Short- Versus Long-Term Duration of Dual-Antiplatelet Therapy After Coronary Stenting

A Randomized Multicenter Trial

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Background—The optimal duration of dual-antiplatelet therapy and the risk-benefit ratio for long-term dual-antiplatelet therapy after coronary stenting remain poorly defined. We evaluated the impact of up to 6 versus 24 months of dual-antiplatelet therapy in a broad all-comers patient population receiving a balanced proportion of Food and Drug Administration–approved drug-eluting or bare-metal stents.

Methods and Results—We randomly assigned 2013 patients to receive bare-metal, zotarolimus-eluting, paclitaxel-eluting, or everolimus-eluting stent implantation. At 30 days, patients in each stent group were randomly allocated to receive up to 6 or 24 months of clopidogrel therapy in addition to aspirin. The primary end point was a composite of death of any cause, myocardial infarction, or cerebrovascular accident. The cumulative risk of the primary outcome at 2 years was 10.1% with 24-month dual-antiplatelet therapy compared with 10.0% with 6-month dual-antiplatelet therapy (hazard ratio, 0.98; 95% confidence interval, 0.74–1.29; $P=0.91$). The individual risks of death, myocardial infarction, cerebrovascular accident, or stent thrombosis did not differ between the study groups; however, there was a consistently greater risk of hemorrhage in the 24-month clopidogrel group according to all prespecified bleeding definitions, including the recently proposed Bleeding Academic Research Consortium classification.

Conclusions—A regimen of 24 months of clopidogrel therapy in patients who had received a balanced mixture of drug-eluting or bare-metal stents was not significantly more effective than a 6-month clopidogrel regimen in reducing the composite of death due to any cause, myocardial infarction, or cerebrovascular accident.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00611286.

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Key Words: antiplatelet therapy ■ aspirin ■ clopidogrel ■ percutaneous coronary intervention ■ dual antiplatelet therapy

Nine to 12 months of clopidogrel therapy after bare-metal stenting has been shown to reduce the composite of death, myocardial infarction, or stroke by nearly 30% in patients with non–ST-segment–elevation acute coronary syndrome compared with 1-month duration of treatment.[1,2] The design of these studies, however, was such that only patients who received preprocedural clopidogrel continued to receive it long-term.[1,2] Therefore, the actual effect of long-term clopidogrel may have been biased by the positive influence of upstream initiation of treatment in these patients. Because of prior experience with patients affected by non–ST-segment–elevation acute coronary syndromes, as well as patients undergoing coronary stenting, long-term therapy with clopidogrel is also

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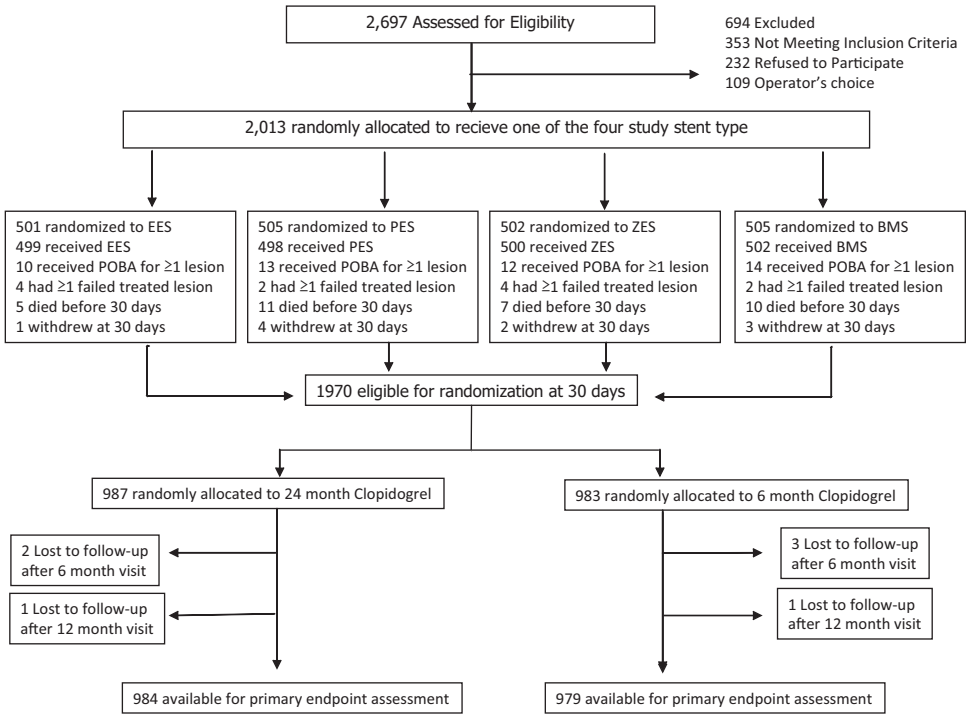

Figure 1. Study profile. BMS indicates bare-metal stent; DAPT, dual-antiplatelet therapy; EES, everolimus-eluting stent; POBA, plain balloon angioplasty; PES, paclitaxel-eluting stent; and ZES, zotarolimus-eluting stent.

recommended for patients with ST-segment elevation myocardial infarction.[3,4]

Editorial see p 1967
Clinical Perspective on p 2026

Clopidogrel therapy should be prolonged for at least 12 months or for 6 to 12 months after drug-eluting stent (DES) implantation, according to the American College of Cardiology/American Heart Association[5] and European Society of Cardiology[6] guidelines, respectively, based on concerns that delayed vessel healing may be responsible for late (>30 days) or very late (>1 year) stent thrombosis. Yet randomized data supporting this recommendation are limited,[7] and findings of observational studies have been inconsistent.[8–11] Therefore, the optimal duration of dual-antiplatelet therapy and the risk-benefit ratio for long-term dual-antiplatelet therapy after percutaneous coronary intervention remain uncertain.

The purpose of the present trial was to assess the effect of using dual-antiplatelet therapy for 6 versus 24 months on long-term clinical outcomes after coronary intervention in a broad all-comers patient population receiving a balanced proportion of Food and Drug Administration–approved DES or bare-metal stents (BMS).

Methods

Study Design and Population

The Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) is a 4-by-2 randomized, multicenter, open-label clinical trial designed to evaluate the efficacy and safety of prolonging the duration of clopidogrel therapy for up to 24 months in all-comer patients receiving a balanced mixture of stents with varying anti-intimal hyperplasia potency and belonging to both first- and second-generation DES.[12] Patients undergoing elective, urgent, or emergent coronary angioplasty with intended stent implantation at 3 referral Italian sites were randomly assigned in a 1:1:1:1 fashion to 1 of 4 stent types, including an everolimus-eluting stent, paclitaxel-eluting stent, zotarolimus-eluting Endeavor Sprint stent, or third-generation thin-strut BMS. At 30 days, patients in each stent group were randomized in a balanced fashion to either 6 or 24 months of dual-antiplatelet treatment (Figure 1). In the 6-month dual-antiplatelet therapy group, clopidogrel discontinuation at any time after 30 days was allowed in patients who were randomized to a BMS if coronary intervention was indicated by the presence of stable coronary artery disease. This was driven by the lack of data showing the value of clopidogrel in addition to aspirin beyond 30 days in this patient population. The inclusion of a BMS group allowed us to prespecify the interaction testing between stent type and duration of therapy.

Individuals eligible for enrolment were patients ≥18 years of age with chronic stable coronary artery disease or acute coronary syndromes, including non–ST-elevation and ST-elevation myocardial infarction. They were eligible if they had at least 1 lesion with a diameter stenosis of ≥50% that was suitable for coronary stent implantation in a vessel with a reference vessel diameter of ≥2.25 mm. Selection criteria were broad, reflecting routine clinical practice. We set no limit for the number of treated lesions, vessels, or lesion length, and we excluded no patients on the basis of comorbid disorders or age, apart from the following prespecified criteria: Known allergy to acetylsalicylic acid or clopidogrel; planned surgery within 24 months of percutaneous coronary intervention unless the dual-antiplatelet therapy could be maintained throughout the perisurgical period; history of bleeding diathesis; major surgery within 15 days; active bleeding or previous stroke in the past 6 months; concomitant or foreseeable need for oral anticoagulation therapy; pregnancy; life expectancy <24 months; participation in another trial; and inability to provide informed consent.

The ethics committees of the 3 participating centers independently approved the protocol, and all participants gave written informed consent.

Randomization Procedures

The treating physician performed allocation of study treatment immediately after eligibility criteria were met and subsequently at 30±5 days after intervention via sealed envelopes. Both randomization procedures were achieved with a computer-generated random sequence that was produced in the coordinating center with random block sizes of 4, 8, and 12. Treatment allocation was not masked.

Stent Randomization

A randomization scheme to stent type based on a 1:1:1:1 ratio to everolimus-eluting, paclitaxel-eluting, zotarolimus-eluting Endeavor Sprint, or BMS (any thin-strut, uncoated-stent type approved by the regulatory agency) was stratified by the center, the presence of ongoing ST-segment–elevation myocardial infarction, diabetes mellitus, or the need for intervention on at least 1 in-stent restenotic lesion. Patients were then treated with aspirin and clopidogrel for the first 30 days after intervention. In the case of intercurrent or staged revascularization procedures that required stent implantation, the study protocol mandated the use of a study stent as per the original randomization scheme.

Clopidogrel Randomization

Random allocation to 1 of the 2 antiplatelet treatment strategies occurred at 30±5 days based on a random scheme that was stratified by the same covariates implemented in the balancing randomization at the time of the index procedure, plus randomized stent group.

Treatment Protocol and Follow-Up Procedures

All patients received aspirin (160 to 325 mg orally or 500 mg IV as a loading dose and then 80 to 160 mg orally indefinitely) and clopidogrel (300 or 600 mg orally as a loading dose) and then 75 mg/d for the treatment duration according to the randomization scheme as follows: For either 6 months in the 6-month dual-antiplatelet group (in patients randomized to BMS and presenting with stable coronary artery disease, a shorter [but not <30 day] duration of dual-antiplatelet treatment was allowed, to comply with available evidence) or 24 months in the 24-month dual-antiplatelet arm irrespective of the previously implanted stent type or indication for the coronary procedure.

Anticoagulation during coronary intervention was accomplished through administration of either unfractionated heparin or bivalirudin. All interventions were performed according to current standard guidelines, and the final interventional strategy, including administration of glycoprotein IIb/IIIa antagonists, predilation or postdilation, or use of intravascular imaging techniques, was left entirely to the discretion of the operator, except for the stent utilization. Angiographic success was defined as residual stenosis <30% by visual analysis in the presence of TIMI (Thrombolysis In Myocardial Infarction) 3 grade flow.

Follow-Up

All randomized patients who were not lost to follow-up, irrespective of their compliance with the assigned treatment schedule, returned for study visits at 30 days, and then every 6 months up to 2 years. During follow-up visits, patients were examined and assessed for adverse events, and 12-lead ECG recordings were obtained. At all follow-up time points, patients were questioned about their compliance with the study medication. Any interruptions or termination, as well as the reasons for this, were documented. To ensure a high adherence rate to the assigned study treatment, a dedicated study nurse per site telephonically contacted each patient on a monthly basis.

Study End Points

The primary objective of the present study was to assess whether 24-month dual-antiplatelet treatment consisting of clopidogrel and aspirin after coronary stenting, evaluated from the time of randomization up to 2 years, was associated with a lower cumulative incidence of death of any cause, nonfatal myocardial infarction, or cerebrovascular accident compared with 6-month clopidogrel and aspirin duration. Because the therapy did not differ between the 2 groups in the first month after stenting, the time frame of interest for the primary end point was from 30 days (ie, after the primary end point randomization) to 24 months.

Secondary end points included each component of the primary end point, cardiovascular death, the incidence of stent thrombosis defined on the basis of the Academic Research Consortium criteria,[13] and bleeding outcomes. The key safety end point was the rate of bleeding according to TIMI criteria and the BleedScore.[14] The study protocol was then amended in March 2010 to incorporate the recently developed Bleeding Academic Research Consortium (BARC) criteria,[15] with the key safety end point being a composite of type 5, 3, or 2 bleeding.

Prespecified analysis of the primary and secondary end points was performed according to age, sex, presence of diabetes mellitus, type of stent implanted (BMS versus DES), clinical presentation, complexity, number of treated lesions, and renal function. All deaths were considered to be of cardiovascular causes unless an unequivocal noncardiovascular cause could be established. The diagnosis of acute myocardial infarction was based on the universal definition of myocardial infarction.[16] Stroke, as detected by the occurrence of a new neurological deficit, was confirmed by a neurologist and on imaging, whereas the occurrence of a transient ischemic attack required hospitalization and clinical confirmation by a neurologist.

All study end points and bleeding events were confirmed on the basis of documentation collected at each hospital and were centrally adjudicated by the clinical events committee, whose members were unaware of patients' treatment-group assignments. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Statistical Analysis

Assuming an event rate of 8.0% at 2 years for the primary end point of death of any cause, nonfatal myocardial infarction, or cerebrovascular accident among patients who were assigned to 6-month clopidogrel duration, we estimated that at least 1700 patients (850 in each group) would need to be enrolled to detect a 40% reduction in the relative risk of the primary end point in the 24-month clopidogrel group compared with 6-month duration of clopidogrel therapy, with statistical power of ≥80% at a 2-sided significance level of 0.05. The assumed rate for the primary end point and the assumed reduction in relative risk were based on historical data.[9,10,12] No interaction was expected between stent type (DES versus BMS) and assigned treatment. The planned sample size was then increased up to 2000 to allow for fatalities occurring within the first 30 days, noncompliance, and loss to follow-up.

Categorical variables were expressed as frequency (percentage), whereas continuous variables were expressed as median (interquartile range). Baseline continuous variables were compared between randomized groups with the Wilcoxon rank sum test, whereas for baseline binary variables, the Fisher exact test was used.

Estimation of the cumulative major adverse cardiovascular event rate was performed by the Kaplan-Meier method, and events were compared by the log-rank test. Hazard ratios with 95% confidence intervals (CIs) were calculated for long-term clopidogrel versus short-term clopidogrel (ie, values >1 indicated increased hazard in the long-term group) with a proportional hazards model. The proportionality assumptions were checked by visual estimation after we plotted the log cumulative hazard versus (log) time at follow-up after the index procedure and by applying a test for nonproportional hazards using Schoenfeld residuals as described previously,[17] which failed to reject the null hypothesis that event rate was affected by time ($P=0.87$). We performed a Cox regression analysis with interaction testing to determine whether the effect of duration of dual-antiplatelet therapy on the primary efficacy end point at 2 years was consistent across important prespecified subgroups. Interaction tests were performed with likelihood ratio tests of the null hypothesis that the interaction coefficient was zero. A 2-sided probability value <0.05 was considered significant. All analyses, performed on the basis of the intention-to-treat principle, were performed with STATA, version 11.1 (Stata Corp, College Station, TX).

Table 1. Baseline Characteristics of Patients

Characteristic	24-Month Clopidogrel (n=987)	6-Month Clopidogrel (n=983)	P
Age, y			
Mean±SD	67.8±11	67.9±11	
Median	69	69	0.85
Interquartile range	61–76	60–77	
Range	29–94	31–99	
Male sex, n (%)	764 (77.4)	747 (76.0)	0.46
Body mass index, kg/m^2			
Median	26.6	26.7	0.68
Interquartile range	24.6–29.4	24.8–29.3	
Diabetes, n (%)	244 (24.7)	233 (23.7)	0.87
Insulin dependent, n (%)	59 (6.0)	55 (5.6)	
Hypertension, n (%)	721 (73.0)	693 (70.4)	0.22
Hyperlipidemia, n (%)	553 (56.0)	525 (53.4)	0.25
Current cigarette use, n (%)	222 (22.5)	247 (25.1)	0.28
Creatinine clearance, mL/min			
Median	74.4	75.4	0.53
Interquartile range	56.5–99.2	57.1–94.8	
Prior myocardial infarction, n (%)	270 (27.3)	258 (26.2)	0.67
Prior percutaneous coronary intervention, n (%)	184 (18.6)	174 (17.7)	0.65
Prior coronary bypass surgery n (%)	110 (11.1)	105 (10.7)	0.79
Prior stroke or transient ischemic attack, n (%)	37 (3.7)	39 (4.0)	0.81
Left ventricular ejection fraction			
Median	55.0	50.0	0.25
Interquartile range	45–60	43.3–60	
Clinical presentation, n (%)			
Stable angina pectoris	257 (26.0)	250 (25.4)	0.75
Acute coronary syndrome	732 (74.2)	733 (74.6)	
Non–ST-elevation acute coronary syndrome	411 (41.6)	406 (41.3)	0.88
Unstable angina	183 (18.5)	182 (18.5)	0.99
Non–ST-elevation MI	226 (22.9)	224 (22.8)	0.95
ST-segment-elevation MI	321 (32.5)	327 (33.3)	0.73
Angiographic features, n (%)			
Single-vessel disease	344 (34.9)	334 (34.0)	
Double-vessel disease	351 (35.6)	350 (35.6)	0.89
Triple-vessel disease	292 (29.6)	299 (30.4)	

MI indicates myocardial infarction.

Table 2. Procedural Results

Patients	24-Month Clopidogrel (n=987)	6-Month Clopidogrel (n=983)	P
No. of treated lesions	1500	1546	
Mean±SD	1.52±0.86	1.57±0.94	
Median	1	1	0.37
Interquartile range	1–2	1–2	
Range	1–7	1–7	
≥2 Treated lesions, n (%)	365 (37)	371 (37.7)	0.73
≥3 Treated lesions, n (%)	108 (10.9)	115 (11.7)	0.57
≥4 Treated lesions, n (%)	38 (3.9)	44 (4.5)	0.49
Multivessel intervention, n (%)	253 (25.6)	273 (27.8)	0.28
LAD treated, n (%)	518 (52.5)	518 (52.7)	0.92
CFX treated, n (%)	321 (32.5)	318 (32.4)	0.93
RCA treated, n (%)	346 (35.1)	363 (36.9)	0.39
LMCA treated, n (%)	55 (5.6)	56 (5.7)	0.90
SVG treated, n (%)	23 (2.3)	17 (1.7)	0.34
At least 1 complex (type B2 or C) lesion, n (%)*	642 (65.1)	664 (67.6)	0.24
Total ACC/AHA score*†			0.19
Median	3	3	
Interquartile range	2–4	2–5	
At least 1 restenotic lesion, n (%)	45 (4.6)	48 (4.9)	0.75
Implanted stent type, n (%)			0.99
Bare-metal stent	246 (24.9)	246 (25.0)	
Everolimus-eluting stent	248 (25.1)	245 (24.9)	
Paclitaxel-eluting stent	245 (24.8)	245 (24.9)	
Everolimus-eluting stent	248 (25.1)	247 (25.1)	
No. of stents implanted			0.27
Mean±SD	1.82±1.23	1.90±1.25	
Median	2	2	
Interquartile range	1–2	1–2	
Range	1–10	1–11	
Length of stent, mm			0.43
Median	30	30	
Interquartile range	20–48	20–48	
Range	8–303	8–250	
Mean stent diameter, mm			0.43
Median	3	3	
Interquartile range	2.65–3.33	2.66–3.25	

LAD indicates left anterior descending artery; CFX, circumflex artery; RCA, right coronary artery; LMCA, left main coronary artery; SVG, saphenous vein graft; and ACC/AHA, American College of Cardiology/American Heart Association.

*Calculated in 952 patients in the 24-month clopidogrel arm and in 943 patients in the 6-month clopidogrel arm who presented with ≥1 de novo lesion; ACC/AHA score was missing in 3 patients.

†As described previously,[18] type A stenoses were coded 1 point, type B1 stenoses 2 points, type B2 stenoses 3 points, and type C stenoses 4 points.

Results

From December 2006 to December 2008, a total of 2789 patients underwent screening, and 2013 were ultimately recruited into the study and randomized to receive 1 of the 4 stent types (Figure 1). Thirty-three patients (1.6%) died within 30 days, and 10 patients withdrew consent; therefore, 1970 patients were randomly allocated at 1 month to undergo 24-month versus 6-month clopidogrel therapy. The 2 groups were well balanced with regard to baseline and angiographic characteristics (Tables 1 and 2).

The median age was 69 years; roughly one fourth of the patient population had a history of diabetes mellitus or prior myocardial infarction. Nearly two thirds of the patients presented with acute coronary syndromes, including acute ST-segment–elevation myocardial infarction in 30% of the

Table 3. Use of Medications During Trial

	24-Month Clopidogrel	6-Month Clopidogrel	*P*
Drug therapy at 30 d, n (%)			
No. evaluated	987	983	
Aspirin	987 (100)	983 (100)	>0.99
Clopidogrel	987 (100)	983 (100)	>0.99
Aspirin and clopidogrel	987 (100)	983 (100)	>0.99
ACE inhibitors	789 (80.0)	743 (75.6)	0.25
Angiotensin II receptor antagonist	69 (7.0)	86 (8.7)	0.18
β-blockers	828 (84.6)	810 (83.6)	0.55
Statins	898 (91.0)	905 (92.1)	0.85
Proton pump inhibitors	375 (38.0)	363 (36.9)	0.62
Drug therapy at 6 mo, n (%)			
No evaluated, total (DES/BMS)	966 (725/241)	963 (723/240)	
Aspirin	960 (99.4)	954 (99.1)	0.43
Clopidogrel	960 (99.4)	805 (83.6)	<0.0001
DES patients	721 (99.5)	711 (98.3)	0.09
BMS patients	239 (99.2)	94 (39.2)	<0.0001
Aspirin and clopidogrel	954 (98.8)	800 (83.1)	<0.0001
ACE inhibitors	754 (78.0)	743 (77.2)	0.87
Angiotensin II receptor antagonist	94 (9.7)	89 (9.2)	0.74
β-blockers	811 (84.0)	802 (83.3)	0.91
Statins	876 (90.7)	866 (89.9)	0.90
Proton pump inhibitors	369 (38.2)	298 (30.9)	0.019
Drug therapy at 12 mo, n (%)			
No. evaluated, total (DES/BMS)	948 (712/236)	942 (710/232)	
Aspirin	939 (99.0)	926 (98.3)	0.15
Clopidogrel	932 (98.3)	33 (3.5)	<0.0001
DES patients	699 (98.2)	25 (3.5)	<0.0001
BMS patients	233 (98.7)	8 (3.5)	<0.0001
Aspirin and clopidogrel	923 (97.4)	32 (3.4)	<0.0001
ACE inhibitors	743 (78.4)	739 (78.5)	0.99
Angiotensin II receptor antagonist	102 (10.8)	102 (10.8)	0.96
β-blockers	770 (81.2)	772 (82.0)	0.90
Statins	845 (89.1)	834 (88.5)	0.92
Proton pump inhibitors	358 (37.8)	294 (31.2)	0.036
Drug therapy at 18 mo, n (%)			
No. evaluated, total (DES/BMS)	933 (699/234)	932 (701/231)	
Aspirin	921 (98.7)	913 (98.0)	0.21
Clopidogrel	904 (96.9)	8 (0.9)	<0.0001
DES patients	673 (96.3)	6 (0.9)	<0.0001
BMS patients	231 (98.7)	2 (0.9)	<0.0001
Aspirin and clopidogrel	895 (95.9)	6 (0.6)	<0.0001
ACE inhibitors	717 (76.8)	712 (76.4)	0.93
Angiotensin II receptor antagonist	104 (11.1)	118 (12.7)	0.37
β-blockers	757 (81.1)	755 (81.0)	0.98
Statins	828 (88.7)	821 (88.1)	0.91
Proton pump inhibitors	352 (37.7)	301 (32.3)	0.088
Drug therapy at 24 mo, n (%)			
No. evaluated, total (DES/BMS)	920 (690/230)	920 (693/227)	
Aspirin	905 (98.4)	897 (97.5)	0.19
Clopidogrel	880 (95.7)	5 (0.5)	<0.0001
DES patients	654 (94.8)	5 (0.7)	<0.0001
BMS patients	226 (98.3)	0	<0.0001
Aspirin and clopidogrel	871 (94.7)	3 (0.3)	<0.0001
ACE inhibitors	707 (76.8)	708 (77.0)	0.97
Angiotensin II receptor antagonist	112 (12.2)	119 (12.9)	0.65
β-blockers	750 (81.5)	749 (81.4)	0.99
Statins	818 (88.9)	811 (88.2)	0.91
Proton pump inhibitors	344 (37.4)	302 (32.8)	0.16

ACE indicates angiotensin-converting enzyme; DES, drug-eluting stent; and BMS, bare-metal stent.

cases, and more than half of the patients had multivessel disease. At least 1 complex lesion, defined according to the American College of Cardiology/American Heart Association scale,[18] was treated in >65% of the patients, and everolimus-eluting, paclitaxel-eluting, or zotarolimus-eluting stents or BMS were implanted in one fourth of the patients, as per the randomization scheme.

Follow-Up and Clinical Outcomes

Overall, there were 118 patients (12%) in the short-term arm who discontinued clopidogrel after the first month versus 2 (0.2%) in the 24-month clopidogrel group. All of these patients received BMS at the time of intervention as per randomization. Among the patients allocated to the DES groups, clopidogrel was discontinued for various reasons before 6 months in 5 and 7 patients in the long- and short-term clopidogrel groups, respectively.

During the follow-up period, adherence to the assigned study treatment progressively increased from 6 to 12 months in both groups, and it was ≈97% at 12 months and ≈95% at 24 months in the 24-month clopidogrel group and >95% at both 12 and 24 months in the 6-month clopidogrel group (Table 3). Clinical follow-up at 2 years with respect to the primary and secondary end points was complete for 99.7% of patients in the long-term clopidogrel group and for 99.6% of those in the short-term clopidogrel group.

During the follow-up period, 130 patients died, 73 of cardiovascular causes. A total of 80 patients had an acute myocardial infarction, 35 had a cerebrovascular accident (of which 14 were confirmed as having intracranial hemorrhage), and 12 had definite stent thrombosis. Overall, there were 181 bleeding events according to the Bleeding Academic Research Consortium classification, of which 107 were included in the key safety end point and 14 were reported to be fatal.

The Kaplan-Meier estimate of the event rate for the primary end point (death of any cause, myocardial infarction, or cerebrovascular accident) at 2 years was 10.1% in the 24-month clopidogrel group compared with 10.0% in the 6-month clopidogrel group (hazard ratio, 0.98; 95% CI,

Table 4. Outcome Rates at 24 Months According to Treatment Group*

	24-Month Clopidogrel (n=987)	6-Month Clopidogrel (n=983)	Hazard Ratio (95% CI)	*P*
Primary efficacy end point, n (%)				
Death of any cause, myocardial infarction, or cerebrovascular accident	100 (10.1)	98 (10.0)	0.98 (0.74–1.29)	0.91
Secondary efficacy end points, n (%)				
Death of any cause or myocardial infarction	88 (8.9)	94 (9.6)	1.07 (0.80–1.43)	0.62
Death of any cause or cerebrovascular accident	77 (7.8)	70 (7.1)	0.91 (0.66–1.26)	0.57
Death of any cause	65 (6.6)	65 (6.6)	1.00 (0.72–1.40)	0.98
Death of cardiovascular cause	36 (3.7)	37 (3.8)	1.03 (0.66–1.61)	0.89
Myocardial infarction	39 (4.0)	41 (4.2)	1.06 (0.69–1.63)	0.80
Cerebrovascular accident	21 (2.1)	14 (1.4)	0.60 (0.29–1.23)	0.17
Confirmed intracranial hemorrhage	10 (1.0)	4 (0.4)	0.40 (0.13–1.28)	0.12
Definite stent thrombosis				
Late	8 (0.8)	4 (0.4)	0.67 (0.19–2.37)	0.53
Very late	0	3 (0.3)	1.51 (0.25–9.00)	0.65
Cumulative	8 (0.8)	7 (0.7)	0.88 (0.32–2.42)	0.80
Definite or probable stent thrombosis				
Late	10 (1.0)	9 (0.9)	0.90 (0.37–2.22)	0.82
Very late	3 (0.3)	6 (0.6)	2.00 (0.50–8.06)	0.32
Cumulative	13 (1.3)	15 (1.5)	1.15 (0.55–2.41)	0.70
Definite, probable, or possible stent thrombosis				
Late	26 (2.6)	28 (2.9)	1.07 (0.64–1.83)	0.78
Very late	12 (1.3)	18 (1.9)	1.50 (0.73–3.12)	0.27
Cumulative	38 (3.9)	46 (4.7)	1.21 (0.79–1.86)	0.38
Safety end points, n (%)				
BARC classification*				
Type 5	9 (0.9)	5 (0.5)	0.56 (0.19–1.66)	0.29
Type 5A	3 (0.3)	0		
Type 5B	6 (0.6)	5 (0.5)		
Type 4	0	2 (0.2)		0.47
Type 3	25 (2.5)	14 (1.4)	0.56 (0.29–1.07)	0.075
Type 3A	16 (1.6)	11 (1.1)		
Type 3B	5 (0.5)	3 (0.3)		
Type 3C	4 (0.4)	0		
Type 2	39 (4.0)	15 (1.5)	0.38 (0.21–0.69)	0.0016
Type 1	11 (1.1)	8 (0.8)	0.72 (0.11–1.47)	0.65
Key safety end point (type 5, 3, or 2)	73 (7.4)	34 (3.5)	0.46 (0.31–0.69)	0.00018
Type 5 or 3	34 (3.4)	19 (1.9)	0.56 (0.32–0.98)	0.037
Type 3 or 2	64 (6.5)	29 (3.0)	0.45 (0.29–0.69)	0.00033
TIMI classification				
Major	16 (1.6)	6 (0.6)	0.38 (0.15–0.97)	0.041
Minor	11 (1.1)	9 (0.9)	0.82 (0.34–1.94)	0.66
Major or minor	27 (2.7)	15 (1.5)	0.55 (0.30–1.04)	0.063
BleedScore				
Total score				
Median	0	0		<0.0001
Interquartile range	0–1	0–0		

(*Continued*)

Table 4. Continued

	24-Month Clopidogrel (n=987)	6-Month Clopidogrel (n=983)	Hazard Ratio (95% CI)	*P*
Range	0–18	0–18		
0	729 (73.9)	845 (86.0)		<0.0001
1	47 (4.8)	20 (2.0)		
2	27 (2.7)	11 (1.1)		
3	104 (10.5)	65 (6.6)		
4	13 (1.3)	4 (0.4)		
≥5	67 (6.8)	38 (3.9)		
Red blood cell transfusion	26 (2.6)	13 (1.3)	0.50 (0.26–0.98)	0.041

CI indicates confidence interval; BARC, Bleeding Academic Research Consortium; and TIMI, Thrombolysis In Myocardial Infarction.

For the total number of events for each type of end point, first events only were counted. Cumulative rates of events were based on Kaplan-Meier estimates.

*Type 5 refers to fatal bleeding. Type 4 refers to coronary artery bypass–related bleeds. Type 3 bleeds are divided into 3A (overt bleeding plus hemoglobin drop of 3 to <5 g/dL or any transfusion with overt bleeding), 3B (overt bleeding plus hemoglobin drop ≥5 g/dL or cardiac tamponade or bleeding requiring surgical intervention for control, excluding dental/nasal/skin/hemorrhoid, or bleeding requiring intravenous inotropes), or 3C (intracranial hemorrhage or intraocular bleed compromising vision). Type 2 bleeds are any overt, actionable sign of hemorrhage that does not fit the criteria for types 3, 4, or 5 but does meet at least 1 of the following criteria: (1) Requires nonsurgical/medical intervention by a healthcare professional; (2) leads to hospitalization or increased level of care; or (3) prompts evaluation. Type I refers to bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional.

0.74–1.29; $P=0.91$; Table 4; Figure 2A). There was no significant difference between the 2 treatment groups regarding the risk of individual secondary end points (death of any cause, death of cardiovascular causes, myocardial infarction, stroke, or stent thrombosis; Table 4; Figures 2B–2F).

Among the patients assigned to receive long-term dual-antiplatelet therapy compared with those assigned to receive short-term clopidogrel plus aspirin, there was a roughly 2-fold greater risk of type 5, 3, or 2 (hazard ratio, 2.17; 95% CI, from 1.44–3.22; $P=0.00018$; Table 4; Figure 1F) and type 5 or 3 bleeding events (hazard ratio, 1.78; 95% CI, from 1.02–3.13; $P=0.037$) according to the Bleeding Academic Research Consortium classification (Table 4).

The risks of TIMI-defined major bleeding and red blood cell transfusion were also increased in the 24-month clopidogrel group (Table 4). Consistent findings were also obtained by application of the BleedScore (Table 4).

Subgroup and Landmark Analysis

As shown in Figure 3, treatment assignment and the ischemic composite end point at 2 years proved to be consistent across the 9 prespecified subgroups. A signal of heterogeneity was noted in younger patients and individuals presenting with stable coronary artery disease, in whom there was a trend toward a lower ischemic composite end point at 2 years in the 6-month dual-antiplatelet therapy group; however, interaction tests did not reach formal significance. The effect of study treatment also proved to be consistent across recruitment sites ($P=0.85$ for interaction; online-only Data Supplement Figure I).

A total of 1924 patients reached the 6-month follow-up, of whom 963 were allocated to the 24-month dual-antiplatelet therapy group and 961 to the short-term clopidogrel duration arm; the incidence of the primary composite end point from 6 to 24 months was 7.2% (69 patients) in the long-term and 6.5% (62 patients) in the short-term clopidogrel therapy group (hazard ratio, 0.89; 95% CI, from 0.64–1.25; $P=0.53$; Figure 4A). Among 1443 patients who were randomly allocated to DES at the time of angioplasty, death of any cause, myocardial infarction, or cerebrovascular accident from the landmark time point of 6 up to 24 months occurred in 49 patients (6.8%) in the 24-month group and in 43 (6.0%) in the 6-month group (hazard ratio, 0.87; 95% CI, from 0.58–1.31; $P=0.51$; Figure 4B). Finally, in this subset of DES-treated patients, all-cause mortality (4.4% versus 4.0%; $P=0.81$), the composite of all-cause death or MI (6.0% versus 5.7%; $P=0.92$), and the rate of definite stent thrombosis (0.42% versus 0.56%; $P>0.99$) did not differ from 6 months onward in the 24-month versus the 6-month treatment groups.

Discussion

The present multicenter trial recruited a largely unselected patient population predominantly presenting with unstable coronary artery disease. Patients received implantation of a balanced proportion among 4 different stents, including 3 Food and Drug Administration–approved DES. We found no significant benefit associated with clopidogrel continuation (use of clopidogrel plus aspirin) compared with clopidogrel discontinuation (use of aspirin alone) after 6 months in reducing the incidence of death of any cause, myocardial infarction, or cerebrovascular accident at 2 years. On the other hand, 2-year clopidogrel therapy resulted in a significant increase in the number of actionable bleeding episodes,[19] which included events that required medical or surgical treatment, red blood cell transfusion, and life-threatening events.

Two randomized controlled studies have shown that 9 to 12 months of dual-antiplatelet therapy reduces the composite ischemic end point of death, myocardial infarction, or stroke compared with a 1-month regimen after BMS implantation.[1,2,12] However, 1-year results of these studies were

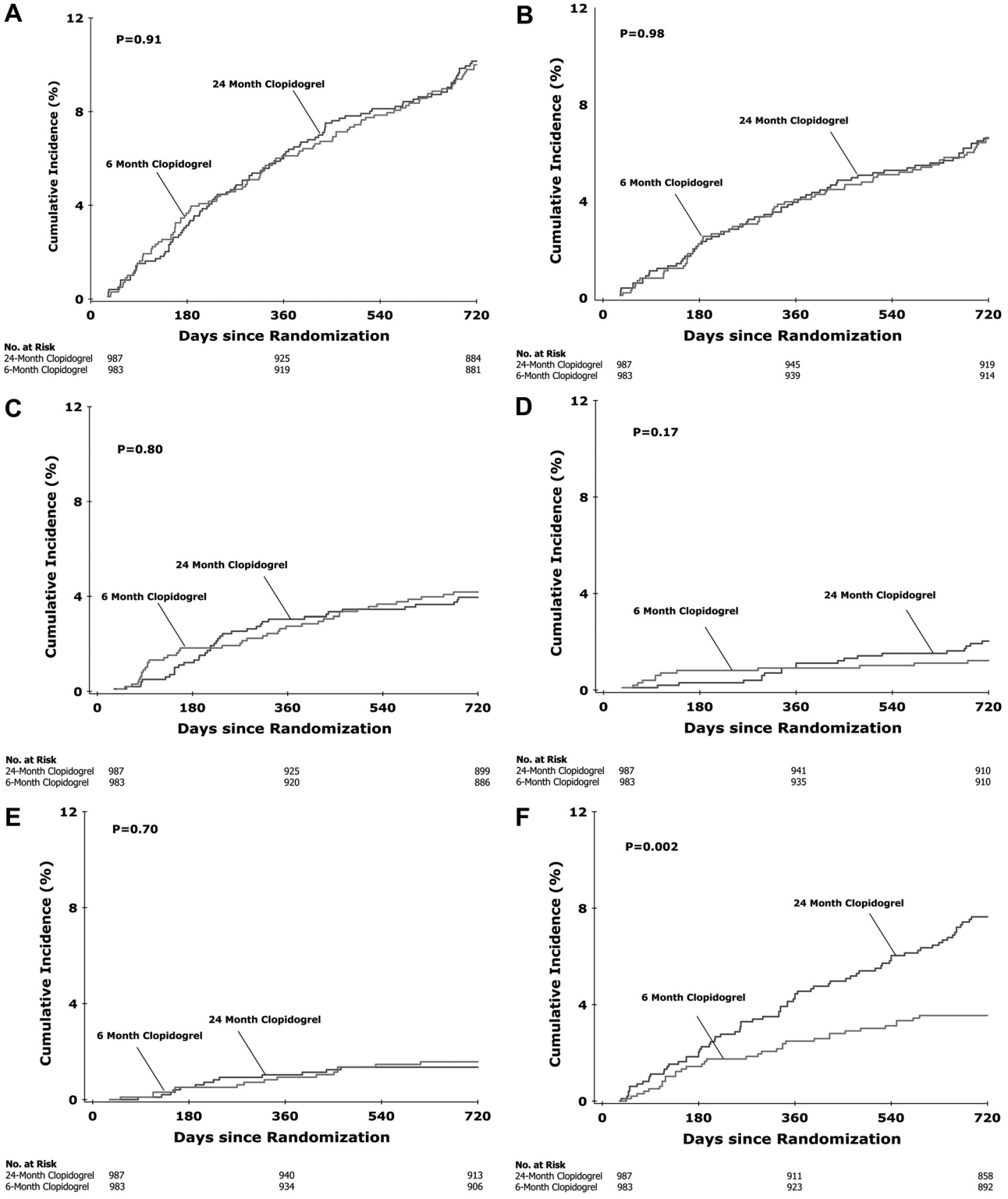

Figure 2. Cumulative incidence of the primary end point and selected secondary end points, according to treatment group. Cumulative incidence curves are shown for the primary end point of death of any cause, myocardial infarction, or cerebrovascular accident (**A**), death of any cause (**B**), myocardial infarction (**C**), any cerebrovascular accident (**D**), definite or probable stent thrombosis (**E**), and cumulative type 5, 3, or 2 bleeding events according to the Bleeding Academic Research Consortium classification (**F**). Probability values were calculated with log-rank test.

potentially biased by the difference in the pretreatment regimen between the 2 groups and were conducted more than a decade ago. Therefore, it remains unclear to what extent they remain relevant to current practice.

In the absence of randomized data, 2 independent observational registries[9,10] have largely influenced the current recommendation to prolong clopidogrel therapy for at least 12 months or for 6 to 12 months after DES implantation,

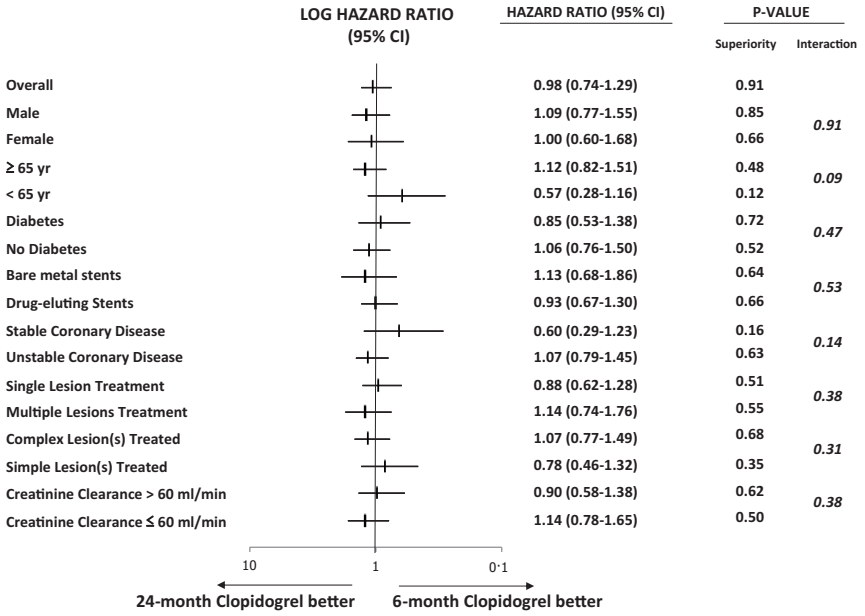

Figure 3. Subgroup analyses of the primary end point. Subgroup analyses are shown with hazard ratios and 95% confidence intervals (CI) for the primary end point of death of any cause, myocardial infarction, or cerebrovascular accident among subgroups of patients randomly assigned to either the 6- or 24-month clopidogrel therapy. The probability value for interaction represents the likelihood of interaction between the variable and the relative treatment effect.

despite the fact that their findings were not confirmed by many others.[8,11,20] The Basel Stent Cost-Effectiveness Trial–Late Thrombotic Events (BASKET-LATE; Current Controlled Trials No. ISRCTN75663024)[10] reported a >70% increase in death or myocardial infarction in DES recipients who discontinued clopidogrel at 6 months compared with patients who were treated with BMS. Similarly, a 50% increase in rates of death of any cause or myocardial infarction was observed in the Duke Heart Center registry in patients treated with DES who discontinued clopidogrel at 6 months compared with those who continued the treatment for 24 months.[9]

Therefore, we designed the present study to prospectively validate or refute previous observational data that would lead one to assume that prolonged and interrupted use of dual-antiplatelet therapy beyond 6 months is critical to achievement of an acceptable safety profile for DES while retaining its higher efficacy on reintervention compared with BMS.[21] Because the benefit of long-term clopidogrel therapy may extend beyond the type of coronary stent type implanted,[1,2] patients treated with BMS were also included in the present study.

The present patient population was minimally selected upfront and prospectively recruited at the time of intervention. As a consequence, the event rate and final study power were adequate, and the results of the present study can be interpreted with confidence.

At variance with previous[7] or ongoing[22–24] studies in which only event-free patients were or will be randomized to stop or continue clopidogrel therapy at 12 or 6 months, in the present

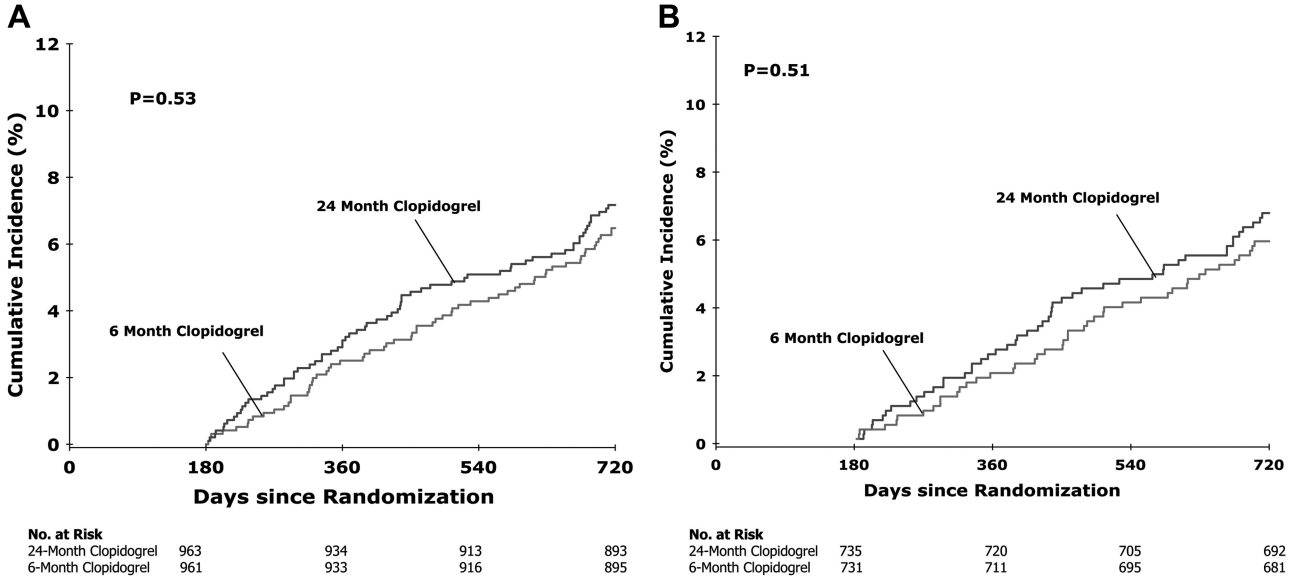

Figure 4. Landmark analyses. Cumulative rates of composite of death, myocardial infarction, or cerebrovascular accident in all recruited patients (**A**) or in patients who were randomly allocated to the drug-eluting stent groups (**B**) using the 6-month landmark analysis.

trial, patients were randomized at 1 month to continue dual-antiplatelet therapy for an additional 5 or 23 months, regardless of previous nonfatal ischemic or bleeding events. This was to avoid the selection of low-risk patients and to enable the provision of unique intention-to-treat data. Considerations regarding the ability to preserve long-term therapy with clopidogrel should influence the stent-type selection process.[3,6] Studies that randomize different durations of antiplatelet therapy as closely as possible to angioplasty may therefore be better suited to inform the decision-making process regarding DES versus BMS.

In this setting, the results of the present study are consistent with those reported previously by Park and colleagues,[7] who showed that the use of dual-antiplatelet therapy for a period of >12 months in patients who had received DES was not significantly more effective than aspirin monotherapy in reducing the rate of myocardial infarction or death of cardiac causes. In that study, ischemic and bleeding events were low, which negatively affected the power of the study and which may have been the consequence of selecting and randomizing event-free patients at 12 months.[7] Contrary to the findings of Park and colleagues,[7] bleeding events and transfusions were found to be higher in the 24-month clopidogrel group in the present study. The difference between the findings by Park et al[7] and our findings concerning bleeding may simply reflect the small number of hemorrhagic events reported in their study.

Stent thrombosis rates did not differ between the 2 groups, yet possible stent thrombosis events were numerically slightly higher in the 6-month dual-antiplatelet therapy group, especially from 12 months onward, when the difference in adherence to the 2 different treatment strategies was highest. Whether this minor difference is a play of chance or a true finding remains to be established.

On the other hand, cerebrovascular accidents trended in the opposite direction and were numerically increased in the 24-month dual-antiplatelet therapy group, which is again in keeping with previous observations.[7] Moreover, bleeding events, including life-threatening and fatal episodes, were numerically consistently higher in the group with 24 months of dual-antiplatelet therapy.

On subgroup analysis, a tendency toward more composite ischemic events in the 24-month dual-antiplatelet group was noted in some low-risk patients, ie, younger patients or individuals who presented with stable coronary artery disease. This observation is supported at least in part by previous evidence[25] and deserves further exploration.

Several limitations of the present study should be considered. The sample size of the present study was meant to confirm or refute the hypothesis that 24-month clopidogrel therapy would result in a ≥40% reduction in patient-oriented ischemic events compared with 6-month clopidogrel duration. Therefore, the present study cannot rule out the possibility that prolonging clopidogrel beyond 6 months would result in a lower than expected benefit or in a reduction in device-oriented end points such as stent thrombosis.

The open-label design may have introduced a potential for bias. We minimized this potential with the requirement that an independent committee that was unaware of the treatment assignments adjudicate all ischemic and hemorrhagic events. Moreover, no placebo therapy was administered to replace clopidogrel after 6 months in the short-term clopidogrel group.

It may be perceived that the inclusion of one fourth of the patients who were treated with BMS in the present study may have diluted the potential benefit of 24 months of dual-antiplatelet therapy in patients treated exclusively with DES implantation. However, the subgroup analysis provided reassuring data, because the point estimate for patients treated exclusively with DES slightly favored the 6-month duration of treatment with respect to the primary end point of the study, and no interaction was noted between stent type and duration of dual-antiplatelet therapy.

In the present study, we allowed BMS-treated patients with stable symptoms to stop treatment with clopidogrel after 1 month if they were allocated to the short-term group. This was justified by the lack of evidence supporting >1 month of treatment in this patient population. Because therapy was expected to start to differ between the 2 groups after 30 days (and actually did so in roughly 50% of the BMS group), the time frame of interest for the primary end point analysis was from 30 days onward. However, it can be argued that the use of clopidogrel did not differ in the vast majority of patients for the first 6 months and that the inclusion of events during the first 6 months, which would dilute the events that were possibly related to clopidogrel, may have biased the long-term clopidogrel group toward the null. Our landmark analysis focusing on events that occurred after 6 months in the whole population or in DES-only treated patients provides reassurance that the null finding of the present study may not be related to the study design but rather to a true biological observation.

In conclusion, the present study shows that the extended use of dual-antiplatelet therapy, for up to 24 months, was not significantly more effective than a 6-month duration of clopidogrel followed by aspirin monotherapy in reducing the risk of death of any cause, myocardial infarction, or cerebrovascular accident among all-comer patients recruited at the time of the index intervention. On the other hand, long-term duration of dual-antiplatelet therapy was associated with higher bleeding events and blood transfusion.

Appendix

Investigators Participating in the Study

Executive Committee: M. Valgimigli (principal investigator), G. Campo, G. Percoco, and R. Ferrari. *Data and Safety Monitoring Board:* N. Avigni and R. Mazzucco. *Clinical Events Committee:* P. Vranckx (chair), Belgium; S. Curello, Italy; G. Guardigli, Italy. *Data Management and Monitoring:* Medical Trial Analysis, Switzerland and Eustrategy Research Coordination, Italy (M. Monti, S. Gambetti, and L. Bristot). *Statistical Committee:* G. Parrinello (chair), University of Brescia.

Clinical Sites

Azienda Ospedaliero Universitaria di Ferrara, Italy: M. Valgimigli, G. Campo, M. Tebaldi, C. Tumscitz, C. Cavazza, E. Cangiano, M. Minarelli, C. Arcozzi, A. Scalone, M. Borghesi, J. Marchesini, and M. Monti. *Valle Oppio Hospital:* G.F. Percoco, M. Kubbajeh, and A. Frangione. *Villa Maria Cecilia Hospital:* A. Cremonesi, F. Castriota,

F. Colombo, K. Oshoala, C. Garattoni, and P. Sbarzaglia. *Cento Hospital:* G. Fucà.

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Disclosures

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CLINICAL PERSPECTIVE

This study focusing on 2013 patients undergoing coronary stent implantation who received bare-metal, zotarolimus-eluting, paclitaxel-eluting, or everolimus-eluting stent implantation and were subsequently allocated to up to 6 months versus 24 months of clopidogrel therapy in addition to aspirin failed to show the anticipated superiority of long-term duration of dual-antiplatelet therapy in terms of a lower composite ischemic end point of overall death, myocardial infarction, or cerebrovascular accidents. The cumulative risk of the primary outcome at 2 years was 10.1% with 24-month dual-antiplatelet therapy compared with 10.0% with 6-month dual-antiplatelet therapy (hazard ratio, 0.98; 95% confidence interval, 0.74–1.29; $P=0.91$). The individual risks of death, myocardial infarction, cerebrovascular accident, or stent thrombosis did not differ between the study groups; however, there was a consistently greater risk of hemorrhage in the 24-month clopidogrel group according to all prespecified bleeding definitions, including the recently proposed Bleeding Academic Research Consortium classification. Two Korean studies have also previously reported a lack of benefit of either 12 or 24 months of clopidogrel therapy over 6 or 12 months of therapy, respectively. Therefore, altogether, the available evidence does not support the concept that the longer the duration of clopidogrel therapy after drug-eluting stent implantation, the better the outcomes. On the contrary, this study identifies the potential for harm with respect to major bleeding associated with prolonged use of dual-antiplatelet therapy.