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Benefits and Risks of Extended Dual Antiplatelet Therapy After Everolimus-Eluting Stents

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on behalf of the DAPT Study Investigators

ABSTRACT

OBJECTIVES The purpose of this study was to characterize outcomes for everolimus-eluting stent (EES)-treated subjects according to treatment with continued thienopyridine plus aspirin versus aspirin alone 12 to 30 months after stenting.

BACKGROUND In the DAPT (Dual Antiplatelet Therapy) study, continued thienopyridine plus aspirin beyond 1 year after coronary stenting reduced ischemic events. Given low rates of stent thrombosis and myocardial infarction (MI) for current drug-eluting stents, we examined outcomes among EES-treated subjects in the DAPT study.

METHODS The DAPT study enrolled 25,682 subjects (11,308 EES-treated) after coronary stenting. Following 12 months of treatment with thienopyridine and aspirin, eligible subjects continued treatment with aspirin and 9,961 (4,703 with EES) were randomized to 18 months of continued thienopyridine or placebo. Stent type was not randomized, and the EES subset analysis was post hoc.

RESULTS Among EES-treated patients, continued thienopyridine reduced stent thrombosis (0.3% vs. 0.7%, hazard ratio [HR]: 0.38, 95% confidence interval [CI]: 0.15 to 0.97; p = 0.04) and MI (2.1% vs. 3.2%, HR: 0.63, 95% CI: 0.44 to 0.91; p = 0.01) versus placebo but did not reduce a composite of death, MI, and stroke (4.3% vs. 4.5%, HR: 0.89, 95% CI: 0.67 to 1.18; p = 0.42), and increased moderate/severe bleeding (2.5% vs. 1.3%, HR: 1.79, 95% CI: 1.15 to 2.80; p = 0.01), and death (2.2% vs. 1.1%, HR: 1.80, 95% CI: 1.11 to 2.92; p = 0.02). Death due to cancer and not related to bleeding was increased (0.64% vs. 0.17%; p = 0.01).

CONCLUSIONS In EES-treated subjects, significant reductions in stent thrombosis and MI and an increase in bleeding were observed with continued thienopyridine beyond 1 year compared with aspirin alone. (The Dual Antiplatelet Therapy Study [DAPT Study]); NCT00977938) (J Am Coll Cardiol Intv 2016;9:138–47) © 2016 by the American College of Cardiology Foundation.

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In the DAPT (Dual Antiplatelet Therapy) study, patients who were free from major ischemic or bleeding events at 1 year after coronary stenting (either drug-eluting stents [DES] or bare-metal stents [BMS]), experienced significant reductions in stent thrombosis and myocardial infarction (MI) but increases in moderate or severe bleeding when treated with 30 months of thienopyridine plus aspirin compared with 12 months (1,2). Approved DES have been designed with different metallic scaffold designs, polymers, and eluted medications, resulting in different effectiveness and safety outcomes in clinical trials. Recent randomized trials and meta-analysis suggest that everolimus-eluting stents (EES), the most commonly used stent type in both the DAPT study as well as current clinical practice, are associated with lower rates of stent thrombosis compared with paclitaxel-eluting stents (3-5).

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Subjects treated with any DES approved and available in the United States at the time of study enrollment were eligible to be enrolled in the DAPT study. Although patients were not randomized to stent types, in adjusted analysis, there was heterogeneity in the relative reduction in major adverse cardiovascular and cerebrovascular events (MACCE) (a composite endpoint of death, MI, or stroke) according to stent type (1), and a large treatment benefit for continued therapy was observed among the subset of patients treated with paclitaxel-eluting stents (n = 2,666 randomized) (6). To determine whether the results of the DAPT study were generalizable to EES, we evaluated the benefits and risks of treatment with thienopyridine plus aspirin for 30 versus 12 months in the large subset of patients (11,308 enrolled, 4,703 randomized).

METHODS

DESIGN. The DAPT study was a double-blind, international, multicenter, randomized, placebo-controlled trial designed (7) to compare 30 versus 12 months of aspirin plus thienopyridine therapy (clopidogrel or prasugrel) after coronary stenting with either DES or BMS (NCT00977938). Randomization was stratified by DES/BMS, hospital site, subject complexity, and thienopyridine drug type. The results comparing randomized treatments among DES- (1) and BMS-treated (2) cohorts on ischemic and bleeding endpoints, as well as comparing BMS- versus DES-treated patients on these endpoints (8), have been reported. The institutional review board at each participating institution approved the study, and each participant provided written, informed consent.

The primary study analysis within all randomized DES-treated patients compared randomized treatments with respect to the primary effectiveness endpoints of stent thrombosis and MACCE from 12 to 30 months post-procedure and the primary safety endpoint of moderate or severe bleeding from 12 to 30 months post-procedure (1). DES types included EES (Xience, Abbott Vascular, Santa Clara, California; PROMUS, Boston Scientific, Marlborough, Massachusetts), sirolimus-eluting stents (Cypher, Cordis, Bridgewater, New Jersey), zotarolimus-eluting stents (Endeavor, Medtronic, Minneapolis, Minnesota), and paclitaxel-eluting stents (TAXUS, Boston Scientific, Marlborough, Massachusetts). Although stent type among various DES was not randomized, assessments of randomized treatment-by-DES type interactions on stent thrombosis and MACCE were pre-specified to determine whether the randomized treatment effect was consistent across DES types. Although randomized treatment effect on stent thrombosis did not vary

ABBREVIATIONS AND ACRONYMS

BMS = bare-metal stent(s)

CI = confidence interval

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

EES = everolimus-eluting stent(s)

HR = hazard ratio

MACCE = major adverse cardiovascular and cerebrovascular events

MI = myocardial infarction

St. Jude Medical; and has received speakers fees from AstraZeneca, Eli Lilly and Company, Abbott, Biotronik, Boston Scientific, Biosensors, Medtronic, and Bayer. Dr. Steg has received research funding from Sanofi and Servier; is a consultant for Amarin, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, CSL-Behring, Daiichi-Sankyo-Lilly, GlaxoSmithKline, Janssen, Medtronic, Merck Sharp & Dohme, Novartis, Pfizer, Regeneron, Sanofi, Servier, and The Medicines Company; and is a stockholder in Aterovax. Dr. Yeh is on an advisory board of Abbott Vascular; and is a consultant for Gilead Sciences, Boston Scientific, and Merck. Dr. Cohen receives research grant support from Eli Lilly, AstraZeneca, Daiichi-Sankyo, Medtronic, Abbott Vascular, and Boston Scientific; is a consultant for Eli Lilly, AstraZeneca, Medtronic, and Abbott Vascular; and receives speaking honoraria from AstraZeneca. Dr. Cutlip received research funding (paid to his institution) from Medtronic, Boston Scientific, and Celonova. Dr. Massaro has received funding from Harvard Clinical Research Institute for statistical services for the paper. Dr. Mauri has received grants (to her institution) from Abbott, Boston Scientific, Cordis, Medtronic, Eli Lilly and Company, Daiichi-Sankyo, Sanofi, Bristol-Myers Squibb, Boehringer Ingelheim, and Biotronik; is a consultant for Amgen, Medtronic, Eli Lilly and Company, Boehringer Ingelheim, Recor, and Biotronik; and has received honoraria from AstraZeneca and Sanofi. Drs. Kereiakes and Hsieh have reported that they have no relationships relevant to the contents of this paper to disclose.

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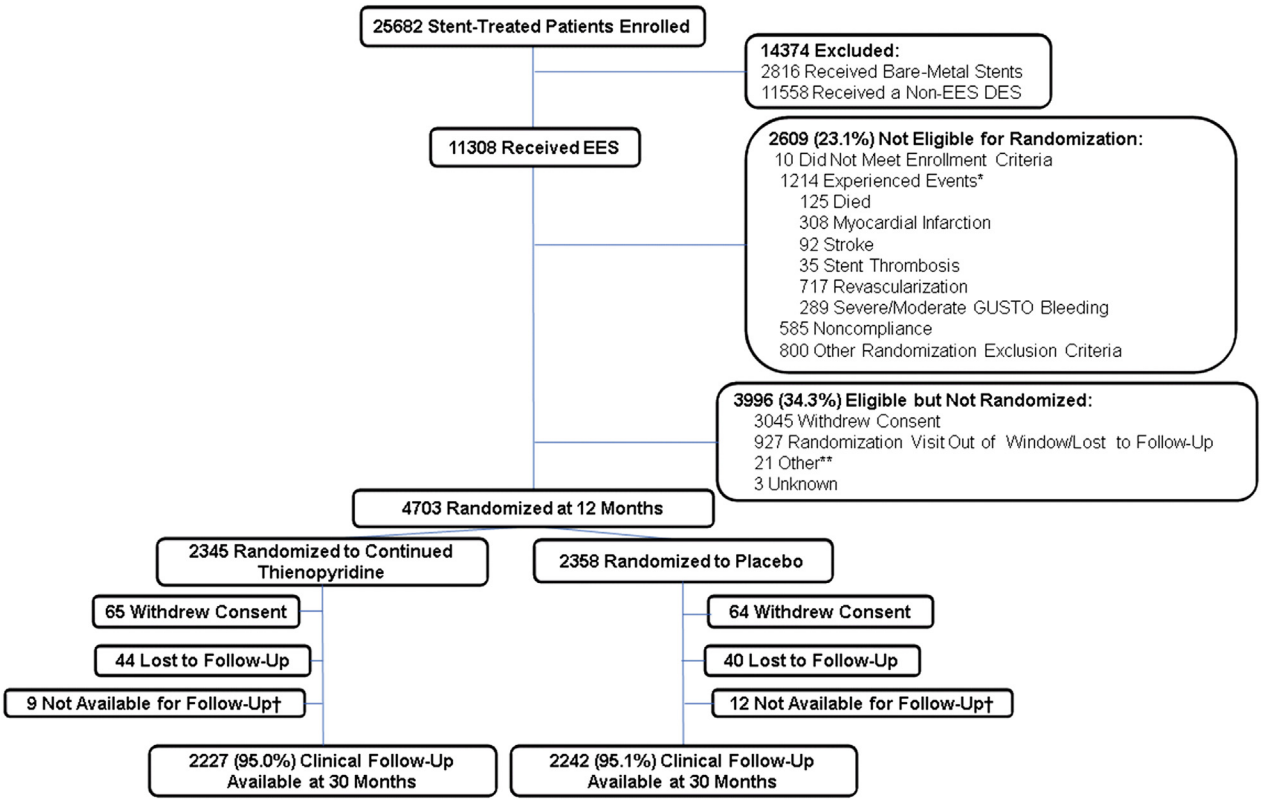
FIGURE 1 Subject Flowchart



Patients were enrolled within 72 h after stent placement and were followed for 12 months while they received open-label treatment with thienopyridine plus aspirin. At 12 months, they were randomly assigned to receive thienopyridine or placebo (each in addition to aspirin) for another 18 months. Although the number of patients with available data on clinical follow-up is reported in each group, the efficacy endpoints were analyzed with the last available follow-up information in the intention-to-treat population. Among the 4,703 randomized patients, at least 30 months of clinical follow-up was complete in 2,227 (95.0%) versus 2,242 (95.1%) subjects and clinical follow-up or vital status was available in 2,233 (95.2%) versus 2,247 (95.3%) of patients receiving continued thienopyridine or placebo, respectively. *Subjects may have >1 event. **Site terminated participation, randomization target met prior to subject follow-up, or subject not recognized to be eligible by site. †Subjects moved, were incarcerated, or were prematurely exited from the study. DES = drug-eluting stent(s); EES = everolimus-eluting stent(s); GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries.

by stent type (interaction p = 0.76), variation in treatment effect on MACCE was observed (interaction p = 0.048) (1). The current analysis was performed among randomized subjects treated only with EES to determine the effects of treatment, particularly on those endpoints that could be presumed to be stent-related (e.g., stent thrombosis, MACCE, and MI). Secondary endpoints included additional components of MACCE (mortality, stroke) and GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries) moderate or severe bleeding.

STUDY POPULATION AND PROCEDURES. Adult candidates for thienopyridine plus aspirin therapy who were treated with Food and Drug Administration-approved coronary stents were enrolled within 3 days of stent placement. All patients received open-label aspirin plus thienopyridine for 12 months after coronary stenting, and at month 12, patients who had tolerated DAPT without a MACCE, repeat revascularization, or moderate or severe bleeding event and who had been adherent to thienopyridine therapy (defined as having taken 80% to 120% of the drug without an interruption of longer than 14 days) continued aspirin and were randomized to either continued thienopyridine or to placebo for a further 18 months.

Endpoint events were adjudicated by a clinical events committee administered by the Harvard Clinical Research Institute and blinded to treatment assignment, as previously described (7). Deaths were classified as cardiac, vascular, or noncardiovascular, according to the Academic Research Consortium definition (9). Cardiovascular procedure-related bleeding

TABLE 1 Baseline Characteristics of All Randomized Subjects Treated With Everolimus-Eluting Stents

	Continued Thienopyridine (n = 2,345)	Placebo (n = 2,358)	p Value
Demographics			
Age, yrs	62.6 ± 10.1	62.0 ± 10.1	0.052
Female	1,774 (24.4)	1,787 (24.2)	0.92
Non-white race*	207 (9.0)	192 (8.4)	0.43
Hispanic or Latino ethnic group*	54 (2.4)	63 (2.7)	0.45
Weight, kg	90.9 ± 19.2	91.2 ± 18.8	0.64
BMI, kg/m^2	30.2 ± 5.6	30.4 ± 5.6	0.33
Medical history			
Diabetes mellitus	671 (28.8)	670 (28.5)	0.87
Hypertension	1,734 (74.3)	1,705 (72.5)	0.18
Cigarette smoker	528 (22.9)	522 (22.5)	0.75
Stroke/TIA	95 (4.1)	97 (4.1)	0.94
Congestive heart failure	83 (3.6)	91 (3.9)	0.59
Peripheral arterial disease	112 (4.9)	114 (5.0)	0.95
Prior PCI	693 (29.8)	672 (28.6)	0.39
Prior CABG	250 (10.7)	256 (10.9)	0.85
Prior MI	503 (21.9)	459 (19.9)	0.10
Indication for index procedure			
Acute coronary syndromes	652 (27.8)	620 (26.3)	0.25
STEMI	258 (11.0)	241 (10.2)	0.39
NSTEMI	394 (16.8)	379 (16.1)	0.50
Unstable angina†	285 (12.2)	298 (12.6)	0.63
Stable angina	960 (40.9)	954 (40.5)	0.74
Other	448 (19.1)	486 (20.6)	0.20
Region			1.00
North American	1,922 (82.0)	1,932 (81.9)	
Europe	308 (13.1)	309 (13.1)	
Australia/New Zealand	115 (4.9)	117 (5.0)	
Any risk factor for stent thrombosis			
STEMI or NSTEMI	652 (27.8)	620 (26.3)	0.25
Renal insufficiency/failure	98 (4.2)	83 (3.5)	0.26
LVEF <30%	32 (1.5)	34 (1.6)	0.81
≥2 vessels stented	10 (0.4)	10 (0.4)	1.00
≥2 lesions/vessel	38 (1.6)	36 (1.5)	0.82
Lesion length ≥30 mm	192 (8.2)	190 (8.1)	0.87
Bifurcation lesion	178 (7.6)	187 (8.0)	0.70
In-stent restenosis	66 (2.8)	71 (3.0)	0.73
Vein bypass graft stented	53 (2.3)	51 (2.2)	0.84
Unprotected left main stented	8 (0.3)	8 (0.3)	1.00
Thrombus-containing lesion	215 (11.3)	183 (9.5)	0.06
Prior brachytherapy	6 (0.3)	4 (0.2)	0.55
Thienopyridine at randomization			1.00
Clopidogrel	1,979 (84.4)	1,989 (84.4)	
Prasugrel	366 (15.6)	369 (15.7)	
No. of treated lesions	1.3 ± 0.5	1.3 ± 0.5	0.20
No. of treated vessels	1.1 ± 0.3	1.1 ± 0.3	0.81
No. of stents	1.5 ± 0.8	1.4 ± 0.7	0.20
Minimum stent diameter			0.52
<3 mm	1,101 (47.0)	1,085 (46.0)	
≥3 mm	1,244 (53.1)	1,273 (54.0)	
Total stent length, mm	27.2 ± 16.3	26.9 ± 16.3	0.51
Lesion(s)			
Treated vessel‡			
Native coronary	2,969 (97.6)	2,946 (98.0)	0.29
Left main	22 (0.7)	28 (0.9)	0.40
Left anterior descending	1,292 (42.5)	1,282 (42.7)	0.90
Right	985 (32.4)	930 (30.9)	0.24
Circumflex	670 (22.0)	706 (23.5)	0.18
Venous graft	64 (2.1)	55 (1.8)	0.46
Arterial graft	9 (0.3)	5 (0.2)	0.42
In-stent restenosis	121 (4.0)	124 (4.1)	0.78
Extreme tortuosity	134 (4.4)	121 (4.1)	0.46
Heavy calcification	277 (9.2)	256 (8.6)	0.44
Modified ACC/AHA lesion class B2 or C	1,299 (45.2)	1,271 (44.9)	0.83

Values are mean ± SD or n (%). *Race and ethnic group were self-reported. †This category included unstable angina without reported elevation of cardiac enzymes. ‡A total of 3,043 lesions were treated in subjects randomized to continued thienopyridine and 3,007 in subjects randomized to placebo.

ACC = American College of Cardiology; AHA = American Heart Association; BMI = body mass index; CABG = coronary bypass artery graft; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TIA = transient ischemic attack.

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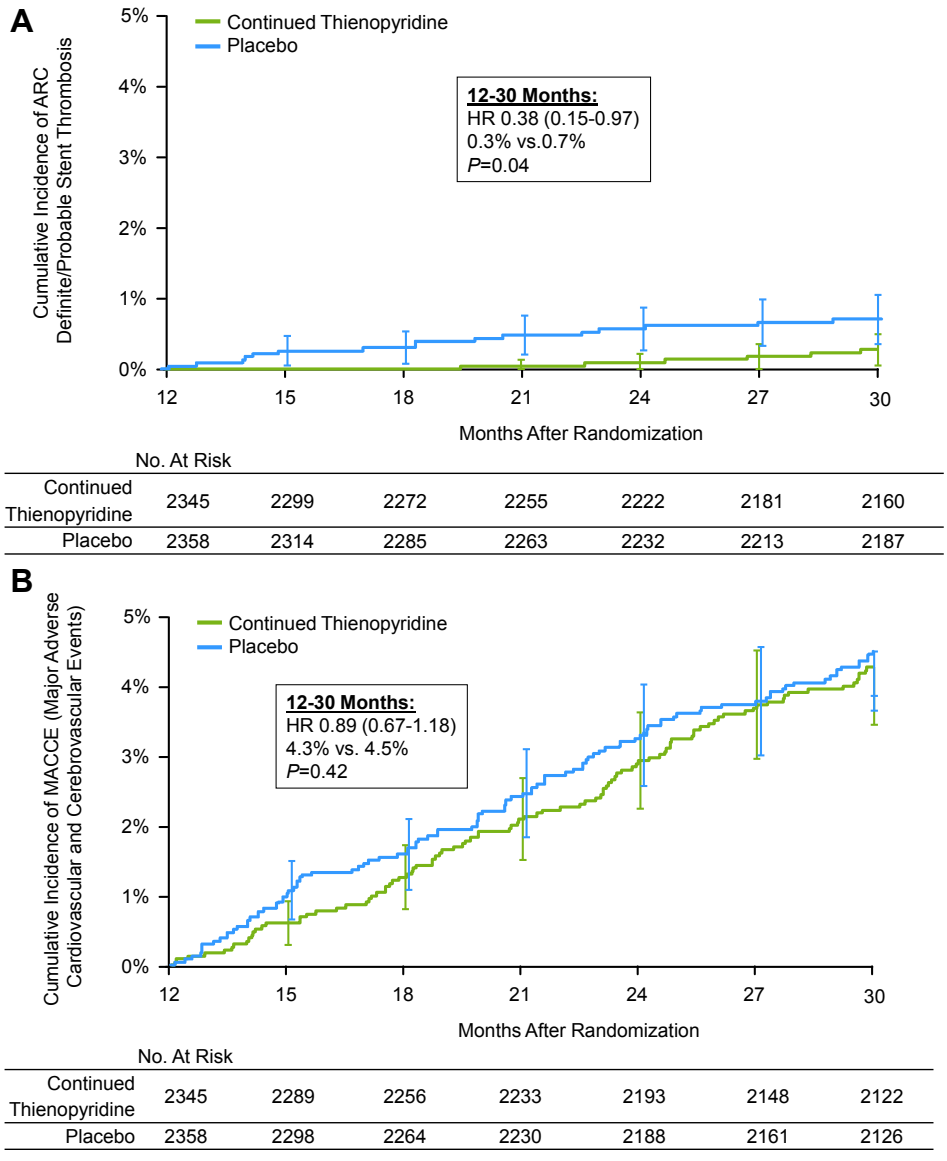
or bleeding related to primarily cardiac or vascular conditions was considered cardiovascular death; other fatal bleeds were considered noncardiovascular. A second blinded clinical events committee evaluated the potential contribution of specific pathological mechanisms to mortality (10). The classification of cardiac, vascular, and noncardiovascular death was not readjudicated. All deaths were reviewed regardless of initial adjudicated cause. Bleeding-related death was adjudicated as any death that was possibly, probably, or definitely related to a prior bleeding event. Cancer-related death was adjudicated as any death that was possibly, probably, or definitely related to a malignancy or complications from treatments specifically administered for the malignancy. Causes of death were not mutually exclusive, that is, a patient could have both a bleeding- and cancer-related death.

A central data safety monitoring board and an independent biostatistician reviewed unblinded data from all subjects at regular intervals.

STATISTICAL ANALYSIS. All analyses were performed on the subset of all randomized EES-treated patients, according to the intention-to-treat principle. Analysis of the interaction of stent type and treatment assignment (duration of antiplatelet therapy) on the outcomes of stent thrombosis, MACCE, and GUSTO severe or moderate bleeding was

FIGURE 2 Cumulative Incidence of Stent Thrombosis, MACCE, a Myocardial Infarction, and GUSTO Moderate/Severe Bleeding According to Randomized Treatment Arm



Kaplan-Meier curves are shown for the endpoints of Academic Research Consortium definite or probable stent thrombosis **(A)**, major adverse cardiovascular and cerebrovascular events (MACCE) **(B)**, myocardial infarction **(C)**, and GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries) moderate/severe bleeding **(D)** in all randomized subjects treated with everolimus-eluting stents (n = 4308) at 12 to 30 months, according to randomized treatment arm (continued thienopyridine vs. placebo). Hazard ratios (HRs) for continued thienopyridine vs. placebo and corresponding Cox regression p values are presented. The number at risk was defined as the number of patients who had not had the event of interest and who were available for subsequent follow-up. *HR for continued thienopyridine versus placebo.

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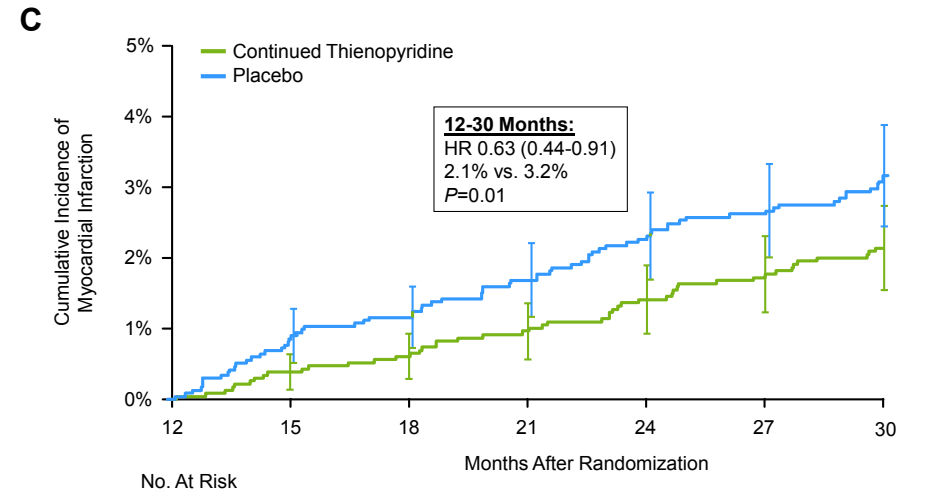
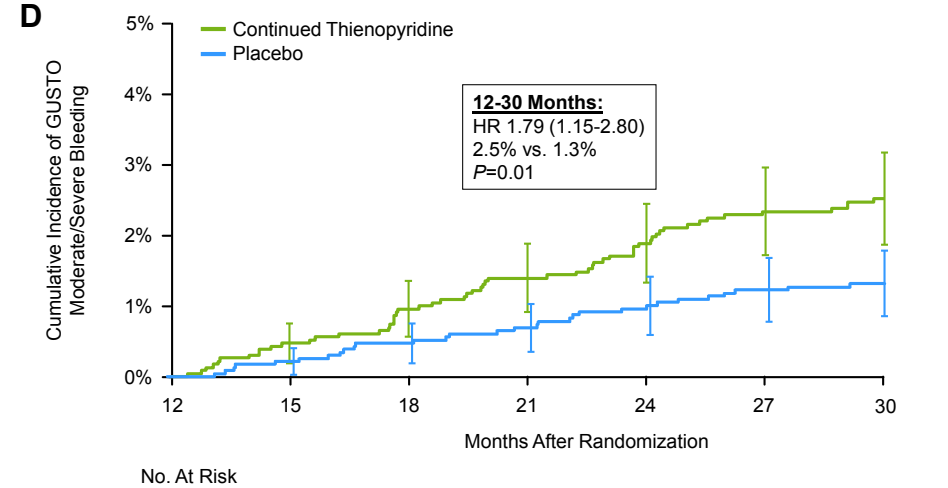
pre-specified, as previously described. The Cox proportional hazards assumption was met for these endpoints for the primary DES cohort and for the EES-treated subset. All other within-subset analyses (i.e., comparing randomized treatment arms within EES-treated subjects) were not pre-specified.

Kaplan-Meier estimates of endpoint events were calculated for each treatment group. For the outcomes of stent thrombosis, MACCE, death, MI, and GUSTO severe or moderate bleeding, hazard ratios (HRs) and 95% confidence intervals (CIs) were adjusted for baseline characteristics; adjusted Cox

FIGURE 2 Continued



No. At Risk							
Continued Thienopyridine	2345	2290	2259	2236	2196	2153	2127
Placebo	2358	2299	2267	2237	2196	2171	2137



No. At Risk							
Continued Thienopyridine	2345	2290	2256	2232	2193	2147	2124
Placebo	2358	2314	2282	2257	2223	2201	2174

proportional hazard regression p values were used to compare the treatment difference and to assess randomized treatment by DES type interaction effects. For all other outcomes, HRs and 95% CIs were stratified by randomization strata. Kaplan-Meier estimates were compared between treatment groups using a log-rank p value stratified by randomization strata.

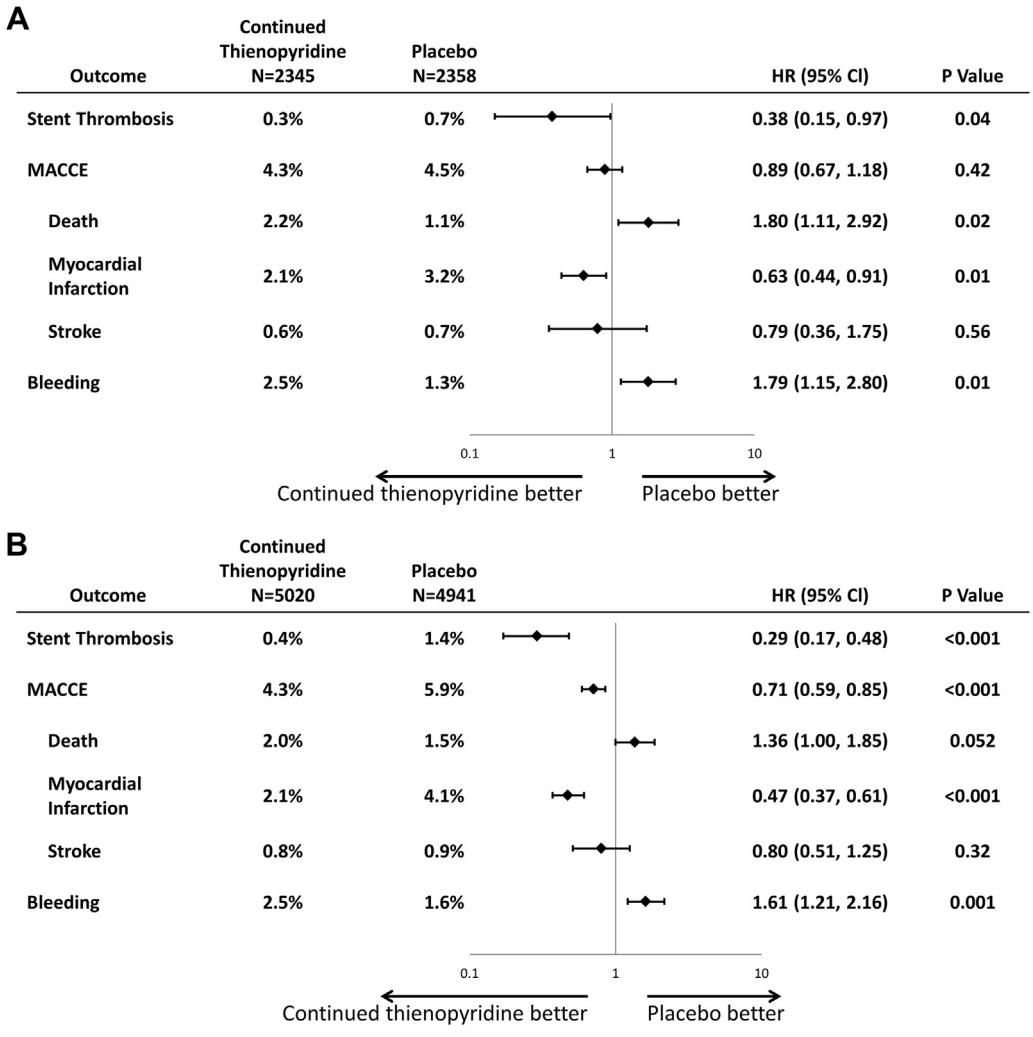
For baseline characteristics, continuous variables were compared using the Student 2-sample *t* test; categorical parameters were compared using the chi-square test or Fisher exact test as appropriate.

All statistical analyses were conducted at the Harvard Clinical Research Institute with the use of SAS software, version 9.2. (SAS Institute Inc., Cary, North Carolina). The authors (L.M., J.M.M.) had full access to the data and vouch for the integrity of the analyses presented.

RESULTS

STUDY POPULATION. Of 25,682 patients enrolled in the DAPT study, 11,308 received an EES. Of 11,648 randomized patients, 9,961 received a DES at the index

FIGURE 3 Outcomes (12 to 30 Months) in Randomized Patients According to Treatment Arm



(A) All randomized EES-treated patients; **(B)** all randomized DES-treated patients. Percentages are Kaplan-Meier estimates. (HRs), confidence intervals (CIs), and p values are adjusted for baseline characteristics as listed in the supplemental appendix of Mauri et al. (1). Stent thrombosis includes Academic Research Consortium definite/probable definitions. Bleeding severity includes GUSTO moderate or severe definitions. MACCE = major adverse cardiovascular and cerebrovascular events; other abbreviations as in Figures 1 and 2.

procedure, with the following stent types: everolimus alone (4,703 [47.2%]), paclitaxel alone (2,666 [26.8%]), zotarolimus alone (1,264 [12.7%]), sirolimus alone (1,118 [11.2%]), and more than 1 type of DES (210 [2.1%]). The Taxus Liberté study, in which all patients received a paclitaxel-eluting stent and prasugrel, contributed 2,191 (31.5%) of the 6,945 patients treated with a non-EES stent in the DAPT study (6). During the open-label period, 11.2% of EES-treated patients and 12.5% of patients treated with other DES had events rendering them ineligible for randomization at 12 months ($p = 0.003$) (Online Table 1). Among 4,703 randomized EES patients, at least 30 months of clinical follow-up was complete in 2,227 (95.0%) versus 2,242 (95.1%) patients (Figure 1) and clinical follow-up or vital status was available in 2,233 (95.2%) versus 2,247 (95.3%) of patients receiving continued thienopyridine or placebo, respectively. Within EES-treated patients, there were no significant differences between randomized groups on baseline characteristics except that those randomized to continued thienopyridine were slightly older (Table 1).

As expected due to lack of randomization to stent type, EES-treated subjects differed from patients

treated with other DES. EES patients were slightly older (mean age 62.3 years vs. 61.2 years), had a lower body mass index (30.3 kg/m^2 vs. 30.8 kg/m^2), were more likely to be treated with clopidogrel (84.4% vs. 48.2%) and less likely to receive prasugrel (15.6% vs. 51.8%), and were more likely to have had a prior history of cancer (all p < 0.001) (Online Table 2). Reduction in stent thrombosis (interaction p = 0.76) and MI (interaction p = 0.11) with continued thienopyridine therapy versus placebo was consistent among all DES after adjustment for differences in patient characteristics and type of thienopyridine, as was the increase in bleeding (interaction p = 0.46) and mortality (interaction p = 0.17), whereas there was variation in the magnitude of risk reduction in MACCE across stent types (interaction p = 0.048) (1).

EFFECT OF CONTINUED THIENOPYRIDINE THERAPY AMONG EES-TREATED PATIENTS. Among EES-treated patients randomized to continued thienopyridine or placebo, continued thienopyridine significantly reduced the rates of stent thrombosis (0.3% vs. 0.7%, HR: 0.38, 95% CI: 0.15 to 0.97; p = 0.04) (**Figure 2A and Figure 3**) and MI (2.1% vs. 3.2%, HR: 0.63, 95% CI: 0.44 to 0.91; p = 0.01) (**Figure 2C**) but not MACCE (4.3% vs. 4.5%, HR: 0.89, 95% CI: 0.67 to 1.19; p = 0.42) (**Figure 2B**, **Table 2**). Moderate or severe bleeding was higher with continued thienopyridine (2.5% vs. 1.3%, HR: 1.79, 95% CI: 1.15 to 2.80; p = 0.01) (**Figure 2D**).

MORTALITY. During the randomized treatment period (12 to 30 months after enrollment), all-cause mortality was 2.2% in the continued thienopyridine arm versus 1.1% in the placebo arm (HR: 1.80, 95% CI: 1.11 to 2.91; p = 0.02). There was no difference in cardiovascular death (1.0% continued thienopyridine vs. 0.8% placebo; HR: 1.42, 95% CI: 0.75 to 2.69; p = 0.28). A difference in noncardiovascular death was observed (1.2% continued thienopyridine vs. 0.4% placebo; HR: 3.46, 95% CI: 1.49 to 8.04; p = 0.002). The most common noncardiovascular condition related to mortality was cancer (n = 18 vs. n = 4; p = 0.002); few of these cancer-related deaths were associated with bleeding (3 of 18 in the continued thienopyridine arm, 0 of 4 in the placebo arm) (**Table 3**). Death related to bleeding occurred in 3 of 18 total cancer-related deaths in the continued thienopyridine arm and in 0 of 4 in the placebo arm. Bleeding was the second most common mechanism of death and occurred more frequently in the continued thienopyridine group versus placebo (n = 9 vs. n = 2; p = 0.04), yet bleeding without cancer or trauma was infrequent (n = 4 vs. n = 2; p = 0.45). Of cancer-related deaths during randomized treatment, 4 were among patients diagnosed prior to enrollment in the continued thienopyridine therapy arm versus 0 in the placebo arm, the majority of which were metastatic at the time of diagnosis.

TABLE 2 Outcomes in All Randomized Subjects Treated With Everolimus-Eluting Stents by Treatment Arm

	Continued Thienopyridine (n = 2,345)	Placebo (n = 2,358)	Hazard Ratio (95% CI)	p Value
Stent thrombosis	6 (0.3)	16 (0.7)	0.38 (0.15–0.97)*	0.04†
ARC definite	5 (0.2)	12 (0.5)	0.40 (0.14–1.14)	0.08
ARC probable	1 (0.1)	4 (0.2)	0.25 (0.03–2.26)	0.18
MACCE (death, MI, stroke)	97 (4.3)	103 (4.5)	0.89 (0.67–1.18)*	0.42†
Death	49 (2.2)	26 (1.1)	1.80 (1.11–2.92)*	0.02†
Cardiovascular	23 (1.0)	18 (0.8)	1.42 (0.75–2.69)	0.28
Noncardiovascular	26 (1.2)	8 (0.4)	3.46 (1.49–8.04)	0.002
MI	48 (2.1)	72 (3.2)	0.63 (0.44–0.91)*	0.01†
Stent thrombosis-related	5 (0.2)	15 (0.7)	0.32 (0.12–0.89)	0.02
Non-stent thrombosis-related	44 (2.0)	59 (2.6)	0.74 (0.49–1.11)	0.15
Stroke (total)	13 (0.6)	15 (0.7)	0.79 (0.36–1.75)	0.56
Ischemic	6 (0.3)	11 (0.5)	0.51 (0.17–1.49)	0.21
Hemorrhagic	7 (0.3)	3 (0.1)	1.99 (0.50–7.97)	0.32
Type uncertain	0 (0.0)	1 (0.04)	0‡	0.33
GUSTO severe/moderate	57 (2.5)	30 (1.3)	1.79 (1.15–2.80)*	0.01†
Severe	21 (0.9)	7 (0.3)	4.01 (1.50–10.67)	0.003
Moderate	36 (1.6)	23 (1.0)	1.55 (0.89–2.69)	0.12

Values are n (%) unless otherwise indicated. Percentages are Kaplan-Meier estimates. This analysis was performed on data from the period of 12 to 30 months after enrollment. Results are for all randomized patients; patients not experiencing the endpoint were censored at 30 months or at last known follow-up, whichever was earlier. *Hazard ratios and 95% CIs adjusted for baseline characteristics. All other hazard ratios and 95% CIs are stratified by randomization strata. †Cox regression p value (factors for adjustment are listed in the Online Appendix). ‡Confidence interval not estimable. All other p values are log-rank stratified by randomization strata.

ARC = Academic Research Consortium; CI = confidence interval; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; MACCE = major adverse cardiovascular and cerebrovascular event(s); MI = myocardial infarction.

DISCUSSION

Technological iterations in coronary DES, including thinner struts, novel metal alloys, biocompatible polymers, and various eluted medications, have been associated with improved clinical outcomes following coronary stenting. As the hazard of very late stent-related events (>1 year) may differ between DES types, the potential for benefit (or harm) associated with continued thienopyridine therapy beyond 1 year may be different as well. The DAPT study allowed operator selection from approved and available coronary stents, while comparing the effect of continued thienopyridine therapy versus placebo, on a background of aspirin and across a range of patient and lesion types. The most commonly used DES in contemporary interventional practice (EES) accounted for almost one-half of all DES used in the DAPT

TABLE 3 Deaths Related to Bleeding, Trauma, and Cancer, at 12 to 30 Months After Enrollment, Per Case Review/Adjudication

	Continued Thienopyridine (n = 2,345)	Placebo (n = 2,358)	Difference	p Value
Related to bleeding, cancer, and/or trauma				
All bleeding-related death	9 (0.38)	2 (0.08)	7 (0.30)	0.04
Bleeding-related death without cancer* or trauma	4 (0.17)	2 (0.08)	2 (0.09)	0.45
Bleeding-related death with cancer	3 (0.13)	0 (0.00)	3 (0.13)	0.12
Bleeding-related death with trauma	2 (0.09)	0 (0.00)	2 (0.09)	0.25
All cancer-related death	18 (0.77)	4 (0.17)	14 (0.60)	0.002
Cancer-related death without bleeding†	15 (0.64)	4 (0.17)	11 (0.47)	0.01
All trauma-related death	3 (0.13)	0 (0.00)	3 (0.13)	0.12
Trauma-related death without bleeding†	1 (0.04)	0 (0.00)	1 (0.04)	0.50
Death with any prior history of bleeding‡				
Death preceded by bleeding within 30 days	7 (0.30)	4 (0.17)	3 (0.13)	0.39
Death preceded by bleeding since randomization	14 (0.60)	8 (0.34)	6 (0.26)	0.21

Values are n (%), and event rates are expressed as absolute percentages. Deaths were classified by a blinded clinical events committee according to relatedness to cancer, trauma, and/or bleeding (not mutually exclusive). Rates in each randomized arm are percentages. *Without possible, probable, or definite cancer-related death. †Without possible, probable, or definite bleeding-related death. ‡Defined as Bleeding Academic Research Consortium type 2, 3, or 5 bleeding, prior to death.

study. Although stent type was not randomized and individual stent type subsets were neither pre-specified nor powered to compare treatment effect, analysis of the consistency of treatment effect was pre-specified.

In this context, the following observations were made. First, continued thienopyridine plus aspirin beyond 1 year (vs. aspirin alone) significantly reduced the incidence of stent thrombosis and MI following EES treatment. Second, although heterogeneity in treatment duration benefit for reduction in the composite endpoint of MACCE was present for EES, this observation appears to be in large part driven by a greater increase in mortality with continued thienopyridine therapy, while the beneficial effect on MI was consistent across stent types. Indeed, the relative increase in mortality among EES-treated patients receiving continued thienopyridine therapy (vs. placebo) appears to mirror the observation on mortality for the overall DAPT DES subset. Compared with prior trials of extended dual antiplatelet therapy, the DAPT study has been an isolated example identifying a relationship between mortality and continued thienopyridine plus aspirin therapy (11), largely due to an increase in noncardiovascular-related mortality. The mortality signal in the overall DAPT study has been analyzed after adjudication of all deaths and appears to be related to higher rates of cancer-related death in patients with pre-existing cancer diagnoses, and not mainly attributable to increased bleeding risks (10). Notably, no increase in mortality was observed in BMS-treated patients receiving continued thienopyridine therapy, suggesting the possible effects of a chance imbalance among DES-treated patients, which was most pronounced in the EES subgroup, perhaps related to the more frequent enrollment of subjects with a history of cancer in this group. Third, bleeding events, particularly those classified as GUSTO severe, were numerically higher in the EES subgroup, although variations in bleeding rates would not necessarily be expected to truly differ between types of stents.

Stent thrombosis rates, particularly beyond 1 year, are low for currently used DES. Randomized trials showing lower rates of stent thrombosis with newer DES compared with first-generation DES confirm that, in part, these lower rates are related to improving stent technology over time (3–5,12). Our findings in the EES-treated subset suggest that the therapeutic window for benefit (vs. risk) of continued thienopyridine therapy may be narrow. The number needed to treat to benefit for stent thrombosis was 235 over 18 months; the number needed to treat to benefit for MI was 98, and the number needed to treat to harm for moderate or severe bleeding was 84. Therefore, meticulous assessment of bleeding risk should always affect decisions regarding thienopyridine therapy duration. Overall treatment benefit should be considered according to the individual patient's risk of events and the effect of these events. Current data suggest a net benefit of continuation of therapy even with small absolute reductions in stent thrombosis or MI of ~0.2%, an effect that was exceeded within the EES subset of patients (13). Ongoing analyses will delineate the individual predictors of the risk and benefit of late continuation of treatment as well as the absolute effect of late ischemic and

bleeding events on overall quantity and quality of life.

STUDY LIMITATIONS. Specific limitations that apply to comparisons of absolute event rates across DES types in this study include the post-hoc nature of the analysis, lack of randomization to DES type, demographic differences between DES treatment groups and smaller stent group sample sizes (lack of power), and the limitations of multiple comparisons. Additionally, despite the relatively large EES group size, tests of interaction on randomized treatment effect between stent groups remain underpowered. Finally, false positives related to multiple testing may also be present within these subgroup analyses.

CONCLUSIONS

Continued thienopyridine therapy beyond 1 year following EES treatment is associated with significant reductions in risk of stent thrombosis or MI and an increased risk of bleeding.

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PERSPECTIVES

WHAT IS KNOWN? Recent randomized trials and a meta-analysis suggest that EES, the most commonly used stent type in the DAPT study, are associated with lower rates of stent thrombosis compared with paclitaxel-eluting stents.

WHAT IS NEW? In a post-hoc subset analysis of the DAPT study in patients treated with EES, continued thienopyridine plus placebo beyond 1 year was associated with reduced rates of stent thrombosis and MI and increased rates of bleeding.

WHAT IS NEXT? This study contributes to the growing body of evidence regarding prevention of stent thrombosis and MI after coronary stenting with continued dual antiplatelet therapy, as well as the risks of increased bleeding. Additional research is needed to further individualize therapy to optimize patient selection for continued thienopyridine therapy.

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KEY WORDS drug-eluting stent(s), dual antiplatelet therapy, everolimus, stent thrombosis

APPENDIX For additional statistical information and supplemental tables, please see the online version of this article.