Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION): 1 year results of a randomised controlled trial

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Summary

Background Everolimus-eluting stent (EES) reduces the risk of restenosis in elective percutaneous coronary intervention. However, the use of drug-eluting stent in patients with ST-segment elevation myocardial infarction (STEMI) is still controversial. Data regarding the performance of second-generation EES in this setting are scarce. We report the 1-year result of the EXAMINATION (clinical Evaluation of the Xience-V stent in Acute Myocardial INfArcTION) trial, comparing EES with bare-metal stents (BMS) in patients with STEMI.

Methods This multicentre, prospective, randomised, all-comer controlled trial was done in 12 medical centres in three countries. Between Dec 31, 2008, and May 15, 2010, we recruited patients with STEMI up to 48 h after the onset of symptoms requiring emergent percutaneous coronary intervention. Patients were randomly assigned (ratio 1:1) to receive EES or BMS. Randomisation was in blocks of four or six patients, stratified by centre and centralised by telephone. Patients were masked to treatment. The primary endpoint was the patient-oriented combined endpoint of all-cause death, any recurrent myocardial infarction, and any revascularisation at 1 year and was analysed by intention to treat. The secondary endpoints of the study included the device-oriented combined endpoint of cardiac death, target vessel myocardial infarction or target lesion revascularisation, and rates of all cause or cardiac death, recurrent myocardial infarction, target lesion or target vessel revascularisation, stent thrombosis, device and procedure success, and major and minor bleeding. This trial is registered with ClinicalTrials.gov, number NCT00828087.

Findings Of the 1504 patients randomised, 1498 patients were randomly assigned to receive EES (n=751) or BMS (n=747). The primary endpoint was similar in both groups (89 [11·9%] of 751 patients in the EES group *vs* 106 [14·2%] of 747 patients in the BMS group; difference –2·34 [95% CI –5·75 to 1·07]; p=0·19). Device-oriented endpoint (44 [5·9%] in the EES group *vs* 63 [8·4%] in the BMS group; difference –2·57 [95% CI –5·18 to 0·03]; p=0·05) did not differ between groups, although rates of target lesion and vessel revascularisation were significantly lower in the EES group (16 [2·1%] *vs* 37 [5·0%], p=0·003, and 28 [3·7%] *vs* 51 [6·8%], p=0·0077, respectively). Rates of all cause (26 [3·5%] for EES *vs* 26 [3·5%] for BMS, p=1·00) or cardiac death (24 [3·2%] for EES *vs* 21 [2·8%] for BMS, p=0·76) or myocardial infarction (10 [1·3%] *vs* 15 [2·0%], p=0·32) did not differ between groups. Stent thrombosis rates were significantly lower in the EES group (4 [0·5%] patients with definite stent thrombosis in the EES group *vs* 14 [1·9%] in the BMS group and seven [0·9%] patients with definite or probable stent thrombosis in the EES group *vs* 19 [2·5%] in the BMS group, both p=0·019). Although device success rate was similar between groups, procedure success rate was significantly higher in the EES group (731 [97·5%] *vs* 705 [94·6%]; p=0·0050). Finally, Bleeding rates at 1 year were comparable between groups (29 [3·9%] patients in the EES group *vs* 39 [5·2%] in the BMS group; p=0·19).

Interpretation The use of EES compared with BMS in the setting of STEMI did not lower the patient-oriented endpoint. However, at the stent level both rates of target lesion revascularisation and stent thrombosis were reduced in recipients of EES.

Funding Spanish Heart Foundation.

Introduction

Percutaneous coronary intervention is the standard of treatment in ST-elevation myocardial infarction (STEMI) when done in experienced centres within adequate time delay after the symptoms onset.[1] In this clinical scenario, the use of bare metal stent (BMS) reduced the rate of re-intervention as compared with balloon angioplasty.[2–7] First generation drug-eluting stents have reduced clinical and angiographic restenosis as compared with BMS in both elective and STEMI context.[2,6,8–12] However, concerns on safety potentially related to reduced endothelialisation and healing restrained their use especially in the setting

of patients with STEMI.[13-18] The long-term follow-up of several pivotal studies showed an increased risk of stent thrombosis after first generation drug-eluting stents implantation in patients with STEMI compared with BMS,[4,19–21] even if this result has not been confirmed by other studies.[10,12]

Second generation everolimus-eluting stent (EES; Xience V; Abbott Vascular, Santa Clara, CA, USA) has been designed with thin (7·8 μm) non-adhesive, durable, biocompatible acrylic polymers and fluorinated copolymer.[22] As compared with first generation drug-eluting stents, the second generation everolimus-eluting stent was able to reduce both the restenosis and the thrombosis rates in randomised controlled trials designed in overall elective context.[23,24]

The purpose of the EXAMINATION trial was to compare the second generation everolimus-eluting stent with the cobalt chromium balloon expandable Multilink Vision BMS (Abbott Vascular, Santa Clara, CA, USA) having the same metallic platform but not containing any drug or polymer, in a multicentre, randomised, controlled, superiority trial in patients undergoing percutaneous coronary intervention for STEMI.

Methods

Patients and study design

This multicentre, multinational, prospective, randomised, single-blind, controlled trial was done in patients with STEMI.

Between Dec 31, 2008, and May 15, 2010, we recruited patients swith STEMI. Inclusion and exclusion criteria were reported elsewhere.[25] Briefly, the study had broad inclusion and few exclusion criteria. Any patient presenting with STEMI with the following electrocardiogram criteria: at least 1 mm in two or more standard leads or at least 2 mm in two or more contiguous precordial leads or left bundle-branch block that was not known to be old, within the first 48 h after the symptoms onset requiring emergent percutaneous coronary intervention with a vessel size ranging between 2·25 mm and 4·0 mm without other anatomical restrictions could be included. Exclusion criteria were age younger than 18 years, pregnancy, patients with known intolerance to aspirin, clopidogrel, heparin, stainless steel, everolimus or contrast material, patients on chronic treatment with anti-vitamin K agents, and STEMI secondary to stent thrombosis.

The patients were included in the trial after signing a written informed consent. Besides, given the emergent

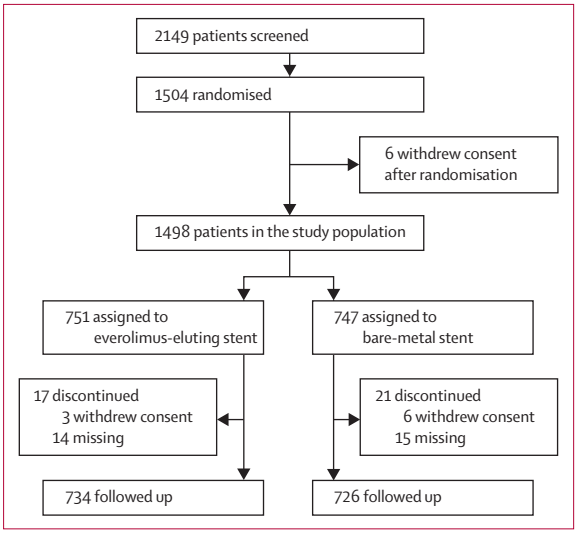


Figure 1: **Trial profile**
EES=everolimus-eluting stent. BMS=bare-metal stent.

	EES group (n=751)	BMS group (n=747)
Age (years, mean [SD])	60·8 (12)	61·6 (13)
Male sex	634 (84%)	610 (82%)
Body-mass index	27·2 (4%)	27·4 (4%)
Coronary risk factors		
(Previous) smoker	544 (72%)	538 (72%)
Diabetes mellitus	137 (18%)	121 (16%)
Arterial hypertension	347 (46%)	378 (51%)
Hyperlipidaemia	354 (47%)	301 (40%)
Family history	134 (18%)	119 (16%)
Cardiovascular history		
Previous myocardial infarction	33 (4%)	47 (6%)
Previous PCI	29 (4%)	32 (4%)
Previous CABG	3 (<1%)	7 (1%)
Previous stroke	12 (2%)	19 (3%)
Peripheral vasculopathy	25 (3%)	30 (4%)
Clinical condition		
Primary PCI (<12 h)	630 (84%)	638 (85%)
Rescue PCI	50 (7%)	48 (6%)
PCI after successful thrombolysis	23 (3%)	11 (1%)
Latecomer (>12 h and <48 h)	48 (6%)	49 (7%)
Clinical status on admission		
Killip I	669 (89%)	668 (90%)
Killip II	59 (8%)	56 (7%)
Killip III	10 (1%)	13 (2%)
Killip IV	11 (1%)	7 (1%)
Infarct-related artery		
Left anterior descending artery	317 (42%)	291 (39%)
Left circumflex	105 (14%)	112 (15%)
Right coronary artery	318 (42%)	334 (45%)
Left main	6 (<1%)	4 (<1%)
Saphenous vein graft	4 (<1%)	6 (<1%)
Single-vessel disease	645 (86%)	656 (88%)
Multivessel disease	100 (13%)	88 (12%)
Ejection fraction (mean [SD])*	51·1 (11)	51·0 (10)

Data are number of patients (%) unless otherwise stated. EES=everolimus-eluting stent. BMS=bare metal stent. PCI=percutaneous coronary intervention. CABG=coronary artery bypass graft. *Ejection fraction calculated in 542 (72%) patients in the EES group and in 515 (69%) patients in the BMS group.

Table 1: **Baseline characteristics of the patients**

clinical context of the study, in case the patient was unable to provide written informed consent (eg, cardiogenic shock, cardiac arrest, severe chest pain making good communication impossible, etc), written assent from a legally acceptable representative was accepted to facilitate enrolment. When the investigator thought the patient was capable of understanding the process and signing the consent form, written consent was signed from the patient.

See Online for appendix

A total of 12 academic hospitals in three countries were involved in the trial (appendix). All centres submitted and received the approval of their Medical Ethics Committee for the protocol and for the informed consent. The study was done in compliance with the protocol, the Declaration of Helsinki, BS EN ISO 14155 Part 1 and Part 2, and applicable local requirements. All patients provided written informed consent. Description of the Data and Safety Monitoring Board, Clinical Event Committee, and the Steering Committee can be found in the appendix.

	EES group	BMS group	Difference (95% CI)*	p value†
TIMI flow before PCI				0·80‡
0	378/751 (50%)	374/747 (50%)	0·81 (–3·60 to 5·21)	
1	56/751 (7%)	60/747 (8%)	–0·39 (–2·74 to 1·96)	
2	92/751(12%)	97/747 (13%)	–1·12 (–4·06 to 1·82)	
3	225/751 (30%)	216/747 (29%)	0·70 (–3·32 to 4·72)	
Anticoagulation regimen				
Unfractioned heparin	599/751 (80%)	590/747 (79%)	0·78 (–3·32 to 4·88)	0·74
Low molecular weight heparin	62/751 (8%)	71/747 (10%)	–1·25 (–4·13 to 1·63)	0·41
Bivalirudin	49/751 (7%)	56/747 (7%)	–0·97 (–3·56 to 1·61)	0·48
Antiplatelet regimen				
Aspirin before PCI	694/751 (92%)	694/747 (93%)	–0·49 (–3·14 to 2·15)	0·76
Clopidogrel before PCI	712/751 (95%)	706/747 (95%)	0·30 (–1·98 to 2·57)	0·81
IIb/IIIa inhibitor	400/751 (53%)	385/747 (52%)	1·72 (–3·33 to 6·78)	0·53
Manual thrombectomy	495/751 (66%)	481/747 (64%)	1·52 (–3·30 to 6·35)	0·55
Type of stent				
EES	748/751 (>99%)	0	..	0·0001
Other drug-eluting stents	3/751 (<1%)	0	..	
Multilink-vision	0	744/747 (>99%)	..	
Other BMS	0	3/747 (<1%)	..	
Direct stenting	451/751 (60%)	434/747 (58%)	1·58 (–3·43 to 6·58)	0·55
Post-dilatation	118/751 (16%)	103/747 (14%)	1·86 (–1·80 to 5·51)	0·34
Overlapping stent	198/751 (26%)	206/747 (28%)	–1·27 (–5·32 to 3·96)	0·77
Number of stents (mean [SD])	1·4 (0·7)	1·4 (0·6)	0·02 (–0·05 to 0·08) §	0·65§
Total stent length-median (IQR)	23 (18–35)	23 (18–33)	0·00 (0·00 to 0·00) ¶	0·87‖
TIMI flow after PCI				0·38‡
0	17/751 (2%)	8/747 (1%)	0·97 (–0·32 to 2·26)	
1	7/751 (<1%)	5/747 (<1%)	0·09 (–0·76 to 0·95)	
2	33/751 (4%)	31/747 (4%)	0·47 (–1·36 to 2·29)	
3	694/751 (92%)	703/747 (94%)	–1·53 (–3·87 to 0·82)	

Dara are number of patients (%) unless otherwise stated. EES=everolimus-eluting stent. BMS=bare metal stent. PCI=percutaneous coronary intervention. IQR: interquartile range. *Normality assumed. †2-sided Fisher's Exact test. ‡Cochran-Mantel-Haenszel test. §t-test procedure. ¶Hodges-Lehmann estimation. ‖Median two-sample test.

Table 2: **Periprocedural characteristics**

Randomisation and masking

All recruited patients were randomly assigned (ratio 1:1) to receive one of the two treatment: EES or cobalt-chromium BMS. We based the allocation schedule on computer-generated random numbers. The randomisation was in blocks of four or six patients (randomly), stratified by centre and centralised by telephone. The design of both platforms (EES or BMS) was the same and corresponded to that of the Multilink Vision stent. Patients were masked to the treatment. As per inclusion criteria, the patient could fall into one of the following categories: STEMI at less than 12 h after the onset of symptoms (namely, primary percutaneous coronary intervention), rescue percutaneous coronary intervention after failed thrombolysis, percutaneous coronary intervention indicated early (<24 h) after effective thrombolysis, and patients presenting late ("latecomers") with STEMI (between 12 h and 48 h after the onset of symptoms).

Procedures

At the index procedure, patients received appropriate anticoagulation and other therapy according to standard hospital practice. Either unfractionated heparin or bivalirudin might be used for procedural anticoagulation. The use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the investigator. Aspirin (loading dose 250–500 mg) and clopidogrel (loading dose of at least 300 mg) had to be given before percutaneous coronary intervention for those patients not on chronic antiplatelet treatment. Neither prasugrel nor ticagrelor were approved during the recruitment period. Clopidogrel was prescribed for at least 1 year (75 mg per day) and aspirin (100 mg) indefinitely. Compliance to dual antiplatelet therapy refers to the concomitant use of both drugs during the prescription time of 1 year. Manual thrombectomy followed by direct stenting was the recommended technique in this setting, although other devices could also be used if considered necessary. Operators were instructed to use only the assigned stent type at the index procedure.

Patients with multivessel disease needing staged percutaneous coronary intervention could also be included. A recommendation was made to implant the same stent type, as per randomisation, in all staged lesions. Importantly, all staged procedures had to be done within the first month following discharge. Any revascularisation done after this timeframe was counted as an unplanned intervention, even if it was undertaken to treat previously-existing coronary lesions.

The follow-up included clinical visit or telephone contacts at 30 days, 6 months, and 1 year, and will be continued yearly up to 5 years. No angiographic follow-up was mandated per protocol.

Statistical analysis

The primary endpoint of the study was the patient-oriented combined endpoint of all-cause death, any myocardial infarction or any revascularisation at 1 year

according to the Academic Research Consortium (ARC).[26] Secondary endpoints of the study were the device-oriented combined endpoint of cardiac death, target vessel myocardial infarction or target lesion revascularisation at 1 year;[26] all cause and cardiac death; recurrent myocardial infarction (WHO extended definition[27]); target lesion and target vessel revascularisation; stent thrombosis (according to the ARC definitions[26]); device and procedure success; and major and minor bleeding. Detailed definitions of the endpoints have been reported elsewhere.[25]

We did all analyses by intention to treat as well as per protocol (if different from allocated by randomisation). The overall sample size for the study of 1500 patients was based on the primary endpoint at 1-year. The sample size calculation was based on a 2-sided type I error rate α of 0·05, a randomisation ratio of 1:1 (EES group: BMS group), and a statistical power of at least 86% to detect about 30% reduction in the rate of the primary endpoint at 1 year from 20·5% in the control group to 14·5% in the EES group. To estimate the rate of events in the BMS group, we used the data available from all-comers Registries (Research, T-Search) and meta-analysis of randomised controlled trials that included patients with STEMI.[9,28]

We tested the primary endpoint statistically with the log-rank test at a two-sided 0·05 significance level for the comparison of the EES group with the BMS group. We presented count variables as percentages, continuous variables as means (medians and interquartile ranges whenever appropriate). For time-to-event variables, we constructed survival curves using Kaplan-Meier estimates.

Prespecified subgroup analyses included the following variables: sex, age (>70 years *vs* ≤70 years), presence of diabetes, primary versus non-primary percutaneous coronary intervention; TIMI after percutaneous coronary intervention (TIMI<3 *vs* TIMI=3), concomitant treatment with glycoprotein IIb/IIIa inhibitors, use of aspiration thrombectomy catheters, multivessel disease *vs* single-vessel disease, ischaemia time (<3 h *vs* ≥3 h), time between first medical contact and first device (<120 min *vs* ≥120 min); ejection fraction (<30% *vs* ≥30%); left anterior descending as infarct-related artery.

During the recruitment period, data of the number of percutaneous coronary interventions in the setting of STEMI done at the institutions involved were obtained, as well as the reasons why these procedures were not included in the trial. This trial is registered with ClinicalTrials.gov, number NCT00828087.

Role of the funding source

The sponsor of the study had no role in the study design. The promoter funded an independent data management and analysis centre (Cardialysis, Rotterdam, Netherlands) for database management and all statistical analyses. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

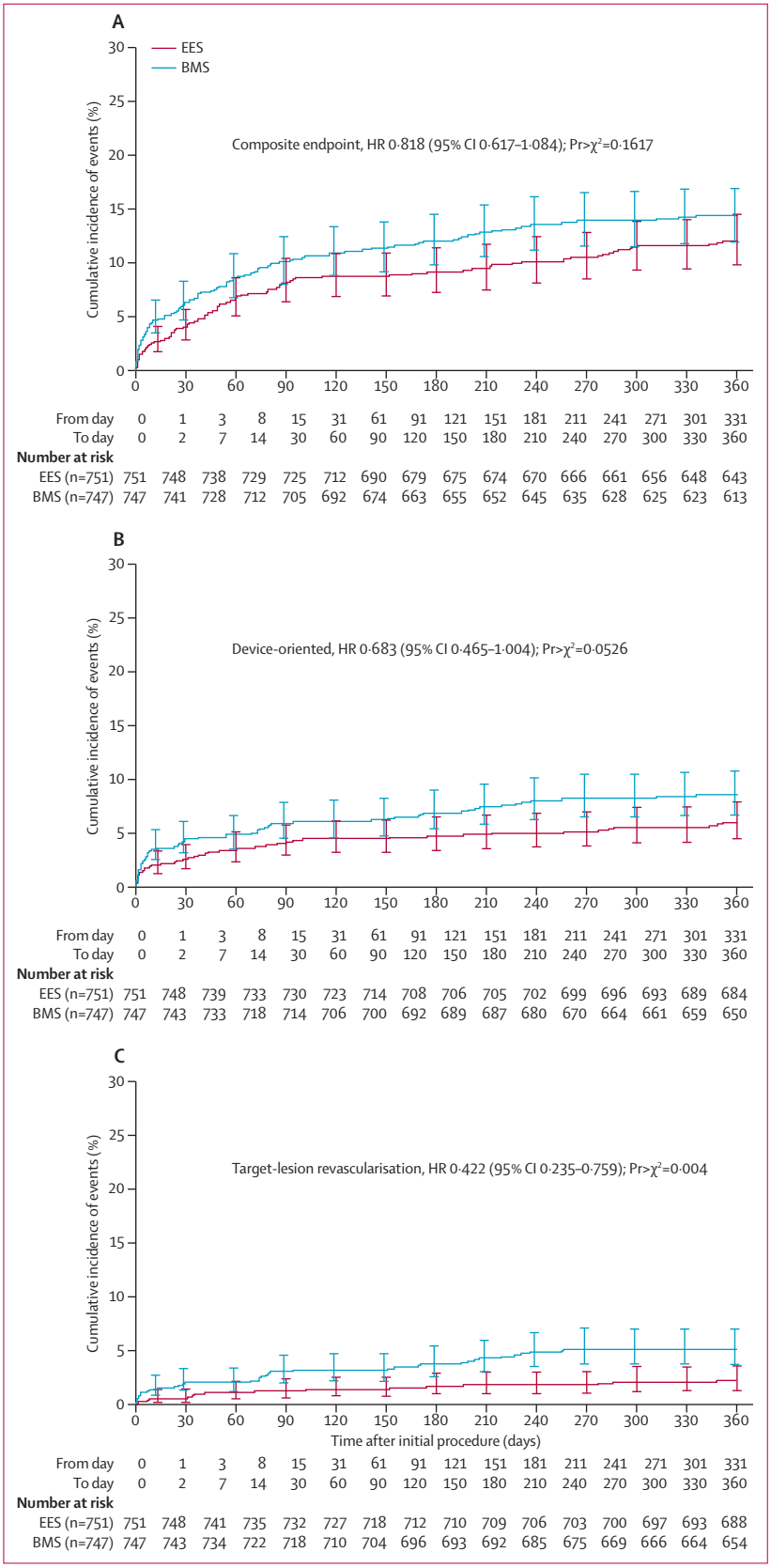
Results

From 2149 patients screened in the centres, 1504 patients were initially recruited, of whom six withdrew consent after randomisation (figure 1). 1498 patients were randomly assigned to receive either an EES (751 patients) or a BMS (747 patients). As a result, this cohort of patients represented 70% of all STEMI presenting at the recruiting centres during the study period. Reasons for non-

	EES group (n=751)	BMS group (n=747)	Difference (95%CI)*	p value†
Up to 30 days				
Death‡	11 (1·5%)	14 (1·9%)	−0·41 (−1·71 to 0·89)	0·55
Cardiac	11 (1·5%)	14 (1·9%)	−0·41 (−1·71 to 0·89)	0·55
Vascular	0	0	..	
Non-cardiovascular	0	0	..	
Myocardial infarction§	5 (0·7%)	9 (1·2%)	−0·54 (−1·51 to 0·44)	0·29
Target-vessel related	5 (0·7%)	9 (1·2%)	−0·54 (−1·51 to 0·44)	0·29
Non-target-vessel related	0	0	..	
Revascularisation	17 (2·3%)	31 (4·2%)	−1·89 (−3·67 to −0·10)	0·0406
Target lesion	4 (0·5%)	15 (2·0%)	−1·48 (−2·61 to −0·34)	0·0111
Target vessel	9 (1·2%)	25 (3·4%)	−2·15 (−3·65 to −0·64)	0·0053
Non-target vessel	8 (1·1%)	13 (1·7%)	−0·68 (−1·87 to 0·52)	0·28
Definite stent thrombosis¶	3 (0·4%)	12 (1·6%)	−1·21 (−2·22 to −0·20)	0·0204
Probable stent thrombosis¶	3 (0·4%)	4 (0·5%)	−0·14 (−0·83 to 0·55)‖	0·72
Definite or probable stent thrombosis¶	6 (0·8%)	16 (2·1%)	−1·34 (−2·56 to −0·13)	0·0330
Procedural success**	731 (97·3%)	705 (94·3%)	−2·90 (−3·30 to −2·40)	0·0050
Up to 360 days				
Primary endpoint (patient oriented)††	89 (11·9%)	106 (14·2%)	−2·34 (−5·75 to 1·07)	0·19
Device-oriented secondary endpoint‡‡	44 (5·9%)	63 (8·4%)	−2·57 (−5·18 to 0·03)	0·05
Death*	26 (3·5%)	26 (3·5%)	−0·02 (−1·87 to 1·84)	1·00
Cardiac	24 (3·2%)	21 (2·83%)	0·38 (−1·34 to 2·11)	0·76
Vascular	1 (0·1%)	3 (0·4%)	−0·27 (−0·79 to 0·25)‖	0·37
Non-cardiovascular	1 (0·1%)	2 (0·3%)	−0·13 (−0·59 to 0·32)‖	0·62
Myocardial infarction§	10 (1·3%)	15 (2·0%)	−0·68 (−1·97 to 0·62)	0·32
Target-vessel related	8 (1·1%)	15 (2·0%)	−0·94 (−2·19 to 0·30)	0·14
Non-target-vessel related	2 (0·3%)	0	0·27 (−0·10 to 0·63)‖	0·49
Revascularisation	60 (8·0%)	79 (10·6%)	−2·59 (−5·52 to 0·35)	0·09
Target lesion	16 (2·1%)	37 (5·0%)	−2·82 (−4·69 to −0·96)	0·0032
Target vessel	28 (3·7%)	51 (6·8%)	−3·10 (−5·36 to −0·84)	0·0077
Non-target vessel	40 (5·3%)	41 (5·5%)	−0·16 (−2·45 to 2·13)	0·90
Definite stent thrombosis¶	4 (0·5%)	14 (1·9%)	−1·34 (−2·44 to −0·24)	0·0183
Probable stent thrombosis¶	3 (0·4%)	5 (0·7%)	−0·27 (−1·01 to 0·47)‖	0·50
Definite or probable stent thrombosis¶	7 (0·9%)	19 (2·5%)	−1·61 (−2·93 to −0·29)	0·0197
Bleeding	29 (4%)	39 (5%)	−1·4 (−3·47 to 0·75)	0·19
Major	9 (1%)	12 (2%)	−0·4 (−1·60 to 0·78)	0·65
Minor	21 (3%)	30 (4%)	−1·2 (−3·06 to 0·62)	0·21

Data are number of patients (%). EES=everolimus-eluting stent. BMS=bare metal stent. *Normality assumed. †2-sided Fisher's Exact test. ‡Death was adjudicated according to the Academic Research Consortium.[26] §Myocardial infarction was adjudicated according to WHO extended definition.[27] ¶Stent thrombosis defined according to the Academic Research Consortium.[26] ‖Insufficient observations to apply normal distribution. **Procedural success defined as successful device implantation without the occurrence of ischaemia-driven major adverse cardiac event during the hospital stay with a maximum of first 7 days post index procedure. ††Combined (hierarchical) of all-cause death, any recurrent myocardial infarction or any revascularisation.[26] ‡‡Combined (hierarchical) of cardiac death, target vessel myocardial infarction or target lesion revascularisation.[26]

Table 3: **Clinical events during follow-up**



randomisation of the patient were: impossibility to obtain informed consent (152 [23%] of 645), impossibility to keep the patient with dual antiplatelet therapy for 1 year (70 [11%]), stent thrombosis (63 [10%]), requirement of subsequent surgery (59 [9%]), patient in transit (53 [8%]), not consented to be in the trial (52 [8%]), terminal patient (32 [5%]), inappropriate vessel size (32 [5%]), treatment with acenocumarol (30 [5%]), drug misuse (16 [2%]), patient already registered in another trial (25 [4%]), and other reasons (61 [9%]). Baseline clinical characteristics were well balanced between study groups (table 1). Procedural characteristics were also similar between the two study groups (table 2). Most patients received the combination of aspirin (250–500 mg) and clopidogrel (300–600 mg) loading doses before the intervention. The anticoagulation regimen did not differ between groups. Overall, the combination of heparin and IIb/IIIa inhibitors accounted for 809 (54%) patients, heparin alone for 614 (41%), bivalirudin alone for 67 (4%), and bivalirudin and IIb/IIIa inhibitors for eight (<1%). Manual thrombus aspiration followed by direct stenting was the most common selected strategy of intervention. At the index procedure, three patients in the EES group received another DES type (Taxus™ stent) and three patients from the BMS group received another BMS type (table 2). No crossover occurred from drug-eluting stents to BMS or vice versa at the index procedure. On average, a total of 1·4 stents were implanted at the culprit lesion with a median total length of 23 mm. Device success rate (defined as successful delivery and deployment of the first inserted study stent [in overlapping stent setting a successful delivery and deployment of the first and second study stent] at the intended target lesion and successful withdrawal of the stent delivery system with attainment of final residual stenosis of less than 50% of the target lesion without use of a device outside the assigned treatment strategy) was similar in both groups (747 [>99%] of 751 patients in the EES group and 742 [99%] of 747 patients in the BMS group). However, procedural success rate (defined as successful device implantation without the occurrence of ischaemia-driven major adverse cardiac event during the hospital stay with a maximum of first 7 days post-index procedure) was significantly higher in the EES group (table 3). Peri-procedural times and biomarker levels were also similar between the two groups (appendix).

Overall, 123 patients (16%) in the EES group and 98 (13%) in the BMS group needed staged procedures, which were

Figure 2: **Patient-oriented primary endpoint and device-oriented endpoint over 360 days**

EES=everolimus-eluting stent. BMS=bare-metal stent. (A) Kaplan-Meier estimates for the patient-oriented primary endpoint over 360 days of follow-up. (B) Kaplan-Meier estimates of the device-oriented endpoint over 360 days of follow-up. (C) Kaplan-Meier estimates of the target lesion revascularisation endpoint over 360 days of follow-up. Error bars indicate a point-wise two-sided 95% CI with a complementary log-log transformation. Standard Error based on the Greenwood Formula.

done after a median time of 9 days (range 5–25 days) in the EES group and 11·5 days (range 6–23) in the BMS group. In 35 (36%) of 98 patients allocated to the BMS group, a crossover to EES was done at the time of the staged procedure. In 14 (11%) of the 123 patients allocated to EES another DES was implanted. No crossover to BMS from EES group was noted at staged procedures.

During follow-up, nine patients withdrew the consent and 29 were lost to follow-up (figure 1). As a result, data of 1-year follow-up were obtained for 734 patients in the EES group and 726 patients in the BMS group (figure 1). Compliance to dual antiplatelet regimen (EES *vs* BMS) did not differ between groups up to 30 days (99·7% *vs* 99·6% at discharge, difference 0·14 [95% CI –0·45 to 0·73], p=0·69; 98·8% *vs* 99·4% at 30 days, –0·58 [–1·57 to 0·40, p=0·26) and became significantly different at 6 months (99·1% *vs* 92·8%, 6·36 [4·26–8·46], p<0·0001) and at 1 year (97·9% *vs* 89·9%, 8·05 [5·53 to 10·57], p<0·0001).

Table 3 presents outcomes at 30-day and 1-year follow-up. The patient-oriented primary endpoint occurred in 89 (11·9%) patients of the EES group and 106 (14·2%) patients of the BMS group (figure 2A and table 3). Hence, the superiority hypothesis was not met for this global primary endpoint. The rates for the individual components of the primary endpoint were similar to those for the composite endpoint between the two groups (table 3). The findings for the primary endpoint were consistent across prespecified stratified analyses (appendix).

The device-oriented secondary endpoint occurred in 44 (5·9%) patients of the EES group and in 63 (8·4%) of the BMS group (table 3 and figure 2B). This benefit of EES was mainly due to a significant reduction in target lesion revascularisation (table 3 and figure 2C). Rate of target vessel revascularisation was also significantly lower in the EES group than in the BMS group (table 3). Conversely, rates of all cause death, cardiac death, and myocardial infarction did not differ between groups (table 3). Results of patients treated specifically with primary percutaneous coronary intervention were consistent with the overall population (appendix).

At 12 months, the rate of definite stent thrombosis was significantly reduced in the EES group compared with the BMS group, which was primarily related to a reduction of definite stent thrombosis at 30 days (table 3). Overall, the rate of definite or probable stent thrombosis was also reduced in the EES group at 1 year (table 3). Figure 3 A and B shows a temporal breakdown of all definite and probable episodes of stent thrombosis, along with the worst hierarchical outcome during a 12-month period.

Overall, bleeding rates at 1 year were similar between groups: 29 (3·9%) patients in the EES arm versus 39 (5·2%) patients in the BMS group (p=0·19). Both TIMI major and minor bleeding rates were similar between groups: nine (1·2%) patients with major bleeding and 21 (2·8%) with minor bleeding in the EES group versus 11 (1·5%) patients with major bleeding and 30 (4·0%) patients with minor bleeding in the BMS group (p=0·65 for major bleeding and p=0·21 for minor bleeding)

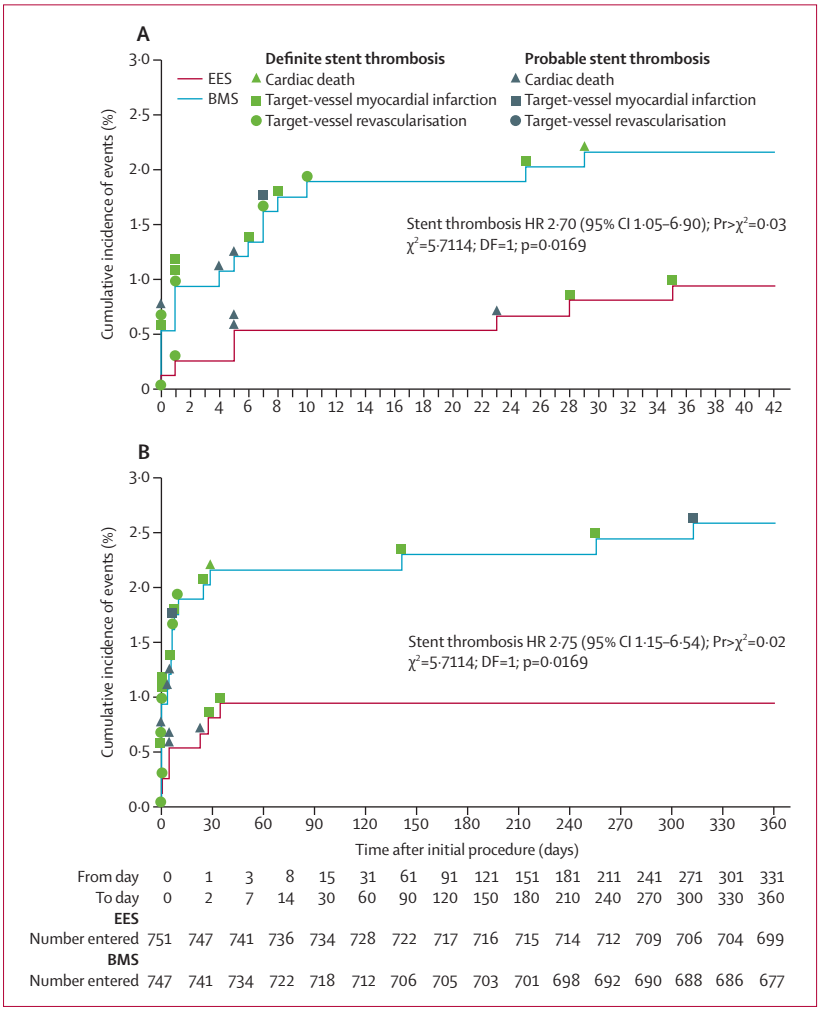


Figure 3: **Cumulative incidences of definite or probable stent thrombosis**
EES=everolimus-eluting stent. BMS=bare-metal stent. (A) Cumulative incidence of definite or probable stent thrombosis over 30 days of follow-up. (B) Cumulative incidence of definite or probable stent thrombosis over 360 days of follow-up.

Discussion

This is the first trial comparing the use of EES, with the conventional BMS in the setting of STEMI (panel). This trial did not show the previously anticipated superiority of EES in the global patient-oriented primary endpoint. The rates of all-cause death or recurrent myocardial infarction were similar in the two groups whereas a small difference in favour of EES was noted for the need of any revascularisation. The recorded low rate of events in the control group might be related to the cobalt-chromium alloy embedded in the thin strut (96×96 μm²) platform.[29] Another factor to take into account is the potential presence of non-viable areas of myocardium

Panel: **Research in context**

Systematic review

We searched PubMed for complete reports of trials comparing drug eluting stents with bare metal stents (BMS) in patients with ST-elevation myocardial infarction (STEMI) from 2005, to 2011, using combinations of the search terms "ST segment elevation myocardial infarction", "primary percutaneous coronary intervention", "randomised controlled trial", "bare metal stent", and "drug eluting stent". In this specific clinical setting, we identified various trials comparing only first-generation drug-eluting stents with BMS. In addition to this finding, we identified the RESOLUTE trial,[35] comparing two different second-generation drug-eluting stents in an all-comer population, including STEMI.

Interpretation

Our study is the first randomised comparison between a second-generation drug-eluting stent and BMS in the clinical context of STEMI. The everolimus-eluting stent (EES) was able to reduce the need for repeat target vessel revascularisation as compared with BMS, although this benefit was diluted in the overall patient-oriented composite endpoint. Additionally, and reported for the first time, EES was able to reduce the rate of definite stent thrombosis in this prothrombotic clinical scenario as compared with BMS. This finding, if corroborated in larger trials and in longer follow-up, might represent a change in the paradigm on the safety of second generation drug-eluting stents in the STEMI population.

distal to the stented segment. In such scenario, the presence of ischaemia is less often demonstrable and reintervention is much less indicated than in non-infarcted arteries. Besides, the absence of mandated angiographic control avoided any unnecessary revascularisation based on the oculo-stenotic reflex,[30] mimicking the current clinical practice.

The main secondary composite device-oriented endpoint did not differ between groups. However, target lesion revascularisation was significantly reduced by the use of EES (figure 2C). The selection of both endpoints in drug-eluting stent trials has been strongly advised by the ARC group. Yet, no study has ever selected this endpoint as primary endpoint.[26] This global patient-oriented endpoint has the merit to reflect the complex interplay between device performance, revascularisation strategy, secondary prevention, residual left ventricle function, and other key patient descriptors. In this regard, the outcomes in the context of STEMI are per se multifactorial and many times unrelated to the stent implanted at the index procedure. The downside of this approach is the potential dilution of the benefit of a device in the global context of the patient. This situation can be explicitly true in presence of multivessel disease that requires additional percutaneous coronary intervention at a later stage. In fact, more than a third of the staged procedures done in patients allocated to the BMS group received EES, as protocol violation. The decision to use EES instead of BMS was indicated by the anatomy of the lesion to be treated and by the clinical profile of the patient as usually done in the real world. Therefore, the concomitant analysis of the device-oriented endpoint, as advised by ARC,[26] was essential to portray the true contribution of EES in the trial.

It is noteworthy that stent thrombosis rates were significantly reduced in the group of patients allocated to EES (table 3 and figure 3A and 3B). The BMS group had an overall number of events (hierarchical) related to stent thrombosis almost three fold higher than the EES group; particularly, the number of target vessel myocardial infarctions secondary to stent thrombosis was five fold in the BMS group compared with that in the EES group. Of note is that the maximum reduction in the thrombosis rate was noted in the acute and subacute phase, in which patients who had STEMI usually exhibit high inflammatory and thrombogenic reactions.[31] Interestingly, compliance to dual antiplatelet treatment was high (almost 100%) in acute and subacute phase after STEMI in both groups, and none of the patients with stent thrombosis has prematurely stopped the dual antiplatelet therapy. In terms of periprocedural antithrombotic regimen, no differences between groups were noted. Certainly, the broad inclusion criteria and other clinical STEMI conditions such as rescue percutaneous coronary intervention, post-thrombolysis, or latecomers, might explain the high percentage of patients receiving heparin as a unique antiocoagulant during the procedure. Additionally, it is noteworthy that both Xience™ V and Multilink Vision share the same stent platform. Thus, the recorded reduction in stent thrombosis by the EES compared with BMS might be explained by the presence of the fluorinated copolymer.[32] This copolymer is composed of vinylidene fluoride and hexafluoropropylene monomers that might confer a certain degree of thromboresistance and haemocompatibility.[32] This benefit can even be extended to incompletely apposed or overlapping stents, where the presence of the copolymer resulted to be less thrombogenic than the BMS with complete absence of polymer.[32] This can be especially relevant in the context of STEMI where the eventual dissolution of the thrombus behind the struts might lead to a high incidence of late acquired malapposition.[33] Overall, the incidence of definite. or definite or probable, stent thrombosis is low and similar to those of other trials that use EES. Particularly, in the COMPARE all-comer[34] and Resolute AC[35] trials, the stent thrombosis rates at 1 year were 0·2% and 0·7%, respectively. Our finding of a low stent thrombosis rate with EES has also been confirmed in a recent comparison with first generation drug-eluting stents in the long-term and in recent metanalyses.[36–38] Besides, our results may be further expanded to other second generation drug-eluting stents (ie, biolimus-eluting stent) that are currently being studied in STEMI (COMFORTABLE-AMI trial).

Several limitations merit being acknowledged. First, the trial was not powered to detect differences in stent thrombosis between the two groups, which could be play of chance. However, it currently represents the only data existing of stent thrombosis of EES in the clinical context of STEMI patients and corroborates data from a recently

published meta-analysis of EES versus BMS in the overall clinical context.[37] Other limitations include the single-blind nature of the trial, the fact that the results of the trial apply only to the Xience V EES and that the rate of the primary endpoint was significantly lower than anticipated in the control group (20·5% planned *vs* 14·2% observed). More than a third of the staged procedures done in patients allocated to the BMS group received EES, as protocol violation, which might explain why the trial was not positive. Given this observed rate of events, the power that the study had to determine a 30% reduction of the endpoint was only 26%. Although the number of potentially eligible patients finally not randomly assigned to treatment was rather small, various patients in whom results do not apply still exist (ie, exclusion criteria). The number and types of stent stratified per operator, implanted in each center, have not been obtained in the case report form. Finally, these results regard only for the 1-year follow-up. Long-term follow-up is needed to rule out late hazards of this second generation drug-eluting stents.

The results of this trial might be adequately representative to the real world population admitted with STEMI. The all-comer design allowed the inclusion of most of patients (70%) presenting at our institutions. By comparison, the Typhoon trial[2] done in STEMI was only able to include 35% of screened patients and the Resolute AC[35] trial included 44% of patients who underwent percutaneous coronary intervention. Besides, patients were treated according to current standard of care in terms of time delays and mechanical approaches. The potential change in the paradigm (namely, reduction in stent thrombosis by EES compared with BMS) will surely be the target of a larger trial properly powered to this aim.

In conclusion, the use of EES in the setting of STEMI is not better than BMS in terms of a global patient-oriented endpoint. However, EES implantation reduced the need for target lesion revascularisation and was associated to a lower incidence of definite and definite or probable stent thrombosis compared with BMS.

Contributors

MS and PWS contributed to the design and execution of the trial. MS drafted the report, which was critically revised by MV, SB, and PWS. AC, AI, AS, RH-A, VM, MV, MT, PdH, AB, NV, JAG-H, JAB, VM-Y, R-JvG, FA, PB, MT, MM, and AS contributed to the execution of the trial. BB, SB, and G-AvE did the statistical analysis. All authors approved the final report.

Conflicts of interest

MS has received consultant and speaker fees from Abbott Vascular, Medtronic, and Cordis J&J. MV received an honorarium as a public speaker Terumo, The Medicines Company, Medtronic, Iroko, Merck, Abbott, Ely Lilly, AstraZeneca, Cordis, CID, and Bayer. BB and G-AvE are employees of Cardialysis. SB has received speaker fees from Abbott Vascular and St Jude Medical. All other authors declare that they have no conflicts of interest.

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