Original Investigation

Three vs Twelve Months of Dual Antiplatelet Therapy After Zotarolimus-Eluting Stents
The OPTIMIZE Randomized Trial

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IMPORTANCE The current recommendation is for at least 12 months of dual antiplatelet therapy after implantation of a drug-eluting stent. However, the optimal duration of dual antiplatelet therapy with specific types of drug-eluting stents remains unknown.

OBJECTIVE To assess the clinical noninferiority of 3 months (short-term) vs 12 months (long-term) of dual antiplatelet therapy in patients undergoing percutaneous coronary intervention (PCI) with zotarolimus-eluting stents.

DESIGN, SETTING, AND PATIENTS The OPTIMIZE trial was an open-label, active-controlled, 1:1 randomized noninferiority study including 3119 patients in 33 sites in Brazil between April 2010 and March 2012. Clinical follow-up was performed at 1, 3, 6, and 12 months. Eligible patients were those with stable coronary artery disease or history of low-risk acute coronary syndrome (ACS) undergoing PCI with zotarolimus-eluting stents.

INTERVENTIONS After PCI with zotarolimus-eluting stents, patients were prescribed aspirin (100-200 mg daily) and clopidogrel (75 mg daily) for 3 months (n = 1563) or 12 months (n = 1556), unless contraindicated because of occurrence of an end point.

MAIN OUTCOMES AND MEASURES The primary end point was net adverse clinical and cerebral events (NACCE; a composite of all-cause death, myocardial infarction [MI], stroke, or major bleeding); the expected event rate at 1 year was 9%, with a noninferiority margin of 2.7%. Secondary end points were major adverse cardiac events (MACE; a composite of all-cause death, MI, emergent coronary artery bypass graft surgery, or target lesion revascularization) and Academic Research Consortium definite or probable stent thrombosis.

RESULTS NACCE occurred in 93 patients receiving short-term and 90 patients receiving long-term therapy (6.0% vs 5.8%, respectively; risk difference, 0.17 [95% CI, −1.52 to 1.86]; P = .002 for noninferiority). Kaplan-Meier estimates demonstrated MACE rates at 1 year of 8.3% (128) in the short-term group and 7.4% (114) in the long-term group (HR, 1.12 [95% CI, 0.87-1.45]). Between 91 and 360 days, no statistically significant association was observed for NACCE (39 [2.6%] vs 38 [2.6%] for the short- and long-term groups, respectively; HR, 1.03 [95% CI, 0.66-1.60]), MACE (78 [5.3%] vs 64 [4.3%]; HR, 1.22 [95% CI, 0.88-1.70]), or stent thrombosis (4 [0.3%] vs 1 [0.1%]; HR, 3.97 [95% CI, 0.44-35.49]).

CONCLUSIONS AND RELEVANCE In patients with stable coronary artery disease or low-risk ACS treated with zotarolimus-eluting stents, 3 months of dual antiplatelet therapy was noninferior to 12 months for NACCE, without significantly increasing the risk of stent thrombosis.

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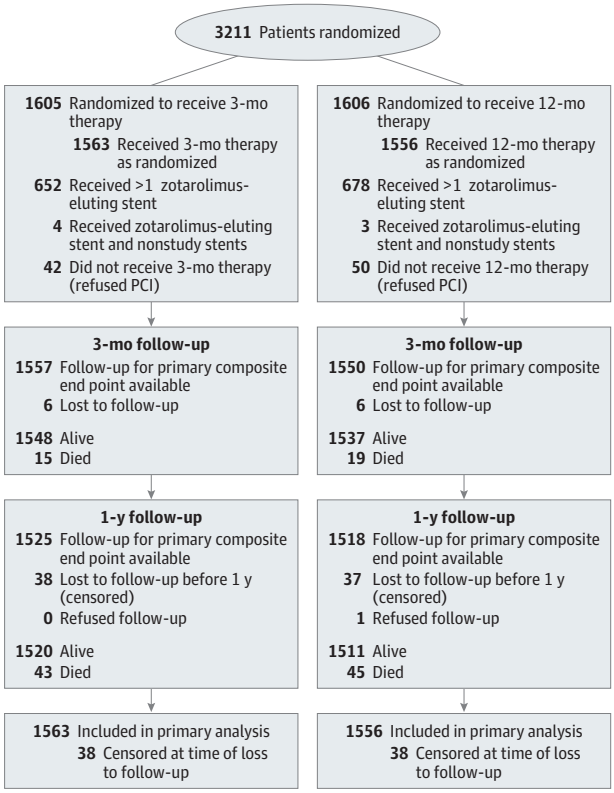
Original recommendations for patients receiving first-generation drug-eluting stents (sirolimus- and paclitaxel-eluting stents) specified that these patients also receive 3 to 6 months of dual antiplatelet therapy with aspirin and a thienopyridine.[1] However, limited trial data and retrospective analyses from real-world registries documented the occurrence of late and very late stent thrombosis and suggested that long-term (≥12 months) dual antiplatelet therapy might be beneficial.[2,3] Such outcomes, along with previous evidence obtained from studies of bare-metal stents, led to current guideline recommendations for prolonged dual antiplatelet therapy for all patients undergoing implantation of a drug-eluting stent.[2-6]

Several observational studies showed a significant association between discontinuation of dual antiplatelet therapy and the occurrence of thrombotic events in the first 6 or 12 months after implantation of a drug-eluting stent, but not afterward.[7-10] Most recently, a few randomized trials of modest size tested different durations of dual antiplatelet therapy (3 or 6 months vs 12 or 24 months) with multiple drug-eluting stents, and results did not show benefits favoring prolonged therapy.[11-13] Moreover, many shortcomings have been identified with prolonged dual antiplatelet therapy, including bleeding and cost issues.[14] At this point, even though recent trials comparing first- and second-generation drug-eluting stents have demonstrated superior safety profiles with newer devices (zotarolimus- and everolimus-eluting stents),[15-19] the optimal duration of dual antiplatelet therapy with specific types of drug-eluting stents remains unknown.[20]

The zotarolimus-eluting stent with a phosphorylcholine durable polymer is a second-generation drug-eluting stent that has demonstrated safety and efficacy in previous reports, despite use of dual antiplatelet therapy of relatively short duration (3 to 6 months) in most trials.[21] In the OPTIMIZE (Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice) trial, we sought to investigate the clinical implications of short-term (3 months) vs standard long-term (12 months) dual antiplatelet therapy in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) solely with a zotarolimus-eluting stent in daily clinical practice and to determine whether short-term dual antiplatelet therapy would be noninferior to long-term dual antiplatelet therapy.[22]

Figure 1. Study Flow



No reliable data for number of patients assessed for eligibility are available.
PCI indicates percutaneous coronary intervention.

Methods

Study Design

The OPTIMIZE trial was a multicenter, open-label, active-controlled, 1:1 randomized clinical trial (**Figure 1**) including patients from daily clinical practice undergoing PCI with the Endeavor zotarolimus-eluting stent (Medtronic Inc). The full description of the methods has been published.[22]

Inclusion criteria were symptoms of stable angina or of silent ischemia or low-risk acute coronary syndrome (ACS) as defined by unstable angina or recent (but not acute) myocardial infarction (MI) (<30 days)—there was a formal recommendation not to enroll patients with elevated biomarker levels at the time of the index procedure and at least 1 lesion with stenosis greater than 50% (multivessel disease was allowed) located in a native vessel at least 2.5 mm in diameter with indication for PCI with stent implantation.

Exclusion criteria were ST-segment elevation MI presenting for primary or rescue PCI; PCI with bare-metal stent(s) in nontarget lesions less than 6 months prior to the index procedure; previous treatment with any drug-eluting stent; scheduled elective surgery within 12 months after the index procedure; contraindication, intolerance, or known hypersensitivity to aspirin, clopidogrel, or both; lesion located in a saphenous vein graft; or in-stent restenosis of a drug-eluting stent. Randomization was conducted in a 1:1 ratio with the use of a block size of 8 for the 2 study groups and was stratified by the presence of diabetes mellitus.

Procedure and Clinical Follow-up

The clinical investigational protocol and informed consent form for this study were reviewed and approved by an appropriately constituted independent ethics committee or institutional review board at each clinical site before the study initiation and by the Brazilian Regulatory Agency for Clinical Trials. The study was conducted in accordance with the principles of the Declaration of Helsinki, International Organization for Standardization guidelines, and Good Clinical Prac-

tices guidelines. All patients provided written informed consent prior to enrollment.

Aspirin (100-200 mg daily) was recommended for patients with chronic (>7 days) aspirin use prior to PCI; otherwise, a loading dose of 300 to 500 mg was given at least 24 hours prior to the procedure. Postprocedure use of aspirin (100-200 mg daily) was prescribed indefinitely.

A loading dose of clopidogrel (300 mg) was given at least 24 hours prior to the procedure, if not already taken (75 mg daily); if less than 24 hours remained prior to PCI, a loading dose of 600 mg was given at least 2 hours prior to the procedure. Postprocedural clopidogrel use (75 mg daily) was maintained according to the randomization scheme (3 vs 12 months). Overall, generic clopidogrel (Medley Pharmaceutics Industry Ltd) was given to patients in an open-label fashion at 2 distinct study points. At hospital discharge, all patients received clopidogrel tablets for the first 90 days of treatment after the index procedure. Patients randomized to receive 12 months of dual antiplatelet therapy were given an additional amount of clopidogrel for the remaining 270 days at a mandatory medical visit at 3 months.

An independent clinical research organization (Cardiovascular Research Center, São Paulo, São Paulo, Brazil), was responsible for all data collection via electronic case report forms, source document verification for all reported events, and electronic and on-site monitoring. All end points were independently adjudicated by a Clinical Events Committee blinded to randomization groups. In addition, interim analyses at enrollment of each 500 patients were evaluated by an independent data and safety monitoring board blinded to study allocation.

Study End Points

The primary end point of net adverse clinical and cerebral events (NACCE) was a composite of death from any cause, MI, stroke, or major bleeding. Myocardial infarction was defined according to the historical extended World Health Organization definition as previously reported.[23] Based on evolving definitions for MI since the design of the OPTIMIZE protocol, the previously considered definition[22,24] was changed to the World Health Organization definition[23] by the steering committee while still blinded to group allocation and results. Protocol-defined major bleeding was based on a combination of 2 different bleeding criteria,[25,26] as previously reported.[22] Specifically, major bleeding incorporated modified major REPLACE-2 (Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events) and severe or life-threatening GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) criteria (intracranial, intraocular, or retroperitoneal hemorrhage; clinically overt blood loss resulting in a decrease in hemoglobin of more than 3 g/dL, any decrease in hemoglobin level of more than 4 g/dL, or transfusion of 1 or more units of packed red blood cells or whole blood; or either intracranial hemorrhage or bleeding that caused hemodynamic compromise and required intervention).

Key secondary end points included stent thrombosis according to the Academic Research Consortium (ARC),[24] target-lesion and target-vessel revascularization, major adverse cardiac events (MACE, including death from any cause, MI, emergent coronary artery bypass graft surgery, or target-lesion revascularization), and any bleeding, which included major bleeding plus bleeding events that did not meet criteria for either major or severe or life-threatening bleeding according to modified major REPLACE-2 and severe or life-threatening GUSTO criteria.

Statistical Analysis

The trial was powered for noninferiority testing of the primary end point between patients enrolled in the short-term group (n = 1560; 3 months of dual antiplatelet therapy) vs the control long-term group (n = 1560; 12 months of dual antiplatelet therapy). The primary analysis was based on the principle of intention-to-treat. Analysis of the primary end points was also performed for the per-protocol population. The per-protocol population was defined as intention-to-treat patients with (1) successful procedure outcome, (2) treatment solely with the zotarolimus-eluting stent, (3) dual antiplatelet therapy according to randomization, and (4) complete clinical follow-up information.

Based on previous data involving a similar patient population profile,[27] a primary end point rate (NACCE at 12 months) of 9% was assumed for both groups. Therefore, with 80% power and a 1-sided type I error of 5%, a sample size of 1404 patients in each group would be able to demonstrate noninferiority between both groups for the primary end point with a noninferiority fixed margin of 2.7%, which is in accordance with noninferiority margins used in contemporary trials of drug-eluting stents.[15,28-30] If the upper bound of the 95% CI of the difference in treatment (short- vs long-term dual antiplatelet therapy) was less than 2.7%, the null hypothesis would be rejected, which would signify that the short-term group was noninferior to the long-term group with regard to 12-month NACCE. Assuming up to 10% loss to follow-up, a minimum of 1544 patients in each group was deemed necessary.

All analyses were performed according to the intention-to-treat principle, with inclusion of all randomized patients according to original group allocation and without imputation. Descriptive statistics for the baseline characteristics and secondary clinical end points were provided. Categorical variables were reported as counts and percentages, and differences were assessed using the χ^2 test or the Fisher exact test in the case of low counts. Continuous variables were presented as mean (SD) and were compared using the 2-sample *t* test. Post hoc superiority analysis was conducted for clinical end points. Time to the primary end point and its components, including landmark analysis at 90 days, was also evaluated using the Kaplan-Meier method, and the log-rank test was used to compare differences. Hazard ratios were calculated using Cox proportional hazards regression.

Ninety days was selected as the time point for the landmark analysis because it was the prespecified time for discontinuation of clopidogrel in the short-term group. Thus, groups were analyzed under 2 situations: (1) considering all patients by intention-to-treat, including end point events or censored events up to 90 days, and (2) considering only those with end

point events or censored events from 91 days up to 1 year. For both scenarios, patients without events were censored at 360 days for the analysis up to 1-year follow-up.

We prespecified analyses of the primary end point at 1 year according to sex, history of diabetes, clinical presentation, bifurcation, lesion complexity, extent of disease, vessel size, lesion length, lesion type, intervention center, and number of stents implanted. All analyses were accompanied by tests for interaction between dual antiplatelet therapy treatment allocation and subgroup.

$P < .05$ (2-sided) was considered significant unless otherwise specified. All statistical analyses were performed using R version 2.13.0 (R Foundation for Statistical Computing).

Results

A total of 3119 patients were randomly assigned to 3 months of dual antiplatelet therapy (1563 patients) vs 12 months of dual antiplatelet therapy (1556 patients). Seventy-six patients refused follow-up or were lost to follow-up, and the majority of patients were treated solely with zotarolimus-eluting stents (Figure 1). Baseline and procedural characteristics were well matched between both groups (**Table 1** and **Table 2**). A radial approach was used in 40% of cases, 4120 coronary lesions were treated, 42% of patients received multiple stents, and mean total stent length was 32.7 (SD, 20) mm per patient. Adherence rates for aspirin and clopidogrel at 90 days were 99.3% and 99.7%, respectively, for the short-term group vs 99.5% and 99.8% for the long-term group. At 1-year clinical follow-up, the rates of aspirin and clopidogrel use were 98.9% and 6.2%, respectively, in the short-term group and 98.8% and 97.9% in the long-term group.

Primary Outcome

The primary outcome (NACCE) at 1 year occurred in 93 patients in the short-term group vs 90 patients in the long-term group (6.0% vs 5.8% based on cumulative incidence of events; risk difference, 0.17 [95% CI, −1.52 to 1.86]; $P = .002$ for noninferiority). From 91 to 360 days, there were also comparable NACCE rates between the groups (**Figure 2**). NACCE rates for the per-protocol population were 5.1% (71 events) in the short-term group and 4.9% (70 events) in the long-term group (risk difference, 0.22 [95% CI, −1.38 to 1.81]; $P = .001$ for noninferiority).

Time-to-event estimates for the composite and individual end points are reported in **Table 3**. **Figure 3** and **Figure 4** show the time-to-event curves for the individual components of NACCE. Overall MACE rates at 1 year were 8.3% with short-term dual antiplatelet therapy vs 7.4% with long-term therapy (hazard ratio [HR], 1.12 [95% CI, 0.87 to 1.45]). Moreover, after 90 days, there was no statistically significant association between duration of dual antiplatelet therapy and the occurrence of death, MI, or stroke (HR, 1.19 [95% CI, 0.74 to 1.90]), cardiac death (HR, 1.00 [95% CI, 0.54 to 1.85]), and cardiac death or MI (HR, 1.13 [95% CI, 0.65 to 1.95]). At 1 year, target lesion revascularization occurred in 53 patients (3.5%) in the short-term group and in 49 patients (3.2%) in the long-term group (HR, 1.08 [95% CI, 0.73 to 1.59]). Any new revascularization after the procedure occurred in 167 patients (5.5% of the total study population) and accounted for all cases of prolonged clopidogrel use in the short-term group (94 patients [6.2%]).

Stent Thrombosis and Subgroup Analysis

Definite or probable stent thrombosis up to 90 days occurred in 9 patients in the short-term group (0.6%) and in 11 patients in the long-term group (0.7%) (HR, 0.81 [95% CI, 0.34 to 1.96]). From 91 to 360 days, rates were 0.3% (4 events) and 0.1% (1 event) for the short- vs long-term groups, respectively (HR, 3.97 [95% CI, 0.44-35.49]) (Table 3).

Results of the prespecified subgroup analysis for the primary end point are shown in **Figure 5**. There was no statistically significant association between duration of dual antiplatelet therapy and the occurrence of NACCE in several subgroups, including history of ACS (risk difference, 1.04 [95% CI, 0.67-1.61]) or diabetes (risk difference, 0.90 [95% CI, 0.58-1.41]).

Bleeding

Any bleeding complications occurred in 80 patients up to 1 year, but only 23 cases were classified as major bleeding according to the study criteria, which represented 29% of all bleeding events (a list of all bleeding events are reported in the eAppendix in Supplement). Between 91 and 360 days postprocedure, major bleeding event rates were 0.2% in the short-term group vs 0.4% in the long-term group (HR, 0.50 [95% CI, 0.12-1.99]) (Table 3 and Figure 4). Considering any bleeding occurring after 90 days, patients in the long-term group had more events than those in the short-term group, but there was no statistically significant association (HR, 0.43 [95% CI, 0.16-1.11]). Furthermore, premature discontinuation of dual antiplatelet therapy according to the study protocol was experienced by 32 patients (9 in the short-term group and 23 in the long-term group); reasons for discontinuation were cardiac surgery (10 patients), hemorrhagic stroke (2 patients), noncardiac surgery (3 patients), and nonadherence or unknown cause (17 patients). Premature interruption of dual antiplatelet therapy was associated with the occurrence of stent thrombosis in 5 patients in the short-term group and in 4 patients in the long-term group.

Discussion

In this study comparing 3 months vs 12 months of dual antiplatelet therapy among patients with coronary artery disease treated with zotarolimus-eluting stents in daily practice, results demonstrated noninferiority for short- vs long-term dual antiplatelet therapy. This result was similar in several key subgroups, including patients with diabetes, history of low-risk ACS, multivessel disease, or bifurcation lesions.

These findings build on those from other randomized noninferiority trials with relatively smaller sample sizes, which suggested safety and efficacy of short-term dual antiplatelet therapy in patients treated with second-generation drug-

eluting stents. In the EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting) trial, 1443 patients were randomized to 6 vs 12 months of dual antiplatelet therapy after implantation of first- and second-generation drug-eluting stents, and the primary outcome of target-vessel failure (cardiac death, MI, or ischemia-driven target-vessel revascularization) was similar; in addition, landmark analysis at 6 months showed comparable event rates with

Table 1. Baseline Clinical and Lesion Characteristics of Patients Receiving Short- and Long-term Dual Antiplatelet Therapy[a]

Characteristic	No. (%) Short-term (n = 1563)	Long-term (n = 1556)
Patients		
Age, mean (SD), y	61.3 (10.4)	61.9 (10.6)
Women	571 (36.5)	574 (36.9)
Cardiovascular risk factors		
Diabetes mellitus	554 (35.4)	549 (35.3)
Insulin dependent	160 (10.2)	161 (10.4)
Hypertension	1350 (86.4)	1371 (88.2)
Dyslipidemia	953 (63.2)	952 (63.7)
Current smoking	290 (18.6)	269 (17.3)
Family history of CAD	564 (41.3)	583 (42.8)
Renal insufficiency[b]	114 (7.4)	89 (5.8)
Peripheral vascular disease	43 (2.8)	46 (3.0)
Cardiac heart failure	67 (4.3)	64 (4.2)
Previous myocardial infarction	541 (34.6)	542 (34.8)
>30 d	382 (24.4)	359 (23.1)
≤30 d	159 (10.2)	183 (11.8)
Previous PCI	327 (20.9)	297 (19.1)
Previous CABG surgery	111 (7.1)	128 (8.2)
History of cerebral vascular accident	38 (2.5)	38 (2.5)
History of bleeding	10 (0.6)	9 (0.6)
Clinical presentation		
Silent ischemia	134 (8.6)	143 (9.2)
Stable angina	935 (59.8)	911 (58.6)
Recent acute coronary syndrome, ≤30 d	494 (31.6)	502 (32.3)
NSTEMI	84 (5.4)	84 (5.4)
Lesions		
Treated in target artery	2058	2062
Left anterior descending	986 (47.9)	960 (46.6)
Left circumflex	481 (23.4)	501 (24.3)
Right coronary	567 (27.6)	571 (27.7)
Left main coronary	24 (1.2)	30 (1.5)
Lesion complexity		
Bifurcation	302 (14.7)	308 (14.9)
Total occlusion	87 (4.2)	74 (3.6)
Lesion class type C[c]	760 (37.0)	766 (37.4)
Pre-TIMI flow grade <3	153 (7.4)	143 (6.9)
Baseline quantitative coronary angiography		
Lesion length, mean (SD), mm	18.28 (10.76)	18.46 (10.89)
Median (IQR)	15.73 (10.64-22.91)	15.78 (10.68-23.33)
Reference diameter, mean (SD), mm	2.76 (0.48)	2.76 (0.47)
Median (IQR)	2.71 (2.41-3.04)	2.72 (2.42-3.04)
Minimal lumen diameter, mean (SD), mm	0.87 (0.41)	0.88 (0.41)
Median (IQR)	0.86 (0.57-1.15)	0.88 (0.60-1.15)
Diameter stenosis, mean (SD), %	68.6 (13.4)	68.2 (13.5)
Median (IQR)	67.2 (58.2-78.3)	66.9 (58.2-77.6)
LVEF <50%[d]	446 (36.1)	446 (35.4)

Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; IQR, interquartile range; LVEF, left ventricular ejection fraction; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

[a] Two-sided *P* values calculated with χ^2 or Fisher exact tests or *t* test (all $P \geq .08$).

[b] Baseline serum creatinine level of 1.5 mg/dL (132.6 µmol/L) or greater.

[c] According to the American College of Cardiology/American Heart Association lesion classification. Type C includes lesion length >20 mm, severe tortuosity of the proximal segment, angulation >90°, bifurcation with inability to protect a major side branch, or total occlusion >3 mo (or degenerated saphenous vein graft—not applicable for this study).

[d] Assessed by angiography or by echocardiography (n = 1234 patients in the short-term group and n = 1259 patients in the long-term group).

6 vs 12 months of dual antiplatelet therapy.[11] In the PRODIGY (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intima Hyperplasia Study), 2013 patients were first randomized to receive bare-metal stents vs zotarolimus-eluting stents vs paclitaxel-eluting stents vs everolimus-eluting stents and 30 days after the procedure underwent a second random-

Table 2. Procedural Outcomes Among Patients Receiving Short- and Long-term Dual Antiplatelet Therapy[a]

Characteristic	No. (%) Short-term (n = 1563)	No. (%) Long-term (n = 1556)
No. of lesions	2058	2062
Multivessel PCI	396 (25.34)	413 (26.54)
Staged procedure	105 (6.7)	114 (7.3)
Lesions treated per patient, mean (SD)	1.3 (0.6)	1.3 (0.6)
Stents implanted, mean (SD)		
Per patient	1.6 (0.8)	1.6 (0.8)
Per lesion	1.2 (0.5)	1.2 (0.5)
Balloon predilatation	826 (40.1)	782 (37.9)
Stent implanted	2056 (99.9)	2060 (99.9)
Additional stent implanted per lesion	294 (14.3)	327 (15.9)
Stent deployment pressure, mean (SD), atm	11.0 (3.4)	11.0 (3.5)
Balloon postdilatation	932 (45.3)	986 (47.8)
Maximum inflation pressure, mean (SD), atm	16.8 (4.1)	17.0 (3.9)
Nominal stent length per patient, mean (SD), mm	32.75 (19.84)	32.73 (20.01)
Angiographic success[b]	1957 (98.1)	1968 (98.7)
Procedure success[c]	1364 (97.3)	1356 (98.2)
Duration of hospital stay, mean (SD), d	1.6 (2.2)	1.5 (1.3)
Median (IQR)	1.0 (1.0-2.0)	1.0 (1.0-2.0)
Baseline antithrombotic medication		
Aspirin, mean (SD), mg	127.38 (51.77)	128.59 (53.09)
Median (IQR)	100.0 (100.0-100.0)	100.0 (100.0-200.0)
Clopidogrel,mean (SD), mg	237.38 (172.11)	233.01 (171.59)
Median (IQR)	300.0 (75.0-300.0)	300 (75.0-300.0)
75 mg (chronic use)[d]	689 (44.1)	711 (45.7)
300 mg (loading dose)	679 (43.4)	658 (42.3)
600 mg (loading dose)	193 (12.3)	186 (12.0)

Abbreviations: IQR, interquartile range; PCI, percutaneous coronary intervention.

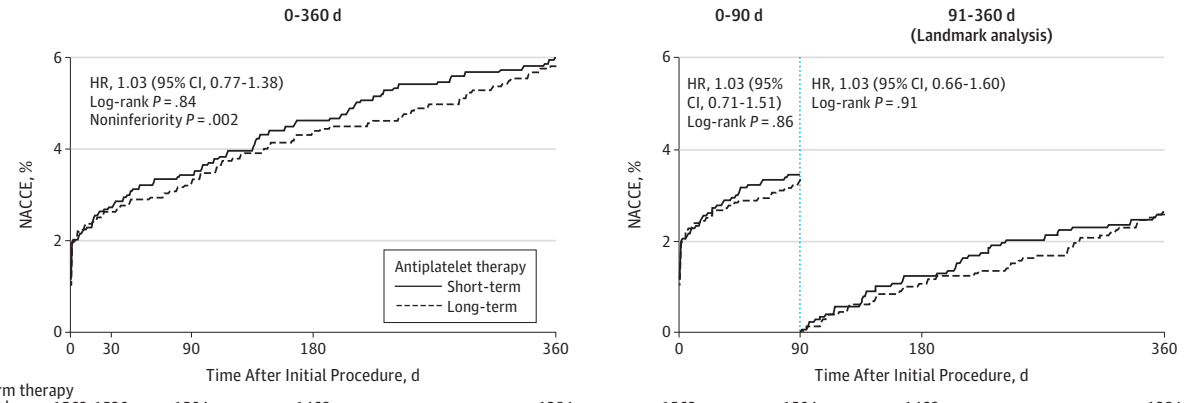
[a] Two-sided *P* values calculated using χ^2 or Fisher exact tests or *t* tests (all $P \geq .07$).

[b] Defined as attainment of <30% diameter stenosis in the segment treated with the study device at final procedure.

[c] Defined as angiographic success plus absence of major adverse cardiac events during index hospitalization.

[d] Clopidogrel use for at least 7 days prior to index procedure.

Figure 2. Time to Event for the Primary Composite End Point (NACCE) Among Patients Receiving Short- and Long-term Dual Antiplatelet Therapy—0-360 Days, 0-90 Days, and 91-360 Days



Short-term therapy										
No. at risk	1563	1520	1504	1468	1384	1563	1504	1468	1384	
No. of events	18	25	11	18	21	18	11	18	21	
Long-term therapy										
No. at risk	1556	1514	1497	1466	1381	1556	1497	1466	1381	
No. of events	16	25	11	16	22	16	11	16	22	

Numbers of events listed under the x-axes are not cumulative but rather incremental numbers of events; numbers of events listed under the x-axes on day 0 represent periprocedural events. HR indicates hazard ratio; NACCE, net adverse clinical and cerebral events (a composite of all-cause death, myocardial infarction, stroke, or major bleeding).

Table 3. Clinical Outcomes of Patients with Short- vs Long-term Dual Antiplatelet Therapy[a]

Clinical Outcomes	Patients, No. (%)		HR (95% CI)	Risk Difference (95% CI)	Log-Rank *P* Value
	Short-term (n = 1563)	Long-term (n = 1556)			
Events up to 1 y					
NACCE[b]	93 (6.0)[c]	90 (5.8)[c]	1.03 (0.77 to 1.38)	0.17 (−1.52 to 1.86)	.84
All-cause death	43 (2.8)	45 (2.9)	0.95 (0.63 to 1.45)	−0.14 (−1.34 to 1.05)	.82
MI	49 (3.2)	42 (2.7)	1.17 (0.77 to 1.76)	0.45 (−0.76 to 1.66)	.47
Stroke	5 (0.3)	5 (0.3)	0.99 (0.29 to 3.44)	0.00 (−0.41 to 0.41)	.99
Major bleeding[d]	10 (0.6)	14 (0.9)	0.71 (0.32 to 1.60)	−0.27 (−0.90 to 0.36)	.41
Stent thrombosis, definite or probable	13 (0.8)	12 (0.8)	1.08 (0.49 to 2.36)	0.06 (−0.58 to 0.70)	.86
Cardiac death	29 (1.9)	32 (2.1)	0.90 (0.55 to 1.49)	−0.21 (−1.20 to 0.79)	.69
Cardiac death or MI	70 (4.5)	62 (4.0)	1.13 (0.80 to 1.59)	0.51 (−0.94 to 1.95)	.49
Cardiac death, MI, or stent thrombosis	72 (4.7)	65 (4.2)	1.11 (0.79 to 1.55)	0.44 (−1.03 to 1.91)	.56
Death, MI, or stroke	87 (5.6)	78 (5.1)	1.14 (0.82 to 1.51)	0.57 (−1.04 to 2.18)	.49
Major adverse cardiac events[e]	128 (8.3)	114 (7.4)	1.12 (0.87 to 1.45)	0.88 (−1.04 to 2.81)	.36
Target-lesion revascularization	53 (3.5)	49 (3.2)	1.08 (0.73 to 1.59)	0.25 (−1.03 to 1.53)	.70
Target-vessel revascularization	70 (4.6)	57 (3.8)	1.23 (0.87 to 1.75)	0.84 (−0.59 to 2.26)	.25
Any bleeding[f]	35 (2.3)	45 (2.9)	0.77 (0.50 to 1.20)	0.67 (−1.81 to 0.47)	.25
0 to 90 d					
NACCE[b]	54 (3.5)	52 (3.3)	1.03 (0.71 to 1.51)	0.11 (−1.16 to 1.39)	.86
All-cause death	15 (1.0)	19 (1.2)	0.79 (0.40 to 1.55)	−0.26 (−0.99 to 0.47)	.48
MI	37 (2.4)	33 (2.1)	1.12 (0.70 to 1.79)	0.25 (−0.80 to 1.29)	.64
Stroke	1 (0.1)	3 (0.2)	0.33 (0.03 to 3.19)	−0.13 (−0.38 to 0.12)	.31
Major bleeding[d]	7 (0.5)	8 (0.5)	0.87 (0.32 to 2.40)	−0.07 (−0.55 to 0.42)	.79
Stent thrombosis, definite or probable	9 (0.6)	11 (0.7)	0.81 (0.34 to 1.96)	−0.13 (−0.69 to 0.43)	.64
Cardiac death	9 (0.6)	12 (0.8)	0.75 (0.31 to 1.77)	−0.20 (−0.77 to 0.38)	.50
Cardiac death or MI	43 (2.8)	38 (2.4)	1.13 (0.73 to 1.75)	0.31 (−0.81 to 1.43)	.59
Cardiac death, MI, or stent thrombosis	44 (2.8)	41 (2.6)	1.07 (0.70 to 1.64)	0.18 (−0.97 to 1.33)	.76
Death, MI, or stroke	49 (3.1)	46 (3.0)	1.06 (0.71 to 1.64)	0.18 (−1.03 to 1.39)	.77
Major adverse cardiac events[e]	50 (3.2)	50 (3.2)	1.00 (0.67 to 1.48)	−0.01 (−1.26 to 1.23)	.99
Target-lesion revascularization	3 (0.2)	9 (0.6)	0.33 (0.09 to 1.22)	−0.39 (−0.82 to 0.05)	.08
Target-vessel revascularization	7 (0.4)	10 (0.6)	0.69 (0.27 to 1.83)	−0.20 (−0.71 to 0.32)	.46
Any bleeding[f]	29 (1.9)	31 (2.0)	0.93 (0.56 to 1.54)	−0.14 (−1.11 to 0.83)	.78
91 d to 1 y					
NACCE[b]	39 (2.6)	38 (2.6)	1.03 (0.66 to 1.60)	0.05 (−1.06 to 1.17)	.91
All-cause death	28 (1.9)	26 (1.7)	1.07 (0.63 to 1.83)	0.12 (−0.81 to 1.06)	.79
MI	12 (0.8)	9 (0.6)	1.34 (0.56 to 3.18)	0.19 (−0.39 to 0.78)	.51
Stroke	4 (0.3)	2 (0.1)	1.99 (0.37 to 10.88)	0.13 (−0.18 to 0.45)	.42
Major bleeding[d]	3 (0.2)	6 (0.4)	0.50 (0.12 to 1.99)	−0.20 (−0.58 to 0.19)	.31
Stent thrombosis, definite or probable	4 (0.3)	1 (0.1)	3.97 (0.44 to 35.49)	0.20 (−0.09 to 0.48)	.18
Cardiac death	20 (1.3)	20 (1.3)	1.00 (0.54 to 1.85)	−0.01 (−0.82 to 0.80)	.99
Cardiac death or MI	27 (1.8)	24 (1.7)	1.13 (0.65 to 1.95)	0.19 (−0.72 to 1.10)	.67
Cardiac death, MI, or stent thrombosis	28 (1.9)	24 (1.6)	1.17 (0.68 to 2.02)	0.26 (−0.67 to 1.18)	.58
Death, MI, or stroke	38 (2.6)	32 (2.2)	1.19 (0.74 to 1.90)	0.38 (−0.68 to 1.45)	.47
Major adverse cardiac events[e]	78 (5.3)	64 (4.3)	1.22 (0.88 to 1.70)	0.90 (−0.60 to 2.40)	.23
Target-lesion revascularization	50 (3.3)	40 (2.7)	1.25 (0.82 to 1.89)	0.64 (−0.56 to 1.85)	.30
Target-vessel revascularization	63 (4.2)	47 (3.2)	1.34 (0.92 to 1.96)	1.03 (−0.29 to 2.36)	.12
Any bleeding[f]	6 (0.4)	14 (1.0)	0.43 (0.16 to 1.11)	−0.53 (−1.10 to 0.05)	.07

Abbreviations: HR, hazard ratio; MI, myocardial infarction; NACCE, net adverse clinical and cerebral events.

[a] Event rates based on Kaplan-Meier estimates; HRs are derived from Cox proportional hazard regression models.

[b] Composite of death from all causes, MI, stroke, or major bleeding. Noninferiority *P* = .002 for primary end point.

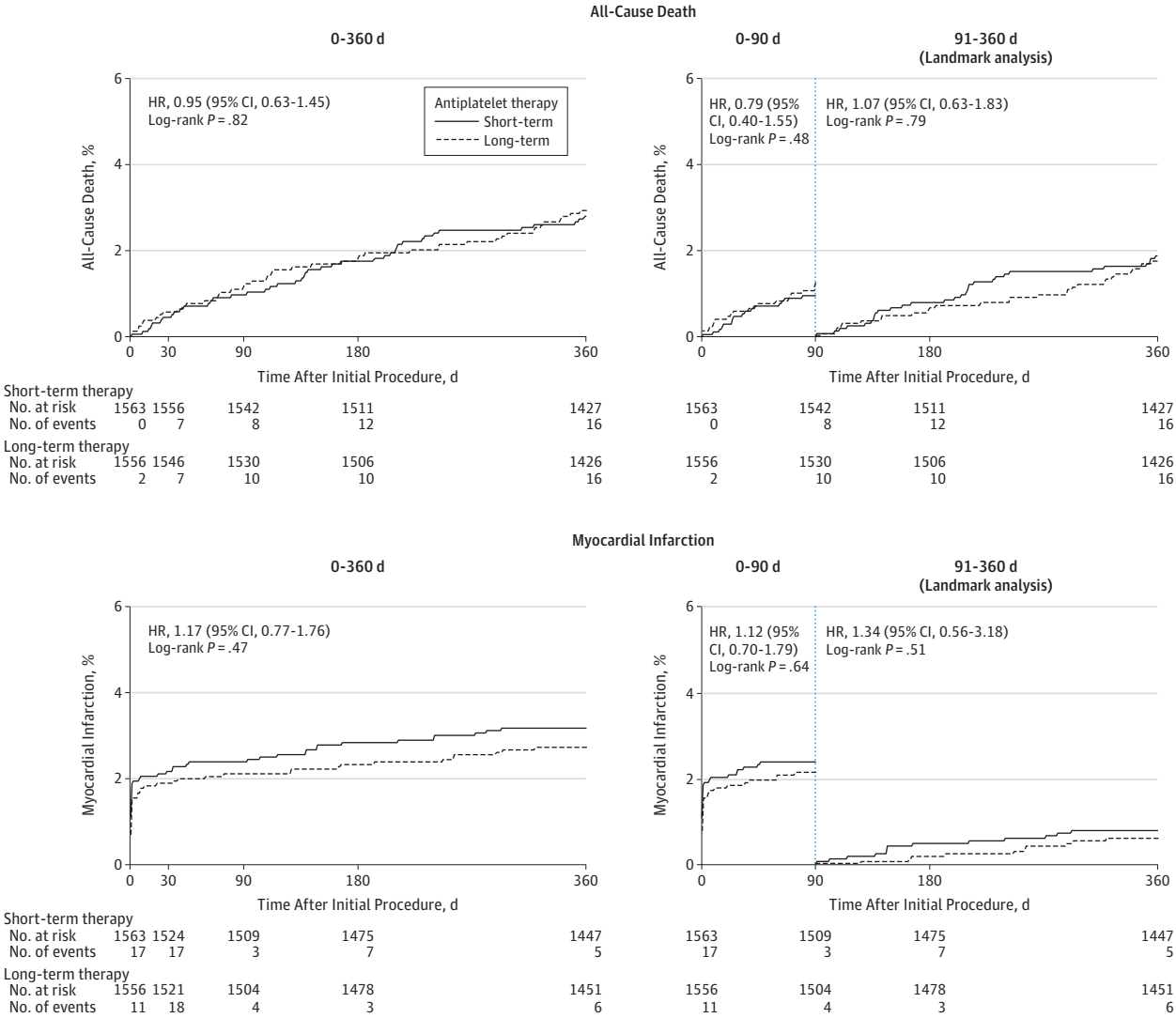
[c] Event rates were 6.1% in the short-term group and 5.9% in the long-term group if based on proportional risk.

[d] Defined as intracranial, intraocular, or retroperitoneal hemorrhage; clinically overt blood loss resulting hemoglobin decrease >3 g/dL, any hemoglobin decrease >4 g/dL, or transfusion of ≥1 units of packed red blood cells or whole blood; or intracranial hemorrhage or bleeding causing hemodynamic compromise and requiring intervention.

[e] Death from all causes, MI, urgent coronary artery bypass graft surgery, or target lesion revascularization.

[f] Any bleeding event (combined modified REPLACE-2 and GUSTO criteria).

Figure 3. Time to Event for Individual Components of the Primary Composite End Point (All-Cause Death, Myocardial Infarction) Among Patients Receiving Short- and Long-term Dual Antiplatelet Therapy at 0-360 Days, 0-90 Days, and 91-360 Days



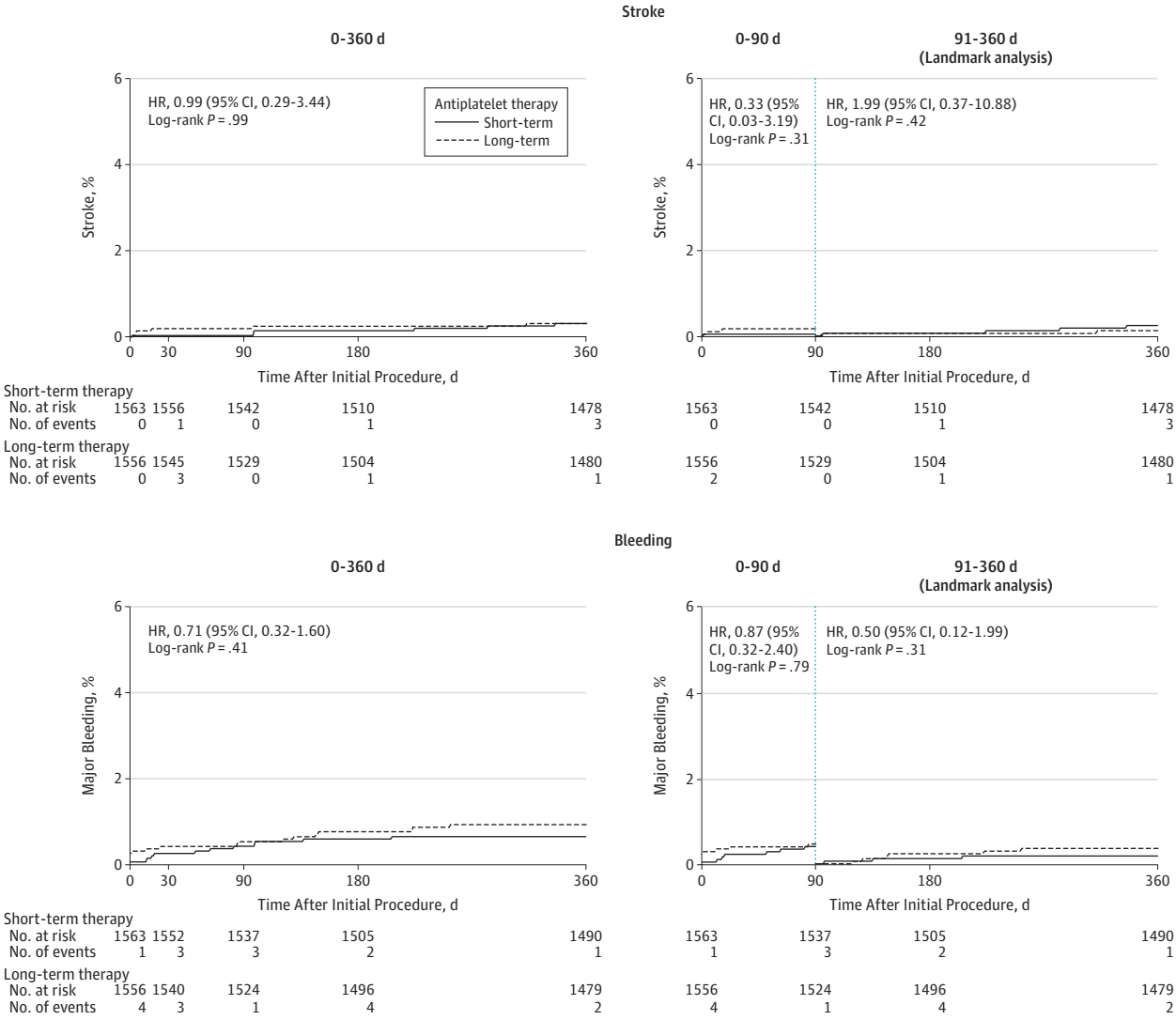
Numbers of events listed under the x-axes are not cumulative but rather incremental numbers of events; numbers of events listed under the x-axes on day 0 represent periprocedural events. HR indicates hazard ratio.

ization for allocation to 6 vs 24 months of dual antiplatelet therapy. At 24 months' follow-up, the primary outcome (death from any cause, MI, or stroke) was also similar with 6 vs 24 months of dual antiplatelet therapy.[12]

In the RESET (Real Safety and Efficacy of 3-Month Dual Antiplatelet Therapy Following Endeavor Zotarolimus-Eluting Stent Implantation) trial, 2117 patients were randomized to treatment with zotarolimus-eluting stents plus 3 months of dual antiplatelet therapy vs first- or second-generation drug-eluting stents plus 12 months of dual antiplatelet therapy. At 12 months' follow-up, the primary outcome (cardiac death, MI, stent thrombosis, or ischemia-driven target-vessel revascularization) was equal in both groups.[13] Although a treatment scheme of 3 months of dual antiplatelet therapy was tested in RESET, multiple types of stents were included.[13] A subanalysis from PRODIGY with landmark analysis at 6 months showed lack of benefit for prolonged (24 months) vs shorter-term (6 months) dual antiplatelet therapy with bare-metal stents and second-generation drug-eluting stents (zotarolimus-eluting stents and everolimus-eluting stents); conversely, patients treated solely with paclitaxel-eluting stents significantly benefited from prolonged dual antiplatelet therapy.[31]

Recent analyses comparing first- and second-generation drug-eluting stents have demonstrated lower rates of stent thrombosis over time with second-generation stents.[15,16,18,31,32] Therefore, it is not possible to determine whether all drug-eluting stents could benefit from short-term regimens of dual antiplatelet therapy based on the previous trials reported.[11-13,31] To our knowledge, our study is the only trial to date of dual antiplatelet therapy duration using a single second-generation drug-eluting stent and in which 3 months of dual antiplatelet therapy demonstrated noninferiority against 12

Figure 4. Time to Event for Individual Components of the Primary Composite End Point (Stroke, Major Bleeding) Among Patients Receiving Short- and Long-term Dual Antiplatelet Therapy at 0-360 Days, 0-90 Days, and 91-360 Days



Numbers of events listed under the x-axes are not cumulative but rather incremental numbers of events; numbers of events listed under the x-axes on day 0 represent periprocedural events. HR indicates hazard ratio.

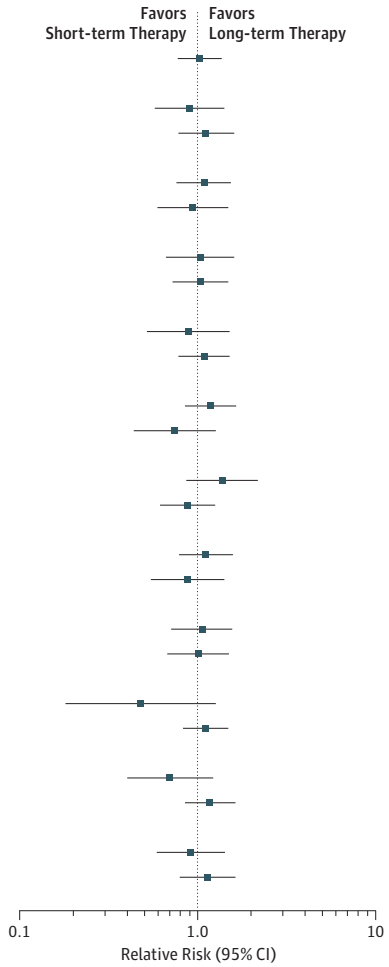
months of therapy with respect to hard end points associated with duration of therapy.

Premature discontinuation of dual antiplatelet therapy has been determined to be one of the most powerful predictors of stent thrombosis following implantation of first-generation drug-eluting stents, mainly within the 6 months after PCI.[7-10] In our study, prespecified cessation of dual antiplatelet therapy at 3 months did not significantly affect the occurrence of either the primary outcome or stent thrombosis. Notably, time-to-event analysis starting at 90 days demonstrated no significant differences between 3 and 12 months. Even when considering the composite outcome of cardiac death, MI, or stent thrombosis, the absolute difference of events occurring between 90 and 360 days was only 0.3%.

Overall, ARC definite or probable stent thrombosis rates up to 1 year were 0.8% with 3 months of dual antiplatelet therapy and 0.8% with 12 months of dual antiplatelet therapy. Similar rates were seen in the pooled analysis with zotarolimus-eluting stents, including an ARC definite or probable stent thrombosis rate of 0.8% up to 5 years follow-up, because most stent thromboses occurred within the first year after the procedure.[21] In general, second-generation drug-eluting stents have demonstrated a better safety profile compared with first-generation devices,[15,16] but because of the rarity of stent thrombosis, most studies are not adequately powered to demonstrate significant differences in this outcome. In the PROTECT (Patient-Related Outcomes With Endeavor Versus Cypher Stenting Trial), significant differences were seen only in the occurrence of very late stent thrombosis, with lower rates found with zotarolimus-eluting stents compared with sirolimus-eluting stents.[33] A possible explanation may be the improved biocompatibility of drug carriers found in newer drug-

Figure 5. Forest Plot for the Primary Composite End Point According to Subgroup and Duration of Antiplatelet Therapy

Subgroup	Short-term Therapy No. of Events	Short-term Therapy Rate	Long-term Therapy No. of Events	Long-term Therapy Rate	Relative Risk (95% CI)	*P* Value	*P* Value for Interaction
All patients (N = 3119)	93	0.06	90	0.06	1.03 (0.78-1.36)	.84	
Diabetes							
Yes (n = 1103)	34	0.06	37	0.07	0.90 (0.58-1.41)	.65	.50
No (n = 2016)	59	0.06	53	0.05	1.12 (0.78-1.60)	.55	
Sex							
Men (n = 1973)	60	0.06	55	0.06	1.08 (0.76-1.55)	.66	.63
Women (n = 1146)	33	0.06	35	0.06	0.94 (0.59-1.49)	.80	
Acute coronary syndrome							
Yes (n = 1000)	36	0.08	37	0.08	1.04 (0.67-1.61)	.88	>.99
No (n = 2119)	57	0.05	53	0.05	1.04 (0.72-1.49)	.84	
Bifurcation							
Yes (n = 547)	23	0.09	26	0.10	0.88 (0.52-1.51)	.65	.52
No (n = 2572)	70	0.06	64	0.05	1.09 (0.78-1.51)	.62	
Lesion							
Complex (n = 1846)	70	0.08	60	0.07	1.18 (0.85-1.65)	.32	.15
Simple (n = 1273)	23	0.04	30	0.05	0.74 (0.44-1.27)	.27	
No. of vessels							
Multiple (n = 809)	38	0.10	29	0.07	1.38 (0.87-2.19)	.17	.13
Single (n = 2310)	55	0.05	61	0.05	0.88 (0.62-1.26)	.48	
Vessel size							
Small (n = 1889)	63	0.07	56	0.06	1.12 (0.79-1.58)	.53	.43
Large (n = 1230)	30	0.05	34	0.06	0.88 (0.55-1.42)	.60	
Lesion length							
Long (n = 1287)	47	0.07	45	0.07	1.06 (0.71-1.57)	.78	.86
Short (n = 1832)	46	0.05	45	0.05	1.01 (0.67-1.50)	.98	
In-stent restenosis							
Yes (n = 324)	6	0.04	11	0.07	0.48 (0.18-1.27)	.13	.10
No (n = 2795)	87	0.06	79	0.06	1.11 (0.83-1.49)	.48	
Center							
Academic (n = 836)	20	0.05	28	0.07	0.70 (0.40-1.22)	.21	.12
Nonacademic (n = 2283)	73	0.07	62	0.06	1.18 (0.85-1.64)	.33	
Stents implanted							
Single (n = 1787)	37	0.04	39	0.05	0.92 (0.59-1.42)	.69	.45
Multiple (n = 1332)	56	0.09	51	0.08	1.14 (0.79-1.64)	.48	



Primary outcome was a composite of all-cause death, myocardial infarction, stroke, or major bleeding.

eluting stents. The main reasons for the selection of the zotarolimus-eluting stent in our trial were that this stent has demonstrated a good safety profile in several trials including a wide range of patient and lesion subsets and that most of the prior studies of zotarolimus-eluting stents used short-term dual antiplatelet therapy.[21] In fact, early vessel healing was the basis for the hypothesis tested in our study for short-term duration of dual antiplatelet therapy with zotarolimus-eluting stents.[34-36]

Although not specifically studied, it is possible that the results of our trial may be especially relevant for patients at high risk of bleeding complications following PCI, such as the elderly and patients with a history of hemorrhagic events. Bleeding complications associated with prolonged dual antiplatelet therapy are reported in 0.7% to 30% of patients undergoing PCI with stent implantation and have ominous consequences.[14,37,38] Premature discontinuation of dual antiplatelet therapy is a relatively common consequence of either major or nuisance bleeding.[37] In our study, no significant differences were observed in the occurrence of major bleeding according to the primary outcome definition. Even when considering any bleeding events, there was no statistically significant association between duration of dual antiplatelet therapy and bleeding occurring after 90 days, although patients assigned to 12 months of dual antiplatelet therapy had a 2.5-fold higher rate compared with those assigned to 3 months of dual antiplatelet therapy. Moreover, noncardiac surgery may occur in a relatively high number of patients following implantation of drug-eluting stents in daily practice.[39,40] Thus, our findings may be reassuring for patients with a high probability of undergoing noncardiac surgery and other invasive procedures and may be applicable to those with less risk for stent thrombosis.

Some limitations must be considered when interpreting our results. First, based on the relatively low event rates observed, our study might not have been powered to detect small differences in ischemic and bleeding events after 90 days. A study specifically designed to detect differences in such outcomes (cardiac death, MI, stent thrombosis, or stroke) would have to be approximately 5 to 10 times as large to exclude a significant influence on these events.[41,42] In OPTIMIZE, a fixed

margin of 2.7% represented 30% of the expected rate for the control group (9%), which we considered acceptable and even conservative compared with other contemporary drug-eluting stent trials with clinical end points; it also appeared to be in accordance with current paradigms used in calculations of noninferiority margin.[15,28-30]

Second, an important issue in our study was that the overall event rate for the primary composite end point (NACCE) was lower than expected (6% vs 9%), even though the MACE rate was approximately 8%. We recognize that when this occurs, it may affect the statistical power to rule out a small degree of excess risk.[43] When this trial was designed, it was expected that both groups would have a 9% composite event rate based on historical data. A fixed 2.7% noninferiority margin was selected, and the trial would have had 80% power to demonstrate noninferiority. The observed event rates (approximately 6%) were less than expected. Considering a new trial with a 6% expected primary end point event rate, with all other assumptions unchanged, then with the same sample size, the power would become 90%. Although the power to detect differences in rates of stent thrombosis was somewhat limited, these are likely the best randomized data available regarding shorter durations of dual antiplatelet therapy.

Third, the patient population represented in our trial mostly comprised patients with stable coronary artery disease or history of low-risk ACS. Nevertheless, 84 patients in each group (5.4%) presented with non-ST-segment elevation MI despite a formal recommendation not to enroll these patients. Even though there was no statistically significant difference in rates of NACCE by duration of dual antiplatelet therapy in the subgroup with history of ACS, caution should be used before generalizing our results to patients with moderate or high risk of ACS. Several high-risk characteristics (diabetes, renal insufficiency, congestive heart failure, previous MI, left ventricular ejection fraction <50%) were well represented in the study. Also, baseline angiographic characteristics demonstrated relatively high lesion complexity, including 15% bifurcations, one-third type C lesions, mean lesion length of 18 mm, and mean vessel size of 2.76 mm. Additionally, overall, mean total stent length was quite long (33 mm).

Fourth, combining efficacy and safety within a single composite outcome may be problematic and may mask important differences. However, analysis of MACE did not show any significant differences between durations of dual antiplatelet therapy. Fifth, randomization was performed at the time of the index procedure and not at the 3-month landmark time point. In clinical practice, sometimes physicians and patients need to decide on the duration of dual antiplatelet therapy prior to the decision to revascularize, because it may be a factor in determining whether to place a drug-eluting stent.

Conclusion

Among patients undergoing PCI with implantation of zotarolimus-eluting stents, short-term (3 months) dual antiplatelet therapy was noninferior to long-term (12 months) dual antiplatelet therapy for the occurrence of death, MI, stroke, or major bleeding, without significantly increasing the risk of stent thrombosis.

ARTICLE INFORMATION

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Conflict of Interest Disclosures: Dr Feres reported receiving speakers honoraria from Biosensors International, Eli Lilly, Medtronic Vascular, sanofi-aventis, and Terumo. Dr Costa reported receiving speakers honoraria from Medtronic Vascular and Biosensors International and research grant support from Abbott Vascular. Dr King reported receiving Data and Safety Monitoring Board honoraria from Merck & Company, Wyeth Pharmaceuticals, and nContact Surgical; receiving consulting fees from Celonova Biosciences Inc; and serving on the speakers bureau of the Network for Continuing Medical Education. Dr Bhatt reported serving on the advisory boards of Elsevier Practice Update Cardiology, Medscape Cardiology, and Regado Biosciences; serving on the boards of directors of Boston Veterans Affairs Research Institute and the Society of Cardiovascular Patient Care; serving as chair of the American Heart Association Get With The Guidelines Steering Committee; receiving honoraria from the American College of Cardiology (editor, *Clinical Trials*, *Cardiosource*), Belvoir Publications (editor in chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees), Population Health Research Institute (clinical trial steering committee), Slack Publications (chief medical editor, *Cardiology Today's Intervention*), and WebMD (CME steering committees); serving as senior associate editor, *Journal of Invasive Cardiology*; serving on the data monitoring committees of the Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, and Population Health Research Institute; receiving research grants from Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic, sanofi-aventis, and The Medicines Company; and conducting unfunded research for FlowCo, PLx Pharma, and Takeda. Dr Negoita and Dr Liu are employees of Medtronic. No other authors reported disclosures.

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