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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

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Objectives This study sought to assess the 2-year outcomes of the population included in the EXAMINATION (Everolimus-Eluting Stents Versus Bare-Metal Stents in ST-Segment Elevation Myocardial Infarction) trial beyond the 1-year prescription period of dual antiplatelet therapy.

Background The EXAMINATION trial compared the performance of everolimus-eluting stents (EES) versus bare-metal stents (BMS) in an all-comer ST-segment elevation myocardial infarction (STEMI) population.

Methods This was a multicenter, multinational, prospective, randomized, single-blind, controlled trial in patients with STEMI. The primary endpoint, which was the combined endpoint of all-cause death, any recurrent myocardial infarction, and any revascularization, and the endpoints target lesion revascularization and stent thrombosis were assessed at 2 years.

Results Between December 31, 2008, and May 15, 2010, 1,498 patients were randomized to receive EES (n = 751) or BMS (n = 747). Compliance with dual antiplatelet regimen was reduced at 2 years to a similar degree (17.3% vs. 17.2%, p = 0.91). At 2 years, the primary endpoint occurred in 108 (14.4%) patients of the EES group and in 129 (17.3%) patients of the BMS group (p = 0.11). Rate of target lesion revascularization was significantly lower in the EES group than in the BMS group (2.9% vs. 5.6%; p = 0.009). Rates of definite and definite or probable stent thrombosis were also significantly reduced in the EES group (0.8% vs. 2.1%; p = 0.03, and 1.3% vs. 2.8%; p = 0.04, respectively).

Conclusions The 2-year follow-up of the EXAMINATION trial confirms the safety and efficacy of the EES compared with BMS in the setting of STEMI. Specifically, both rates of target lesion revascularization and stent thrombosis were reduced in recipients of EES without any signs of late attrition for either of these endpoints. (A Clinical Evaluation of Everolimus Eluting Coronary Stents in the Treatment of Patients With ST-Segment Elevation Myocardial Infarction: EXAMINATION Study; NCT00828087) (J Am Coll Cardiol Intv 2014;7:64–71) © 2014 by the American College of Cardiology Foundation

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First-generation drug-eluting stents (DES) have been shown to be more efficacious as compared with bare-metal stents (BMS) during the first year after the index procedure (1–3). However, beyond that period, they may suffer from late hazard, namely stent thrombosis (4,5). The observed increased rate of stent thrombosis may be related to a persistent inflammatory reaction to the remnant polymeric coating, delayed endothelialization of the stent or concomitant presence of mechanical abnormalities (i.e., stent malapposition, underexpansion, etc.), and reduced antithrombotic protective effect of antiplatelet agents (i.e., rebound effect of clopidogrel withdrawal) (6–9). Second-generation DES have been shown to improve both the efficacy and safety outcomes compared with first-generation DES and even BMS (10,11). Improvements in hemocompatibility and thromboresistance of new coatings may have played a role in this regard (12).

ST-segment elevation myocardial infarction (STEMI) represents the paradigm of a thrombotic milieu and a challenging clinical scenario to test new intracoronary devices (13,14). The EXAMINATION (Everolimus-Eluting Stents Versus Bare-Metal Stents in ST-Segment Elevation Myocardial Infarction) trial (15) was specifically designed to evaluate the performance of everolimus-eluting stents (EES) as compared with BMS in the setting of STEMI. At 1-year follow-up, rates of both target lesion revascularization and stent thrombosis were reduced in recipients of EES (16). Although the results of EES in the EXAMINATION trial were in accordance with those in more elective contexts (11), it is unknown whether its safety and efficacy are maintained beyond 1 year, once dual antiplatelet therapy is usually withdrawn. Therefore, we sought to evaluate the performance of EES at 2-year clinical follow-up of patients included in the EXAMINATION trial.

Methods

Study design and patient population. This was a multicenter multinational, prospective, randomized, single-blind, controlled trial in patients with STEMI (NCT00828087). The study design has been previously reported (15). Briefly, the study had broad inclusion and few exclusion criteria. Any patient presenting with STEMI within the first 48 h after symptom onset, requiring emergent percutaneous coronary intervention, with a vessel size ranging between 2.25 mm and 4.0 mm without other anatomic restrictions could be included. Exclusion criteria were age younger than 18 years; pregnancy; known intolerance to aspirin, clopidogrel, heparin, stainless steel, everolimus, or contrast material; being on chronic treatment with anti-vitamin K agents; and STEMI secondary to stent thrombosis.

All recruited patients were randomly assigned (ratio 1:1) to receive 1 of the 2 treatments: EES or cobalt-chromium BMS. The design of both platforms (EES or BMS) was the same and corresponded to that of the Multilink Vision stent (Abbott Vascular, Santa Clara, California). Patients were blinded to which treatment they received.

Procedures were performed following current practice. At the index procedure, patients received appropriate anticoagulation with either unfractionated heparin or bivalirudin. The use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the investigator. Aspirin (loading dose 250 to 500 mg) and clopidogrel (loading dose of at least 300 mg) had to be given before percutaneous coronary intervention. Clopidogrel was prescribed for 1 year (75 mg per day) and aspirin (100 mg) indefinitely. Manual thrombectomy was recommended, 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 randomization, in all staged lesions.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
EES = everolimus-eluting stent(s)
STEMI = ST-segment elevation myocardial infarction

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

Endpoints. The primary endpoint of the study was the patient-oriented combined endpoint of all-cause death, any myocardial infarction, or any revascularization at 1 year (16,17). For the purpose of the current 2-year follow-up, we have analyzed the patient-oriented endpoint and its individual components together with the following stent-derived endpoints: target vessel myocardial infarction (18); target vessel and target lesion revascularization; and stent thrombosis (17). Detailed definitions of the endpoints have been reported elsewhere (15).

Statistical analysis. All analyses were performed by intention to treat as well as per protocol (if different from allocated by randomization). Categorical variables were presented as percentages, and continuous variables as means (medians

Spain; |||Erasmus Medical Center, Interventional Cardiology Unit, Rotterdam, the Netherlands; and ¶¶Cardialysis, Rotterdam, the Netherlands. Dr. Sabaté is a consultant for and has received speaker's fees from Abbott Vascular, Boston Scientific, and Medtronic. Dr. Brugaletta has received speaker's fees from Abbott Vascular and St. Jude Medical. Dr. Valgimigli has received honoraria as a public speaker for Terumo, The Medicines Company, Medtronic, Iroko, Merck & Co., Abbott, Eli Lilly and Company, AstraZeneca, Cordis, CID, and Bayer. Ms. Backx is an employee of Cardialysis. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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and interquartile ranges whenever appropriate). The sample size calculation was based on a 2-sided type I error rate alpha of 0.05, a randomization ratio of 1:1 (EES group/BMS group), and a statistical power of at least 86% to detect about a 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. We tested the endpoints statistically with the log-rank test at a 2-sided 0.05 significance level for the comparison of the EES group with the BMS group. For time-to-event variables, we constructed survival curves using Kaplan-Meier estimates. Landmark analyses were performed for primary endpoint, target vessel revascularization, and definite/probable stent thrombosis between 1- and 2-year follow-up. Statistical analyses were performed with SPSS statistical package, version 19.0 (SPSS, Chicago, Illinois).

Results

Patient demographics and flow chart. Between December 31, 2008 and May 15, 2010, a total of 1,504 patients with STEMI were recruited, of whom 6 withdrew consent after randomization. As a result, 1,498 patients were randomly assigned to receive either an EES (n = 751) or a BMS (n = 747). Complete 2-year clinical follow-up was obtained in 741 (98.7%) patients of the EES arm and in 733 (98.1%) of the BMS arm. A flowchart of the study is presented in Figure 1. Baseline clinical and procedural characteristics were comparable between both arms (Table 1), and published elsewhere (16). Compliance to dual antiplatelet regimen (EES vs. BMS) did not differ between groups up to 30 days (99.7% vs. 99.6% at discharge; p = 0.69; 98.8% vs. 99.4% at 30 days, p = 0.26) and became significantly different at 6 months (99.1% vs. 92.8%, p < 0.0001) and at 1 year (97.9% vs. 89.9%, p < 0.0001). Following current guidelines, the protocol mandated withdrawal of clopidogrel at 12 months unless it was clinically indicated (i.e., patient with repeat revascularization within the first year). As a result, compliance with dual antiplatelet regimen was reduced at 2-year follow-up to a similar degree (17.3% vs. 17.2%, p = 0.91) (Fig. 2).

Clinical outcomes at 2 years. Clinical outcomes at 2 years are presented in Table 2. The patient-oriented endpoint occurred in 108 (14.4%) patients in the EES group, and 129 (17.3%) patients in the BMS group (p = 0.11). No significant differences were observed between groups in the rates of all-cause and cardiac death and any recurrent myocardial infarction. Rates of target vessel and target lesion revascularization were significantly lower in the EES group than in the BMS group (4.8% vs. 7.9%; p = 0.014, and 2.9% vs. 5.6%; p = 0.009, respectively). The rate of definite stent thrombosis was significantly reduced in the EES group compared with the BMS group (0.8% vs. 2.1%; p = 0.03). There were 2 episodes of very late definite stent thrombosis in both groups. Overall, the rate of definite or probable stent thrombosis was also reduced in the EES group at 2 years (1.3% vs. 2.8%; p = 0.04). There were 3 episodes of very late definite or probable stent thrombosis in the EES arm and 2 in the BMS arm. None of the instances of very late stent thrombosis were chronologically related to clopidogrel discontinuation. Kaplan-Meier estimates for the aforementioned outcomes

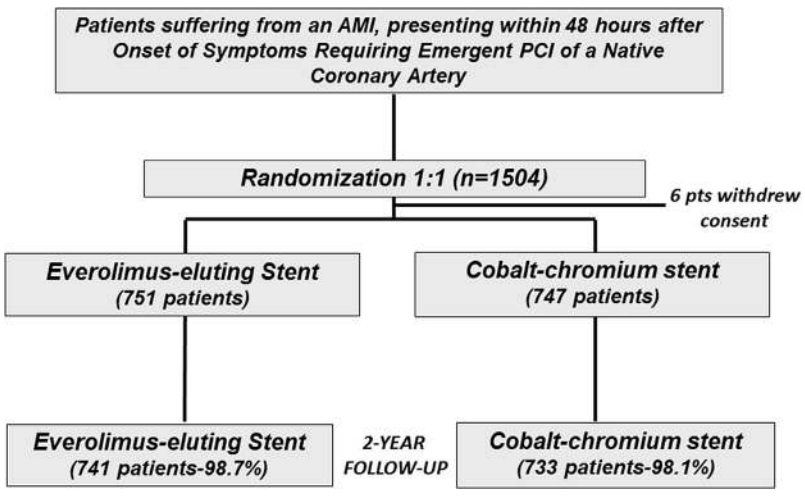

Figure 1. Flowchart of the Study up to 2-Year Follow-Up

A total of 1,504 patients were initially randomized 1:1 to receive either everolimus-eluting stents or cobalt-chromium bare-metal stents. At 2 years, clinical follow-up was obtained in 98.7% of the patients treated with everolimus-eluting stents and 98.1% of the patients treated with bare-metal stents. AMI = acute myocardial infarction; PCI = percutaneous coronary intervention; pts = patients.

Table 1. Baseline Clinical and Procedural Characteristics of the Patients

Variable	EES Group (n = 751)	BMS Group (n = 747)
Age, yrs	60.8 ± 12	61.6 ± 13
Female	117 (16.6)	137 (18.3)
Coronary risk factors		
Smoker	544 (62.5)	538 (62.0)
Diabetes mellitus	137 (18.3)	121 (16.2)
Arterial hypertension	347 (46.3)	378 (50.6)
Hyperlipidemia	354 (47.2)	301 (40.3)
Family history of ischemic heart disease	134 (17.9)	119 (16.0)
Cardiovascular history		
Prior MI	33 (4.4)	47 (6.3)
Prior PCI	29 (3.9)	32 (4.3)
Prior CABG	3 (0.4)	7 (0.9)
Prior stroke	12 (1.6)	19 (2.5)
Infarct-related artery		
LAD	379 (42.2)	343 (38.9)
LCX	130 (14.5)	132 (15.0)
RCA	380 (42.3)	396 (44.9)
Other	10 (1.1)	10 (1.2)
Total ischemia time, min		
Primary PCI, <12 h	215 [150–315]	210 [155–327]
Rescue PCI	449 [330–705]	453 [340–580]
After successful thrombolysis	828 [284–1,323]	1,105 [750–1,210]
Late-comers, ≥12 h <48 h	981 [783–1,264]	1,060 [923–1,340]
Anticoagulation regimen		
Unfractioned heparin	597 (79.5)	588 (78.7)
Low-molecular-weight heparin	62 (8.3)	71 (9.5)
Bivalirudin	49 (6.5)	56 (7.5)
Antiplatelet regimen		
ASA pre-PCI	692 (92.1)	692 (92.6)
Clopidogrel pre-PCI	710 (94.5)	704 (94.2)
IIb/IIIa inhibitor	400 (53.3)	385 (51.5)
Manual thrombectomy	495 (65.9)	481 (64.4)
Direct stenting	451 (61%)	434 (59.5)
Post-dilation	118 (15.7)	103 (13.7)
Number of stents	1.39 ± 0.7	1.38 ± 0.6
Total stent length	23 [18–35]	23 [18–33]
Biomarkers (peak value)		
CK total, IU/l	1,374 [604–3,053]	1,464 [663–2,849]
CK-MB, IU/l	149 [62–321]	142 [60–323]
Troponin, ng/ml	16.4 [4.2–74]	18.2 [4.3–68]

Values are mean ± SD, n (%), or median [interquartile range]. p = NS for all variables.

ASA = aspirin; BMS = bare-metal stent; CABG = coronary artery bypass graft; CI = confidence interval; CK = creatine kinase; CK-MB = creatine kinase–myocardial band; EES = everolimus-eluting stent; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery.

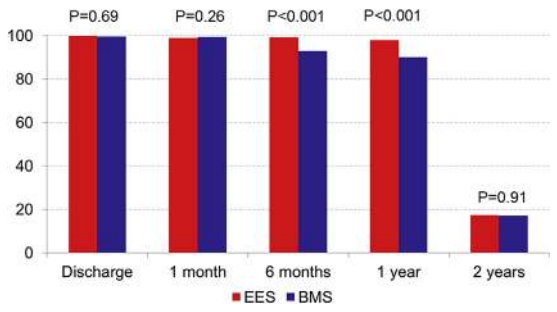

Figure 2. Dual Antiplatelet Compliance Between Groups for 2 Years

This figure depicts the percentage of patients receiving dual antiplatelet treatment at different time points. As per protocol, clopidogrel had to be withdrawn at 1-year follow-up unless the clinical condition of the patient dictated the opposite. At 2 years, no difference in the percentage of patients with aspirin alone was observed between groups. BMS = bare-metal stent(s); EES = everolimus-eluting stent(s).

over 720 days of follow-up are presented in Figures 3A to 3F. Landmark analyses between 1- and 2-year follow-up did not demonstrate any significant differences regarding the patient-oriented endpoint (p = 0.461), clinically driven target lesion revascularization (p = 0.511), or probable/definite stent thrombosis (p = 0.672).

Discussion

This report summarizes the long-term outcomes of the first randomized trial specifically designed in patients with STEMI who have been treated either with EES, as a second-generation DES, or with BMS. The main findings of the current study are the following. First, the rate of the patient-oriented composite endpoint did not differ between groups. Second, the repeat revascularization rate was also reduced by EES at 2-year follow-up. Third, the rate of definite or probable stent thrombosis remained lower with the use of EES as compared with BMS in the setting of STEMI. None of these endpoints had very late (>1 year) attrition following the discontinuation of dual antiplatelet therapy at 12 months.

Matching the results of the 1-year follow-up (16), this extended follow-up beyond the prescribed period of dual antiplatelet therapy did not demonstrate any difference in favor of the use of EES as assessed by the patient-oriented composite endpoint. In the same way, the rates of all-cause death, cardiac death, or recurrent myocardial infarction were similar between the 2 groups. The use of the patient-related endpoint has been advocated by the Academic Research Consortium (17), because this endpoint may more closely reflect the outcomes of patients' underlying global disease rather than the specific effect of the study stent. In this regard, the patient-oriented endpoint also included any noncardiac death, any myocardial infarction not related to the target vessel, and any revascularizations not related to the target vessel. Similarly, the RESOLUTE AC (RESOLUTE All Comers) trial (19) showed a doubled rate of patient-related outcomes as compared with stent-related

Table 2. Clinical Events at 2 Years

	EES Group (n = 751)	BMS Group (n = 747)	Difference (95% CI)	p Value
Primary endpoint, patient-oriented*	108 (14.4)	129 (17.3)	−2.9 (−6.6 to 0.8)	0.11
Death†	32 (4.3)	37 (5.0)	−0.7 (−2.8 to 1.4)	0.52
Cardiac	28 (3.7)	28 (3.7)	0.0 (−1.9 to 1.9)	1.0
Vascular	3 (0.4)	3 (0.4)	0.0 (−0.6 to −0.6)	0.99
Non-cardiovascular	1 (0.1)	6 (0.8)	−0.7 (−1.4 to 0.0)	0.57
Myocardial infarction‡	14 (1.9)	18 (2.4)	−0.3 (−1.5 to 0.9)	0.45
Target vessel related	11 (1.5)	16 (2.1)	−0.4 (−1.5 to 0.7)	0.46
Non-target vessel related	3 (0.4)	3 (0.4)	0.0 (−0.6 to −0.6)	0.99
Revascularization	73 (9.7)	95 (12.7)	−3.0 (−6.2 to 0.0)	0.05
Target lesion	22 (2.9)	42 (5.6)	−2.7 (−4.7 to −0.6)	0.01
Target vessel	36 (4.8)	59 (7.9)	−3.1 (−5.6 to −0.6)	0.009
Non-target vessel	46 (6.1)	52 (7.0)	−0.8 (−3.3 to 1.7)	0.51
Definite stent thrombosis§	6 (0.8)	16 (2.1)	−1.3 (−2.6 to −0.1)	0.03
Definite/probable stent thrombosis§	10 (1.3)	21 (2.8)	−1.5 (−2.9 to 0.0)	0.04

Values are n (%), except as noted. *Combined (hierarchical) endpoint of all-cause death, any recurrent myocardial infarction, and any revascularization (16). †Death was adjudicated according to Academic Research Consortium (ARC) definitions (17). ‡Myocardial infarction was adjudicated according to the World Health Organization extended definition (18). §Stent thrombosis defined according to ARC definitions (17).
Abbreviations as in Table 1.

outcomes at 2-year follow-up, reinforcing the importance of secondary prevention as adjunctive therapy to revascularization.

Despite offering no advantages in the primary endpoint as compared with BMS, EES reduced the need for subsequent revascularization at 2-year follow-up. For reducing intimal hyperplasia in stent segments, DES are known to be superior to BMS (2,20). The time course of restenosis, however, may differ between types of stents. After BMS implantation, intimal hyperplasia peaks in the first 6 months, and lumen enlargement may occur from 6 months to 3 years after stent implantation (21). Conversely, first-generation DES exhibit a potent antiproliferative effect within the first months after implantation, that may vanish over time. In this regard, Byrne et al. (22) reported the results of angiographic data during 2-year follow-up in 1,331 patients who were treated with DES. They found ongoing erosion of the lumen caliber beyond 6 to 8 months post-index procedure, up to 2-year follow-up. In a 3-year follow-up study of patients in the J-Cypher registry, incidences of target lesion revascularization in sirolimus-eluting stent–treated lesions were reported to be 5.5% at 1 year, 8.1% at 2 years, and 10% at 3 years (23). This phenomenon, called "late catch-up phenomenon," was initially advocated also for EES based on the 2-year imaging outcome data from the SPIRIT II (SPIRIT II: A Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) trial (24). Finally, the concerns were proven unfounded when the recently published 5-year data confirmed a reduction in main cardiac events with the use of EES as compared with first-generation DES (25). In a recent analysis (26), data from 76 randomized trials involving 117,762 patient-years of follow-up demonstrated a continued benefit at long term (>1 year) by the use of DES. Among the 5 DES analyzed in that study, EES was the stent with the lowest target vessel revascularization rate.

In accordance with these previous findings, our report extended the benefit of EES over BMS in reducing target lesion revascularization, to STEMI patients, in whom restenosis of stented segments supplying infarcted arteries may be silent or not clinically relevant. To define the clinical relevance of the restenosis in STEMI, it is necessary to design trials that do not include mandatory angiographic follow-up to avoid the potential oculostenotic reflex. In this regard, all angiographies performed during follow-up in the EXAMINATION trial were clinically mandated (i.e., ischemia-driven) in order to reflect real-world clinical practice.

Stent thrombosis was reduced at 2 years by the use of EES. Stent thrombosis is an infrequent, but serious, complication with a high mortality rate. In fact, it can be manifested by fatal and nonfatal STEMI in >80% of patients, with a mortality rate up to 25% within 30 days (6,27). Slow coronary flow, delayed and incomplete healing, stent malapposition and/or underexpansion, stent length, lack of stent thrombosis resolution, dissection, exposure of the blood to prothrombotic subendothelial tissue, failure to inhibit platelet adhesion and aggregation, and chronic eosinophilic infiltration are some of the mechanisms of stent thrombosis (8,28–32). Besides these factors, in most clinical registries, acute coronary syndrome as a clinical condition at the time of the index procedure repeatedly appears as an independent predictor of stent thrombosis (13,14). The timing of stent thrombosis differs between the types of

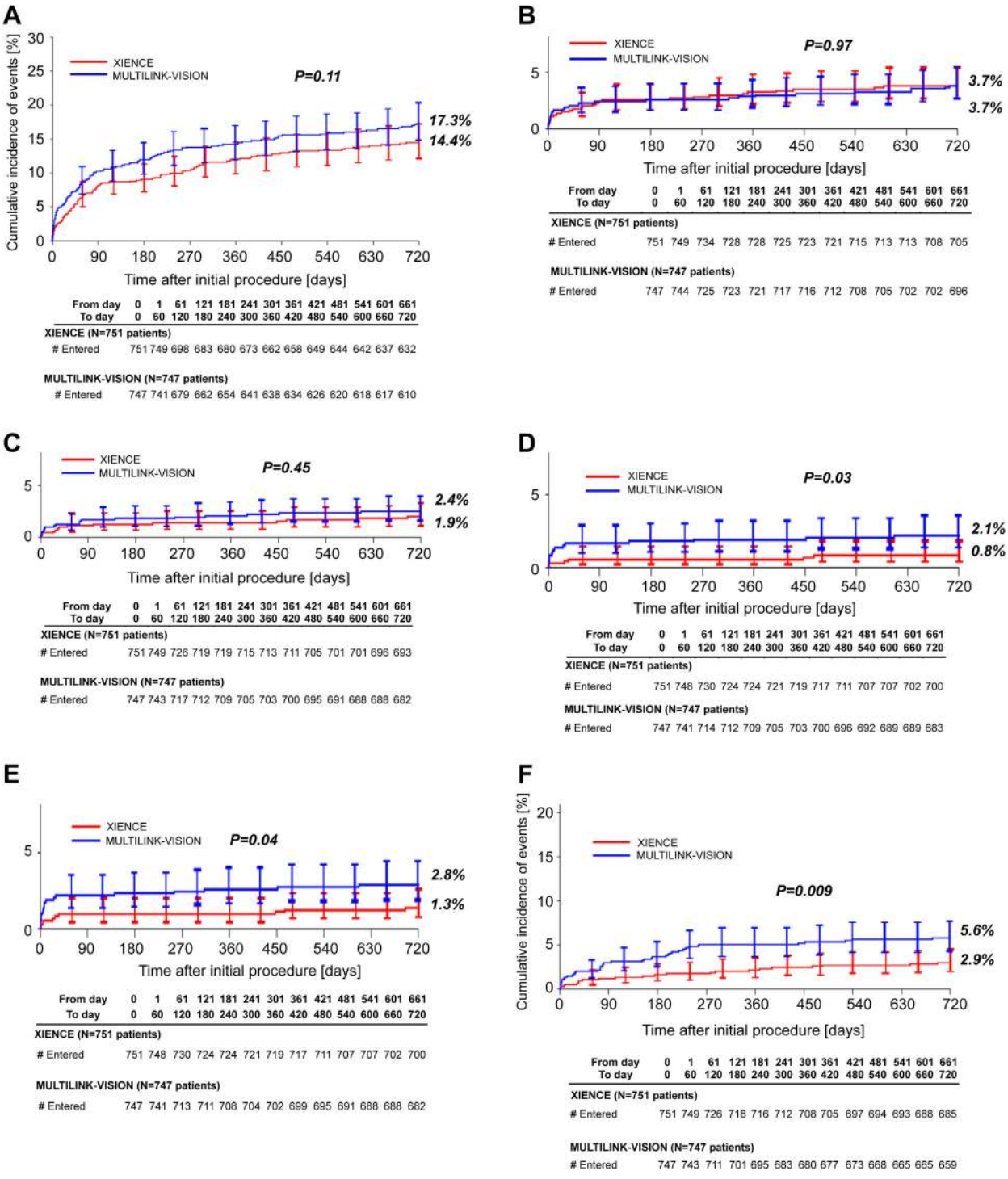

Figure 3. Kaplan-Meier Estimates for Different Endpoints for 720 Days of Follow-Up

(A) Kaplan-Meier estimates for the primary endpoint. **(B)** Kaplan-Meier estimates for cardiac death. **(C)** Kaplan-Meier estimates for recurrent myocardial infarction. **(D)** Kaplan-Meier estimates for definite stent thrombosis. **(E)** Kaplan-Meier estimates for definite or probable stent thrombosis. **(F)** Kaplan-Meier estimates for target lesion revascularization. At 2-year follow-up, no significant differences were observed in the first 3 endpoints **(A, B, C)** between groups. Conversely, significant reductions were observed for the latter 3 endpoints **(D, E, F)** in favor of the everolimus-eluting stent group. Error bars indicate a point-wise 2-sided 95% confidence interval with a complementary log-log transformation. Standard error is based on the Greenwood formula.

stents. During the first months, it may occur after both BMS and DES implantation; however, beyond 1 year, it is more frequently observed after first-generation DES implantation. BMS was therefore considered the benchmark for safety standards for stent evaluation. However, recent studies and meta-analyses (10,33–35) have demonstrated an excellent safety profile for second-generation DES. Newer-generation stents such as the EES have changes in stent design, including thinner struts, use of cobalt-chromium rather than stainless steel stents, and thinner and more biocompatible polymers that may elicit less inflammatory response with a consequent decrease in stent thrombosis. In particular, EES carries a fluorinated copolymer that may confer a specific resistance to thrombosis (12). This may explain the results of the current study in which 2 stents with an identical platform (except for the presence of everolimus and durable polymeric and copolymeric coatings) have been assessed. In this regard, we could identify the BMS as the most potent independent predictor of stent thrombosis at 1-year follow-up (30). Of interest, stent thrombosis was reduced in the early phase, and this benefit persisted up to 2 years without any signs of late erosion of the benefit beyond 1 year. Certainly, the percentage of patients on dual antiplatelet regimen at 2 years was comparably reduced (<20%) in both groups. The present results are consistent with the similar low rates of stent thrombosis with EES seen in the Bern-Rotterdam cohort study (versus other DES) (33) and in an updated analysis from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) (36), in which there was a 67% reduction in the risk of stent thrombosis compared with BMS. In a recently published probability analyses, EES had a >80% probability of having the lowest stent thrombosis rate compared with all other stent types, including BMS (26).

Study limitations. This study was underpowered to detect differences in the primary endpoint at any time period. In fact, the power that the study had to determine a 30% reduction of the primary endpoint was only 26% at 1 year (16). In the same vein, this trial was also not powered to detect differences in rare events such as stent thrombosis. Although data are reassuring and consistent with other reports on the use of EES, only larger trials with stent thrombosis as the primary endpoint or a meta-analysis will provide definite conclusions in this regard.

Conclusions

The 2-year follow-up of the EXAMINATION trial confirms the safety and efficacy of EES compared with BMS in the setting of STEMI. Specifically, the rates of both target lesion revascularization and stent thrombosis were reduced in recipients of EES, without any signs of late attrition for both endpoints.

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