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10-Year Follow-Up of Patients With Everolimus-Eluting Versus Bare-Metal Stents After ST-Segment Elevation Myocardial Infarction

Salvatore Brugaletta, MD, PhD,[a,*] Josep Gomez-Lara, MD, PhD,[b,*] Luis Ortega-Paz, MD, PhD,[a] Victor Jimenez-Diaz, MD, PhD,[c] Marcelo Jimenez, MD,[d] Pilar Jiménez-Quevedo, MD, PhD,[e] Roberto Diletti, MD, PhD,[f] Vicente Mainar, MD, PhD,[g] Gianluca Campo, MD, PhD,[h] Antonio Silvestro, MD,[i] Jaume Maristany, MD, PhD,[j] Xacobe Flores, MD, PhD,[k] Loreto Oyarzabal, MD,[b] Antonio De Miguel-Castro, MD,[c] Andrés Iñiguez, MD, PhD,[c] Antonio Serra, MD, PhD,[d] Luis Nombela-Franco, MD, PhD,[e] Alfonso Ielasi, MD, PhD,[i] Maurizio Tespili, MD, PhD,[i] Mattie Lenzen, MD, PhD,[f] Nieves Gonzalo, MD, PhD,[e] Pascual Bordes, MD,[g] Matteo Tebaldi, MD,[h] Simone Biscaglia, MD,[h] Juan Jose Rodriguez-Arias, MD,[a] Soheil Al-Shaibani, MD,[f] Victor Arevalos, MD,[a] Rafael Romaguera, MD,[b] Joan Antoni Gomez-Hospital, MD, PhD,[b] Patrick W. Serruys, MD, PhD,[l,m] Manel Sabaté, MD, PhD[a,n]

ABSTRACT

BACKGROUND Outcomes data for a durable-polymer everolimus-eluting stent (EES) at extended long-term follow-up in patients with ST-segment elevation myocardial infarction (STEMI) are unknown.

OBJECTIVES The aim of this study was to assess the 10-year outcomes of patients enrolled in the EXAMINATION (A Clinical Evaluation of Everolimus Eluting Coronary Stents in the Treatment of Patients With ST-Segment Elevation Myocardial Infarction) trial.

METHODS The EXAMINATION-EXTEND (10-Years Follow-Up of the EXAMINATION Trial) study is an investigator-driven 10-year follow-up of the EXAMINATION trial, which randomly assigned 1,498 patients with STEMI in a 1:1 ratio to receive either EES (n = 751) or bare-metal stents (n = 747). The primary endpoint was a patient-oriented composite endpoint of all-cause death, any myocardial infarction, or any revascularization. Secondary endpoints included a device-oriented composite endpoint of cardiac death, target vessel myocardial infarction, or target lesion revascularization; the individual components of the combined endpoints; and stent thrombosis.

RESULTS Complete 10-year clinical follow-up was obtained in 94.5% of the EES group and 95.9% of the bare-metal stent group. Rates of the patient-oriented composite endpoint and device-oriented composite endpoint were significantly reduced in the EES group (32.4% vs. 38.0% [hazard ratio: 0.81; 95% confidence interval: 0.68 to 0.96; p = 0.013] and 13.6% vs. 18.4% [hazard ratio: 0.72; 95% confidence interval: 0.55 to 0.93; p = 0.012], respectively), driven mainly by target lesion revascularization (5.7% vs. 8.8%; p = 0.018). The rate of definite stent thrombosis was similar in both groups (2.2% vs. 2.5%; p = 0.590). No differences were found between the groups in terms of target lesion revascularization (1.4% vs. 1.3%; p = 0.963) and definite or probable stent thrombosis (0.6% vs. 0.4%; p = 0.703) between 5 and 10 years.

CONCLUSIONS At 10-year follow-up, EES demonstrated confirmed superiority in combined patient- and device-oriented composite endpoints compared with bare-metal stents in patients with STEMI requiring primary percutaneous coronary intervention. Between 5- and 10-year follow-up, a low incidence of adverse cardiovascular events related to device failure was found in both groups. (10-Years Follow-Up of the EXAMINATION Trial; NCT04462315) (J Am Coll Cardiol 2021;77:1165–78) © 2021 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

BMS = bare-metal stent(s)

CI = confidence interval

DES = drug-eluting stent(s)

EES = everolimus-eluting stent(s)

HR = hazard ratio

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

TLR = target lesion revascularization

ST-segment elevation myocardial infarction (STEMI) is an emergency clinical situation for which primary percutaneous coronary intervention (PCI) constitutes the standard of treatment (1). It also represents a challenging clinical setting, usually chosen to test new intracoronary devices because of its thrombotic milieu (2,3). First-generation drug-eluting stents (DES) were shown to reduce clinical and angiographic restenosis compared with bare-metal stents (BMS) (4–6) at the expense of an increased risk for very late stent thrombosis (7–9), caused mainly by incomplete endothelialization, delayed arterial healing, and vessel remodeling due to chronic inflammation (10–13).

The second-generation everolimus-eluting stent (EES; Xience V, Abbott Vascular, Santa Clara, California) was designed with a thin, nonadhesive, durable, and biocompatible fluorinated copolymer aimed to overcome the aforementioned limitations (14). It has indeed exhibited a better clinical profile compared with both BMS and first-generation DES in many randomized clinical trials and meta-analyses (15–17). On the basis of these studies, current guidelines recommend the use of second-generation DES in the context of STEMI (1).

Nevertheless, there are still concerns about the potential adverse long-term impact of durable-polymer coatings in patients with STEMI (18). Autopsy studies and studies of patients presenting with acute stent failure suggest that delayed arterial healing and accelerated in-stent atherosclerosis may be widespread months and years after stenting, caused at least partly by an inflammatory reaction to polymer coatings (16,19). Moreover, current evidence is limited to 5-year follow-up, although the overall life expectancy of most patients included in these studies exceeded this follow-up time. Longer-term follow-up beyond 5 years is required to determine the relative effectiveness and safety of EES versus BMS in patients with STEMI.

The EXAMINATION (A Clinical Evaluation of Everolimus Eluting Coronary Stents in the Treatment of Patients With ST-Segment Elevation Myocardial Infarction) all-comers trial compared clinical outcomes of EES and BMS placement in 1,498 patients with STEMI (20). At 5-year follow-up, it demonstrated a significant reduction in patient-oriented and device-oriented composite endpoints in patients who received EES compared with BMS (21). The present study, the EXAMINATION-EXTEND (10-Years Follow-Up of the EXAMINATION Trial) study, examined patient- and device-oriented composite endpoints after 10 years of follow-up in patients with STEMI randomly assigned to EES or BMS in the EXAMINATION trial, specifically focusing on the differences between 5 and 10 years of follow-up.

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METHODS

STUDY DESIGN AND PATIENTS. The EXAMINATION trial (NCT00828087) was an all-comers, multicenter, prospective, randomized, 2-arm, single-blind, controlled trial conducted at 12 centers in 3 countries, with the aim of assessing the superiority of EES versus BMS in patients with STEMI for the primary endpoint, a patient-oriented composite endpoint of all-cause death, any myocardial infarction, and any revascularization at 1 year. The study had broad inclusion criteria and few exclusion criteria, to ensure an all-comers STEMI population representative of routine clinical practice. The EXAMINATION trial included any adult patient presenting with STEMI and meeting the following electrocardiographic criteria: at least 1 mm in 2 or more standard leads or at least 2 mm in 2 or more contiguous precordial leads or new left bundle branch block within the first 48 h after symptom onset that required emergency PCI and a vessel size of 2.25 to 4.0 mm without other

From the [a]Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Barcelona, Spain; [b]Hospital Universitari de Bellvitge, Institut d'Investigació Biomedica de Bellvitge, L'Hospitalet de Llobregat, Spain; [c]Hospital Alvaro Cunqueiro, Vigo, Spain; [d]University Hospital of Sant Pau, Barcelona, Spain; [e]University Hospital San Carlos, Madrid, Spain; [f]Thoraxcenter, Rotterdam, the Netherlands; [g]Hospital General of Alicante, Alicante, Spain; [h]Cardiology Unit, Azienda Ospedaliera Universitaria di Ferrara, Cona, Italy; [i]University Hospital Bolognini Seriate; Bergamo; Italy; [j]Hospital Son Dureta, Palma de Mallorca, Spain; [k]Hospital Universitario, A Coruña, Spain; [l]International Center of Circulatory Health, Imperial College London, London, United Kingdom; [m]Department of Cardiology, National University of Ireland, Galway, Galway, Ireland; and the [n]CIBER-CV, Instituto de Salud Carlos III, Spain. *Drs. Brugaletta and Gomez-Lara contributed equally to this work.

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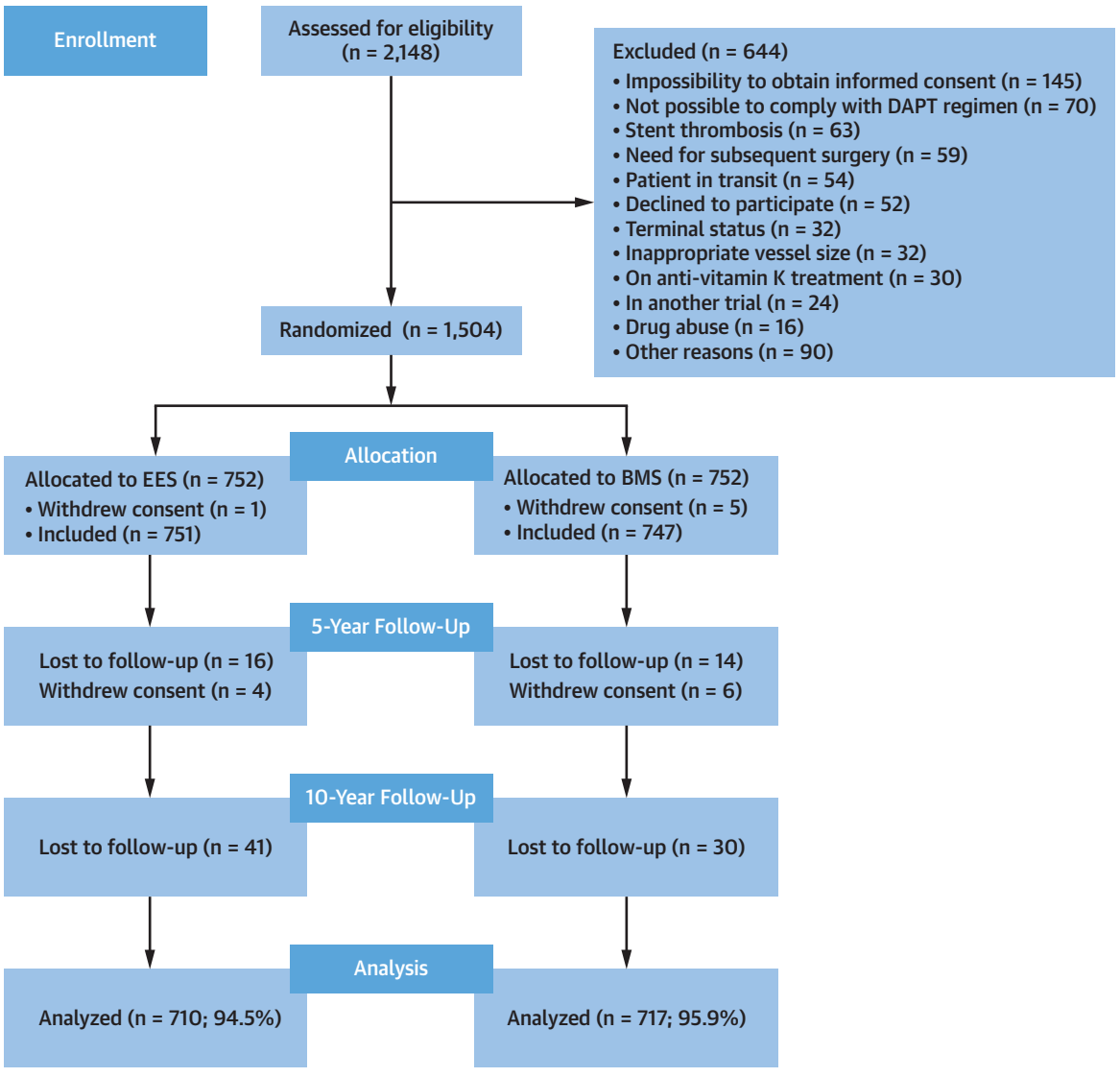
FIGURE 1 Flowchart of the Study Up to 10-Year Follow-Up



A total of 1,504 patients were initially randomized 1:1 to receive either everolimus-eluting stents (EES) or cobalt-chromium bare-metal stents (BMS). At 10 years, clinical follow-up was obtained in 95.2% of the patients in both groups. DAPT = dual antiplatelet therapy.

anatomic restrictions. Exclusion criteria were age <18 years, pregnancy, long-term treatment with anti-vitamin K agents, STEMI secondary to stent thrombosis, and known intolerance to aspirin, clopidogrel, heparin, stainless steel, everolimus, or contrast material. The rationale, design, and 1-year primary endpoint results of the EXAMINATION trial have been published previously, as have results at 2- and 5-year follow-up (20–23).

The EXAMINATION trial completed follow-up at 5 years and was reinitiated as the EXAMINATION-EXTEND study to evaluate patient- and device-oriented composite endpoints at 10 years. The EXAMINATION-EXTEND study is registered at ClinicalTrial.gov (NCT04462315) as an investigator-driven extension of follow-up of the EXAMINATION trial. Medical ethics committee approval for this study was granted at the institutions of the principal investigators (Hospital Clinic and Hospital Bellvitge, Barcelona, Spain). The requirement to obtain informed consent to gather information on 10-year events was waived, and follow-up was performed in

TABLE 1 Clinical Events Up to 10 Years

	EES	BMS	HR (95%CI)	p value
1-yr follow-up				
Patient-oriented composite endpoint*	89 (11.9)	106 (14.2)	0.83 (0.62-1.09)	0.19
Device-oriented composite endpoint†	44 (5.9)	63 (8.4)	0.69 (0.48-0.10)	0.0568
Death‡	26 (3.5)	26 (3.5)	0.99 (0.58-1.71)	1.00
Cardiac	24 (3.2)	21 (2.8)	0.67 (0.32-2.04)	0.76
Myocardial infarction§	10 (1.3)	15 (2.0)	0.60 (0.22-1.64)	0.32
Target vessel related	8 (1.1)	15 (2.0)	0.44 (0.14-1.43)	0.14
Non-target vessel related	2 (0.3)	0 (0)	1.99 (0.18-21.95)	0.49
Revascularization	60 (8.0)	79 (10.6)	0.75 (0.54-1.05)	0.09
Target lesion	16 (2.1)	37 (5.0)	0.42 (0.24-0.76)	0.0032
Target vessel	28 (3.7)	51 (6.8)	0.54 (0.34-0.85)	0.0077
Non-target vessel	40 (5.3)	41 (5.5)	1.00 (0.64-1.5)	0.90
Definite stent thrombosis‖	4 (0.5)	14 (1.9)	0.28 (0.09-0.86)	0.0183
Definite/probable stent thrombosis‖	7 (0.9)	19 (2.5)	0.36 (0.15-0.87)	0.0197
5-yr follow-up				
Patient-oriented composite endpoint*	159 (21.2)	192 (25.7)	0.80 (0.65-0.98)	0.033
Device-oriented composite endpoint†	88 (11.7)	113 (15.1)	0.75 (0.57-0.99)	0.043
Death‡	65 (8.7)	88 (11.8)	0.72 (0.52-1.00)	0.047
Cardiac	47 (6.3)	55 (7.4)	0.84 (0.57-1.24)	0.37
Myocardial infarction§	35 (4.7)	27 (3.6)	1.27 (0.77-2.10)	0.35
Target vessel related	21 (2.8)	23 (3.1)	0.90 (0.50-1.62)	0.71
Non-target vessel related	15 (2.0)	6 (0.8)	2.44 (0.95-6.29)	0.07
Revascularization	93 (12.4)	116 (15.5)	0.77 (0.59-1.01)	0.06
Target lesion	32 (4.3)	54 (7.2)	0.57 (0.37-0.89)	0.012
Target vessel	49 (6.5)	76 (10.2)	0.62 (0.43-0.89)	0.009
Non-target vessel	62 (8.3)	62 (8.3)	0.98 (0.69-1.39)	0.91
Definite stent thrombosis‖	12 (1.6)	18 (2.4)	0.65 (0.31-1.36)	0.25
Definite/probable stent thrombosis‖	15 (2.0)	23 (3.1)	0.64 (0.33-1.23)	0.18
10-yr follow-up				
Patient-oriented composite endpoint*	243 (32.4)	286 (38.0)	0.81 (0.68-0.96)	0.013
Device-oriented composite endpoint†	97 (13.6)	129 (18.4)	0.72 (0.55-0.93)	0.012
Death‡	140 (19.4)	172 (23.2)	0.81 (0.65-1.01)	0.061
Cardiac	86 (11.8)	81 (10.9)	1.07 (0.79-1.46)	0.649
Myocardial infarction§	40 (5.5)	45 (6.2)	0.89 (0.58-1.36)	0.559
Target vessel related	22 (3.0)	30 (4.1)	0.73 (0.42-1.27)	0.262
Non-target vessel related	18 (2.4)	15 (2.0)	2.32 (0.60-8.97)	0.223
Revascularization	122 (16.5)	147 (19.9)	0.80 (0.63-1.02)	0.073
Target lesion	42 (5.7)	65 (8.8)	0.63 (0.43-0.93)	0.018
Target vessel	71 (9.6)	93 (12.5)	0.74 (0.54-1.01)	0.054
Non-target vessel	80 (10.2)	82 (10.9)	1.06 (0.69-1.63)	0.771
Definite stent thrombosis‖	16 (2.2)	19 (2.5)	0.83 (0.43-1.62)	0.590
Definite/probable stent thrombosis‖	19 (2.6)	26 (3.5)	0.72 (0.40-1.30)	0.277

Values are n (%) unless otherwise indicated. No corrections for multiple testing were applied. *Combined endpoint of all-cause death, any recurrent myocardial infarction, and any revascularization (24). †Combined endpoint of cardiac death, target vessel myocardial infarction, and target lesion revascularization (24). ‡Death was adjudicated according to the Academic Research Consortium definition (24). §Myocardial infarction was adjudicated according to the World Health Organization extended definition (25). ‖Stent thrombosis was defined according to the Academic Research Consortium definition (24).

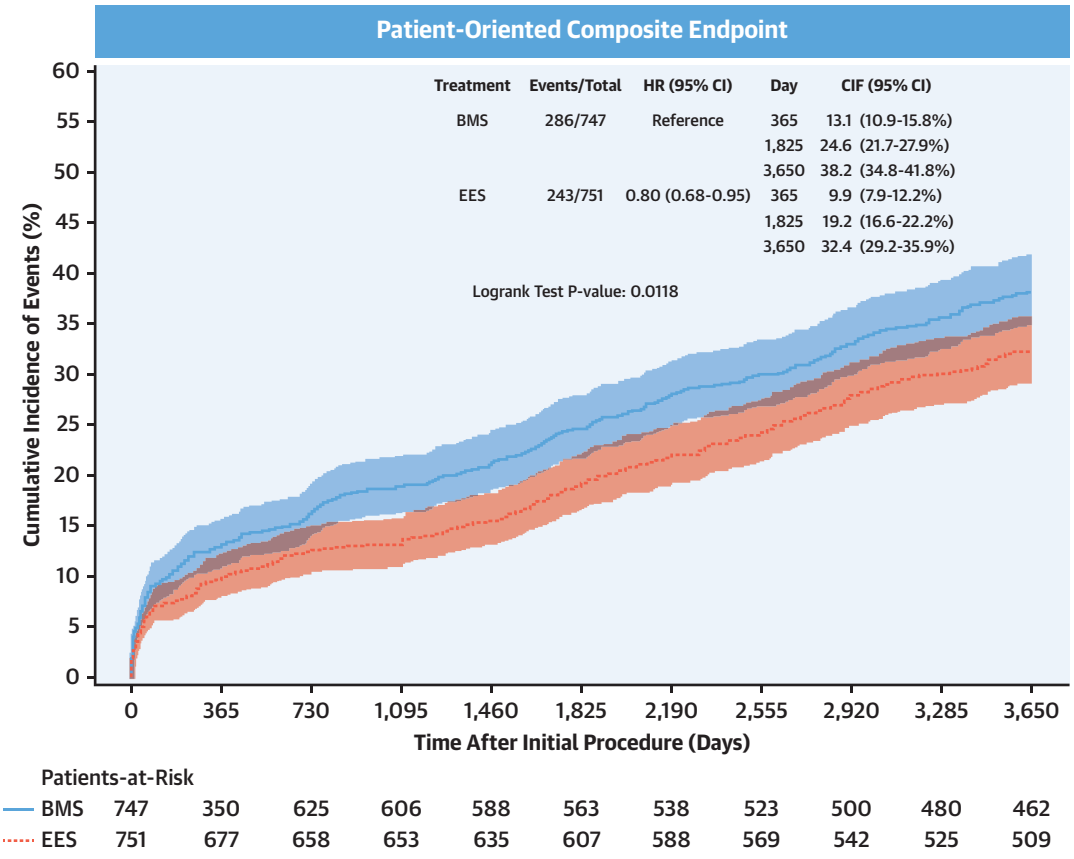
BMS = bare-metal stent; CI = confidence interval; EES = everolimus-eluting stent; HR = hazard ratio.

accordance with local law and the regulations of each participating site and complied with the Declaration of Helsinki.

RANDOMIZATION. All recruited patients were randomized 1:1 to the EES (Xience V) or cobalt-chromium BMS (Multilink Vision, Abbott Vascular) treatment arm. The allocation schedule was based on computer-generated random numbers. Central randomization (by telephone) of randomly allocated blocks of 4 or 6 patients was stratified by center.

PROCEDURES. Both platforms (EES and BMS) have the same design as the Multilink Vision stent. At the

FIGURE 2 **10-Year Time-to-Event Curves for the Primary Endpoint of All-Cause Death, Any Recurrent Myocardial Infarction, or Any Revascularization**



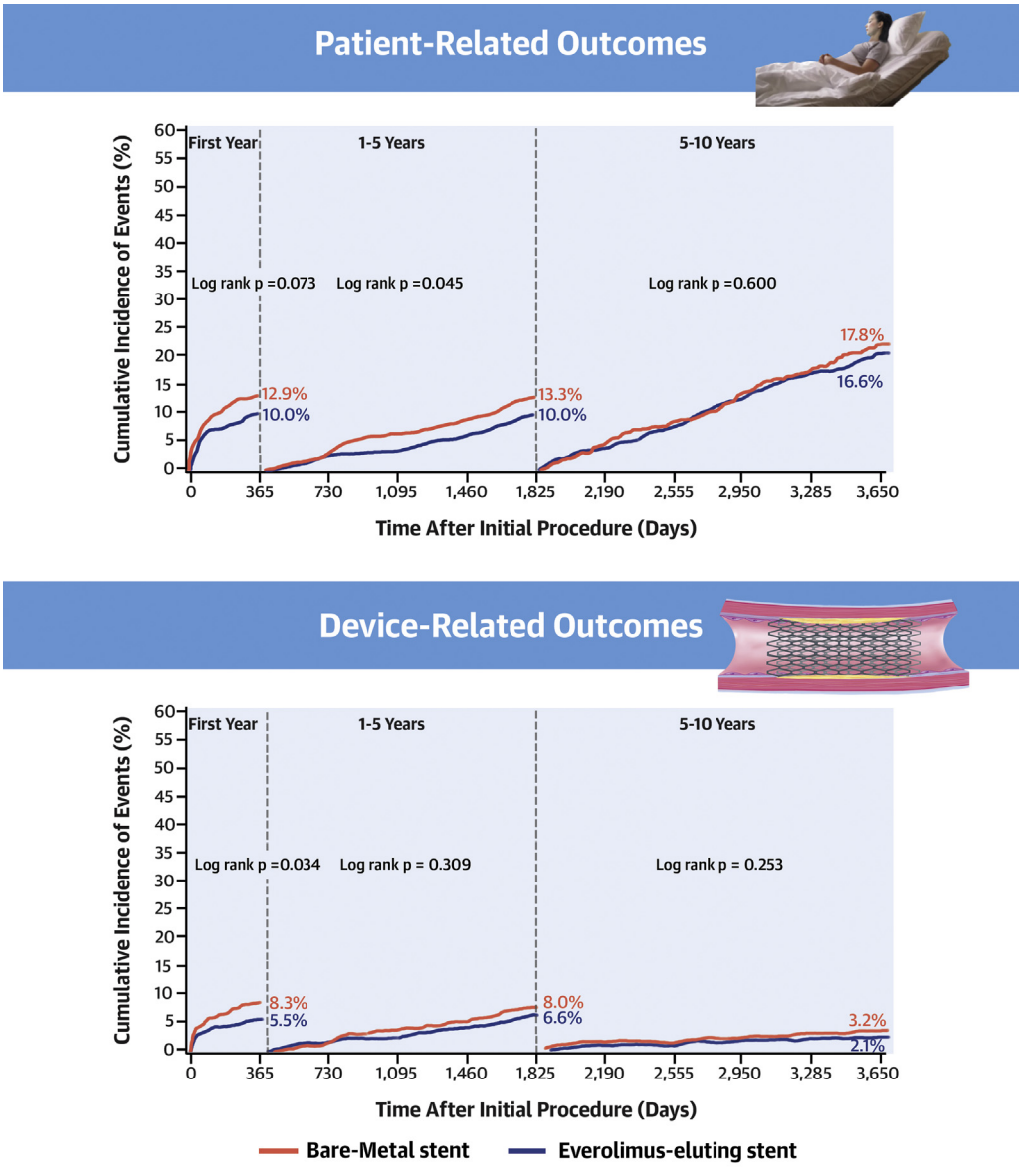
Cumulative 10-year incidence is shown with Kaplan-Meier yearly event rates. CI = confidence interval; CIF = cumulative incidence frequency; HR = hazard ratio; other abbreviations as in Figure 1.

index procedure, anticoagulation was achieved using either unfractionated heparin or bivalirudin. The use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the operator. Administration of aspirin (loading dose 250 to 500 mg) and clopidogrel (loading dose of at least 300 mg) was required before PCI for those patients not receiving long-term antiplatelet treatment (neither prasugrel nor ticagrelor was available at the time of recruitment). Clopidogrel (75 mg/day) was prescribed for at least 1 year and aspirin (100 mg) indefinitely. Manual thrombectomy followed by direct stenting was the recommended technique during PCI, although other devices could also be used if considered necessary. Operators were instructed to use only the randomly assigned stent type for the index procedure. Patients with multivessel disease necessitating staged PCI could also be included. Staged procedures had to be done within the first month following discharge and by the use of the same stent as per randomization.

STUDY ENDPOINTS. The pre-specified primary endpoint of the EXAMINATION-EXTEND study was the patient-oriented composite endpoint of all-cause death, any myocardial infarction, or any revascularization at 10 years according to the Academic Research Consortium definition (24). Secondary endpoints included a device-oriented composite endpoint of cardiac death, target vessel myocardial infarction, or target lesion revascularization (TLR) (24); all-cause and cardiac death; target vessel revascularization; and stent thrombosis (according to Academic Research Consortium definitions) (24). Detailed descriptions of the study endpoints and definitions have been reported previously (22).

Patients were systematically evaluated at a clinical visit or by telephone contact at 30 days, 6 months,

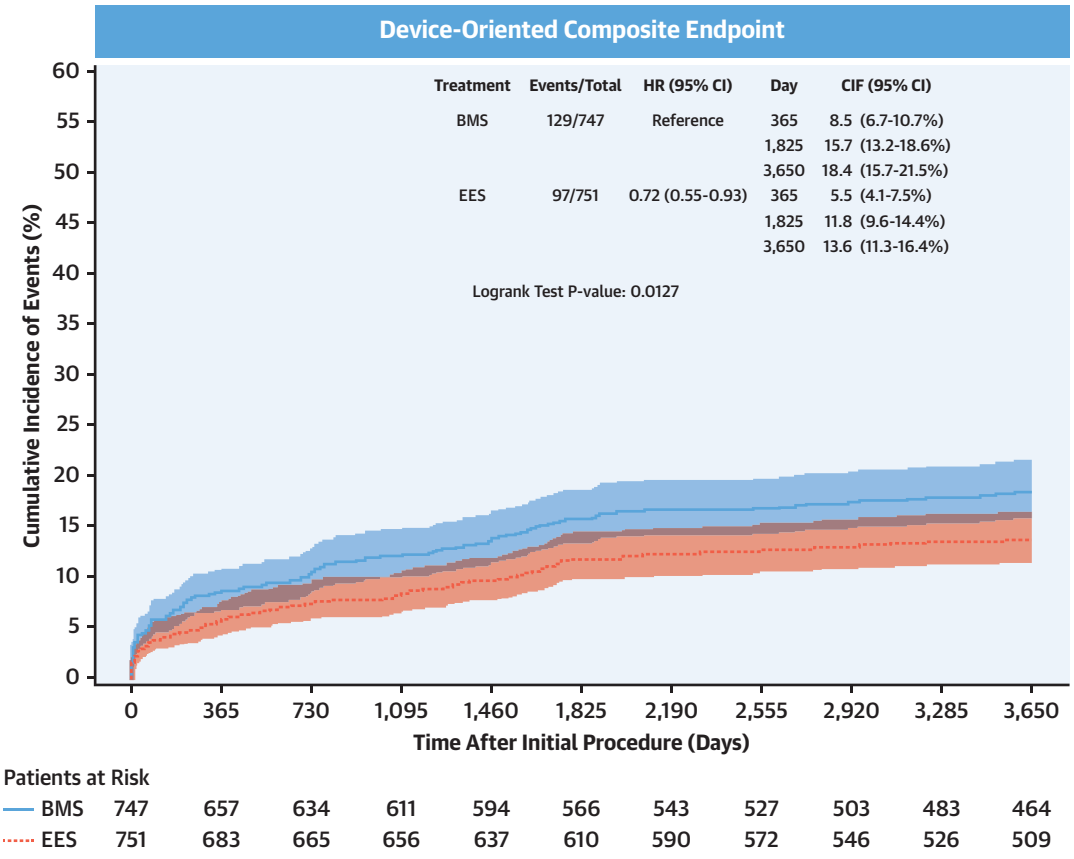
CENTRAL ILLUSTRATION **Landmark Analysis of Patient- and Device-Oriented Outcomes After ST-Segment Elevation Myocardial Infarction, According to Treatment Groups**



Brugaletta, S. et al. J Am Coll Cardiol. 2021;77(9):1165-78.

Shown is a landmark analysis at 0 to 1, 1 to 5, and 5 to 10 years, with time-to-event curves for the incidence of the patient-oriented outcomes (all-cause death, any myocardial infarction, or any revascularization) and of the device-oriented outcomes (cardiac death, target vessel myocardial infarction, and target lesion revascularization). Whereas patient-oriented outcomes continued to increase over time, device-oriented outcomes decreased.

FIGURE 3 **10-Year Time-to-Event Curves for the Device-Oriented Endpoint of Cardiac Death, Target Vessel Myocardial Infarction, or Target Lesion Revascularization**



Cumulative 10-year incidence is shown with Kaplan-Meier yearly event rates. Abbreviations as in Figures 1 and 2.

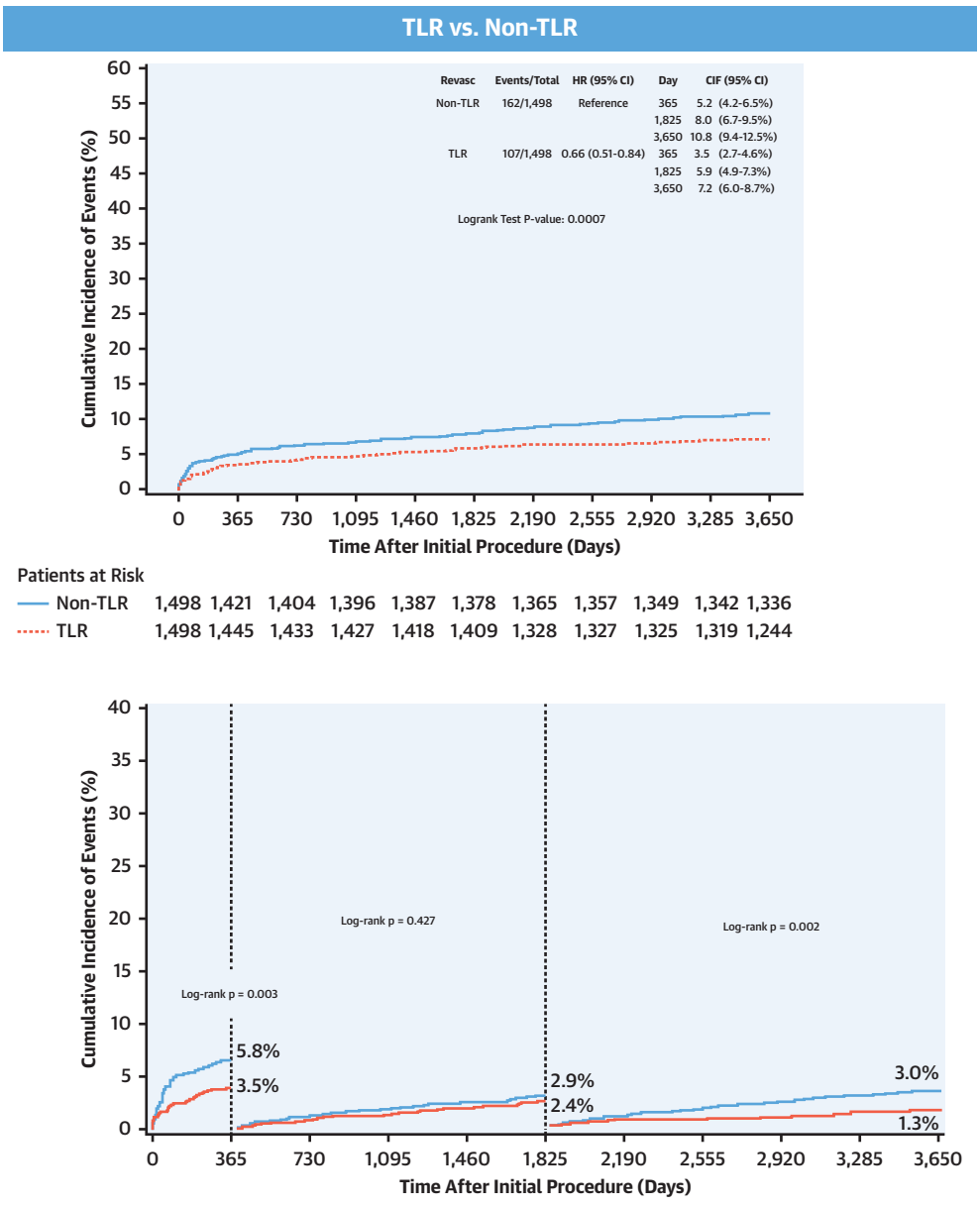
and 1 year and then annually up to 5 years. No angiographic follow-up was mandated per protocol. Extended 10-year follow-up was performed in the setting of routine care by either telephone call or office visit.

Independent study monitors (ADKNOMA, Barcelona, Spain) verified the adequacy of the extended follow-up and events reported, conducting auditing among 50% of all patients included. All events were adjudicated and classified by an independent event adjudication committee blinded to the treatment groups by reviewing source documents (including angiograms) provided by each center (Barcicore Lab, Barcelona, Spain).

STATISTICAL ANALYSIS. All analyses were performed according to the intention-to-treat principle. Patients with missing follow-up data were included in the analysis and censored at the time they were lost to follow-up or at 5 years if their recruiting hospitals did not participate in 10-year follow-up. We analyzed the 10-year patient-oriented composite endpoint using Kaplan-Meier curves, with a log-rank p values to test between-group differences. We used Cox proportional hazards models to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) comparing EES with BMS. Landmark analyses were conducted in the overall population, setting the landmark points at 1 and 5 years to distinguish the results of the EXAMINATION trial from the extended follow-up of the EXAMINATION-EXTEND study. The same was done for the device-oriented composite endpoint and for the other secondary endpoints.

Subgroup analyses included the following specified variables: sex, age >75 years, presence of diabetes, post-PCI TIMI (Thrombolysis In Myocardial Infarction) flow grade <3, multivessel disease, ejection fraction <30%, Killip class >I, ST-segment resolution >70%, use of aspiration thrombectomy

FIGURE 4 TLR Versus Non-TLR



Time-to-event curves for the incidence of target lesion revascularization (TLR) versus non-TLR during the study **(left)** with landmark analysis at 0 to 1, 1 to 5, and 5 to 10 years. HRs and p values are derived from Cox model. Abbreviations as in Figure 2.

catheters, primary PCI (STEMI <12 h), and the left anterior descending coronary artery as the infarct-related artery.

Two-tailed p values <0.05 were considered to indicate statistical significance. P values and 95% CIs presented in this report have not been adjusted for multiplicity, and therefore inferences drawn from these statistics may not be reproducible.

RESULTS

PATIENTS. Between December 31, 2008, and May 15, 2010, 1,504 patients with STEMI up to 48 h after the onset of symptoms were recruited; 6 withdrew consent after randomization. A total of 1,498 patients were randomly assigned to receive either the EES (751 participants) or the BMS (747 participants). Baseline

and procedural characteristics, well matched between groups, have been published previously (20,21) and are included in Supplemental Tables 1 to 4.

Information on 10-year outcomes was collected between January 2019 and May 2020. One hospital, which included 14 patients (0.9%), did not participate in the EXAMINATION-EXTEND study. At 10 years, complete clinical follow-up was obtained in 710 patients (94.5%) treated with EES and 717 patients (95.9%) treated with BMS (**Figure 1**).

Clinical outcomes up to 10 years are presented in **Table 1**. The primary patient-oriented composite endpoint occurred in 243 patients (32.4%) in the EES group and 286 patients (38.0%) in the BMS group (HR: 0.81; 95% CI: 0.68 to 0.96; p = 0.013) (**Figure 2**). This difference was driven mainly by a reduction in the rate of any revascularization. Landmark analysis identified that this difference was acquired during the first 5 years of follow-up, whereas no difference was found between 5 and 10 years (**Central Illustration**).

The device-oriented composite endpoint occurred in 97 patients (13.6%) in the EES group and 129 patients (18.4%) in the BMS group (HR: 0.72; 95% CI: 0.55 to 0.93; p = 0.012) (**Figure 3**). Landmark analysis identified that this difference was acquired during the first 5 years of follow-up, with low rates of events between 5 and 10 years (**Central Illustration**). This difference was driven mainly by a significant reduction in the rate of TLR, acquired during the first 5 years of follow-up, without any difference in the landmark analysis between 5 and 10 years. Landmark analyses of the individual components of the device-oriented composite endpoint showed that between 5 and 10 years, there was no difference between groups in terms of target vessel myocardial infarction or TLR. Time-to-event curves for individual components of the patient- and device-oriented composite endpoints and landmark curves are presented in the Supplemental Appendix.

Regardless of type of stent implanted, non-TLR occurred in a higher proportion of patients than TLR (p = 0.0007), especially in the first year and between 5 and 10 years (**Figure 4**). The findings for the patient-oriented and device-oriented composite endpoints were consistent across the stratified analysis, with a significant interaction between diabetes and stent outcomes (**Figure 5**).

At 10 years, the EES and BMS groups had comparable rates of definite stent thrombosis (2.2% vs. 2.5%; HR: 0.83; 95% CI: 0.43 to 1.62; p = 0.59) and definite or probable stent thrombosis (2.6% vs. 3.5%, respectively; HR: 0.72; 95% CI: 0.40 to 1.3; p = 0.27) (**Table 1**). Kaplan-Meier estimates for definite or probable stent thrombosis and landmark analysis (0 to 1, 1 to 5, and 5 to 10 years) are presented in **Figure 6**. Time-to-event curves for any and definite stent thrombosis and landmark analyses (0 to 1, 1 to 5, and 5 to 10 years) are presented in the Supplemental Appendix.

DISCUSSION

We herein report the 10-year outcomes of everolimus-eluting durable-polymer second-generation DES in the context of patients with STEMI undergoing primary intervention. The main findings of this very long-term follow-up can be summarized as follows: 1) the EES was superior to the BMS for the patient- and device-oriented composite endpoints; 2) the benefit of the EES was driven mainly by a reduction in the rate of TLR; 3) this advantage was acquired during the first 5 years of follow-up, without any attrition of the benefit over the BMS between 5 and 10 years; and 4) the rate of definite or probable stent thrombosis was similar between the EES and BMS at 10 years. Specifically, the incidence of definite or probable stent thrombosis was mitigated with time, and it was very low between 5 and 10 years in both groups.

Randomized clinical trials comparing stents in patients with coronary artery disease usually have limited follow-up duration. As stent failure is expected to occur within 12 months, and because of logistical and funding challenges, only a few trials have follow-up longer than 1 year, occasionally up to 5 years (25). Although most patients enrolled in clinical trials are in middle age with a long life expectancy (21), data beyond 5 years are currently scarce to further investigate whether the implantation of new-generation DES results in persistent attenuation of clinical events or to capture very late events, especially those related to the development of neoatherosclerosis, which takes a long time to occur in DES (11,19).

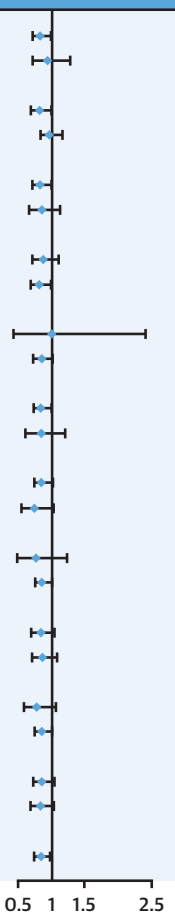
EXAMINATION-EXTEND is the first study reporting 10-year outcomes after primary PCI with second-generation DES compared with BMS, analyzing the full lifecycle risk for adverse events associated with coronary stents. Our study has the strength of having complete 10-year follow-up in 95% of patients included, with all events adjudicated by dedicated study personnel. Besides, our study represents very long-term follow-up of patients with STEMI treated with durable-polymer EES, which are frequently used in clinical practice, whose safety beyond 5 years has not yet been documented. There are indeed still concerns about the potential adverse long-term impact of durable-polymer coatings, with studies suggesting delayed arterial healing and accelerated in-stent atherosclerosis caused at least partly by an

FIGURE 5 Subgroup Analysis

A

Patient-Oriented Endpoint (All-Cause Death, All Myocardial Infarction, All Revascularization) at 10 Years in Subgroups

Subgroups	No. Events (%) EES	No. Events (%) BMS	p-value	RR (95% CI)	Relative Risk (95% CI) EES Better BMS Better	p-Value for Interaction
Male	197/634 (31%)	229/610 (38%)	0.016	0.83 (0.71-0.97)		0.497
Female	46/117 (39%)	57/137 (42%)	0.711	0.94 (0.70-1.28)		
<75 years	166/638 (26%)	194/615 (32%)	0.031	0.82 (0.69-0.98)		0.516
≥75 years	77/113 (68%)	92/132 (70%)	0.793	0.98 (0.83-1.16)		
No diabetes	184/613 (30%)	225/626 (36%)	0.027	0.84 (0.71-0.98)		0.923
Diabetes	59/137 (43%)	61/121(50%)	0.238	0.85 (0.66-1.11)		
No thrombectomy catheter	91/256 (36%)	107/266 (40%)	0.271	0.88 (0.71-1.10)		0.685
Thrombectomy catheter	152/495 (31%)	179/481 (37%)	0.032	0.83 (0.69-0.98)		
<30% ejection fraction	6/10 (60%)	3/5 (60%)	1.000	1.00 (0.42-2.40)		0.831
≥30% ejection fraction	170/531 (32%)	191/510 (37%)	0.066	0.85 (0.72-1.01)		
Primary PCI (STEMI <12h)	202/630 (32%)	243/638 (38%)	0.025	0.84 (0.72-0.98)		0.974
No Primary PCI	41/121 (34%)	43/108 (40%)	0.353	0.85 (0.61-1.20)		
Single-vessel disease	203/651 (31%)	239/659 (36%)	0.052	0.86 (0.74-1.00)		0.323
Multivessel disease	40/100 (40%)	47/88 (53%)	0.066	0.75 (0.55-1.02)		
TIMI flow <3 post procedure	19/50 (38%)	23/47 (49%)	0.277	0.78 (0.49-1.23)		0.626
TIMI flow 3 post procedure	224/699 (32%)	261/697 (37%)	0.034	0.86 (0.74-0.99)		
ST-resolution >70%	121/414 (29%)	152/438 (35%)	0.087	0.84 (0.69-1.03)		0.955
ST-resolution ≤70%	100/264 (38%)	103/236 (44%)	0.190	0.87 (0.70-1.07)		
Killip class >1 on admission	37/80 (46%)	45/76 (59%)	0.105	0.78 (0.58-1.06)		0.409
Killip class 1 on admission	205/669 (31%)	240/668 (36%)	0.040	0.85 (0.73-0.99)		
Culprit lesion not in LAD	140/428 (33%)	169/442 (38%)	0.088	0.86 (0.71-1.02)		0.845
Culprit lesion in LAD	103/323 (32%)	117/305 (38%)	0.089	0.83 (0.67-1.03)		
Overall	243/751 (32%)	286/747 (38%)	0.017	0.85 (0.74-0.97)		



Subgroup analysis for the 10-year rate of the patient-oriented composite endpoint **(A)** and device-oriented composite endpoint **(B)** among patients randomized to EES or BMS is shown. LAD = left anterior descending coronary artery; PCI = percutaneous coronary intervention; RR = relative risk; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Figure 1.

Continued on the next page

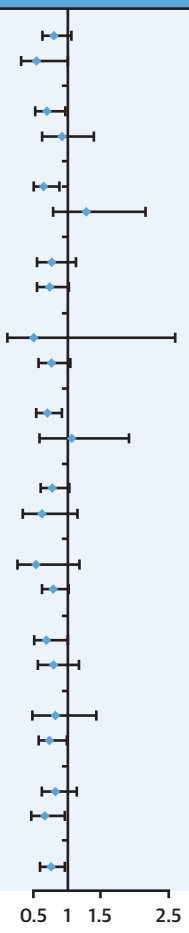
inflammatory reaction to polymer coatings, which may take years to accrue. These concerns have redirected research in this field toward biodegradable-polymer-based metallic DES, polymer-free DES, and completely bioresorbable scaffolds (19). Our findings may dispel these concerns.

At 10-year follow-up, EES are confirmed to be superior to BMS in patients with STEMI, in terms of both patient- and device-oriented composite endpoints. Although the use of BMS has virtually ceased in many countries worldwide, our findings are of interest because they provide reassuring data regarding the long-term safety of durable-polymer EES beyond 5 years in patients with STEMI. The superiority of the EES over the BMS was driven by reduced rate of revascularization. As matter of fact, the benefit gained by EES during the first 5 years of follow-up was maintained thereafter, without any additional value in this extended follow-up from 5 to 10 years. A significant interaction was found between diabetes

FIGURE 5 Continued

B Device-Oriented Endpoint (Cardiac Death, Target Vessel Myocardial Infarction or Target Lesion Revascularization) at 10 Years in Subgroups

Subgroups	No. Events (%) EES	No. Events (%) BMS	p-value	RR (95% CI)	p-Value for Interaction
Male	84/634 (13%)	101/610 (17%)	0.101	0.80 (0.61-1.05)	0.247
Female	13/117 (11%)	28/137 (20%)	0.059	0.54 (0.30-1.00)	
<75 years	66/638 (10%)	90/615 (15%)	0.022	0.71 (0.52-0.95)	0.380
≥75 years	31/113 (27%)	39/132 (30%)	0.715	0.93 (0.62-1.38)	
No diabetes	68/613 (11%)	109/626 (17%)	0.001	0.64 (0.48-0.84)	0.022
Diabetes	29/137 (21%)	20/121(17%)	0.343	1.28 (0.77-2.14)	
No thrombectomy catheter	41/256 (16%)	55/266 (21%)	0.169	0.77 (0.54-1.12)	0.888
Thrombectomy catheter	56/495 (11%)	74/481 (15%)	0.061	0.74 (0.53-1.02)	
<30% ejection fraction	2/10 (20%)	2/5 (40%)	0.560	0.50 (0.10-2.58)	0.587
≥30% ejection fraction	65/531 (12%)	82/510 (16%)	0.076	0.76 (0.56-1.03)	
Primary PCI (STEMI <12h)	77/630 (12%)	112/638 (18%)	0.008	0.70 (0.53-0.91)	0.221
No Primary PCI	20/121 (17%)	17/108 (16%)	0.872	1.05 (0.58-1.90)	
Single-vessel disease	83/651 (13%)	109/659 (17%)	0.052	0.77 (0.59-1.00)	0.490
Multivessel disease	14/100 (14%)	20/88 (23%)	0.121	0.62 (0.33-1.15)	
TIMI flow <3 post procedure	8/50 (16%)	14/47 (30%)	0.105	0.54 (0.25-1.16)	0.322
TIMI flow 3 post procedure	89/699 (13%)	113/697 (16%)	0.065	0.79 (0.61-1.02)	
ST-resolution >70%	48/414 (12%)	73/438 (17%)	0.034	0.70 (0.50-0.98)	0.642
ST-resolution ≤70%	40/264 (15%)	45/236 (19%)	0.244	0.79 (0.54-1.17)	
Killip class >1 on admission	18/80 (23%)	21/76 (28%)	0.459	0.81 (0.47-1.41)	0.843
Killip class 1 on admission	79/669 (12%)	107/668 (16%)	0.026	0.74 (0.56-0.97)	
Culprit lesion not in LAD	59/428 (14%)	74/442 (17%)	0.225	0.82 (0.60-1.13)	0.360
Culprit lesion in LAD	38/323 (12%)	55/305 (18%)	0.027	0.65 (0.44-0.96)	
Overall	97/751 (13%)	129/747 (17%)	0.021	0.75 (0.59-0.95)	

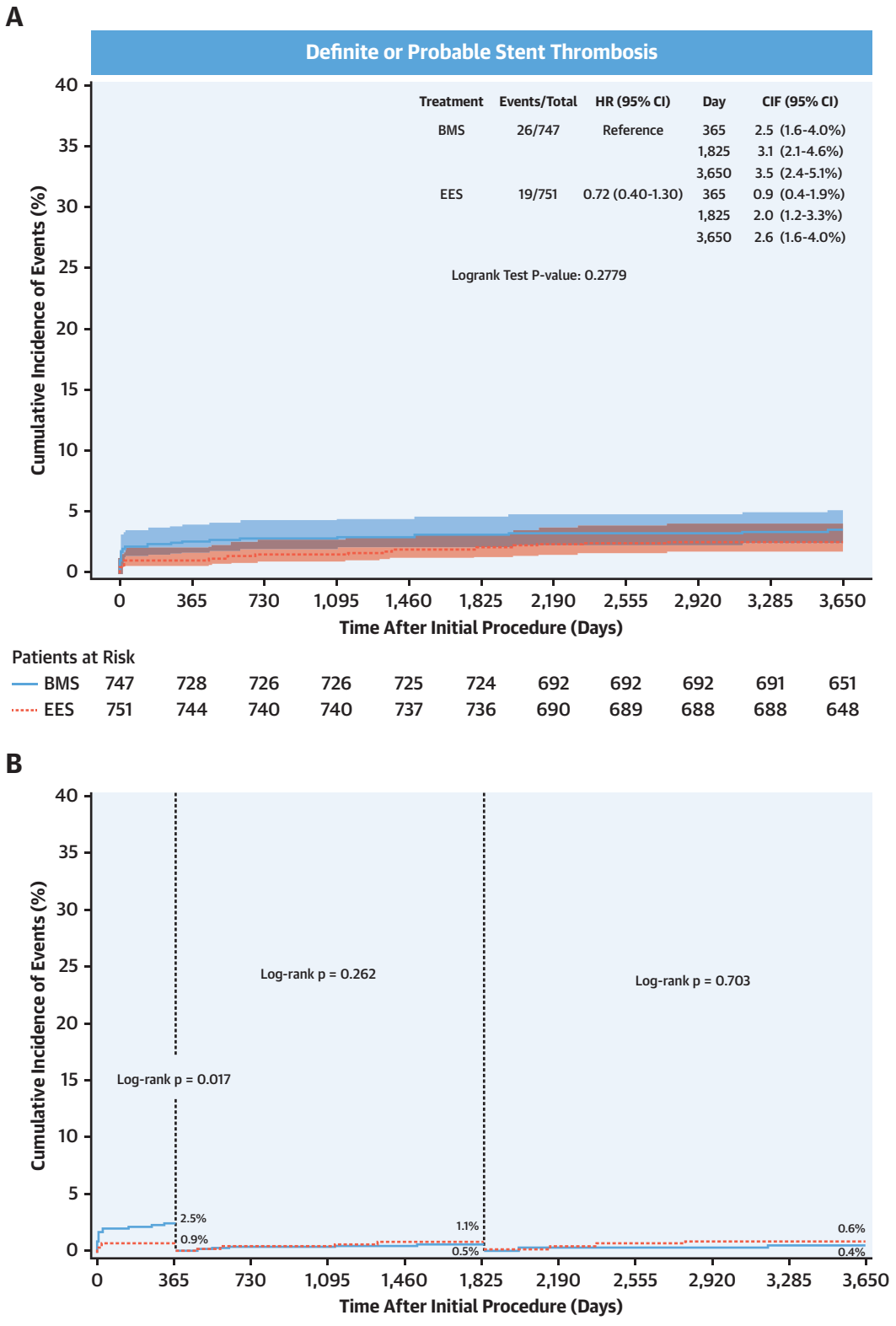


and stent outcomes. Considering that 20 subgroup analyses were performed for the 2 endpoints of interest and that this statistically significant interaction for the device-oriented composite endpoint is not matched by an interaction of the patient-oriented composite endpoint ($p = 0.92$), this finding may be explained by the play of chance.

Specifically looking at mortality, comparing the 2 devices, there was a trend toward a lower incidence of all-cause death with the EES compared with the BMS. This difference, which was already present at 5 years (21), cannot be explained by an increased rate of cardiac death and may be a play of chance.

Similar trends were observed for the revascularization and TLR endpoints, for which the early advantage of EES over BMS acquired during the first year after implantation was still maintained at 10-year follow-up (20,21). Either between 1 and 5 years or between 5 and 10 years, the rate of TLR was similar in both groups, which may suggest that the differing healing process immediately following stent implantation may be responsible for the variability in terms of revascularization between the 2 devices, but once this process is over, no additional advantage of either stent may be seen. In any case, this finding dispels any concern regarding a restenosis "late

FIGURE 6 Ten-Year Time-to-Event Curves for Definite or Probable Stent Thrombosis



Cumulative 10-year incidence is shown with Kaplan-Meier yearly event rates **(A)** and landmark analyses (0 to 1, 1 to 5, and 5 to 10 years) **(B)**. Abbreviations as in Figures 1 and 2.

catch-up" phenomenon, as initially suspected with EES on the basis of the 2-year imaging outcome data from SPIRIT II (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions) (26). The reduced 1-year incidence of EES thrombosis over BMS may have also contributed to build up this early EES advantage. The fluoropolymer coating present on the EES may result in greater thromboresistance relative to the BMS because of a phenomenon called fluoropassivation (27). This is especially relevant in the context of STEMI, in which the dissolution of the thrombus behind the struts may lead to a high incidence of late acquired malapposition (28,29). Of note, this early advantage of EES over BMS in terms of thrombosis dissipated over the 10 years of follow-up with, notably, a low incidence of very late stent thrombosis in both groups (about 0.1% to 0.2% yearly). Given the consistency of the results across multiple stents and in either a stable or STEMI population, the prior fears of late thrombosis with permanent polymer should be put to rest. Of note, between 1 and 10 years, there was a numeric excess of stent thrombosis in the DES arm; given the underpowered nature of this analysis, this may be due to chance, and one cannot exclude a rare increase in inflammation or neoatherosclerosis in the DES arm.

Last but not least, it should be emphasized, in line with previous observations, that the rate of any revascularization was 2-fold higher than the rate of TLR and that long-term mortality is driven mainly by noncardiac death, with a temporal switch from predominantly cardiac to predominantly noncardiac death (30,31). These findings suggest that atherosclerotic disease progression and comorbidities are stronger prognostic factors for patient-related outcomes than recurrent events in the intervened lesion. For all these reasons, it should be noted that secondary prevention measures and a holistic approach in the care of patients with STEMI should be an important part of future clinical investigations (32) (**Central Illustration**).

STUDY LIMITATIONS. The outcomes of this trial refer to patients with STEMI treated with aspirin and 1 year of clopidogrel as dual antiplatelet therapy. The potential role of ticagrelor or prasugrel in the further prevention of events (e.g., stent thrombosis, recurrent myocardial infarction, mortality) in this context was not evaluated, because these therapies were not available at the time of recruitment. Data on prolonged dual antiplatelet therapy beyond 5 years were not collected, so any effect on outcomes cannot be evaluated.

CONCLUSIONS

In this unique 10-year follow-up study, among patients with STEMI requiring emergency primary PCI, the use of durable-polymer-based EES was associated with reductions in patient-oriented and device-oriented composite endpoints compared with BMS. In particular, this advantage was built up during the first years of follow-up, without further divergence of outcomes between 5 and 10 years. A low incidence of TLR and stent thrombosis was registered in both groups between 5 and 10 years. These results may be taken as a landmark reference for the future evaluation of new devices and clinical approaches in patients with STEMI.

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ADDRESS FOR CORRESPONDENCE: Dr. Salvatore Brugaletta, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, c/ Villarroel 170, 08036 Barcelona, Spain. E-mail: sabrugaletta@gmail.com. Twitter: @sbrugaletta, @hospitalclinic, @idibaps.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with STEMI undergoing PCI, deployment of EES was associated with better clinical outcomes than BMS implantation after 10-year follow-up, though event rates were low between 5 and 10 years.

TRANSLATIONAL OUTLOOK: Future studies should focus on the prevention of events unrelated to the initial culprit lesion during the years following acute management of patients with STEMI.

REFERENCES

1. Ibanez B, James S, Agewall S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the Management of Acute Myocardial Infarction in Patients Presenting With ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119–77.

2. Steg PG, Fox KA, Eagle KA, et al. Mortality following placement of drug-eluting and bare-metal stents for ST-segment elevation acute myocardial infarction in the Global Registry of Acute Coronary Events. Eur Heart J 2009;30:321–9.

3. Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2010;31:2501–55.

4. Kastrati A, Dibra A, Spaulding C, et al. Meta-analysis of randomized trials on drug-eluting stents vs. bare-metal stents in patients with acute myocardial infarction. Eur Heart J 2007;28:2706–13.

5. Spaulding C, Henry P, Teiger E, et al. Sirolimus-eluting versus uncoated stents in acute myocardial infarction. N Engl J Med 2006;355:1093–104.

6. Stone GW, Witzenbichler B, Guagliumi G, et al. Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): final 3-year results from a multicentre, randomised controlled trial. Lancet 2011;377:2193–204.

7. Wenaweser P, Daemen J, Zwahlen M, et al. Incidence and correlates of drug-eluting stent thrombosis in routine clinical practice. 4-Year results from a large 2-institutional cohort study. J Am Coll Cardiol 2008;52:1134–40.

8. Kastrati A, Mehilli J, Pache J, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007;356:1030–9.

9. Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007;356:989–97.

10. Nakazawa G, Finn AV, Joner M, et al. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. Circulation 2008;118:1138–45.

11. Finn AV, Nakazawa G, Joner M, et al. Vascular responses to drug eluting stents: importance of delayed healing. Arterioscler Thromb Vasc Biol 2007;27:1500–10.

12. Cook S, Ladich E, Nakazawa G, et al. Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. Circulation 2009;120:391–9.

13. Wilson GJ, Nakazawa G, Schwartz RS, et al. Comparison of inflammatory response after implantation of sirolimus- and paclitaxel-eluting stents in porcine coronary arteries. Circulation 2009;120:141–9.

14. Sheiban I, Villata G, Bollati M, Sillano D, Lotrionte M, Biondi-Zoccai G. Next-generation drug-eluting stents in coronary artery disease: focus on everolimus-eluting stent (Xience V). Vasc Health Risk Manag 2008;4:31–8.

15. Baber U, Mehran R, Sharma SK, et al. Impact of the everolimus-eluting stent on stent thrombosis: a meta-analysis of 13 randomized trials. J Am Coll Cardiol 2011;58:1569–77.

16. Valgimigli M, Sabate M, Kaiser C, et al. Effects of cobalt-chromium everolimus eluting stents or bare metal stent on fatal and non-fatal cardiovascular events: patient level meta-analysis. BMJ 2014;349:g6427.

17. Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Clinical outcomes with drug-eluting and bare-metal stents in patients with ST-segment elevation myocardial infarction: evidence from a comprehensive network meta-analysis. J Am Coll Cardiol 2013;62:496–504.

18. Iglesias JF, Muller O, Heg D, et al. Biodegradable polymer sirolimus-eluting stents versus durable polymer everolimus-eluting stents in patients with ST-segment elevation myocardial infarction (BIOSTEMI): a single-blind, prospective, randomised superiority trial. Lancet 2019;394:1243–53.

19. Finn AV, Joner M, Nakazawa G, et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. Circulation 2007;115:2435–41.

20. Sabate M, Cequier A, Iniguez A, et al. Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION):1 year results of a randomised controlled trial. Lancet 2012;380:1482–90.

21. Sabate M, Brugaletta S, Cequier A, et al. 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. Lancet 2016;387:357–66.

22. Sabate M, Cequier A, Iniguez A, et al. Rationale and design of the EXAMINATION trial: a randomised comparison between everolimus-eluting stents and cobalt-chromium bare-metal stents in ST-elevation myocardial infarction. EuroIntervention 2011;7:977–84.

23. Sabate M, Brugaletta S, Cequier A, et al. The EXAMINATION trial (Everolimus-Eluting Stents Versus Bare-Metal Stents in ST-Segment Elevation Myocardial Infarction): 2-year results from a multicenter randomized controlled trial. J Am Coll Cardiol Intv 2014;7:64–71.

24. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.

25. Byrne RA, Stone GW, Ormiston J, Kastrati A. Coronary balloon angioplasty, stents, and scaffolds. Lancet 2017;390:781–92.

26. Claessen BE, Beijk MA, Legrand V, et al. Two-year clinical, angiographic, and intravascular ultrasound follow-up of the XIENCE V everolimus-eluting stent in the treatment of patients with de novo native coronary artery lesions: the SPIRIT II trial. Circ Cardiovasc Interv 2009;2:339–47.

27. Torii S, Cheng Q, Mori H, et al. Acute thrombogenicity of fluoropolymer-coated versus biodegradable and polymer-free stents. EuroIntervention 2019;14:1685–93.

28. Guagliumi G, Costa MA, Sirbu V, et al. Strut coverage and late malapposition with paclitaxel-eluting stents compared with bare metal stents in acute myocardial infarction: optical coherence tomography substudy of the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial. Circulation 2011;123:274–81.

29. Gomez-Lara J, Brugaletta S, Jacobi F, et al. Five-year optical coherence tomography in patients with ST-segment-elevation myocardial infarction treated with bare-metal versus everolimus-eluting stents. Circ Cardiovasc Interv 2016;9:e003670.

30. Spoon DB, Psaltis PJ, Singh M, et al. Trends in cause of death after percutaneous coronary intervention. Circulation 2014;129:1286–94.

31. Kufner S, Ernst M, Cassese S, et al. 10-Year outcomes from a randomized trial of polymer-free versus durable polymer drug-eluting coronary stents. J Am Coll Cardiol 2020;76:146–58.

32. Sabate M, Mack M. Very late outcomes after stent implantation: it is time to target the nontarget sites. J Am Coll Cardiol 2020;75:605–7.

KEY WORDS everolimus, randomized controlled trial, stent, stent thrombosis, ST-segment elevation myocardial infarction

APPENDIX For EXAMINATION-EXTEND study organization, participating sites with local investigators, sample size calculation, supplemental tables, supplemental figures and their legends, a Consolidated Standards of Reporting Trials randomized controlled trial checklist, the EXAMINATION-EXTEND study protocol, the EXAMINATION-EXTEND statistical plan analysis, the original and final EXAMINATION trial protocol rationale and design, and supplemental references, please see the online version of this paper.