Clinical outcomes in patients with ST-segment elevation myocardial infarction treated with everolimus-eluting stents versus bare-metal stents (EXAMINATION): 5-year results of a randomised trial

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Summary

Background **Data for the safety and efficacy of new-generation drug-eluting stents at long-term follow-up, and specifically in patients with ST-segment elevation myocardial infarction, are scarce. In the EXAMINATION trial, we compared everolimus-eluting stents (EES) with bare-metal stents (BMS) in an all-comer population with ST-segment elevation myocardial infarction. In this study, we assessed the 5-year outcomes of the population in the EXAMINATION trial.**

Methods **In the multicentre EXAMINATION trial, done in Italy, Spain, and the Netherlands, patients with ST-segment elevation myocardial infarction were randomly assigned in a 1:1 ratio to receive EES or BMS. The random allocation schedule was computer-generated and central randomisation (by telephone) was used to allocate patients in blocks of four or six, stratified by centre. Patients were masked to treatment assignment. At 5 years, we assessed the combined patient-oriented outcome of all-cause death, any myocardial infarction, or any revascularisation. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00828087.**

Findings **1498 patients were randomly assigned to receive either EES (n=751) or BMS (n=747). At 5 years, complete clinical follow-up data were obtained for 731 patients treated with EES and 727 treated with BMS (97% of both groups). The patient-oriented endpoint occurred in 159 (21%) patients in the EES group versus 192 (26%) in the BMS group (hazard ratio 0·80, 95% CI 0·65–0·98; p=0·033). This difference was mainly driven by a reduced rate of all-cause mortality (65 [9%] *vs* 88 [12%]; 0·72, 0·52–0·10; p=0·047).**

Interpretation **Our findings should be taken as a point of reference for the assessment of new bioresorbable polymer-based metallic stents or bioresorbable scaffolds in patients with ST-segment elevation myocardial infarction.**

Funding **Spanish Heart Foundation.**

Introduction

Percutaneous coronary intervention (PCI) is the standard of treatment for patients with ST-elevation myocardial infarction when done at specialist centres within the time from onset of symptoms as per guidelines.[1] ST-elevation myocardial infarction represents both a model of a thrombotic setting and a challenging clinical scenario to test new intracoronary devices.[2] In this clinical setting, first-generation drug-eluting stents (DES) reduced clinical and angiographic restenosis, compared with bare-metal stents (BMS).[3–7] Conversely, these benefits were counterbalanced by an increased risk of very late stent thrombosis,[8–11] safety concerns that were confirmed on autopsy, and intravascular imaging studies showing evidence of incomplete endothelialisation, delayed arterial healing, and vessel remodelling because of chronic inflammation.[12–15] The development of neoatherosclerosis,[16] which might occur earlier after DES than after BMS,[17] has also been identified as a potential cause.

Compared with BMS and first-generation DES, the Xience V stent (Abbott Vascular, Santa Clara, CA, USA) reduced rates of cardiovascular events in randomised controlled trials and meta-analysis at short-term and mid-term follow-up.[18,19] The 2014 myocardial revascularisation guidelines recommend the use of second-generation DES for ST-elevation myocardial infarction.[1] However, long-term follow-up data are lacking.

The EXAMINATION (clinical Evaluation of the Xience-V stent in Acute Myocardial INfArcTION) all-comers trial was designed to compare clinical outcomes in patients with ST-elevation myocardial infarction receiving EES with those receiving BMS.[20] At a maximum follow-up of 2 years, the use of EES was associated with a reduced rate of repeat revascularisation and stent thrombosis, although it did not reduce the combined patient-oriented primary endpoint.[21,22] In this study, we compared 5-year clinical outcomes in patients with ST-elevation myocardial infarction treated with EES versus BMS in the EXAMINATION trial,[20] focusing on differences between the first and subsequent years of follow-up.

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Research in context

Systematic review

We searched PubMed from Jan 10, 2005, to Aug 10, 2015, for complete reports of trials in which drug-eluting stents (DES) were compared with bare-metal stents (BMS) in patients with ST-elevation myocardial infarction. We found several trials comparing first-generation DES versus BMS in this specific clinical setting. By narrowing our search to second-generation DES, we identified the COMFORTABLE-AMI trial of the comparison of biolimus-eluting stent with BMS and the XAMI trial of the comparison of everolimus-eluting stent (EES) versus first-generation DES. Follow-up of these studies was 2 years and 1 year. Additionally, we identified other trials in an all-comer population including ST-elevation myocardial infarction (RESOLUTE AC, LEADERS, and COMPARE trials) of the comparison of two different second-generation DES or second-generation versus first-generation DES.

Added value of this study

Our study is the first report of a randomised comparison of a second-generation DES and BMS in the clinical setting of ST-elevation myocardial infarction with long-term follow-up (up to 5 years). At 5 years, patients allocated to EES had a reduction in both the combined patient-oriented and device-oriented endpoints mainly driven by a reduction in all-cause mortality and revascularisation. Additionally, these results were obtained in the absence of very late hazards (namely stent thrombosis, target vessel myocardial infarction, or restenosis).

Interpretation of all the available evidence

The benefit of EES in ST-elevation myocardial infarction at long term is reassuring and confirms the use of second-generation stents as the current gold standard treatment in this clinical context.

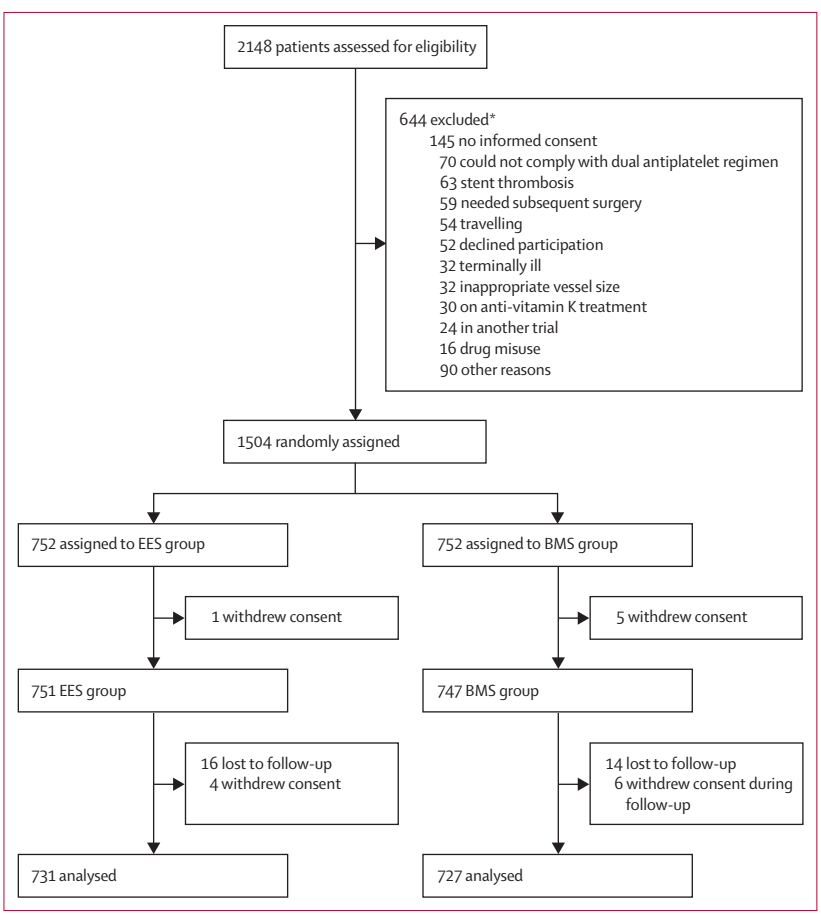

Figure 1: **Trial profile**
EES=everolimus-eluting stents. BMS=bare-metal stents. *Some patients had more than one reason for exclusion.

Methods

Study design and participants

The EXAMINATION study was a multicentre, multinational, prospective, randomised, two-arm, single-blind, controlled trial in patients with ST-elevation myocardial infarction; the detailed study design has been previously reported.[20] Briefly, the study had broad inclusion and few exclusion criteria to ensure an all-comers population with ST-elevation myocardial infarction, representative of routine clinical practice. The inclusion criteria were any adult presenting with ST-elevation myocardial infarction and meeting the following electrocardiograph (ECG) criteria: at least 1 mm in two or more standard leads, at least 2 mm in two or more contiguous precordial leads, or new left bundle-branch block within the first 48 h after onset of symptoms that required emergency PCI, and a vessel size of 2·25–4·00 mm without other anatomical restrictions. Exclusion criteria were age younger than 18 years, pregnancy, chronic treatment with anti-vitamin K agents, ST-elevation myocardial infarction secondary to stent thrombosis, and known intolerance to aspirin, clopidogrel, heparin, stainless steel, everolimus, or contrast material.

12 centres in Italy, Spain, and the Netherlands participated in the trial. All centres received the approval of their medical ethics committee for the protocol and for the acquisition of informed consent. The study complied with the Declaration of Helsinki and applicable local requirements. All patients provided written informed consent for participation in the trial.

Randomisation and masking

All recruited patients were randomly allocated in a 1:1 ratio to the EES (Xience V stent) or cobalt-chromium BMS (Multilink Vision stent, Abbott Vascular, Santa Clara, CA) groups. The allocation sequence with

block sizes of four or six was computer-generated. Central randomisation (by telephone) was stratified by centre. Patients were masked to treatment assignment.

Procedures

Both EES and BMS have the same design. At the index procedure, anticoagulation was achieved with either unfractionated heparin or bivalirudin. The use of glycoprotein IIb/IIIa inhibitors was at the discretion of the operator. Administration of aspirin (loading dose 250–500 mg) and clopidogrel (loading dose ≥300 mg) was required before PCI for patients not on chronic antiplatelet treatment (neither prasugrel nor ticagrelor had become available at the time of recruitment). Clopidogrel (75 mg/day) was prescribed for at least 1 year and aspirin (100 mg/day) indefinitely. Manual thrombectomy followed by direct stenting was the recommended technique during PCI, although other devices could also be used if thought to be necessary. Operators were instructed to use only the randomly assigned stent type for the index procedure.

Outcomes

Primary and secondary endpoints of the study have been reported elsewhere.[21] Briefly, the primary endpoint was the patient-oriented combined endpoint of all-cause death, any myocardial infarction, or any revascularisation at 1 year as per the definition by the Academic Research Consortium (ARC) definition.[23] The main secondary endpoints were the device-oriented combined endpoint of cardiac death, target vessel myocardial infarction, or target lesion revascularisation;[23] all-cause and cardiac death; any myocardial infarction (WHO extended definition[24]); target lesion revascularisation; target vessel revascularisation; and stent thrombosis (as per ARC definitions[23]). All the above endpoints had been assessed up to the 5-year follow-up. Detailed definitions of the endpoints have been reported elsewhere.[20] Patients with multivessel disease needing staged PCI could also be included. Staged procedures had to be done within the first month after discharge and with the same stent as per randomisation.

Follow-up included a clinical visit or telephone contact at 30 days, 6 months, and 1 year, and then yearly contact for up to 5 years. No angiographic follow-up was mandated in the protocol.

Independent study monitors verified all case reports from data on site. Data were stored in a central database, which was maintained by a contract research organisation (Cardialysis, Rotterdam, Netherlands). A clinical event committee, whose members were masked to the assigned stent, independently adjudicated all deaths, potential myocardial infarctions, stent thrombosis, and revascularisation procedures.

Statistical analysis

The trial was powered for superiority of the primary endpoint at 1 year.[20,21] The sample size calculation was based on a two-sided type I error rate α of 0·05, EES to BMS randomisation ratio of 1:1, and a statistical power of at least 86% to detect a 30% reduction in the rate of the primary endpoint at 1 year (ie, to an approximate event rate of 20·5% in the control group and 14·5% in the EES group). For the purpose of this analysis, we calculated two-sided 95% CI and two-sided p values for

	EES group (n=751)	BMS group (n=747)	Hazard ratio (95% CI)	p value
1-year follow-up				
Primary endpoint, patient oriented*	89 (12%)	106 (14%)	0·83 (0·62–1·09)	0·19
Device-oriented endpoint†	44 (6%)	63 (8%)	0·69 (0·48–0·10)	0·0568
Death‡	26 (3%)	26 (3%)	0·99 (0·58–1·71)	1·00
Cardiac	24 (3%)	21 (3%)	0·67 (0·32–2·04)	0·76
Vascular	1 (<1%)	3 (<1%)	0·33 (0·03–3·19)	0·37
Non-cardiovascular	1 (<1%)	2 (<1%)	0·50 (0·05–5·48)	0·62
Myocardial infarction§	10 (1%)	15 (2%)	0·60 (0·22–1·64)	0·32
Target vessel related	8 (1%)	15 (2%)	0·44 (0·14–1·43)	0·14
Non-target vessel related	2 (<1)	0 (0%)	1·99 (0·18–21·95)	0·49
Revascularisation	60 (8%)	79 (11%)	0·75 (0·54–1·05)	0·09
Target lesion	16 (2%)	37 (5%)	0·42 (0·24–0·76)	0·0032
Target vessel	28 (4%)	51 (7%)	0·54 (0·34–0·85)	0·0077
Non-target vessel	40 (5%)	41 (5%)	1·00 (0·64–1·52)	0·90
Definite stent thrombosis¶	4 (1%)	14 (2%)	0·28 (0·09–0·86)	0·0183
Definite or probable stent thrombosis¶	7 (1%)	19 (3%)	0·36 (0·15–0·87)	0·022
2-year follow-up				
Patient-oriented endpoint‡	108 (14%)	129 (17%)	0·81 (0·63–1·05)	0·11
Device-oriented endpoint†	61 (8%)	82 (11%)	0·72 (0·52–1·01)	0·055
Death§	32 (4%)	37 (5%)	0·86 (0·54–1·38)	0·52
Cardiac	28 (4%)	28 (4%)	0·99 (0·59–1·68)	1·0
Vascular	3 (<1%)	3 (<1%)	0·99 (0·20–4·92)	0·99
Non-cardiovascular	1 (<1%)	6 (<1%)	0·17 (0·02–1·37)	0·10
Myocardial infarction*	14 (2%)	18 (2%)	0·77 (0·38–1·55)	0·45
Target vessel related	11 (1%)	16 (2%)	0·68 (0·32–1·47)	0·46
Non-target vessel related	3 (<1%)	3 (<1%)	1·00 (0·20–4·93)	0·99
Revascularisation	73 (10%)	95 (13%)	0·75 (0·55–1·01)	0·05
Target lesion	22 (3%)	42 (6%)	0·51 (0·31–0·86)	0·01
Target vessel	36 (5%)	59 (8%)	0·59 (0·39–0·90)	0·009
Non-target vessel	46 (6%)	52 (7%)	0·87 (0·59–1·30)	0·51
Definite stent thrombosis¶	6 (1%)	16 (2%)	0·37 (0·15–0·95)	0·03
Definite or probable stent thrombosis¶	10 (1%)	21 (3%)	0·47 (0·22–1·00)	0·04
3-year follow-up				
Patient-oriented‡	116 (15%)	151 (20%)	0·75 (0·59–0·95)	0·017
Device-oriented endpoint†	66 (9%)	97 (13%)	0·66 (0·48–0·90)	0·010
Death§	36 (5%)	55 (7%)	0·65 (0·43–0·99)	0·043
Cardiac	30 (4%)	39 (5%)	0·76 (0·48–1·23)	0·27
Vascular	3 (<1%)	3 (<1%)	0·99 (0·20–4·92)	0·99
Non-cardiovascular	6 (1%)	20 (3%)	0·23 (0·07–0·80)	0·021
Myocardial infarction*	14 (2%)	13 (2%)	1·07 (0·50–2·27)	0·86
Target vessel related	10 (1%)	11 (1%)	0·90 (0·38–2·12)	0·81
Non-target vessel related	5 (<1%)	3 (<1%)	1·66 (0·40–6·94)	0·49
Revascularisation	77 (10%)	102 (14%)	0·73 (0·55–0·99)	0·040

(Table continues on next page)

	EES group (n=751)	BMS group (n=747)	Hazard ratio (95% CI)	p value
(Continued from previous page)				
Target lesion	24 (3%)	47 (6%)	0·50 (0·31–0·82)	0·006
Target vessel	40 (5%)	66 (9%)	0·59 (0·40–0·87)	0·008
Non-target vessel	51 (7%)	56 (7%)	0·90 (0·62–1·32)	0·59
Definite stent thrombosis¶	8 (1%)	16 (2%)	0·49 (0·21–1·15)	0·10
Definite or probable stent thrombosis¶	11 (1%)	21 (3%)	0·52 (0·25–1·07)	0·08
4-year follow-up				
Patient-oriented‡	134 (18%)	166 (22%)	0·78 (0·62–0·98)	0·033
Device-oriented endpoint†	76 (10%)	106 (14%)	0·70 (0·52–0·93)	0·016
Death§	46 (6%)	67 (9%)	0·68 (0·47–0·99)	0·042
Cardiac	36 (5%)	43 (6%)	0·83 (0·53–1·29)	0·41
Vascular	3 (<1%)	4 (1%)	0·75 (0·17–3·33)	0·70
Non-cardiovascular	10 (1%)	28 (4%)	0·35 (0·15–0·82)	0·015
Myocardial infarction*	20 (3%)	16 (2%)	1·24 (0·64–2·40)	0·52
Target vessel related	13 (2%)	13 (2%)	0·99 (0·46–2·14)	0·98
Non-target vessel related	8 (1%)	4 (1%)	1·99 (0·60–6·62)	0·26
Revascularisation	86 (11%)	110 (15%)	0·76 (0·57–1·01)	0·055
Target lesion	28 (4%)	52 (7%)	0·53 (0·33–0·83)	0·006
Target vessel	44 (6%)	72 (10%)	0·59 (0·41–0·86)	0·006
Non-target vessel	58 (8%)	60 (8%)	0·96 (0·67–1·37)	0·80
Definite stent thrombosis¶	11 (1%)	17 (2%)	0·64 (0·30–1·64)	0·25
Definite or probable stent thrombosis¶	14 (2%)	22 (3%)	0·63 (0·32–1·23)	0·17
5-year follow-up				
Patient-oriented endpoint‡	159 (21%)	192 (26%)	0·80 (0·65–0·98)	0·033
Device-oriented endpoint†	88 (12%)	113 (15%)	0·75 (0·57–0·99)	0·043
Death§	65 (9%)	88 (12%)	0·72 (0·52–1·00)	0·047
Cardiac	47 (6%)	55 (7%)	0·84 (0·57–1·24)	0·37
Vascular	4 (1%)	5 (1%)	0·79 (0·21–2·92)	0·72
Non-cardiovascular	14 (2%)	28 (4%)	0·49 (0·26–0·92)	0·027
Myocardial infarction*	35 (5%)	27 (4%)	1·27 (0·77–2·10)	0·35
Target vessel related	21 (3%)	23 (3%)	0·90 (0·50–1·62)	0·71
Non-target vessel related	15 (2%)	6 (1%)	2·44 (0·95–6·29)	0·07
Revascularisation	93 (12%)	116 (16%)	0·77 (0·59–1·01)	0·06
Target lesion	32 (4%)	54 (7%)	0·57 (0·37–0·89)	0·012
Target vessel	49 (7%)	76 (10%)	0·62 (0·43–0·89)	0·009
Non-target vessel	62 (8%)	62 (8%)	0·98 (0·69–1·39)	0·91
Definite stent thrombosis¶	12 (2%)	18 (2%)	0·65 (0·31–1·36)	0·25
Definite or probable stent thrombosis¶	15 (2%)	23 (3%)	0·64 (0·33–1·23)	0·18

Data are number (%), unless otherwise indicated. EES=everolimus-eluting stent. BMS=bare metal stent. ARC=Academic Research Consortium. *Myocardial infarction was adjudicated in accordance with WHO's extended definition.[24] †Combined (hierarchical) endpoint of cardiac death, target vessel myocardial infarction, and target lesion revascularisation.[23] ‡Combined (hierarchical) endpoint of all-cause death, any recurrent myocardial infarction, and any revascularisation.[23] §Death was adjudicated in accordance with the ARC's recommendations.[23] ¶Stent thrombosis was defined in accordance with ARC's recommendations.[23]

Table: **Follow-up of clinical events for up to 5 years**

See Online for appendix

superiority for all endpoints to allow conventional interpretation of results.

Continuous variables are presented as mean and SD, and categorical data are presented as counts and percentages. All analyses were by intention to treat; patients who were lost to follow-up were censored at their last known contact. We used the Mantel-Cox method to calculate rate ratios (RR), 95% CI for comparisons of clinical outcomes between groups, and the log-rank test to calculate corresponding p values. We constructed survival curves for time-to-event variables using Kaplan-Meier estimates. Landmark analyses were done from 0 to 1 year and from 1 year to 5 years of follow-up to assess the effect of time on the occurrence of events.

Subgroup analyses were the following prespecified variables: sex, age greater than 75 years, presence of diabetes, primary PCI, post-PCI thrombolysis in myocardial infarction flow of less than 3, multivessel disease, ischaemia time of less than 3 h, time to first medical contact or first device placement of less than 120 min, ejection fraction of less than 30%, Killip class greater than I, ST-segment resolution of greater than 70%, use of aspiration thrombectomy catheters, left anterior descending as infarct-related artery, and need for staged procedure.

This trial is registered with ClinicalTrials.gov identifier, NCT00828087.

Role of the funding source

The funder of the study provided funding for independent data management and all statistical analyses by Cardialysis (Rotterdam, Netherlands) and had no role in the study design or the decision to submit for publication. The principal investigators had full access to the data in the study. The corresponding author had full responsibility for the decision to submit the report for publication.

Results

Between Dec 31, 2008, and May 15, 2010, 1504 patients with ST-elevation myocardial infarction for up to 48 h after the onset of symptoms were recruited; six withdrew consent after randomisation. 1498 patients were randomly assigned to receive either an EES (n=751) or a BMS (n=747). At 5 years, complete clinical follow-up was obtained for 731 patients treated with EES and 727 treated with BMS (97% of both groups; figure 1). Baseline and procedural characteristics were similar between the two groups[21] (appendix). Use of dual antiplatelet therapy beyond the 1-year prescription time was reduced similarly in both groups during the follow-up (appendix). At 5 years, 57 (9%) of 622 participants in the BMS group and 64 (10%) of 648 in the EES group were still on a dual antiplatelet regimen (appendix).

At the 5-year follow-up, the patient-oriented combined endpoint occurred in 159 (21%) of 751 patients in the EES group and 192 (26%) of 747 patients in the BMS group (hazard ratio [HR] 0·80; 95% CI 0·65–0·98; p=0·033; table). This difference was mainly attributable to a significant reduction in the rate of all-cause death and a non-significant reduction in any revascularisation (table).

The overall reduction in all-cause death was attributable to a non-significant reduction in cardiac and vascular deaths (absolute reduction 1%) and a significant reduction in non-cardiovascular death (absolute reduction 2%; table). The specific causes of non-cardiovascular death are shown in the appendix. Most common causes of non-cardiac death included cancer and infection or sepsis. No significant differences were noted between the groups in the rate of any myocardial infarction. The device-oriented combined endpoint occurred in 88 (12%) patients in the EES group and 113 (15%) patients in the BMS group (HR 0·75, 95% CI

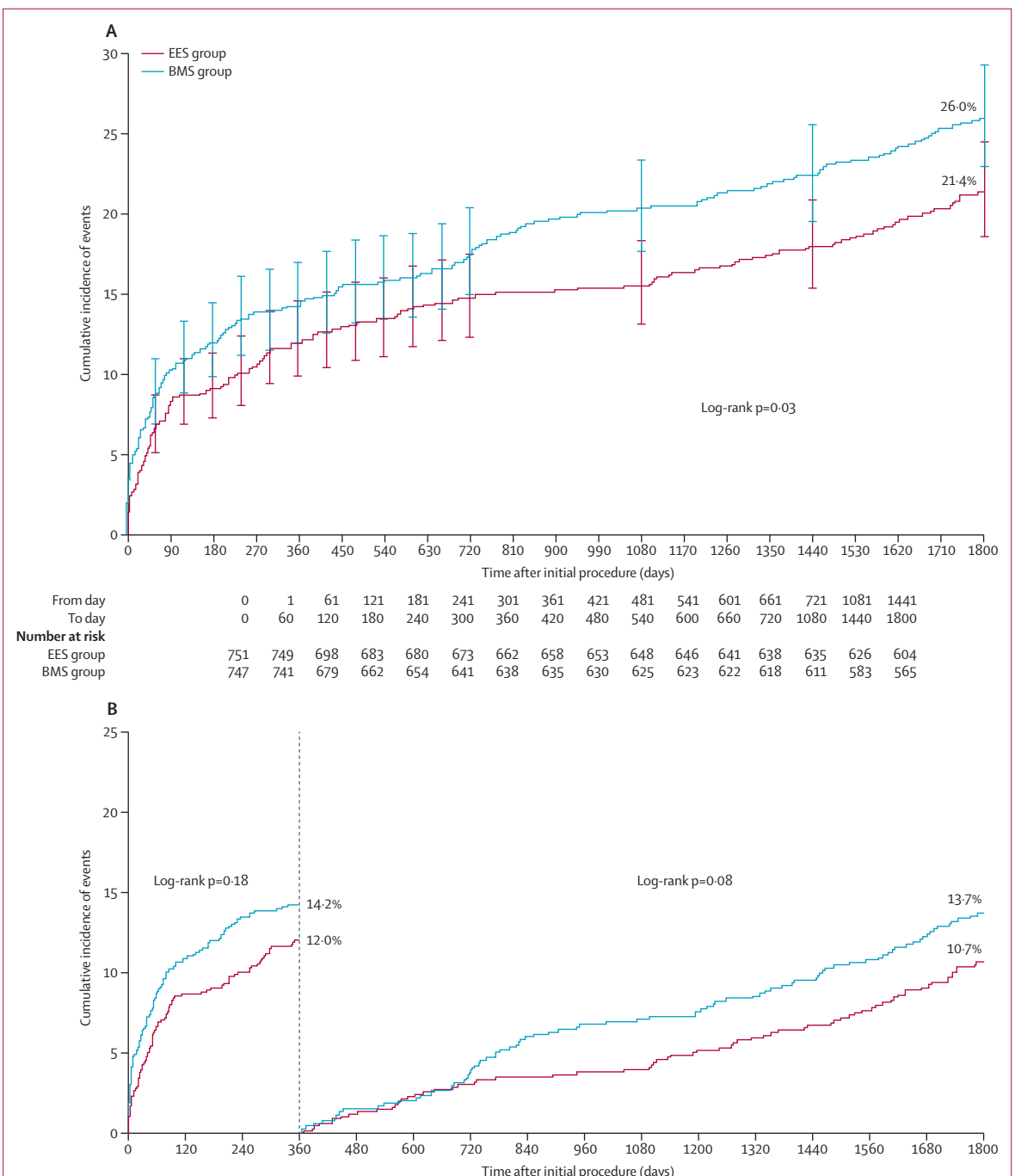

***Figure 2*: Time-to-event analysis of the patient-oriented endpoint of all-cause death, any myocardial infarction, or any revascularisation over 5 years**
(A) Kaplan-Meier analysis of cumulative 5-year incidence. (B) Landmark analyses for 0–1 year and 1–5 years. Error bars indicate point-wise two-sided 95% CI with a complementary log-log transformation. SE was calculated with the Greenwood Formula.

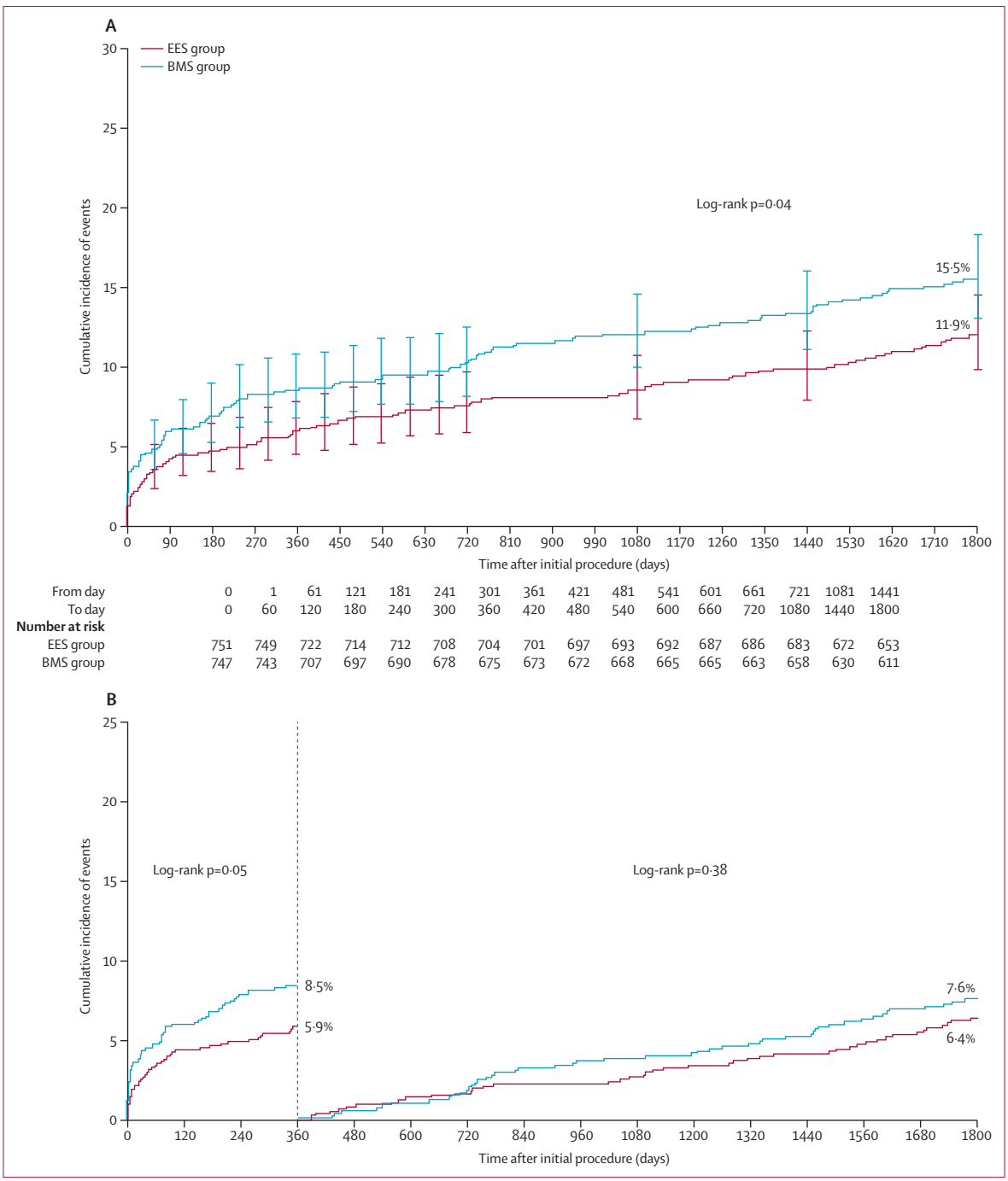

Figure 3: **Time-to-event curves for the device-oriented endpoint of cardiac death, target vessel myocardial infarction, or target lesion revascularisation over 5 years**

EES=everolimus-eluting stents. BMS=bare-metal stents. (A) Kaplan-Meier analysis of cumulative 5-year incidence. (B) Landmark analyses for 0–1 year and 1–5 years. Error bars indicate point-wise 2-sided 95% CI with a complementary log-log transformation. SE was calculated with the Greenwood Formula.

0·57–0·99; p=0·043; table). This difference was mainly attributable to a significant reduction in the rate of target lesion revascularisation (table). No differences between groups were noted in the rates of cardiac death and target vessel myocardial infarction (table).

From day 0, Kaplan-Meier curves began to diverge for the patient-oriented endpoint in favour of EES for up to 1 year, and later diverged again from year 2 to year 5 (figure 2A, B). A test for interaction between treatment effect and time (day 0 to 1 year and 1–5 years) was

	EES group	BMS group	p value	Relative risk (95% CI)	$p_{interaction}$
Sex					
Male	139/634 (22%)	151/610 (25%)	0·238	0·89 (0·72–1·08)	0·140
Female	20/117 (17%)	41/137 (30%)	0·017	0·57 (0·36–0·92)	
Age (years)					
<75	112/638 (18%)	132/615 (21%)	0·081	0·82 (0·65–1·03)	0·631
≥75	47/113 (42%)	60/132 (45%)	0·544	0·92 (0·69–1·22)	
Diabetes					
No	114/613 (19%)	153/626 (24%)	0·012	0·76 (0·61–0·94)	0·245
Yes	45/137 (33%)	39/121 (32%)	0·916	1·02 (0·72–1·45)	
Thrombectomy catheter					
No	60/256 (23%)	75/266 (28%)	0·215	0·83 (0·62–1·11)	0·961
Yes	99/495 (20%)	117/481 (24%)	0·104	0·82 (0·65–1·04)	
Ejection fraction					
<30%	4/10 (40%)	3/5 (60%)	0·464	0·67 (0·23–1·89)	0·768
≥30%	109/531 (21%)	125/510 (25%)	0·124	0·84 (0·67–1·05)	
Primary PCI					
Yes*	133/630 (21%)	161/638 (25%)	0·082	0·84 (0·68–1·02)	0·702
No	26/121 (21%)	31/108 (29%)	0·207	0·75 (0·48–1·18)	
Door to balloon (min)					
<120	65/302 (22%)	70/280 (25%)	0·321	0·86 (0·64–1·16)	0·926
≥120	80/356 (22%)	93/364 (26%)	0·334	0·88 (0·68–1·14)	
Ischaemia (min)					
<180	46/199 (23%)	48/196 (24%)	0·748	0·94 (0·66–1·34)	0·652
≥180	91/433 (21%)	103/413 (25%)	0·175	0·84 (0·66–1·08)	
Vessel disease					
One	130/649 (20%)	156/659 (24%)	0·111	0·85 (0·69–1·04)	0·446
Two or more	28/100 (28%)	36/88 (41%)	0·062	0·68 (0·46–1·02)	
Culprit lesion in LAD					
No	95/423 (22%)	113/439 (26%)	0·260	0·87 (0·69–1·11)	0·530
Yes	64/328 (20%)	79/308 (26%)	0·064	0·76 (0·57–1·02)	
Post-procedure TIMI flow					
<3	10/46 (22%)	18/44 (41%)	0·050	0·53 (0·28–1·02)	0·237
3	149/703 (21%)	172/700 (25%)	0·132	0·86 (0·71–1·05)	
ST resolution					
>70%	78/414 (19%)	96/438 (22%)	0·265	0·86 (0·66–1·12)	0·741
≤70%	66/264 (25%)	74/236 (31%)	0·114	0·80 (0·60–1·06)	
Killip class on admission					
>1	21/80 (26%)	34/76 (45%)	0·016	0·59 (0·38–0·91)	0·181
1	138/669 (21%)	157/668 (24%)	0·205	0·88 (0·72–1·07)	
Staged procedure					
No	121/625 (19%)	156/648 (24%)	0·042	0·80 (0·65–0·99)	0·918
Yes	35/123 (28%)	36/99 (36%)	0·209	0·78 (0·53–1·15)	
Overall	**159/751 (21%)**	**192/747 (26%)**	**0·038**	**0·82 (0·69–0·99)**	

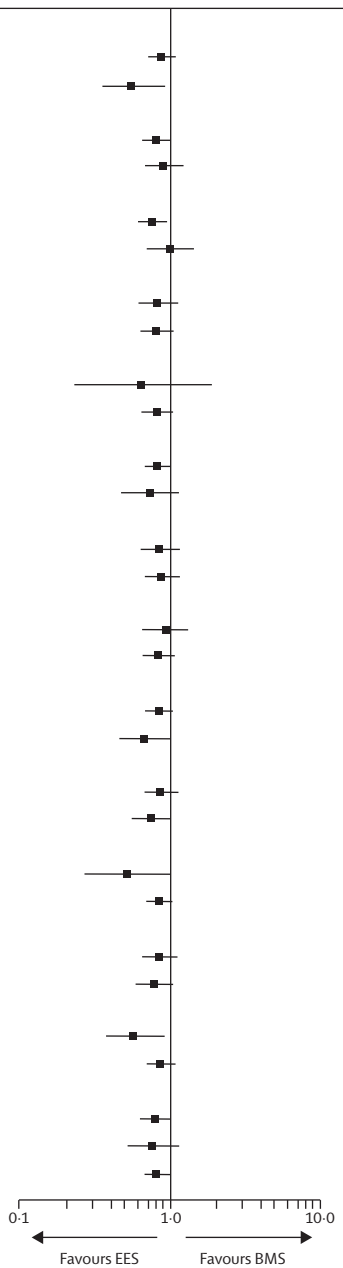

Figure 4: **Subgroup analysis of the patient-oriented endpoint of all-cause death, any myocardial infarction, and any revascularisation at 5 years in the EES and BMS groups**

Data are n/N (%), unless otherwise indicated. EES=everolimus-eluting stents. BMS=bare-metal stents. LAD=left anterior descending artery. PCI=percutaneous coronary intervention. TIMI=thrombolysis in myocardial infarction. *ST-elevation myocardial infarction for less than 12 h.

negative ($p_{interaction}$=0·69 for the patient-oriented outcome and $p_{interaction}$=0·65 for the device-oriented outcome). The same pattern was noted in the time-to-event curves for the device-oriented endpoint (figure 3A, B). The results for the patient-oriented (figure 4) and device-oriented endpoints (appendix) were consistent across the stratified analysis. Time-to-event curves for individual components of the patient-oriented and device-oriented endpoints are presented in the appendix. Of note, the difference in all-cause death was evident beyond the 2 years of follow-up and the difference in target lesion revascularisation in the period between day 0 to 1 year.

At 5 years, the EES and BMS groups had similar rates of definite stent thrombosis (2% *vs* 2%; HR 0·65, 95% CI

0·31–1·36; p=0·25) and of definite or probable stent thrombosis (2% *vs* 3%; 0·64, 0·33–1·23; p=0·18; table). From day 0, Kaplan-Meier curves began to diverge for definite or probable stent thrombosis in favour of EES for up to 30 days, and remained parallel thereafter (appendix). Interaction between day 0 to 1 year and year 1 to year 5 was significant ($p_{interaction}$=0·02). The combined endpoints of all-cause death or definite (76 [10%] of 751 patients *vs* 105 [14%] of 747 patients; HR 1·44, 95% CI 1·05–1·97, p=0·024) and all-cause death or definite or probable stent thrombosis showed significant reductions also favouring the use of EES (76 [10%] *vs* 104 [14%]; 1·45, 1·06–1·99, p=0·020).

Discussion

In patients with ST-elevation myocardial infarction requiring emergency primary PCI, durable polymer-based EES was superior to BMS in the patient-oriented and in the device-oriented endpoints. The benefits of EES were driven by reductions in the rates of all-cause death, non-cardiac death, and target lesion revascularisation. The results of this landmark analysis showed the absence of very late (>1 year) hazards and a benefit of EES compared with BMS over time.

The use of these endpoints in DES trials has been strongly recommended by the ARC group[23] and yet the patient-oriented endpoint was not selected as a primary endpoint in reported studies of stents. The global patient-oriented endpoint was specifically focused on the patients' outcomes rather than the specific effect of a study stent. It has the potential to show the complex interplay between device performance, revascularisation strategy, concomitant antithrombotic regimen, secondary prevention, residual left ventricle function, and other key descriptors for patients (eg, diabetes mellitus and renal function).

An improved global perspective is of utmost importance because outcomes in the context of ST-elevation myocardial infarction are multifactorial and often not directly related to the stent implanted at the index procedure. Differences in the patient-oriented endpoint might accrue over a longer period than previously thought, as shown by the results in this study. We found no differences in this endpoint for up to 2 years,[21,22] but significant differences were noted at 5 years. Furthermore, concomitant reporting of the device-oriented endpoint, as recommended by the ARC, might help to define the true contribution of the stent.

The superiority of the EES over BMS was slight overall (5% absolute reduction in the rate of the patient-oriented endpoint) and it was mainly attributable to reduced rate of all-cause death and revascularisation. The reduction in all-cause and non-cardiac mortality rates cannot be directly explained. According to the results of landmark analyses, there was no interaction between treatment effect and time. The benefit of EES occurred immediately after implantation and up to 1 year and also at long-term follow-up beyond 2 years (figures 2 and 3). We could hypothesise that the actual reduction in early stent thrombosis and repeated revascularisation rates might have improved preservation of the left ventricle ejection fraction, leading to improved long-term outcomes and reduced need for readmission to hospital as potential cause of further complications including infections or sepsis, which seemed to be the second major cause of non-cardiac death in our population (appendix). Therefore, this finding should be further investigated and confirmed in trials specifically focused on this endpoint.

Our results show the extended benefit of EES over BMS in terms of target lesion and target vessel revascularisation in patients with ST-elevation myocardial infarction for up to 5-years of follow-up. This finding dispels any concern about a restenosis late catch-up phenomenon, as initially suggested for EES based on the 2-year imaging outcome data from SPIRIT II.[25]

Very late hazards such as stent thrombosis or target vessel myocardial infarction have not been reported in the extended clinical follow-up. In our trial, stent thrombosis remained at a low level and was lower at 5 years in patients who received EES (2%). Of note, the benefit in stent thrombosis occurred mainly during the early phase (up to 30 days) with no thrombotic late catch-up phenomenon thereafter ($p_{interaction}$=0·02; appendix). The overall reduction in the patient-oriented endpoint was consistent across all prespecified subgroups (figure 4). Stenting did not seem to have an effect in people with diabetes and the interaction between diabetes and treatment effect was not significant.

The only differences between the two stent platforms used in this trial were the presence or absence of drug delivery and EES had a durable polymer and co-polymer composed of vinylidene fluoride and hexafluoropropylene monomers, which might have induced healthy endothelialisation of the stent and some thrombo-resistance and haemocompatibility, as suggested by the results of laboratory tests.[26] This haemocompatibility could be especially relevant in the context of ST-elevation myocardial infarction, in which the eventual dissolution of the thrombus behind the struts might lead to a high incidence of late-acquired malapposition.[27] Furthermore, thrombus-containing plaques, commonly found in patients with ST-elevation myocardial infarction, have been the model of delayed arterial healing after DES implantation. Specifically, the mean rate of uncovered stents seemed to be as high as 49% in culprit lesions from patients with ST-elevation myocardial infarction, compared with 9% in stable plaques after sirolimus-eluting stent implantation.[11] In this clinical context, long-term presence of a durable polymer has been proposed as a point of origin for a chronic inflammatory response that might delay the healing process.[12] Therefore, research in this field has been redirected toward biodegradable polymer-based metallic DES, polymer-free DES, or completely bioresorbable scaffolds.[28–30] Although these pathological findings were noted after implantation of first-generation DES, the use of EES has provided

reassuring data in imaging studies in animals and people[31–33] that have been confirmed in a network meta-analysis of ST-elevation myocardial infarction.[34] However, this meta-analysis was limited by the availability of only two trials specifically designed for patients with ST-elevation myocardial infarction (the EXAMINATION trial[21] and the XAMI trial[35] of the comparison of EES *vs* first-generation sirolimus-eluting stents) and by the shorter follow-up (1 year and 2 years). Our 5-year follow-up findings provide reassurance about safety of using a second-generation durable polymer stent.

Because our study was single-blind, bias cannot be completely ruled out. Results of this long-term follow-up have to be regarded as exploratory because outcomes were not significant at the time of the primary endpoint analysis (1 year).[21] Specifically, the benefit in reduction of the mortality rate with the use of EES should be thought of as hypothesis-generating. Further assessment in a properly powered trial is needed with an endpoint of reducing the mortality rate.

In this trial, patients with ST-elevation myocardial infarction were treated with aspirin and 1 year of clopidogrel as dual antiplatelet therapy. The potential role of ticagrelor or prasugrel in further prevention of events (eg, stent thrombosis, recurrent myocardial infarction, or mortality) in this context was not assessed because these treatments were not available at the time of recruitment. Thus, the potential extended benefit of new antiplatelet agents beyond 1 year of follow-up[36] has not been addressed in our study.

Although trial participants might adequately represent the real-world population admitted with ST-elevation myocardial infarction, because the all-comers design allowed the inclusion of most patients (70%) presenting at our institutions,[21] there are still some patients to whom the reported results do not apply (excluded population). Further long-term research in the excluded populations is needed.

Our results lay the foundation for future developments in stent technologies and should be taken as a point of reference for the assessment of new bioresorbable polymer-based metallic stents or bioresorbable scaffolds in this clinical context.

Contributors

MS and PWS contributed to the design and execution of the trial. MS drafted the report, which was critically revised by MV, SB, AC, PJ-Q, and PWS. AC, AI, SB, AS, PJ-Q, VM, MV, GC, MT, PdH, AB, and NV contributed to the execution of the trial. BB and G-AvE did the statistical analysis. All authors approved the final report.

Declaration of interests

MS has received consultancy and speakers' fees from Abbott Vascular and Medtronic. SB has received speakers' fees from Abbott Vascular and St Jude Medical. MV has received an honorarium as a public speaker for Terumo, the Medicines Company, Medtronic, Iroko, Merck, Abbott, Ely Lilly, AstraZeneca, Cordis, Carbostent and Implantable Devices, and Bayer. BB and G-AvE are employees of Cardialysis. The other authors declare no competing interests.

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