rate of stent thrombosis were reduced in recipients of EES. The same result on stent thrombosis was found in a subgroup of patients with NSTE-ACS from the BASKET-PROVE trial;[15] however, neither trial was sufficiently powered for this end point and the latter was a post hoc analysis.

Although there is growing evidence that the cobalt-chromium (CoCr)-EES is safe, there is still debate about the relative safety of DES compared to BMS related to stent thrombosis. Pathological studies suggest that the permanent presence of polymers may result in chronic arterial inflammation, resulting in delayed endothelial healing and late thrombotic events.[16]

A large meta-analysis in 2007 comparing BMS and first-generation DES strengthened concerns about late and very late stent thrombosis with paclitaxel-eluting stents.[17] Recently, however, it has been shown that second-generation polymers (ie, polyvinylidene fluoride-co-hexafluoropropene (PVDF-HFP)) used in current DES provide a more biocompatible surface than early-generation polymers[18] and Kolandaivelu et al[19] showed in a controlled model of early ST that drug-eluting polymer-coated stents are even consistently less, not more, thrombogenic than matched bare metal platforms.

Table 5 MACE, TVR and ST at 2 years follow-up

Follow-up at 2 years	EES (%)	BMS (%)	p Value
Elisa-3 (n=173)			
MACE	10.7	14.6	0.442
TVR	4.8	11.2	0.119
ST	1.2	3.4	0.621
Elisa Registry (n=282)			
MACE	13.6	16.9	0.437
TVR	3.6	9.9	0.035
ST	1.4	2.8	0.684
Pooled Analysis (n=455)			
MACE	12.5	16.0	0.284
TVR	4.0	10.4	0.009
ST	1.3	3.0	0.339

BMS, bare-metal stent; EES, everolimus-eluting stent; MACE, major adverse cardiac events (composite of death, myocardial infarction and target vessel revascularisation); TVR, target vessel revascularisation; ST, stent thrombosis.

Continuous refinement in stent design and the development of thinner stent struts has resulted in significantly lower rates of stent thrombosis; thus nowadays even larger sample sizes are required to accurately estimate differences between stents and as such many RCTs are presently underpowered for this endpoint. For this reason, Palmerini et al[20] conducted a large network meta-analysis of RCTs comparing the risk of thrombosis between bare-metal, first-generation and second-generation DES. They reported a profound reduction of stent thrombosis with cobalt-chromium EES, compared with other DES as well as with BMS at 2-year follow-up. These findings were corroborated by the results of another meta-analysis of 4896 patients comparing the cobalt-chromium EES with its uncoated otherwise identical metallic counterpart, showing improvement in cardiovascular outcomes including cardiac survival, MI and overall stent thrombosis with the cobalt-chromium EES.[21]

The issue of restenosis is often thought of as trivial, not having any influence at clinical end points, but there is evidence that in ~10% of cases, patients with in-stent restenosis present with reMI instead of just angina.[22]

In our study, restenosis rates were highly significantly lower in the EES group at 9 months angiographic follow-up, which is consistent with findings in previous trials.

Our study, however, is the first randomised trial to investigate the safety and efficacy of second-generation DES in a NSTEMI population. Patients with NSTEMI differ from those with STEMI. In STEMI, the culprit artery is usually occluded by a thrombus, whereas in NSTEMI the culprit artery is usually patent with a non-occlusive thrombus, but both conditions stem from the same pathophysiological process.[10 23 24] Thereby, patients with STEMI are older and have more comorbidity as compared to patients with STEMI, reflecting their worse long-term clinical outcome. This study shows that
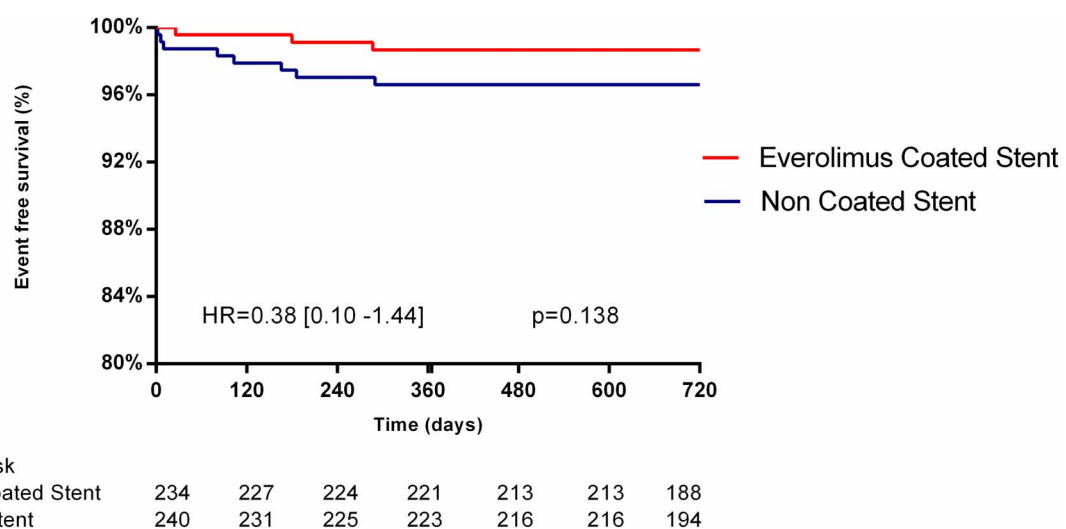

Figure 3 Kaplan-Meier curves showing freedom from stent thrombosis up to 720 days after the index procedure in the pooled population.

DE stenting in this patient population is safe and improves long-term target vessel revascularisation.

Limitations of the study

Several limitations of the present study should be acknowledged. Most important was the lower than expected inclusion rate in the ELISA-3 angiographic substudy. When inclusion in the main study was finished, of 344 eligible patients only 178 were randomised in this angiographic substudy, giving an ~78% power to prove superiority of the DES, while we anticipated to recruit 280 patients in our power calculations.

Furthermore, we encountered a higher than expected loss of angiographic follow-up at 9 months. We conducted a pooled analysis of the ELISA-3 and the ELISA Registry patients to have more power with regard to the safety of DE versus BM stenting in terms of clinical outcome; this study, however, was not powered to show differences in MACE.

Conclusion

In patients with NSTEMI, the use of an EES second-generation DES is safe and decreases both angiographic and clinical restenosis as compared to a cobalt chromium BMS.

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