ORIGINAL CONTRIBUTION

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Effect of Biolimus-Eluting Stents With Biodegradable Polymer vs Bare-Metal Stents on Cardiovascular Events Among Patients With Acute Myocardial Infarction

The COMFORTABLE AMI Randomized Trial

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Context The efficacy and safety of drug-eluting stents compared with bare-metal stents remains controversial in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI).

Objective To compare stents eluting biolimus from a biodegradable polymer with bare-metal stents in primary PCI.

Design, Setting, and Patients A prospective, randomized, single-blinded, controlled trial of 1161 patients presenting with STEMI at 11 sites in Europe and Israel between September 19, 2009, and January 25, 2011. Clinical follow-up was performed at 1 and 12 months.

Intervention Patients were randomized 1:1 to receive the biolimus-eluting stent (n=575) or the bare-metal stent (n=582).

Main Outcome Measures Primary end point was the rate of major adverse cardiac events, a composite of cardiac death, target vessel–related reinfarction, and ischemia-driven target-lesion revascularization at 1 year.

Results Major adverse cardiac events at 1 year occurred in 24 patients (4.3%) receiving biolimus-eluting stents with biodegradable polymer and 49 patients (8.7%) receiving bare-metal stents (hazard ratio [HR], 0.49; 95% CI, 0.30-0.80; $P=.004$). The difference was driven by a lower risk of target vessel–related reinfarction (3 [0.5%] vs 15 [2.7%]; HR, 0.20; 95% CI, 0.06-0.69; $P=.01$) and ischemia-driven target-lesion revascularization (9 [1.6%] vs 32 [5.7%]; HR, 0.28; 95% CI, 0.13-0.59; $P<.001$) in patients receiving biolimus-eluting stents compared with those receiving bare-metal stents. Rates of cardiac death were not significantly different (16 [2.9%] vs 20 [3.5%], $P=.53$). Definite stent thrombosis occurred in 5 patients (0.9%) treated with biolimus-eluting stents and 12 patients (2.1%; HR, 0.42; 95% CI, 0.15-1.19; $P=.10$) treated with bare-metal stents.

Conclusion Compared with a bare-metal stent, the use of biolimus-eluting stents with a biodegradable polymer resulted in a lower rate of the composite of major adverse cardiac events at 1 year among patients with STEMI undergoing primary PCI.

Trial Registration clinicaltrials.gov Identifier: NCT00962416

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PRIMARY PERCUTANEOUS CORONARY intervention (PCI) is the reperfusion therapy of choice among patients with ST-segment elevation myocardial infarction (STEMI) owing to a lower risk of reinfarction and improved survival compared with fibrinolysis.[1,2] Bare-metal stents minimize the risk of infarct vessel reocclusion and reinfarction compared with balloon angioplasty, but are associated with restenosis due to neointimal hyperplasia.[3,4] Early generation drug-eluting stents releasing sirolimus or paclitaxel from durable polymers reduce the need for repeat revascularization compared with bare-metal stents.[5-7] However, vessel healing is delayed with evidence of chronic in-

For editorial comment see p 814.

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flammation related at least in part to the persistence of durable polymer components in patients with acute STEMI.[8]

In addition, acute myocardial infarction (MI) is a predictor of thrombotic stent complications occurring late after drug-eluting stent implantation, particularly in the presence of a high thrombus burden, raising concerns regarding the balance of risks and benefits of these devices in this clinical setting.[9,10] Two meta-analyses in patients with acute MI confirmed a lower risk of repeat revascularization with early generation drug-eluting stents compared with bare-metal stents, however, at the expense of a 2-fold increased risk of very late stent thrombosis.[11,12]

Newer-generation drug-eluting stents with biodegradable polymers provide controlled drug release with subsequent degradation of the polymer rendering the stent surface more closely to a bare-metal stent after the period of biodegradation. The unrestricted use of stents eluting biolimus, an equipotent sirolimus analogue, from biodegradable polylactic acid was noninferior and potentially better than sirolimus-eluting stents in terms of major adverse clinical events in a large clinical trial with follow-up of 4 years, with a substantially reduced risk (80%) of stent thrombosis occurring beyond 1 year.[13,14] A stratified analysis suggested a particularly pronounced benefit among patients with acute STEMI. We therefore performed a multicenter, randomized trial to compare the efficacy and safety of stents eluting biolimus from a biodegradable polymer with bare-metal stents of otherwise identical design.

METHODS

Study Design

The COMFORTABLE AMI trial (Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction) was a multicenter, randomized, assessor-blinded, superiority trial in patients presenting with STEMI undergoing primary PCI. The full study design was reported elsewhere.[15] The study complied with the Declaration of Helsinki and was approved by all institutional ethics committees. All patients provided written informed consent.

Patient Population

Patients aged 18 years or older with symptom onset within 24 hours and ST-segment elevation of at least 1 mm in 2 or more contiguous leads, true posterior MI, or new left bundle branch block were eligible for randomization in the presence of at least 1 culprit lesion within the infarct vessel. There was no limit regarding the number of treated lesions, vessels, or complexity. Exclusion criteria were presence of mechanical complications of acute MI, known allergy to any study medication, use of vitamin K antagonists, planned surgery unless dual antiplatelet therapy could be maintained throughout the perisurgical period, history of bleeding diathesis or known coagulopathy, pregnancy, participation in another trial before reaching the primary end point, inability to provide informed consent, and noncardiac comorbid conditions with life expectancy of less than 1 year. Patients were recruited between September 19, 2009, and January 25, 2011, in 11 centers throughout Europe and Israel (Denmark [n=1], Israel [n=1], the Netherlands [n=1], Serbia [n=1], Switzerland [n=6], and the United Kingdom [n=1]).

Procedures

Randomization was performed via a web-based system after diagnostic angiography. The allocation sequence was computer generated in randomly varying blocks of 2, 4, and 6, and stratified by center. Patients were randomly allocated on a 1:1 basis to treatment with stents eluting biolimus from a biodegradable polylactic acid polymer (BioMatrix, Biosensors Europe SA) or bare-metal stents of otherwise identical design (Gazelle, Biosensors Europe SA).

Both stent types were available in diameters of 2.25, 2.50, 2.75, 3.00, 3.50, and 4.00 mm and in lengths of 8, 11, 14, 18, 24, and 28 mm. Before stent implantation, thrombus aspiration was recommended in all patients whenever aspiration was deemed technically feasible. Predilation of the culprit lesion was left to the discretion of the operator. Complete revascularization of all lesions within the infarct vessel had to be performed with the randomly allocated study stent. Nonculprit vessels were treated by default with biolimus-eluting stents at baseline and during follow-up and did not contribute to the primary end point. Staged procedures for the treatment of nonculprit vessels were permitted within 3 months with the uniform use of biolimus-eluting stent in all lesions.

Acetylsalicylic acid (≥250 mg) was administered before the procedure. In centers where prasugrel was available, an initial dose of 60 mg (including patients preloaded with clopidogrel) was administered followed up with a daily dose of 10 mg. If prasugrel was not available or contraindicated, clopidogrel was administered at a loading dose of 600 mg, followed up with a dose of 75 mg twice daily for 7 days, followed up with a maintenance dose of 75 mg once daily. Dual antiplatelet therapy was prescribed for the duration of at least 1 year in all patients. Unfractionated heparin was routinely administered with a minimal dose of 5000 IE or a dose of 70 to 100 IU/kg to maintain an activated clotting time of 250 seconds. Bivalirudin was administered at a dose of 0.75 mg/kg intravenously followed up with an infusion of 1.75 mg/kg per hour during the duration of the procedure. The use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the operator.

We assessed creatinine kinase, creatinin kinase-MB, and troponin at admission and thereafter every 8 hours until the peak creatinine kinase had been reached. A 12-lead electrocardiogram was performed before the procedure, within 24 hours after the procedure, before discharge, and in case of recurrent signs of ischemia.

Data Management

Independent study monitors verified source data according to a prespeci-

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fied monitoring plan.[15] Data were stored in a central database (Cardiobase, Clinical Trials Unit, and Department of Cardiology, Bern University Hospital, Switzerland, and 2mT, Ulm, Germany). Follow-up appointments were scheduled at 30 days and 1 year, and patients were questioned about the occurrence of angina, any adverse events, hospitalization, and cardiovascular medication intake. All serious adverse events were submitted to Clinical Trials Unit, University of Bern, Bern, Switzerland, in a blinded fashion. Any death, reinfarction, revascularization, stent thrombosis, cerebrovascular accident, and bleeding event was independently adjudicated by a blinded clinical event committee. An independent data and safety monitoring board blinded to treatment groups periodically reviewed all event information and compared safety outcomes between groups.

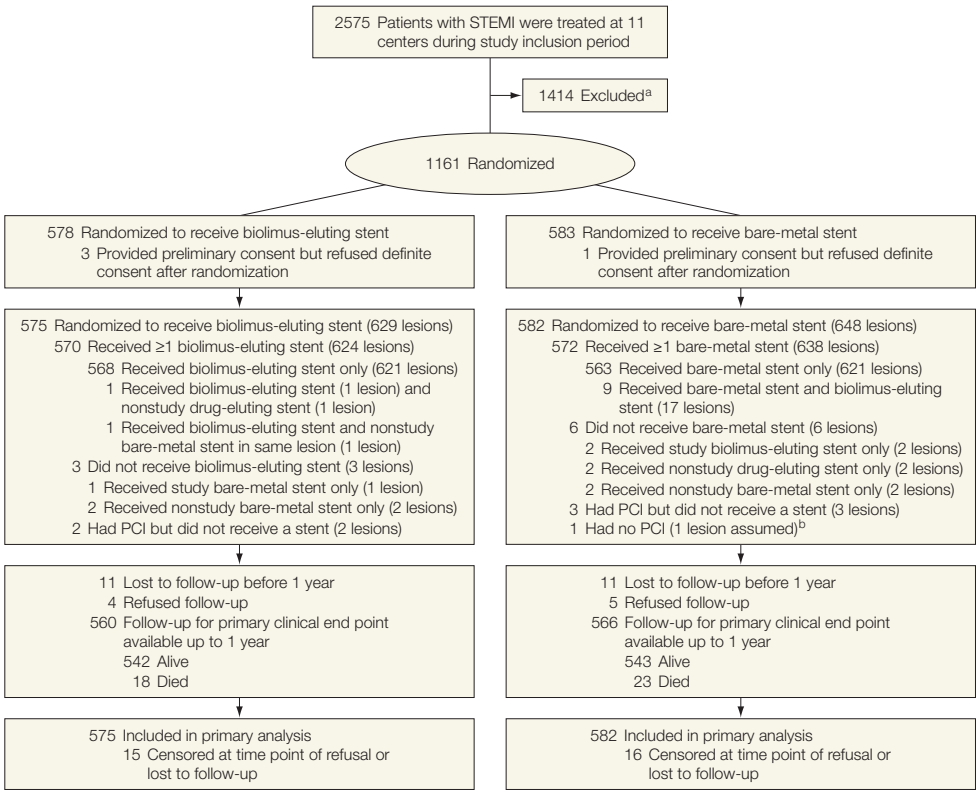
Angiograms were centrally assessed by the core laboratory at Bern University Hospital by blinded personnel. The bare-metal stent and biodegradable polymer-based drug-eluting stent were indistinguishable on angiography. The core laboratory assessment encompassed quantitative coronary angiography using dedicated software (XAangio XA 7.1, Medis) and the assessment of the SYNTAX MI score,[16] and thrombolysis in MI (TIMI) flow grade.

Study End Points

The prespecified primary end point was the device-oriented composite of cardiac death, target vessel–related reinfarction, and ischemia-driven target-lesion revascularization at 1 year. Secondary end points included the patient-oriented composite of death, any reinfarction, and any revascularization, as well as target vessel–related reinfarction and any revascularization (percutaneous and surgical procedures), cardiac death, all-cause mortality, Q-wave and non–Q-wave reinfarction, stroke, stent thrombosis according to the definitions of the Academic Research Consortium, and device and lesion success. Detailed definitions of all primary and secondary end points were reported elsewhere.[15]

Target-lesion revascularization was defined as a repeated revascularization due to a stenosis within the stent or within the 5-mm borders proximal or distal to the stent. Target-vessel revascularization was defined as any repeat PCI or surgical bypass of any segment within the entire major coronary vessel proximal and distal to a target le-

Figure 1. Trial Profile and Flow of Patients



STEMI indicates ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention.
[a] A total of 2575 patients underwent primary PCI for treatment of STEMI at 11 international sites during the inclusion period. No reliable data for patients assessed for eligibility are available.
[b] One patient treated with bare-metal stent did not undergo PCI and was assumed to have 1 lesion.

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sion, including upstream and downstream branches and the target lesion itself. A revascularization was considered ischemia-driven if the diameter stenosis of the treated lesion was at least 50% on the basis of quantitative coronary angiography in the presence of ischemic signs or symptoms, or if there was a diameter stenosis of at least 70% irrespective of the presence of ischemic signs or symptoms.

Table 1. Baseline Clinical Characteristics of Patients Receiving Either Biolimus-Eluting Stents or Bare-Metal Stents[a]

Characteristics	Biolimus-Eluting Stents (n = 575)	Bare-Metal Stents (n = 582)
Patients		
Age, mean (SD), y	60.7 (11.6)	60.4 (11.9)
Male sex	463 (80.5)	455 (78.2)
BMI, mean (SD)	27.3 (4.5)	27.2 (4.0)
Cardiovascular risk factors		
Diabetes	84 (14.6)	90 (15.5)
Hypertension	279 (48.5)	265 (45.5)
Hyperlipidemia	324 (56.6)	328 (56.7)
Current smoker	272 (47.9)	301 (52.3)
Family history of CAD	193 (34.3)	179 (31.3)
Renal failure	79 (14.1)	86 (15.1)
Previous MI	31 (5.4)	32 (5.5)
Previous PCI	19 (3.3)	27 (4.6)
Previous CABG surgery	10 (1.7)	4 (0.7)
Laboratory findings		
Anemia	87 (15.6)	79 (13.9)
Thrombocytopenia	22 (4.0)	30 (5.3)
Clinical presentation		
Time to balloon inflation, median (IQR), min		
From symptom onset	232 (164-380)	236 (163-400)
0-6	421 (73.2)	421 (72.6)
6-12	109 (19.0)	100 (17.2)
12-24	45 (7.8)	59 (10.2)
From hospital admission	44 (32-70)	44 (32-74)
Killip class II, III, or IV	40 (7.0)	37 (6.4)
Resuscitation before hospital arrival	16 (2.8)	9 (1.5)
LVEF, mean (SD), %[b]	49 (11)	50 (10)
Electrocardiographic localization of MI		
Anterior	211 (36.9)	213 (36.9)
Lateral	18 (3.1)	13 (2.2)
Inferior	236 (41.3)	249 (43.1)
Posterior	29 (5.1)	23 (4.0)
Inferior and posterior	78 (13.6)	80 (13.8)
Right ventricular MI	52 (9.1)	55 (9.5)
Lesion complexity[c]		
Bifurcation lesion	52 (9.0)	49 (8.4)
Small vessel	74 (12.9)	79 (13.7)
Long lesion	204 (35.7)	183 (31.7)
SYNTAX MI score, mean (SD)[d]	15.1 (8.2)	14.8 (8.1)

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; CABG, coronary artery bypass graft; CAD, coronary artery disease; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

[a] Data are expressed as No. (%) unless otherwise specified. Anemia was defined as a hemoglobin concentration of less than 120 g/L for women and less than 130 g/L for men, according to the definition of the World Health Organization. Thrombocytopenia was defined as less than 150 000 platelets/μL. Renal failure was defined as glomerular filtration rate of less than 60 mL/min.

[b] Left ventricular function as assessed by angiography or by echocardiography, in case angiography was not available.

[c] Small vessel indicates reference vessel diameter of 2.5 mm or less and long lesion is a lesion length of 20 mm or more.

[d] SYNTAX score was assessed before recanalization according to Magro et al.[16] The SYNTAX score provides a numerical score summarizing a comprehensive angiographic assessment of the entire coronary artery tree, with higher scores indicating increasing complexity of CAD. In the absence of significant CAD (absence of a stenosis ≥50% in a vessel with a reference diameter ≥1.5 mm), the score amounts to 0. The score increases with more complex CAD. The highest score as reported in the SYNTAX trial amounted to 84.[17]

Statistical Analysis

Our trial was powered for superiority on the primary clinical end point at 1 year. On the basis of the HORIZON-AMI[6] and LEADERS trials,[13] we assumed an incidence of major adverse cardiac events of 14% within 1 year in the bare-metal stent group and a 40% relative risk reduction associated with the biolimus-eluting stent, corresponding to a rate of major adverse cardiac events of 8.4%. Enrollment of 1064 patients would therefore provide 80% power to detect a relative risk of 0.60 with 2-sided $\alpha = .05$.

All analyses were performed according to the intention-to-treat principle, with inclusion of all randomized patients in the analysis according to the group they were originally allocated. Cox proportional hazards regression models were used to compare clinical outcomes between the groups, with patients censored at the time of their last known contact. Correspondingly, we constructed time-to-event curves using Kaplan-Meier estimates and the proportional hazards assumption was tested and met in each case.

Categorical variables are reported as numbers and percentages, and groups are compared using χ^2 or Fisher exact tests (low counts). Continuous variables are reported as means ±standard deviations, and groups are compared using unpaired *t* tests. Times are reported as medians (interquartile ranges [IQRs]), and groups are compared using Wilcoxon Mann-Whitney rank sum test.

We prespecified stratified analyses of the primary end point at 1 year according to age, sex, diabetes, renal failure, lesion length, and vessel size. In addition, we performed post hoc analyses stratified according to left ventricular ejection fraction, left anterior descending artery lesion localization, preprocedural TIMI flow, time from pain onset to balloon time, thrombus aspiration, and multivessel treatment. All stratified analyses were accompanied by tests for

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interaction between stent type and subgroup. There were positive treatment × patient characteristics interactions for age and sex. In view of a correlation between age and sex ($P<.001$), we explored treatment × age interactions separately in men and women. All analyses were performed with STATA version 12.1 (StataCorp) and 2-sided $P<.05$ was considered statistically significant.

RESULTS

A total of 1161 patients were randomly assigned to receive biolimus-eluting stents with biodegradable polymer (578 patients) or bare-metal stents (583 patients). Three patients allocated to the biolimus-eluting stent and 1 patient allocated to the bare-metal stent did not confirm their initial written consent and had to be excluded, resulting in 575 patients with 629 infarct-vessel lesions randomly assigned to biolimus-eluting stents and 582 patients with 648 infarct-vessel lesions randomly assigned to bare-metal stents for final analyses (FIGURE 1). A total of 31 patients refused or were lost to follow-up at a median of 31 days in the biolimus-eluting stent group and 32 days in the bare-metal stent group.

Baseline medications and clinical, angiographic, and procedural characteristics were similar in both groups (TABLE 1, TABLE 2, and TABLE 3). The mean (SD) age of patients was 60.6 (11.8) years and 79% were men. The median (IQR) time from symptom onset to balloon inflation was 234 (164-386) minutes and from hospital admission to balloon inflation was 44 (32-72) minutes. Thrombus aspiration was performed in 62% of patients and 47% received a glycoprotein IIb/IIIa antagonist during the procedure. No differences were observed in lesion complexity between both groups including the SYNTAX MI score (mean, 15; SD, 8). At discharge, 43% of patients received prasugrel and 57% of patients received clopidogrel. The use of dual antiplatelet therapy was high and balanced in both treatment groups throughout the entire follow-up period up to 1 year (Table 2).

Clinical outcomes during follow-up are shown in TABLE 4. At 1 year, the primary end point of major adverse cardiac events (cardiac death, target vessel–related reinfarction, and ischemia-driven target-lesion revascularization) occurred in 4.3% of patients receiving biolimus-eluting stents and 8.7% of patients receiving bare-metal stents (hazard ratio [HR], 0.49; 95% CI, 0.30-0.80; $P=.004$) (FIGURE 2A). For cardiac death alone, the percentages were smaller (2.9% of patients received biolimus-eluting stents and 3.5% of patients received bare-metal stents; HR, 0.81; 95% CI, 0.42-1.56; $P=.53$) (Figure 2B). The treatment effect in favor of patients receiving biolimus-eluting stents was attributable to both a lower risk of target vessel–related reinfarction (0.5% vs 2.7%; HR, 0.20; 95% CI, 0.06-0.69; $P=.01$) (Figure 2C) and ischemia-driven target-lesion revascularization (1.6% vs 5.7%; HR, 0.28; 95% CI, 0.13-0.59; $P<.001$) (Figure 2D). Differences between stent types with respect to the primary outcome emerged early and continued throughout the study period.

Among patients treated with biolimus-eluting stents, 3 target vessel–related reinfarctions resulted from defi-

Table 2. Medication Use Among Patients Receiving Either Biolimus-Eluting Stents or Bare-Metal Stents[a]

Medications	Biolimus-Eluting Stents (n = 575)	Bare-Metal Stents (n = 582)
During primary PCI		
Unfractionated heparin	510 (88.7)	523 (89.9)
Bivalirudin	74 (12.9)	67 (11.5)
Low molecular weight heparin	19 (3.3)	19 (3.3)
Glycoprotein IIb/IIIa antagonists	276 (48.0)	266 (45.7)
Loading dose of clopidogrel and prasugrel		
None	2 (0.3)	6 (1.0)
Clopidogrel only (600 mg)	320 (55.8)	330 (57.0)
Prasugrel only (60 mg)	104 (18.2)	110 (19.0)
Both	126 (22.0)	128 (22.1)
At discharge		
Acetylsalicylic acid	568 (99.8)	576 (99.7)
Clopidogrel	323 (56.8)	327 (56.6)
Prasugrel	245 (43.1)	248 (42.9)
Any dual antiplatelet therapy	567 (99.6)	574 (99.3)
β-Blockers	491 (86.3)	476 (82.4)
ACE inhibitors or receptor blockers	410 (72.1)	411 (71.1)
Statins	559 (98.2)	571 (98.8)
At 30 d		
Acetylsalicylic acid	555 (99.3)	565 (99.1)
Clopidogrel	323 (57.6)	322 (56.5)
Prasugrel	241 (43.0)	245 (43.0)
Any dual antiplatelet therapy	554 (98.9)	559 (98.1)
β-Blockers	487 (87.0)	482 (84.6)
ACE inhibitors or receptor blockers	396 (70.7)	401 (70.4)
Statins	534 (95.5)	550 (96.5)
At 1 y		
Acetylsalicylic acid	529 (97.6)	524 (96.3)
Clopidogrel	284 (52.4)	266 (48.9)
Prasugrel	214 (39.6)	222 (40.8)
Any dual antiplatelet therapy	488 (90.0)	478 (87.9)
β-Blockers	435 (80.4)	428 (78.8)
ACE inhibitors or receptor blockers	330 (61.0)	338 (62.2)
Statins	496 (91.7)	506 (93.2)

Abbreviations: ACE, angiotensin-converting enzyme; PCI, percutaneous coronary intervention.
[a]Data are expressed as No. (%). Two-sided P values were calculated using χ^2 or Fisher exact texts (all $P \geq .07$).

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Table 3. Angiographic and Procedural Characteristics of Patients Receiving Either Biolimus-Eluting Stents or Bare-Metal Stents[a]

Characteristics	Biolimus-Eluting Stents (n = 629)	Bare-Metal Stents (n = 648)	*P* Value
Lesions			
Treated in infarct vessel, No.	629	648[b]	
Treated per patient, mean (SD)	1.1 (0.3)	1.1 (0.4)	.61
>2 treated in infarct vessel	49 (8.5)	59 (10.1)	.34
Infarct vessel localization			
Left main coronary artery	2 (0.3)	1 (0.2)	.74
Left anterior descending artery	226 (39.3)	230 (39.6)	
Left circumflex artery	82 (14.3)	90 (15.5)	
Right coronary artery	264 (45.9)	259 (44.6)	
Saphenous vein graft	1 (0.2)	1 (0.2)	
Baseline TIMI flow			
0 or 1	437 (69.6)	423 (65.6)	.31
2	81 (12.9)	95 (14.7)	
3	110 (17.5)	127 (19.7)	
Baseline quantitative coronary angiographic data			
Reference vessel diameter, mm			
Mean (SD)	3.04 (0.47)	3.01 (0.46)	.17
Median (IQR)	3.02 (2.72-3.33)	2.97 (2.67-3.29)	.17
Minimum lumen diameter, mm			
Mean (SD)	0.42 (0.59)	0.44 (0.57)	.47
Median (IQR)	0 (0-0.80)	0 (0-0.88)	.41
Diameter stenosis, %			
Mean (SD)	86.44 (18.37)	85.24 (18.37)	.25
Median (IQR)	100.0 (72.6-100.0)	100.0 (70.4-100.0)	.21
Lesion length, mm			
Mean (SD)	18.19 (9.73)	17.77 (9.57)	.44
Median (IQR)	15.46 (11.79-21.97)	15.63 (11.52-21.30)	.46
Primary PCI procedure			
No. of stents per lesion, mean (SD)	1.32 (0.61)	1.26 (0.60)	.16
Type of stent[c]			
Study biolimus-eluting	623 (99.4)	12 (1.9)	<.001
Other drug-eluting	0	2 (0.3)	.50
Study bare-metal	1 (0.2)	633 (98.3)	<.001
Other bare-metal	4 (0.6)	2 (0.3)	.44
No stent implanted	2 (0.3)	4 (0.6)	.69
Stent length per lesion, mean (SD), mm	25.2 (12.7)	24.1 (12.3)	.10
Stent diameter per lesion, mean (SD), mm	3.2 (0.4)	3.2 (1.1)	.42
Direct stenting	236 (37.6)	240 (37.3)	.89
Maximal balloon pressure, mean (SD), atm	15.2 (3.5)	15.1 (3.4)	.50
Overlapping stents	148 (23.6)	120 (18.7)	.03
Thrombus aspiration	350 (60.9)	374 (64.4)	.22
Intraaortic balloon counterpulsation	14 (2.4)	15 (2.6)	.88
Intravenous vasopressors	18 (3.1)	19 (3.3)	.90
TIMI flow			
0 or 1	3 (0.5)	3 (0.5)	.70
2	25 (4.0)	32 (5.0)	
3	601 (95.5)	611 (94.6)	
Postprocedural QCA, mean (SD)			
Reference vessel diameter, mm	3.06 (0.50)	3.02 (0.48)	.07
Minimum lumen diameter, mm	2.59 (0.50)	2.56 (0.48)	.19
Diameter stenosis, %	15.53 (8.35)	15.22 (7.81)	.49

Abbreviations: IQR, interquartile range; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography; TIMI, thrombolysis in myocardial infarction.

[a] Data are expressed as No. (%) unless otherwise specified. Two-sided *P* values were calculated using a χ^2 test for categorical variables and using *t* test for continuous variables.

[b] Includes 1 patient randomly allocated to bare-metal stents who had no PCI and where 1 lesion was assumed; 2 patients randomly allocated to biolimus-eluting stents and 1 patient randomly allocated to bare-metal stents did not have QCA due to missing angiography cardiovascular disease.

[c] In 1 patient who was randomly allocated to the biolimus-eluting stent group, a biolimus-eluting stent and a bare-metal stent were implanted within the same lesion; and in 5 patients who were randomly allocated to the bare-metal stent group, a biolimus-eluting stent and a bare-metal stent were implanted within the same lesion.

nite stent thrombosis in 2 patients and restenosis in 1 patient. Among patients treated with bare-metal stents, 15 target vessel–related reinfarctions resulted from definite stent thrombosis in 10 patients, restenosis in 4 patients, and spontaneous MI in 1 patient. The risk of target vessel–related reinfarction associated with stent thrombosis or restenosis was lower among patients treated with biolimus-eluting stents vs bare-metal stents (HR, 0.22; 95% CI, 0.06-0.75; *P*=.02).

The findings for the primary end point were consistent across stratified analyses for diabetes, renal failure, left ventricular ejection fraction, left anterior descending artery, thrombus aspiration, time from pain onset to balloon inflation, multivessel treatment, small vessel disease, and lesion length (FIGURE 3). A significant interaction with stent type was observed for age and sex. Men were on average 6.5 years younger than women. In exploratory analyses, we found HRs below the point estimate of the primary end point in the overall cohort (HR=0.49) in women younger than 65 years (HR, 0.40; 95% CI, 0.80-1.95), in men younger than 65 years (HR, 0.25; 95% CI, 0.10-0.61), and in men 65 years or older (HR, 0.43; 95% CI, 0.16-1.11), but not in women 65 years or older (HR, 1.89; 95% CI, 0.65-5.54).

At 1 year, rates of definite stent thrombosis amounted to 0.9% among patients receiving biolimus-eluting stents and 2.1% among patients receiving bare-metal stents (HR, 0.42; 95% CI, 0.15-1.19; *P*=.10). Five patients treated with biolimus-eluting stents experienced definite stent thrombosis while receiving dual antiplatelet therapy, whereas 12 patients treated with bare-metal stents experienced definite stent thrombosis with 11 patients receiving dual antiplatelet therapy and 1 patient not taking acetylsalicylic acid and clopidogrel. We observed no differences in all-cause and cardiac mortality between the groups at 1 year. In addition to the device-oriented primary outcome measure, we recorded a lower risk of the comprehensive patient-oriented composite of death,

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any reinfarction, and any revascularization in favor of biolimus-eluting stents (8.4% vs 12.2%; HR, 0.68; 95% CI, 0.47-0.98; *P*=.04).

Staged procedures were performed after a median duration of 12.0 days (IQR, 4.0-41.5 days) among patients treated with biolimus-eluting stents and after a median duration of 6 days (IQR, 3-33 days; *P*=.25). A total of 1 ischemia-driven target-lesion revascularization was associated with a staged procedure in the biolimus-eluting stent group compared with 2 ischemia-driven target-lesion revascularization events in the bare-metal stent group.

Table 4. Clinical Outcomes at 1 Year of Patients Receiving Either Biolimus-Eluting Stents or Bare-Metal Stents[a]

Clinical Outcomes	No. (%) of Patients: Biolimus-Eluting Stents (n = 575)	No. (%) of Patients: Bare-Metal Stents (n = 582)	Hazard Ratio (95% CI)	*P* Value
Death	18 (3.2)	23 (4.1)	0.79 (0.43-1.47)	.46
Cardiac death	16 (2.9)	20 (3.5)	0.81 (0.42-1.56)	.53
Reinfarction	11 (2.0)	21 (3.7)	0.53 (0.25-1.09)	.08
Q-wave	2 (0.4)	7 (1.2)	0.29 (0.06-1.39)	.12
Non–Q-wave	9 (1.6)	14 (2.5)	0.65 (0.28-1.50)	.31
Target vessel–related reinfarction	3 (0.5)	15 (2.7)	0.20 (0.06-0.69)	.01
Q-wave	1 (0.2)	7 (1.2)	0.14 (0.02-1.17)	.07
Non–Q-wave	2 (0.4)	8 (1.4)	0.25 (0.05-1.19)	.08
Cardiac death or target vessel–related reinfarction	19 (3.4)	32 (5.7)	0.60 (0.34-1.05)	.07
Any target-lesion revascularization	9 (1.6)	34 (6.0)	0.26 (0.13-0.55)	<.001
Ischemia-driven target-lesion revascularization	9 (1.6)	32 (5.7)	0.28 (0.13-0.59)	<.001
Any target-vessel revascularization	11 (2.0)	37 (6.5)	0.30 (0.15-0.58)	<.001
Ischemia-driven target-vessel revascularization	11 (2.0)	35 (6.2)	0.31 (0.16-0.62)	<.001
Major adverse cardiac events[b]	24 (4.3)	49 (8.7)	0.49 (0.30-0.80)	.004
Death, any reinfarction, any revascularization	47 (8.4)	69 (12.2)	0.68 (0.47-0.98)	.04
Stroke	6 (1.1)	4 (0.7)	1.52 (0.43-5.40)	.51
Stent thrombosis				
Definite	5 (0.9)	12 (2.1)	0.42 (0.15-1.19)	.10
Definite or probable	14 (2.5)	21 (3.7)	0.67 (0.34-1.32)	.25

[a] Hazard ratios are derived from Cox proportional hazard regression models. *P* values are 2-sided from superiority testing with a χ^2 test.
[b] Composite of cardiac death, target vessel–related reinfarction, and ischemia-driven target-lesion revascularization.

COMMENT

In this randomized, multicenter, assessor-blinded trial in patients with STEMI, compared with the use of bare-metal stents, the use of biolimus-eluting stents with a biodegradable polymer was associated with a significant 4.4% absolute reduction and 51% relative reduction in the risk of major adverse cardiac events at 1 year, which prevents 42 events per 1000 patients treated with biolimus-eluting stents compared with bare-metal stents at 1 year. Findings were also robust for the more comprehensive patient-oriented composite of any death, reinfarction, or revascularization. Accordingly, our results suggest better clinical outcomes in terms of major adverse cardiac events of a stent releasing biolimus from a biodegradable polymer compared with a bare-metal stent for the treatment of patients with STEMI.

In the single largest trial enrolling patients with STEMI,[6] paclitaxel-eluting stents resulted in a 41% lower risk of target-lesion revascularization compared with bare-metal stents. In our trial, biolimus-eluting stents were associated with a 4.1% absolute reduction and a 72% relative reduction in the risk of ischemia-driven target-lesion revascularization compared with bare-metal stents. This risk reduction is notable as repeat revascularizations were due to recurrent ischemia in the absence of protocol-mandated angiographic follow-up before assessment of the primary end point at 1 year. Rates of revascularization with the biolimus-eluting stent in our study were lower than in the LEADERS trial,[13] which enrolled patients with a broad spectrum of indications and lesions. Explanations for this finding include the larger reference vessel diameter in vessels causing acute MI (3.0 vs 2.6 mm) and the lack of routine angiographic follow-up, as well as less ischemia in vessels subtending previously infarcted myocardium.[13]

Despite a similar risk profile and mortality in our study compared with patients with STEMI enrolled into previous large-scale randomized trials,[5,6] we observed a lower absolute rate of repeat revascularization in both treatment groups. This observation is consistent with a recent trial comparing newer-generation everolimus-eluting stents with bare-metal stents among patients with STEMI[18] and is potentially related to improved lesion preparation due to thrombus aspiration[19] and more potent antithrombotic medications, such as prasugrel,[20] reducing the risk of stent thrombosis–related revascularization. Notwithstanding, the absolute risk reduction of 4.1% in our trial means that 24 patients need to be treated with biolimus-eluting stents to prevent 1 major adverse cardiac event.

Differences in favor of biolimus-eluting stents over bare-metal stents in our study with respect to the primary end point were not limited to efficacy but also driven by an 80% lower risk of target vessel–related reinfarction. This difference in safety has not been observed in previous randomized trials comparing drug-eluting and bare-metal stents among patients with STEMI,[5,6,21-26] but is consistent with the findings of a recent meta-analysis[12] reporting a lower risk of reinfarction during the first year with a number needed

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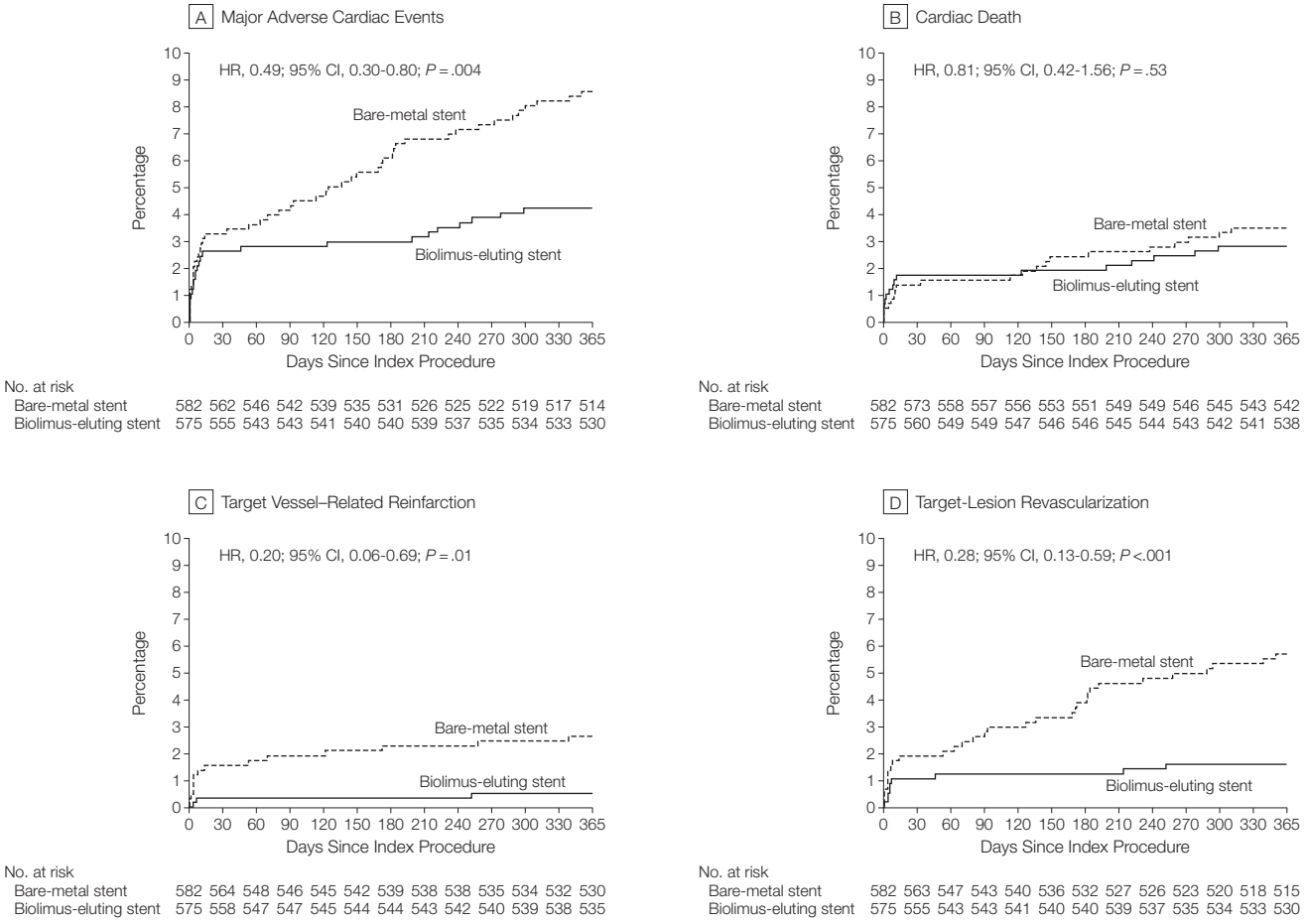
to treat of 79 compared with 45 in our study.

In exploring the mechanism for the lower risk of target vessel–related reinfarction, we observed that the device-related adverse events definite stent thrombosis or target-lesion revascularization due to restenosis were responsible for target vessel–related reinfarction in 17 of 18 cases and were less common among patients receiving biolimus-eluting stents than patients receiving bare-metal stents (3 vs 14, respectively; $P = .01$). In contrast with most previous trials among patients with STEMI, dual antiplatelet therapy was balanced between patients receiving biolimus-eluting stents and those receiving bare-metal stents throughout the entire study period rendering differences in antiplatelet therapy unlikely as an explanation for the differential in target vessel–related reinfarction.

We found positive interactions between stent type and age and sex. Because age and sex were correlated, we further explored these interactions and found estimated HRs below the point estimate of the primary end point for the overall cohort (HR = 0.49) in younger women and men irrespective of age, but not in women aged 65 years or older. It is unclear whether our results reflect a lack of benefit in women or in those aged 65 years or older, or in the subgroup of elderly women only. We are unaware of biological mechanisms that might explain interactions with age or sex, and in view of the lack of mechanisms and the large number of stratified analyzes, chance should also be considered as an explanation of our findings.

A numerically lower rate of definite stent thrombosis was observed (0.9% vs 2.1%, $P = .10$) with the use of biolimus-eluting stents vs bare-metal stents at 1 year, with most events occurring during the peri-interventional period. Although this finding has to be interpreted cautiously, a similar statistically nonsignificant reduction at up to 1 year among patients with STEMI has been observed in a recent meta-

Figure 2. Kaplan-Meier Curves for Major Adverse Cardiac Events, Cardiac Death, Target Vessel–Related Reinfarction, and Ischemia-Driven Target-Lesion Revascularization Among Patients Randomized to Receive Either the Biolimus-Eluting Stent or the Bare-Metal Stent



Major adverse cardiac events included a composite of cardiac death, target vessel–related reinfarction, and ischemia-driven target-lesion revascularization. *P* values are 2-sided from Cox proportional hazards regression models χ^2 test. HR indicates hazard ratio.

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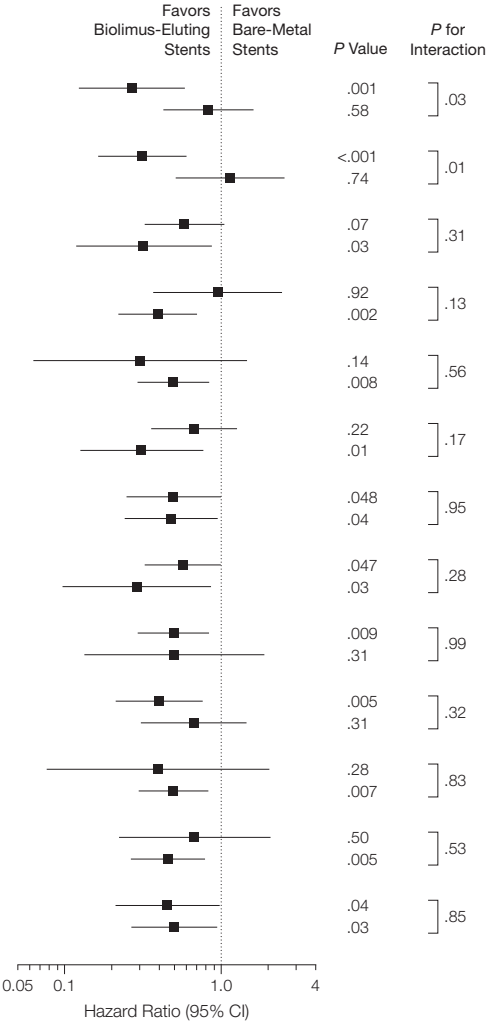
analysis[12] comparing early generation drug-eluting stents with bare-metal stents. Moreover, a significant reduction in the risk of stent thrombosis has been reported in the EXAMINATION trial[18] comparing newer-generation everolimus-eluting stents with bare-metal stents (0.5% vs 1.9%, $P=.01$). Experimental data indicate lower thrombogenicity of drug-eluting stents compared with bare-metal stents suggesting a possible thromboresistant effect of polymer coatings during the immediate peri-interventional period.[27] The latter may be particularly important among patients with STEMI who carry a higher baseline risk of stent thrombosis due to a large thrombus burden[9] and increased platelet activation.[28]

In addition, biolimus is the limus analogue with the highest lipophilicity used for drug elution on currently available stent platforms.[29] Among patients with STEMI, the acute coronary lesions predominantly consist of lipid-rich, ruptured plaques with large necrotic cores.[30] Theoretically, the increased lipophilicity of the drug biolimus may provide a more rapid and homogeneous drug distribution, potentially leading to a more potent anti-inflammatory and antithrombotic local effect. However, this hypothesis requires validation in dedicated studies assessing the properties of various drugs used for elution on drug-eluting stents in the presence of lipid-rich plaques.

Figure 3. Subgroup Analyses of the 1-Year Rates of Major Adverse Cardiac Events Among Patients Randomized to Receive Either the Biolimus-Eluting Stent or the Bare-Metal Stent

	Major Adverse Cardiac Events, No.		Major Adverse Cardiac Events, Total No.					
	Biolimus-Eluting Stents	Bare-Metal Stents	Biolimus-Eluting Stents	Bare-Metal Stents	Hazard Ratio (95% CI)	*P* Value	*P* for Interaction
Age, y							
<65	8	30	370	381	0.27 (0.12-0.59)	.001	.03
≥65	16	19	205	201	0.83 (0.43-1.61)	.58	
Sex							
Male	12	37	463	455	0.31 (0.16-0.60)	<.001	.01
Female	12	12	112	127	1.14 (0.51-2.55)	.74	
BMI							
<30	18	30	447	441	0.58 (0.33-1.05)	.07	.31
≥30	5	17	122	136	0.32 (0.12-0.87)	.03	
Diabetes							
Yes	8	9	84	90	0.95 (0.37-2.47)	.92	.13
No	16	40	491	492	0.39 (0.22-0.70)	.002	
Renal failure							
Yes	2	7	79	86	0.30 (0.06-1.46)	.14	.56
No	21	42	483	483	0.49 (0.29-0.83)	.008	
LVEF, %							
<50	17	22	248	215	0.67 (0.36-1.26)	.22	.17
≥50	6	21	290	322	0.31 (0.13-0.77)	.01	
Infarct lesion in left anterior descending artery							
Yes	12	24	238	239	0.50 (0.25-0.99)	.048	.95
No	12	25	337	342	0.48 (0.24-0.96)	.04	
Preprocedural TIMI flow							
0-1	20	33	430	407	0.57 (0.33-0.99)	.047	.28
2-3	4	16	144	172	0.29 (0.10-0.86)	.03	
Pain onset to balloon, h							
0-12	21	41	530	521	0.50 (0.29-0.84)	.009	.99
12-24	3	8	45	59	0.50 (0.13-1.89)	.31	
Thrombus aspiration							
Yes	13	34	350	374	0.40 (0.21-0.76)	.005	.32
No	11	15	225	207	0.67 (0.31-1.46)	.31	
Multivessel treatment							
Yes	2	5	32	35	0.41 (0.08-2.10)	.28	.83
No	22	44	543	546	0.50 (0.30-0.83)	.007	
Reference vessel diameter, mm							
≤2.50	5	8	74	79	0.68 (0.22-2.07)	.50	.53
>2.50	19	41	498	501	0.46 (0.27-0.79)	.005	
Lesion length, mm							
≥20	10	19	204	184	0.46 (0.21-0.98)	.04	.85
<20	14	30	368	396	0.50 (0.27-0.95)	.03	



BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); LVEF, left ventricular ejection fraction; TIMI, thrombolysis in myocardial infarction. Two patients randomized to receive the biolimus-eluting stent and 1 patient randomized to receive the bare-metal stent could not be included in the stratified analyses for lesion characteristics (reference vessel diameter and lesion length) due to missing angiography.

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Our results have to be interpreted in view of the following limitations. First, the trial indicated superiority on the primary composite outcome but was not powered to address individual components of efficacy or safety. Moreover, observed event rates were lower than anticipated. In view of the size of the observed treatment effect and results of previous trials, we consider it unlikely that estimates of efficacy would substantially differ in a larger patient cohort. The inclusion of safety outcomes in the primary composite outcome is meaningful as cardiac death or target vessel–related reinfarction may be device related. Event rates of cardiac death or target vessel–related reinfarction were of similar magnitude as ischemia-driven target-lesion revascularization in our trial providing a similar weight of efficacy and safety parameters within the composite end point.

Second, the biolimus-eluting stent used in our study is currently not approved by the US Federal Drug Administration and not considered as standard of care in the United States. The biolimus-eluting stent has been shown to be noninferior compared with the sirolimus-eluting CYPHER stent in a randomized trial of 1707 all-comer patients for the composite clinical end point of major adverse events at 9 months and 4 years.[13,14] On the basis of these data, the biolimus-eluting stent is recommended as one of a few drug-eluting stents for clinical use in the European guidelines on myocardial revascularization.[31] It remains to be determined how this stent platform performs compared with newer-generation durable polymer-based drug-eluting stents. Similarly, the optimal duration of dual antiplatelet therapy after implantation of biolimus-eluting stents with a biodegradable polymer has not been established.

Third, although our trial had very few exclusion criteria, the results apply only to patients with characteristics similar to those enrolled. Patients who were unable to provide written informed consent before the procedure had to be excluded from participation in this trial introducing an element of selection bias. Because no reliable data for reasons leading to patient exclusion were collected, we cannot determine the proportion of patients excluded due to poor clinical condition and those refusing participation in the trial.

Fourth, the P2Y12 inhibitor prasugrel was administered instead of clopidogrel in 40% of patients and may have contributed to the low overall event rates in our study. Although the use of prasugrel was higher than in previous trials comparing drug-eluting stents with bare-metal stents among patients with STEMI, it conforms to the recommendations of the American College of Cardiology/American Heart Association guidelines for the management of STEMI and reflects contemporary practice.

Fifth, our study does not address late events beyond 1 year. However, in a previous study,[14] biolimus-eluting stents were shown to reduce the risk of stent thrombosis beyond 1 year by 80% compared with early generation sirolimus-eluting stents providing support for the improved long-term biocompatibility of drug-eluting stents with biodegradable polymer coatings.

In conclusion, compared with a bare-metal stent, the use of a biolimus-eluting stent with a biodegradable polymer resulted in a lower rate of the composite of major adverse cardiac events at 1 year among patients with STEMI undergoing primary PCI.

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Online-Only Material: The Author Video Interview is available at http://www.jama.com.

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