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Antiplatelet Therapy Duration Following Bare Metal or Drug-Eluting Coronary Stents

The Dual Antiplatelet Therapy Randomized Clinical Trial

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IMPORTANCE Despite antirestenotic efficacy of coronary drug-eluting stents (DES) compared with bare metal stents (BMS), the relative risk of stent thrombosis and adverse cardiovascular events is unclear. Although dual antiplatelet therapy (DAPT) beyond 1 year provides ischemic event protection after DES, ischemic event risk is perceived to be less after BMS, and the appropriate duration of DAPT after BMS is unknown.

OBJECTIVE To compare (1) rates of stent thrombosis and major adverse cardiac and cerebrovascular events (MACCE; composite of death, myocardial infarction, or stroke) after 30 vs 12 months of thienopyridine in patients treated with BMS taking aspirin and (2) treatment duration effect within the combined cohorts of randomized patients treated with DES or BMS as prespecified secondary analyses.

DESIGN, SETTING, AND PARTICIPANTS International, multicenter, randomized, double-blinded, placebo-controlled trial comparing extended (30-months) thienopyridine vs placebo in patients taking aspirin who completed 12 months of DAPT without bleeding or ischemic events after receiving stents. The study was initiated in August 2009 with the last follow-up visit in May 2014.

INTERVENTIONS Continued thienopyridine or placebo at months 12 through 30 after stent placement, in 11 648 randomized patients treated with aspirin, of whom 1687 received BMS and 9961 DES.

MAIN OUTCOMES AND MEASURES Stent thrombosis, MACCE, and moderate or severe bleeding.

RESULTS Among 1687 patients treated with BMS who were randomized to continued thienopyridine vs placebo, rates of stent thrombosis were 0.5% vs 1.11% (n = 4 vs 9; hazard ratio [HR], 0.49; 95% CI, 0.15-1.64; *P* = .24), rates of MACCE were 4.04% vs 4.69% (n = 33 vs 38; HR, 0.92; 95% CI, 0.57-1.47; *P* = .72), and rates of moderate/severe bleeding were 2.03% vs 0.90% (n = 16 vs 7; *P* = .07), respectively. Among all 11 648 randomized patients (both BMS and DES), stent thrombosis rates were 0.41% vs 1.32% (n = 23 vs 74; HR, 0.31; 95% CI, 0.19-0.50; *P* < .001), rates of MACCE were 4.29% vs 5.74% (n = 244 vs 323; HR, 0.73; 95% CI, 0.62-0.87; *P* < .001), and rates of moderate/severe bleeding were 2.45% vs 1.47% (n = 135 vs 80; *P* < .001).

CONCLUSIONS AND RELEVANCE Among patients undergoing coronary stent placement with BMS and who tolerated 12 months of thienopyridine, continuing thienopyridine for an additional 18 months compared with placebo did not result in statistically significant differences in rates of stent thrombosis, MACCE, or moderate or severe bleeding. However, the BMS subset may have been underpowered to identify such differences, and further trials are suggested.

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Current clinical practice guidelines recommend a minimum of only 1 month of dual antiplatelet therapy (DAPT) after bare metal stent (BMS) placement following elective percutaneous coronary intervention (PCI), compared with 6 to 12 months for drug-eluting stents (DES),[1,2] and patients with acute coronary syndromes benefit from 12 months of therapy whether or not PCI with stent placement is performed.[3] Although randomized trial results[4] showed a reduction in stent thrombosis and nonstent-related myocardial infarction (MI) with thienopyridine therapy beyond 12 months after DES placement (among patients tolerating DAPT to 12 months), few trials have assessed optimal duration of DAPT after BMS.[5] Because BMS remain a commonly used alternative treatment strategy to DES, particularly for patients who present with acute coronary syndromes or in whom DAPT has perceived increased bleeding risk,[6,7] we compared (1) rates of stent thrombosis or major adverse cardiovascular and cerebrovascular events (MACCE) among randomized patients treated with BMS and (2) treatment duration effect among all randomized patients in the Dual Antiplatelet Therapy (DAPT) Study.

BARC *Bleeding Academic Research Consortium*

BMS *bare metal stent*

DES *drug-eluting stent*

DAPT *dual antiplatelet therapy*

GUSTO *Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries*

MACCE *major adverse cardiovascular and cerebrovascular events*

MI *myocardial infarction*

PCI *percutaneous coronary intervention*

Methods

We compared the randomized treatment effect of continuing to receive thienopyridine vs receiving placebo beyond 12 months with regard to stent thrombosis, MACCE, and bleeding after randomization until the completion of study drug treatment at 30 months among patients treated with BMS as well as the combined cohort of patients treated with BMS or DES. As a prespecified analysis, we assessed the consistency of treatment duration effect between patients treated with BMS or DES.

Study Design

The DAPT Study design has previously been described.[8] This double-blind, international, randomized clinical trial compared the risks and benefits of continued thienopyridine (clopidogrel or prasugrel) vs placebo, when given in addition to aspirin for the prevention of stent thrombosis or MACCE after coronary stent placement with either DES or BMS in patients who tolerated DAPT to 12 months. The results comparing randomized treatments in the DES-treated cohort have been reported separately.[4]

All institutions received approval from their institutional review boards, and each patient provided written informed consent for study participation.

Study Population and Procedures

In brief, patients who were candidates for DAPT and who received treatment with either DES or BMS were recruited. Stent treatment was performed according to site standards of care using only US Food and Drug Administration–approved DES and BMS devices. Types of DES included Cypher sirolimus-eluting stent (Cordis), Endeavor zotarolimus-eluting stent (Medtronic), TAXUS paclitaxel-eluting stent (Boston Scientific), and Xience/Promus everolimus-eluting stents (Abbott Vascular or Boston Scientific). All patients older than 18 years who met all enrollment inclusion and none of the exclusion criteria (eTable 1 in the Supplement) and signed the consent were enrolled into the trial within 3 days of the index procedure, and all received open-label aspirin plus thienopyridine for the first 12 months. As permitted by regulatory authorities, race and ethnicity data were collected via patient self-report. Race categories for this study were prespecified as American Indian or Alaska Native, Asian, black or African American, Native Hawaiian or other Pacific Islander, white, and other. Ethnicity was collected as Hispanic or Latino and not Hispanic or Latino.

At 12 months, patients who were alive and free from MI, stroke, repeat coronary revascularization, stent thrombosis, and moderate or severe bleeding and who demonstrated adherence with thienopyridine treatment were then eligible for randomization (**Figure**) to continue receiving thienopyridine or to receive placebo, and all continued aspirin. A computer-generated randomization schedule stratified patients according to the type of stent they had received (DES vs BMS), hospital site, thienopyridine type, and presence or absence of at least 1 prespecified clinical- or lesion-related risk factor for stent thrombosis (eTable 2 in the Supplement). Postrandomization study procedures and follow-up were the same for all patients regardless of whether they had BMS or DES.

Study End Points

The co-primary effectiveness end points were cumulative incidence of definite or probable stent thrombosis according to the Academic Research Consortium classification[9] and incidence of MACCE at 12 to 30 months. For randomized comparison of DAPT duration among patients treated with BMS, the primary safety end point was moderate or severe bleeding (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries [GUSTO] classification)[10] at 12 to 30 months. Finally, clinically actionable bleeding not related to coronary artery bypass graft procedures was also evaluated according to the Bleeding Academic Research Consortium definitions (BARC type 2, 3, or 5).[11] These events were adjudicated by an independent clinical events committee blinded to treatment assignment and administered by the Harvard Clinical Research Institute (HCRI). An unblinded independent central data monitoring committee oversaw the safety of all patients.

Statistical Analysis

Among patients treated with BMS and randomized to continued thienopyridine vs placebo, the cumulative incidence of stent thrombosis and of MACCE are presented according to intention-to-treat. Treatments were compared using a log-rank test stratified by geographic region (North America, Europe, and Australia/New Zealand), thienopyridine type, and pres-

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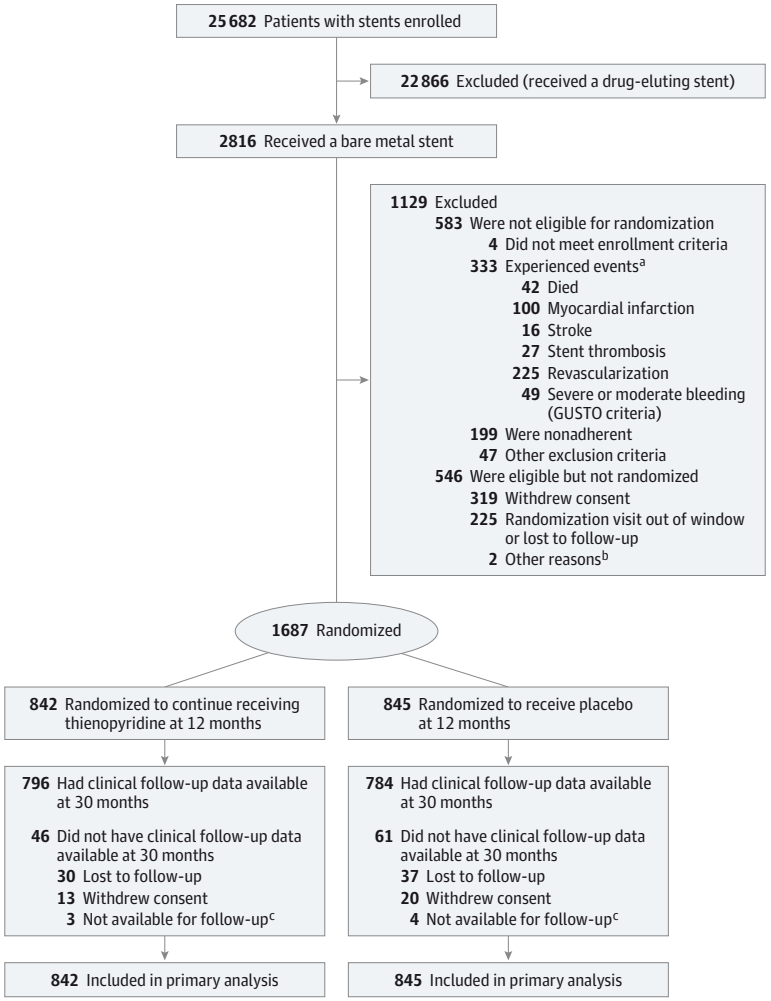
Figure. Enrollment, Randomization, and Follow-up Among Randomized Patients Treated With Bare Metal Stents



Screening for eligibility data were not available to report. Although the number of patients with available data on clinical follow-up at 30 months is reported in each group, the efficacy end points were analyzed with the last available follow-up information in the intention-to-treat population, which included all patients who underwent randomization. GUSTO indicates Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries.

[a] Participants may have experienced more than 1 event.

[b] Site terminated participation; participant was not recognized to be eligible by site.

[c] Patients moved, were incarcerated, or were prematurely exited from the study.

ence or absence of stent thrombosis risk factors (**Table 1**).[8] For each end point, the stratified hazard ratio (HR) and its 2-sided 95% CI comparing continued thienopyridine vs placebo are presented. Patients not experiencing the co-primary end points at 12 to 30 months after the index procedure were censored at the time of last known contact or 30 months, whichever was earlier.

The analysis of the BMS cohort comparing randomized treatment groups was a prespecified secondary analysis of the DAPT Study that was not powered to compare treatment groups within this cohort (the powered DES-treated cohort has been previously presented[4]) but was performed to assess consistency of the randomized treatment effect among patients treated with BMS vs DES from the DAPT Study. As a prespecified analysis, stent type × randomized treatment interaction was assessed using Cox proportional hazards regression for ischemic events and logistic regression for bleeding events; stratified HR for ischemic events and non-stratified risk difference for bleeding events, their 95% CI, and *P* values for interaction are presented. All other analyses presented were prespecified.

All statistical analyses were conducted at HCRI with SAS version 9.2 (SAS Institute). All *P* values are 2-sided and considered significant at the .05 level.

Results

Enrollment in the DAPT Study was conducted between August 2009 and July 2011, with the last follow-up visit conducted in May 2014. Of 2816 enrolled patients treated with BMS, 583 (20.7%) were not eligible for randomization (mainly due to clinical events requiring continuation of DAPT, such as MI or repeat revascularization procedures) after 12 months of follow-up, 546 (19.4%) were eligible but not randomized, and 1687 (59.9%) were randomized (Figure). Of 25 682 total enrolled patients, 5844 (22.8%) were not eligible for randomization after 12 months of follow-up, 8190 (31.9%) were eligible but not randomized, and 11 648 (45.4%) were randomized, with median follow-up of 990 days (interquartile range, 981-990) (eFigure in the Supplement). The most common reason eligible patients were not randomized was withdrawal of consent.

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Table 1. Baseline Characteristics of Randomized Patients Treated With Bare Metal Stents[a]

	No. (%)	
	Continued Thienopyridine (n = 842)	Received Placebo (n = 845)
Age, mean (SD), y	58.9 (10.5)	59.2 (11.1)
Female sex	215 (25.5)	184 (21.8)
Nonwhite race[b]	62 (7.5)	61 (7.3)
Weight, mean (SD), kg	88.0 (18.4)	88.5 (18.8)
BMI, mean (SD)	29.5 (5.2)	29.6 (5.6)
Diabetes mellitus	181 (21.7)	173 (20.7)
Hypertension	534 (64.0)	543 (64.6)
Cigarette smoker	360 (43.3)	350 (43.3)
Stroke/TIA	43 (5.1)	34 (4.0)
Congestive heart failure	35 (4.2)	28 (3.3)
Peripheral arterial disease	35 (4.2)	46 (5.5)
Prior PCI	150 (17.9)	171 (20.3)
Prior CABG	50 (6.0)	50 (5.9)
Prior MI	160 (19.4)	178 (21.5)
Indication for PCI		
STEMI	311 (36.9)	324 (38.3)
NSTEMI	184 (21.9)	169 (20.0)
Unstable angina[c]	77 (9.1)	81 (9.6)
Stable angina	199 (23.6)	198 (23.4)
Other	71 (8.4)	73 (8.6)
Any risk factor for stent thrombosis	568 (69.2)	569 (69.0)
Any clinical	525 (64.0)	521 (63.2)
Enzyme-positive ACS (STEMI or NSTEMI)	495 (58.8)	493 (58.3)
Renal insufficiency/failure	28 (3.4)	20 (2.4)
LVEF <30%	32 (4.0)	29 (3.6)
Any lesion-related	325 (38.7)	316 (37.5)
>2 vessels stented	0	1 (0.1)
>2 lesions per vessel	9 (1.1)	8 (1.0)
Lesion length ≥30 mm	55 (6.5)	56 (6.6)
Bifurcation lesion side branch ≥2.5 mm	38 (4.5)	34 (4.0)
In-stent restenosis of a DES	3 (0.4)	6 (0.7)
Vein bypass graft stented	22 (2.6)	20 (2.4)
Unprotected left main stented	0	1 (0.1)
Thrombus-containing lesion	243 (28.9)	219 (25.9)
Prior brachytherapy	1 (0.1)	1 (0.1)
Region		
North America	509 (60.5)	519 (61.4)
Europe	304 (36.1)	300 (35.5)
Australia or New Zealand	29 (3.4)	26 (3.1)
Thienopyridine drug at randomization		
Clopidogrel	730 (86.7)	732 (86.6)
Prasugrel	112 (13.3)	113 (13.4)
No. of treated lesions, mean (SD)	1.2 (0.4)	1.2 (0.4)

(continued)

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Table 1. Baseline Characteristics of Randomized Patients Treated With Bare Metal Stents[a] (continued)

	No. (%)	
	Continued Thienopyridine (n = 842)	Received Placebo (n = 845)
No. of treated vessels, mean (SD)	1.0 (0.2)	1.1 (0.2)
No. of stents, mean (SD)	1.3 (0.6)	1.3 (0.6)
Minimum stent diameter (per patient)		
<3 mm	201 (23.9)	206 (24.4)
≥3 mm	641 (76.1)	639 (75.6)
Total stent length, mean (SD), mm	24.0 (13.0)	23.9 (13.1)
Lesion characteristics, No. (%)[d]		
Treated vessel		
Left main	0	1 (0.1)
LAD	308 (31.6)	306 (30.9)
RCA	437 (44.8)	452 (45.6)
Circumflex	206 (21.1)	207 (20.9)
Venous graft	24 (2.5)	25 (2.5)
Arterial graft	0	0
Modified ACC/AHA lesion class B2 or C[e]	440 (47.6)	450 (47.8)

Abbreviations: ACC, American College of Cardiology; ACS, acute coronary syndrome; AHA, American Heart Association; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CABG, coronary artery bypass graft procedure; DES, drug-eluting stent; LAD, left anterior descending; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST elevation MI; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-elevation MI; TIA, transient ischemic attack.

[a] For all variables, 0%-4% of patients had missing values.

[b] Race was self-reported.

[c] This category included unstable angina without reported elevation of cardiac enzymes.

[d] A total of 975 lesions were treated in the continued thienopyridine group and 991 in the placebo group.

[e] The definitions of class B2 and class C lesions according to the modified ACC/AHA criteria.[12]

Baseline characteristics of randomized patients treated with BMS were similar between the groups (Table 1). While the same inclusion and exclusion criteria were applied to all enrolled patients, DES- and BMS-treated patients differed according to clinical and procedural characteristics (eTable 2 in the Supplement). Patients treated with DES were more likely to have a history of diabetes mellitus (30.6% vs 21.2%, $P < .001$), hypertension, and previous PCI and to have longer lesions, with smaller reference vessel diameter, while patients treated with BMS were more likely to present with ST-elevation MI (STEMI, 37.6% vs 10.5%, $P < .001$) or non-STEMI (20.9% vs 15.5%, $P < .001$) and were more likely to have thrombus noted in the treated lesion. The baseline characteristics of the randomized patients treated with DES have been previously published.[4] Baseline characteristics of all randomized patients were similar between the randomly assigned treatment groups (eTable 2 in the Supplement). Predefined risk factors for stent thrombosis were present in 54% of patients in each randomly assigned treatment group.

Effect of Continued Thienopyridine Therapy Among Patients Treated With BMS

Among randomized patients treated with BMS, the cumulative incidence of stent thrombosis and MACCE were 0.5% vs 1.1% (HR, 0.49; 95% CI, 0.15-1.64; log-rank $P = .24$) and 4.0% vs 4.7% (HR, 0.92; 95% CI, 0.57-1.47; log-rank $P = .72$), respectively, for continued thienopyridine vs placebo at 12 to 30 months after the index procedure (**Table 2**). Moderate or severe GUSTO bleeding events occurred in 2.03% vs 0.90% among patients treated with BMS randomized to continued thienopyridine vs placebo ($P = .07$); BARC type 2, 3, or 5 bleeding events occurred in 4.56% vs 1.80%, respectively ($P = .002$). Severe bleeding was uncommon, fatal bleeding events (BARC type 5) were rare, and rates were not different between treatment groups (Table 2).

The results comparing continued thienopyridine vs placebo in the cohort treated with DES have been reported previously and demonstrated significant reductions in study co-primary end points of stent thrombosis (0.4% vs 1.4%, respectively; HR, 0.29; 95% CI, 0.17-0.48) and MACCE (4.3% vs 5.9%, respectively; HR, 0.71; 95% CI, 0.59-0.85) (driven by a reduction in both stent-related and non-stent-related MI) (**Table 3**). An increase in moderate/severe bleeding events was observed (2.5% vs 1.6%, respectively; $P = .001$), and a difference in all-cause mortality rate that was not statistically significant was seen (2.0% vs 1.5%; $P = .052$), yet mortality was infrequently related to bleeding (0.15% vs 0.09% with fatal bleeding, $P = .38$, and 0.22% vs 0.06% with bleeding-related mortality within the full 33-month follow-up, $P = .057$).[4]

Consistency of Effects of Continued Thienopyridine Across BMS- and DES-Treated Patients

The prespecified analysis of the effect of continued thienopyridine found nonsignificant interactions between randomized BMS- and DES-treated patients for both stent thrombosis (HR, 0.49 vs 0.29; interaction $P = .42$) and MACCE (HR, 0.92 vs 0.71; interaction $P = .32$) (Table 3).

Among all randomized patients, the co-primary effectiveness end points of stent thrombosis (0.41% vs 1.32%; HR, 0.31; 95% CI, 0.19 to 0.50; $P < .001$) and MACCE (4.29% vs 5.74%; HR, 0.73; 95% CI, 0.62 to 0.87; $P < .001$) were reduced by continued thienopyridine vs placebo, respectively (**Table 4**). The reduction in stent thrombosis was

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Table 2. Ischemic and Bleeding Outcomes of Randomized Patients Treated With Bare Metal Stents

	Patients, No. (%)[a]			
	Continued Thienopyridine (n = 842)	Received Placebo (n = 845)	Hazard Ratio (95% CI)	*P* Value
Ischemic Outcomes				
Stent thrombosis	4 (0.50)	9 (1.11)	0.49 (0.15 to 1.64)	.24
Definite	4 (0.50)	9 (1.11)	0.49 (0.15 to 1.64)	.24
Probable	0	0		
MACCE (death, MI, stroke)	33 (4.04)	38 (4.69)	0.92 (0.57 to 1.47)	.72
Death, all cause	8 (0.99)	10 (1.24)	0.90 (0.35 to 2.33)	.83
MI	22 (2.70)	25 (3.10)	0.91 (0.51 to 1.62)	.74
Related to stent thrombosis	4 (0.50)	9 (1.11)	0.49 (0.15 to 1.64)	.24
Not related to stent thrombosis	18 (2.21)	16 (1.99)	1.12 (0.57 to 2.20)	.74
Stroke (total)	6 (0.73)	5 (0.62)	1.22 (0.37 to 4.01)	.74
Ischemic	4 (0.49)	5 (0.62)	0.82 (0.22 to 3.05)	.77
Hemorrhagic	1 (0.12)	0		.32
Type uncertain	1 (0.12)	0		.32
Bleeding Complications	**(n = 790)**	**(n = 776)**	**Risk Difference, % Points (95% CI)**	
GUSTO severe or moderate	16 (2.03)	7 (0.90)	1.12 (−0.06 to 2.31)	.07
Severe	6 (0.76)	3 (0.39)	0.37 (−0.37 to 1.12)	.33
Moderate	10 (1.27)	4 (0.52)	0.75(−0.18 to 1.68)	.12
BARC type	36 (4.56)	14 (1.80)	2.75 (1.02 to 4.48)	.002
Type 2	22 (2.78)	7 (0.90)	1.88 (0.56 to 3.21)	.01
Type 3	16 (2.03)	6 (0.77)	1.25 (0.09 to 2.41)	.04
Type 5 (fatal)	0	1 (0.13)	−0.13 (−0.38 to 0.12)	.31

Abbreviations: ARC, Academic Research Consortium; BARC, Bleeding Academic Research Consortium; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction.

[a] Patients were randomized to continue receiving thienopyridine or to receive placebo plus aspirin 12 months after receiving a bare metal stent. The effectiveness end points, stent thrombosis and MACCE, are shown over the primary analysis period, eg, 12-30 months after enrollment. Percentages are Kaplan-Meier estimates. For the safety end point of GUSTO severe or moderate bleeding, patients whose last contact date was ≥510 days after randomization or who experienced any adjudicated bleeding outcome at or before 540 days were included. See eTable 3 in the Supplement for GUSTO and BARC definitions.

Table 3. Treatment × Stent Type Interaction and Outcomes[a]

	No. (%)			
	Continued Thienopyridine	Received Placebo	Hazard Ratio (95% CI)	*P* Value for Interaction
Definite or probable stent thrombosis				
DES	19 (0.4)	65 (1.4)	0.29 (0.17 to 0.48)	.42
BMS	4 (0.5)	9 (1.1)	0.49 (0.15 to 1.64)	
MACCE				
DES	211 (4.3)	285 (5.9)	0.71 (0.59 to 0.85)	.32
BMS	33 (4.0)	38 (4.7)	0.92 (0.57 to 1.47)	
Death				
DES	98 (2.0)	74 (1.5)	1.36 (1.00 to 1.85)	.41
BMS	8 (1.0)	10 (1.2)	0.90 (0.35 to 2.33)	
GUSTO severe/moderate bleeding			**Risk Difference (95% CI)**	
DES	119 (2.5)	73 (1.6)	0.96 (0.38 to 1.53)	.49
BMS	16 (2.0)	7 (0.9)	1.12 (−0.06 to 2.31)	

Abbreviations: BMS, bare metal stents; DES, drug-eluting stents; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; MACCE, major adverse cardiovascular and cerebrovascular events.

[a] Analyses of treatment interaction by stent type, shown for efficacy and safety outcomes at 12-30 months among all randomized patients (9961 treated with DES and 1687 treated with BMS).

largely explained by a reduction in definite stent thrombosis, and the reduction in MACCE was largely explained by a 48% relative reduction (1.83% absolute) in MI. Significant reductions were observed in MI related to stent thrombosis (0.38% vs 1.28%, HR, 0.29; 95% CI, 0.18 to 0.48; $P < .001$) as well as MI not related to stent thrombosis (1.84% vs 2.75%, HR, 0.65; 95% CI, 0.50 to 0.84; $P < .001$). In contrast, there was an increased incidence of severe/moderate bleeding events (2.45% vs 1.47%, risk difference, 0.98; 95% CI, 0.46 to 1.50; $P < .001$) largely explained by the relative increase in moderate bleeding (1.65% vs 0.96%, risk difference, 0.70; 95% CI, 0.27 to 1.12; $P = .001$). Similarly, BARC type 2, 3, or 5 bleeding events were significantly increased in the continued thienopyridine treatment group (5.44% vs 2.78%; HR, 2.65; 95% CI, 1.91 to 3.40; $P < .001$), yet fatal bleeding events (BARC type 5) were rare (0.13% vs 0.09%; $P = .58$) (Table 4).

Discussion

Among patients undergoing coronary stent placement with BMS and who tolerated 12 months of thienopyridine, con-

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Table 4. Ischemic and Bleeding Outcomes in All Randomized Patients (Treated With Bare Metal or Drug-Eluting Stent) Comparing Continued Thienopyridine vs Placebo

	Patients, No. (%)[a]			
	Continued Thienopyridine (n = 5862)	Received Placebo (n = 5786)	Hazard Ratio (95% CI)	*P* Value
Ischemic Outcomes				
Stent thrombosis	23 (0.41)	74 (1.32)	0.31 (0.19 to 0.50)	<.001
Definite	19 (0.34)	67 (1.20)	0.28 (0.17 to 0.47)	<.001
Probable	5 (0.09)	7 (0.12)	0.71 (0.23 to 2.24)	.56
MACCE (death, MI, stroke)	244 (4.29)	323 (5.74)	0.73 (0.62 to 0.87)	<.001
Death, all cause	106 (1.87)	84 (1.50)	1.31 (0.97 to 1.75)	.07
MI	121 (2.15)	223 (3.98)	0.52 (0.42 to 0.65)	<.001
Related to stent thrombosis	21 (0.38)	72 (1.28)	0.29 (0.18 to 0.48)	<.001
Not related to stent thrombosis	104 (1.84)	154 (2.75)	0.65 (0.50 to 0.84)	<.001
Stroke (total)	43 (0.76)	48 (0.86)	0.84 (0.55 to 1.28)	.42
Ischemic	28 (0.50)	39 (0.70)	0.70 (0.43 to 1.15)	.16
Hemorrhagic	14 (0.25)	9 (0.16)	1.31 (0.55 to 3.12)	.53
Type uncertain	1 (0.02)	1 (0.02)	1.01 (0.06 to 16.09)	>.99
Bleeding Complications	**(n = 5500)**	**(n = 5425)**	**Risk Difference, % Points (95% CI)**	
GUSTO severe or moderate	135 (2.45)	80 (1.47)	0.98 (0.46 to 1.50)	<.001
Severe	44 (0.80)	29 (0.53)	0.27 (−0.04 to 0.57)	.09
Moderate	91 (1.65)	52 (0.96)	0.70 (0.27 to 1.12)	.001
BARC type	299 (5.44)	151 (2.78)	2.65 (1.91 to 3.40)	<.001
Type 2	167 (3.04)	79 (1.46)	1.58 (1.03 to 2.13)	<.001
Type 3	138 (2.51)	74 (1.36)	1.15 (0.63 to 1.66)	<.001
Type 5 (fatal)	7 (0.13)	5 (0.09)	0.04 (−0.09 to 0.16)	.58

Abbreviations: BARC, Bleeding Academic Research Consortium; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction.

[a] Patients were randomized to continue receiving thienopyridine or to receive placebo plus aspirin 12 months after receiving a bare metal stent. The effectiveness end points, stent thrombosis and MACCE, are shown over the primary analysis period, eg, 12-30 months after enrollment. Percentages are Kaplan-Meier estimates. For the safety end point of GUSTO severe or moderate bleeding, patients whose last contact date was ≥510 days after randomization or who experienced any adjudicated bleeding outcome at or before 540 days were included. See eTable 3 in the Supplement for GUSTO and BARC definitions.

tinuing thienopyridine for an additional 18 months compared with placebo did not result in statistically significant differences in rates of stent thrombosis, MACCE, or moderate or severe bleeding. However, limitations in sample size and power make definitive conclusions regarding DAPT treatment duration effects within BMS difficult. While fewer patients treated with BMS were enrolled and randomized because of the prevailing use of DES in clinical practice, among patients eligible for continued DAPT, a prespecified analysis found nonsignificant interactions for the effect of continued thienopyridine therapy on stent thrombosis among BMS- and DES-treated patients who were randomized in the DAPT Study.[4] As this comparison of treatment interaction was not adequately powered for definitive interpretations, true differences in treatment effect size may not have been detected, and any interpretation that continued thienopyridine therapy beyond 1 year (among patients who tolerated DAPT for 1 year without major bleeding) may prevent ischemic events independent of stent type (DES or BMS) should be considered hypothesis-generating.

Indeed, over late-term follow-up (≥5 years), patients treated with BMS accrue cardiac events related to the target lesion at a rate of 2% or more per year[13] and beyond the target lesion at a rate of 5% or more per year.[14,15] Late atherothrombotic events after BMS may be due to lack of healing or uncovered stent struts, neoatherosclerosis,[16] restenosis,[17] or disease progression outside the stent, in other regions or vessels. The largest portion of MI prevented by extended-duration thienopyridine therapy in this study did not involve the stented coronary segments for either DES or BMS. While bleeding events were similarly increased with continued thienopyridine therapy beyond 1 year among both BMS- and DES-treated patients, these events were infrequently severe and rarely fatal (BARC type 5).[11] The numeric increase in mortality associated with continued thienopyridine therapy (2.0% vs 1.5%, *P* = .052) that was observed in the cohort treated with DES was not evident among randomized patients treated with BMS (1.0% vs 1.2%, *P* = .83).

The lack of apparent treatment interaction between DES and BMS supports the combined analysis of treatment effects of continued duration of therapy independent of stent type. Among the combined BMS and DES cohort, the reductions in stent thrombosis and MACCE were 69% and 27%, respectively, in patients continuing thienopyridine therapy together with aspirin. Fifty percent of the MIs prevented by continued DAPT were not related to stent thrombosis. These ischemic event benefits were balanced by a 67% relative increase in moderate or severe bleeding.

The major limitation of the BMS randomized comparison of DAPT duration is small sample size and lack of power, which limits the interpretability of the findings. However, an adequately powered randomized BMS cohort would require approximately 8000 additional patients, which was practically not feasible. An adequate number of patients treated with BMS were enrolled to allow a powered comparison of stent thrombosis and MACCE rates with patients

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treated with DES,[8] the results of which have been presented separately.[18] In this context, the design of the BMS randomized comparison was to evaluate for consistency or heterogeneity compared with the DES treatment effect in an exploratory fashion, rather than to be powered for a separate, independent analysis. Nonetheless, the BMS cohort sample size exceeds that of prior randomized BMS cohorts evaluating duration of antiplatelet therapy[5] and is similar in size to many prior randomized trials of DAPT duration in DES.[5,19-22] Although similar inclusion criteria were required of BMS- and DES-treated patients, there were systematic differences between BMS- and DES-treated patients, with a higher frequency of MI presentation before the index PCI procedure for patients treated with BMS and a higher prevalence of restenosis risk factors for patients treated with DES. Nevertheless, each cohort was balanced across randomized treatment groups as expected according to the stratified randomization.

Conclusions

Among patients undergoing coronary stent placement with BMS who tolerated 12 months of thienopyridine and aspirin therapy without major bleeding, continuing thienopyridine therapy in addition to aspirin beyond 12 months did not result in statistically significant differences in rates of stent thrombosis, MACCE, or moderate or severe bleeding. However, the BMS subset may have been underpowered to determine such differences.

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