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

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Abstract

Background: In the Dual Antiplatelet Therapy (DAPT) 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 DES, we examined outcomes among everolimus-eluting stent (EES)-treated subjects in the DAPT Study.

Objective(s): To characterize outcomes for EES-treated subjects according to treatment with continued thienopyridine plus aspirin vs. aspirin alone 12-30 months after stenting.

Methods: The DAPT Study enrolled 25682 subjects (11308 EES-treated) after coronary stenting. Following 12 months of treatment with thienopyridine and aspirin, eligible subjects continued aspirin and 9961 (4703 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% CI 0.15-0.97, p=0.04) and MI (2.1% vs. 3.2%, HR 0.63, 95% CI 0.44-0.91, p=0.01) vs. placebo, but did not reduce a composite of death, MI and stroke (4.3% vs. 4.5%, HR 0.89, 95% CI 0.67-1.18, p=0.42), and increased moderate/severe bleeding (2.5% vs. 1.3%, HR 1.79, 95% CI 1.15-2.80, p=0.01) and death (2.2% vs. 1.1%, HR 1.80, 95% CI 1.11-2.92, p=0.02). Death due to cancer 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 was observed with continued thienopyridine beyond one year compared with aspirin alone.

Key words: dual antiplatelet therapy, drug-eluting stents, everolimus, stent thrombosis

Condensed Abstract

We examined outcomes, *post hoc*, among 4703 randomized everolimus-eluting stent (EES)-treated subjects in the Dual Antiplatelet Therapy Study. Among EES treated patients, continued thienopyridine reduced stent thrombosis (0.3% vs. 0.7%, p=0.04) and myocardial infarction (MI; 2.1% vs. 3.2%, p=0.01) vs. placebo, but not a composite of death, MI, or stroke (4.3% vs. 4.5%, p=0.42), and increased moderate/severe bleeding (2.5% vs. 1.3%, p=0.01) 12-30 months post-stenting. These outcomes were consistent among EES and other DES (interaction p=0.76 stent thrombosis, p=0.11 MI, p=0.46, bleeding). In EES-treated subjects, continued thienopyridine beyond one year (vs. aspirin alone) reduced stent thrombosis and MI, and increased bleeding.

Abbreviations:

BMS: bare-metal stent

CI: confidence interval

DAPT: dual antiplatelet therapy

DES: drug-eluting stent

EES: everolimus-eluting stent

FDA: Food and Drug Administration

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

HCRI: Harvard Clinical Research Institute

HR: hazard ratio

MACCE: major adverse cardiovascular and cerebrovascular events

MI: myocardial infarction

PES: paclitaxel-eluting stent

SES: sirolimus-eluting stent

ZES: zotarolimus-eluting stent

INTRODUCTION

In the Dual Antiplatelet Therapy (DAPT) Study, patients who were free from major ischemic or bleeding events at 1 year after coronary stenting (either drug-eluting [DES] or bare metal [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 as 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)

Subjects treated with any drug-eluting stent (DES) approved and available in the United States at the time of study enrollment were eligible to be enrolled in the DAPT Study. While patients were not randomized to stent types, in adjusted analysis there was heterogeneity in the relative reduction in MACCE (major adverse cardiovascular and cerebrovascular events; 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=2666 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 vs. 12 months in the large subset of patients (11308 enrolled, 4703 randomized).

METHODS

Design

The DAPT Study was a double-blind, international, multi-center, 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 (ClinicalTrials.gov # 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- vs. DES-treated patients(8) on these endpoints, 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 end points 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; PROMUS, Boston Scientific), sirolimus-eluting (SES; Cypher, Cordis), zotarolimus-eluting (ZES; Endeavor, Medtronic), and paclitaxel-eluting (PES; TAXUS, Boston Scientific). While stent type among various DES was not randomized, assessments of randomized treatment-by-DES type interactions on stent thrombosis and MACCE were prespecified to determine whether the randomized treatment effect was consistent across DES types. While randomized treatment effect on stent thrombosis did not vary 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 end points that could be

presumed to be stent-related, e.g. stent thrombosis, MACCE and MI. Secondary end points 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 (FDA)-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 further18 months.

Endpoint events were adjudicated by a clinical events committee (CEC) administered by the Harvard Clinical Research Institute (HCRI) and blinded to treatment assignment, as previously described.(7) Deaths were classified as cardiac, vascular, or non-cardiovascular, according to Academic Research Consortium definition.(9) Cardiovascular procedure-related bleeding or bleeding related to primarily cardiac or vascular conditions was considered cardiovascular death, other fatal bleeds were considered non-cardiovascular. A second blinded CEC evaluated the potential contribution of specific pathologic mechanisms to mortality.(10) The classification of cardiac, vascular and non-cardiovascular death was not re-adjudicated. 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, i.e. a patient could have both a bleeding-related and a 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 prespecified, as described above. The Cox proportion 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 prespecified.

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 and 95% confidence intervals (CIs) were adjusted for baseline characteristics; adjusted Cox 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, hazard ratios and 95% CIs were stratified by randomization strata; Kaplan-Meier estimates were compared between treatment groups using log-rank p value stratified by randomization strata.

For baseline characteristics, continuous variables were compared using the two-sample t-test; categorical parameters were compared using the chi-square test or Fisher's exact test as appropriate.

All statistical analyses were conducted at HCRI with the use of SAS software, version 9.2. (SAS Institute Inc., Cary, NC, USA). The authors (LM, JMM) had full access to the data and vouch for the integrity of the analyses presented.

RESULTS

Study Population

Of 25,682 patients enrolled into the DAPT Study, 11,308 received an EES; of 11,648 randomized patients, 9961 received a DES at the index procedure, with the following stent types: everolimus alone (4703 [47.2%]), paclitaxel alone (2666 [26.8%]), zotarolimus alone (1264 [12.7%]), sirolimus alone (1118 [11.2%]); and 210 (2.1%) had more than one type of DES. The Taxus Liberté study, in which all patients received a PES and prasugrel, contributed 2191 (31.5%) of the 6945 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 Appendix Table 1). Among 4703 randomized EES patients, at least 30 months of clinical follow-up was complete in 2227 (95.0%) vs. 2242 (95.1%) patients (Figure 1) and clinical follow-up or vital status was available in 2233 (95.2%) vs. 2247 (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 vs 61.2 years), had a lower body mass index (30.3 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 Appendix Table 2). Reduction in stent thrombosis (interaction p=0.76) and MI (interaction p=0.11) with continued thienopyridine therapy vs. 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), while 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

Amongst 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 0.15-0.97, p=0.04; Figure 2A) and MI (2.1% vs. 3.2%, HR 0.63, 95% CI 0.44-0.91, p=0.01; Figure 2C), but not MACCE (4.3% vs. 4.5%, HR 0.89, 95% CI 0.67-1.19, 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 1.15-2.80, p=0.01; Figure 2D).

Mortality

During the randomized treatment period (12-30 months after enrollment), all-cause mortality was 2.2% vs. 1.1% in the continued thienopyridine arm vs placebo (HR 1.80, 95% CI 1.11-2.91, p=0.02). There was no difference in cardiovascular death (1.0% continued thienopyridine vs. 0.8% placebo; HR=1.42, 95% CI 0.75-2.69; p=0.28). A difference in non-cardiovascular death was observed (1.2 % continued thienopyridine vs. 0.4% placebo; HR=3.46, 95% CI 1.49-8.04; p=0.002). The most common non-cardiovascular condition related to mortality was cancer (N=18 vs. 4, p=0.002); few of these cancers-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 cancer and also 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 vs. placebo (N=9 vs. 2, p=0.04), yet bleeding without cancer or trauma was

infrequent (n=4 vs. 2, p=0.45). Of cancer-related deaths during randomized treatment, 4 vs. 0 were among patients diagnosed prior to enrollment in the continued thienopyridine therapy arm vs. placebo arms, the majority of which were metastatic at the time of diagnosis.

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 vs. 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 half of all DES used in the DAPT Study. While stent type was not randomized and individual stent type subsets were not prespecified nor powered to compare treatment effect, analysis of the consistency of treatment effect was prespecified.

In this context, the following observations were made. First, continued thienopyridine plus aspirin beyond 1 year (versus 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 (versus 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 non-cardiovascular 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 one 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 [NNTB] for stent thrombosis was 235 over 18 months; the NNTB 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 impact decisions regarding thienopyridine therapy duration. Overall treatment benefit should be considered according to the individual patient's risk of events and the impact 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 impact 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 positive 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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CLINICAL PERSPECTIVES

What is Known?

Recent randomized trials and meta-analysis suggest that everolimus-eluting stents (EES), the most commonly used stent type in the Dual Antiplatelet Therapy (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 one year was associated with reduced rates of stent thrombosis and myocardial infarction, and increased rates of bleeding.

What is Next?

This study contributes to the growing body of evidence regarding prevention of stent thrombosis and myocardial infarction 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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Figure Legends (and footnotes, if applicable):

Figure 1. Subject Flowchart. Patients were enrolled within 72 hours 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 end points were analyzed with the last available follow-up information in the intention-to-treat population. GUSTO denotes Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries. Among the 4703 randomized patients, at least 30 months clinical follow-up was complete in 2227 (95.0%) vs. 2242 (95.1%) subjects and clinical follow-up or vital status was available in 2233 (95.2%) vs. 2247 (95.3%) of patients receiving continued thienopyridine or placebo, respectively.

Figure 2. Cumulative incidence of stent thrombosis and myocardial infarction, according to randomized treatment arm.

Kaplan-Meier curves are shown for the end points of ARC definite or probable stent thrombosis (Panel A), major adverse cardiovascular and cerebrovascular events (MACCE; Panel B), myocardial infarction (Panel C), and GUSTO moderate/severe bleeding (Panel D) in all randomized subjects treated with everolimus-eluting stents (N=4308) at 12-30 months, according to randomized treatment arm (continued thienopyridine vs. placebo). Hazard ratios 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.

Panel A. Definite or Probable Stent Thrombosis

Panel B. MACCE

Panel C. Myocardial Infarction

Panel D. GUSTO Moderate/Severe Bleeding.

*HR = Hazard ratio. Hazard ratio for continued thienopyridine vs. placebo.

Figure 3. Outcomes (12-30 months) in randomized atients according to treatment arm.

Percentages are Kaplan–Meier estimates. Hazard ratios, confidence intervals and p values are adjusted for baseline characteristics as listed in the supplementary appendix of the Mauri et al. manuscript.(1) Stent thrombosis includes Academic Research Consortium definite/probable definitions. Bleeding severity includes GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries) moderate or severe definitions. MACCE denotes major adverse cardiovascular and cerebrovascular events.

Panel A: All randomized EES-treated patients.

Panel B: All randomized DES-treated patients.

Table 1. Baseline characteristics of all randomized subjects treated with everolimus-eluting stents.

Measure*	Continued Thienopyridine N=2345	Placebo N=2358	P-value
Demographics			
Age (years)	62.6±10.1	62.0±10.1	0.052
Female	1774 (24.4%)	1787 (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	1734 (74.3%)	1705 (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	1922 (82.0%)	1932 (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 per 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

Measure*	Continued Thienopyridine N=2345	Placebo N=2358	P-value
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	1979 (84.4%)	1989 (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	1101 (47.0%)	1085 (46.0%)	
≥ 3 mm	1244 (53.1%)	1273 (54.0%)	
Total stent length – mm	27.2±16.3	26.9±16.3	0.51
Lesion(s)			
Treated vessel‡			
Native Coronary	2969 (97.6%)	2946 (98.0%	0.29
Left main	22 (0.7%)	28 (0.9%	0.40
Left anterior descending	1292 (42.5%)	1282 (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	1299 (45.2%)	1271 (44.9%)	0.83

*Plus–minus values are means ±SD; all other numbers are N (%).

** Race and ethnic group were self-reported.

† This category included unstable angina without reported elevation of cardiac enzymes.

‡A total of 3043 lesions were treated in subjects randomized to continued thienopyridine and 3007 in subjects randomized to placebo.

Abbreviations: 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-elevation myocardial infarction; PCI,

percutaneous coronary intervention; TIA, transient ischemic attack; SD, standard deviation; STEMI, ST-elevation myocardial infarction.

Table 2. Outcomes in all randomized subjects treated with everolimus-eluting stents by treatment arm. This analysis was performed on data from the period of 12 to 30 months after enrollment. Percentages are Kaplan–Meier estimates. Results are for all randomized patients; patients not experiencing the endpoint are censored at 30 months or at last known follow-up, whichever is earlier.

Outcome	Continued Thienopyridine N=2345	Placebo N=2358	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
Non-Cardiovascular	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†
GUSTO Severe	21 (0.9%)	7 (0.3%)	4.01 (1.50, 10.67)	0.003
GUSTO Moderate	36 (1.6%)	23 (1.0%)	1.55 (0.89, 2.69)	0.12

*Hazard ratios and 95% CIs adjusted for baseline characteristics. All other hazard ratios and 95% CIs are stratified by randomization strata.

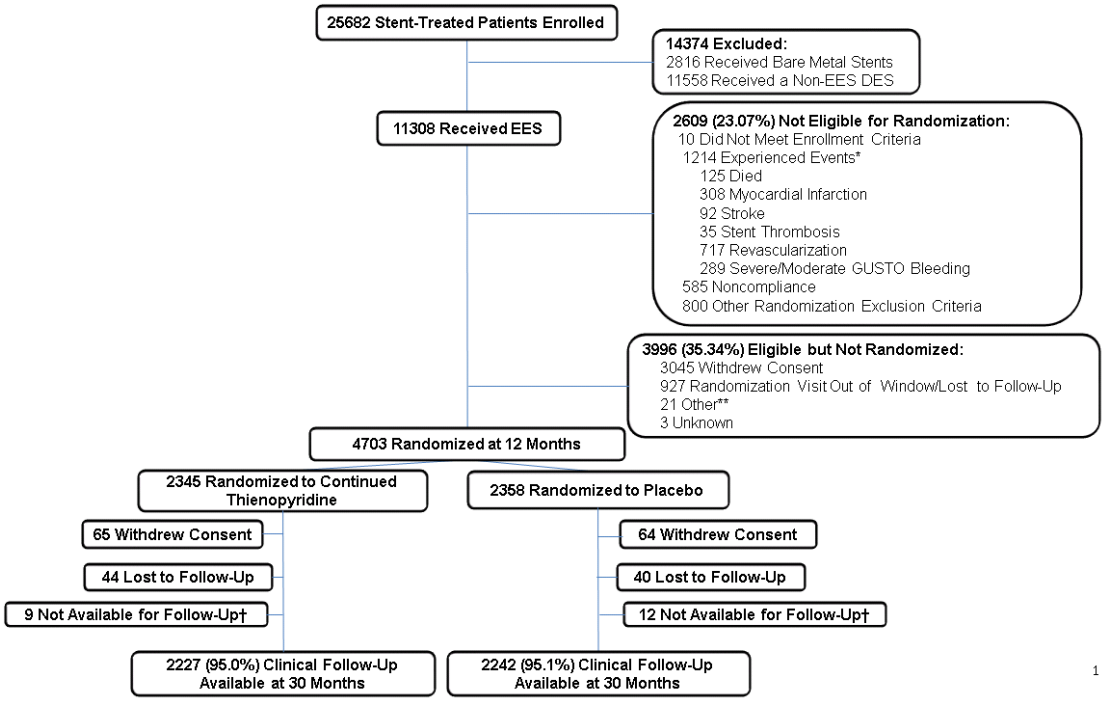
†Cox regression p value (factors for adjustment are listed in the appendix). All other p values are log rank stratified by randomization strata.

Abbreviations: ARC, 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.

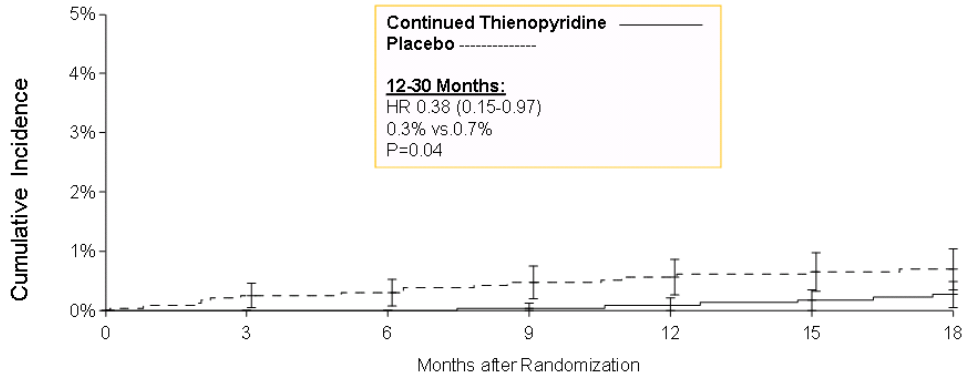
Table 3. Deaths related to bleeding, trauma, and cancer, at 12-30 months after enrollment, per case review/adjudication. Deaths were classified by a blinded clinical events committee according to relatedness to cancer, trauma, and/or bleeding (not mutually exclusive). Rates in each randomized arm are percentages.

N (%)	Continued Thienopyridine N=2345	Placebo N=2358	Difference	P Value
Relatedness 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

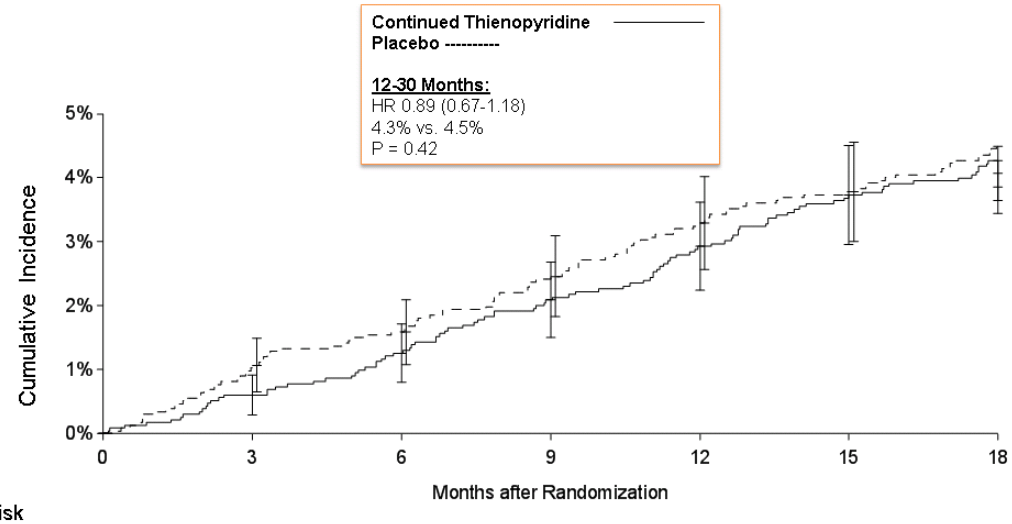
*Without possible, probable, or definite cancer-related death.
†Without possible, probably, or definite bleeding-related death.
‡Defined as BARC type 2, 3, or 5 bleeding, prior to death.
Event rates are expressed as absolute percentages.



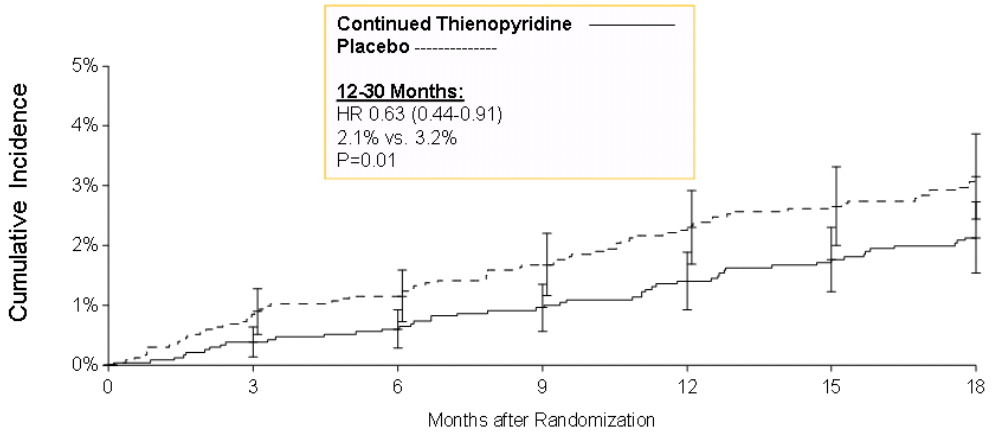
*Subjects may have >1 event.
**Site terminated participation, randomization target met prior to subject follow-up, or subject not recognized to be eligible by site.
† Subjects moved, were incarcerated, or were prematurely exited from the study.



No. at Risk							
Thienopyridine	2345	2299	2272	2255	2222	2181	2160
Placebo	2358	2314	2285	2263	2232	2213	2187

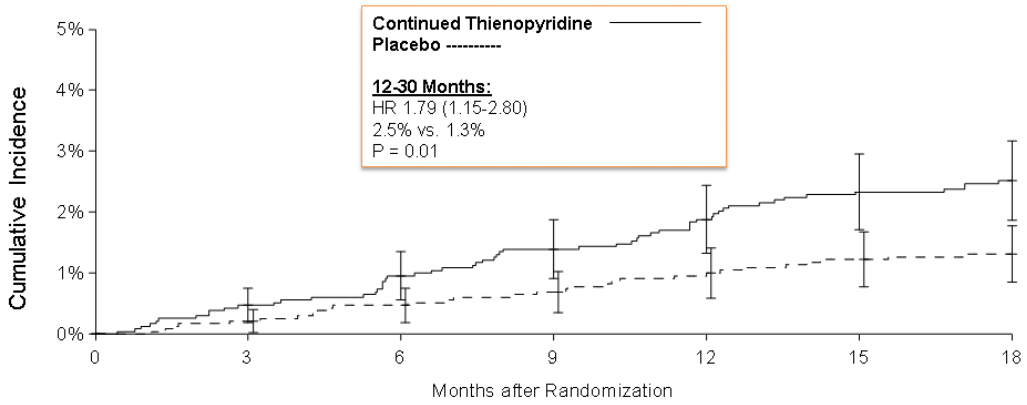


No. at Risk							
Thienopyridine	2345	2289	2256	2233	2193	2148	2122
Placebo	2358	2298	2264	2230	2188	2161	2126



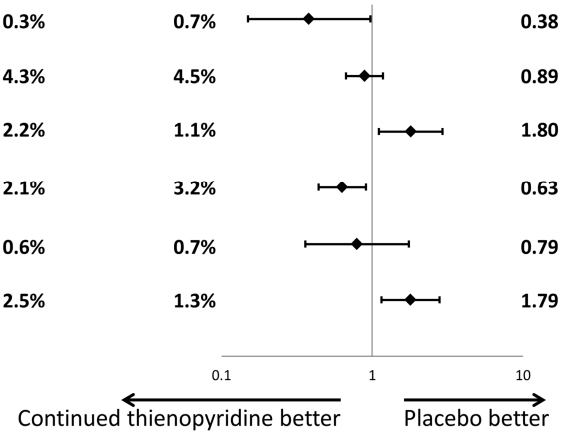
No. at Risk

Thienopyridine	2345	2290	2259	2236	2196	2153	2127
Placebo	2358	2299	2267	2237	2196	2171	2137

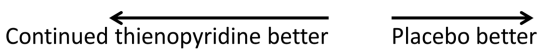


No. at Risk							
Thienopyridine	2345	2290	2256	2232	2193	2147	2124
Placebo	2358	2314	2282	2257	2223	2201	2174

Outcome	Continued Thienopyridine N=2345	Placebo N=2358	HR (95% CI)	P Value
Stent Thrombosis	0.3%	0.7%	0.38 (0.15, 0.97)	0.04
MACCE	4.3%	4.5%	0.89 (0.67, 1.18)	0.42
Death	2.2%	1.1%	1.80 (1.11, 2.92)	0.02
Myocardial Infarction	2.1%	3.2%	0.63 (0.44, 0.91)	0.01
Stroke	0.6%	0.7%	0.79 (0.36, 1.75)	0.56
Bleeding	2.5%	1.3%	1.79 (1.15, 2.80)	0.01



Outcome	Continued Thienopyridine N=5020	Placebo N=4941	HR (95% CI)	P Value
Stent Thrombosis	0.4%	1.4%	0.29 (0.17, 0.48)	<0.001
MACCE	4.3%	5.9%	0.71 (0.59, 0.85)	<0.001
Death	2.0%	1.5%	1.36 (1.00, 1.85)	0.052
Myocardial Infarction	2.1%	4.1%	0.47 (0.37, 0.61)	<0.001
Stroke	0.8%	0.9%	0.80 (0.51, 1.25)	0.32
Bleeding	2.5%	1.6%	1.61 (1.21, 2.16)	0.001



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

James B. Hermiller, Mitchell W. Krucoff, Dean J. Kereiakes, Stephan Windecker, P. Gabriel Steg, Robert W. Yeh, David J. Cohen, Donald E. Cutlip, Joseph M. Massaro, Wen-Hua Hsieh, and Laura Mauri, on behalf of the DAPT Study Investigators.

Supplemental Appendix

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Additional Statistical Information

Baseline Covariates Used for Adjustment of Treatment Interaction

In the Table 2, Cox regression P values were adjusted for baseline covariates as follows:

For the outcomes of Death, MACCE, MI: Variables used in adjustment were imputed, including Age, Gender, Race (White vs. Non-White), Body Mass Index, Diabetes Mellitus, Hypertension, Cigarette smoker, Stroke, Congestive Heart Failure, Peripheral Arterial Disease, Prior Percutaneous Coronary Revascularization, Prior CABG, Atrial fibrillation, History of Cancer, Prior MI, STEMI, Non-STEMI, Renal Insufficiency or Failure, LVEF $< 30\%$, Bifurcation lesion with side branch ≥ 2.5 mm, Lesion classification (B2/C vs. A/B1), TIMI Flow, Pre procedure (grade 0, 1 vs 2, 3), Reference Vessel Diameter (mm) - Pre-Procedure, % Stenosis - Pre-Procedure, Lesion Length (mm)- Pre-Procedure, Number of Stents implanted, Minimum Stent Diameter (mm), Total Stent Length (mm), Number of Treated Lesions, Number of Treated Vessels, Thienopyridine Type at randomization, Vessel Location (LAD/LM vs Others).

For the outcomes of Definite/Probable Stent Thrombosis: Variables used in adjustment were imputed, including age, thienopyridine type at randomization, STEMI and Non-STEMI.

For the outcomes of GUSTO severe or moderate bleeding: Variables used in adjustment were imputed, including Age, Gender, Race (White vs. Non-White), BMI, Diabetes Mellitus, Hypertension, Cigarette smoker, Congestive Heart Failure, Peripheral Arterial Disease, Prior Percutaneous Coronary Revascularization, Prior CABG, Atrial fibrillation, History of Cancer, Prior MI, Non-STEMI, Renal Insufficiency or Failure, Bifurcation lesion with side branch ≥ 2.5 mm, Lesion classification (B2/C vs A/B1), TIMI Flow, Pre procedure (grade 0, 1 vs 2, 3), Reference Vessel Diameter (mm) - Pre-Procedure, % Stenosis - Pre-Procedure, Lesion Length (mm)- Pre-Procedure, % Stenosis - Post-Procedure, Number of Stents implanted, Minimum Stent Diameter (mm), Total Stent Length (mm), Number of Treated Lesions, Number of Treated Vessels, Thienopyridine Type at randomization, Vessel Location (LAD/LM vs. Others).

Tables

Table 1. Events occurring from index stenting procedure to 12 months, unadjusted for baseline characteristics of patients.

Measure	Enrolled Patients with Everolimus-Eluting Stents N=11308	Enrolled Patients with Other Drug-Eluting Stents N=11558	P Value
Events*	1269 (11.2%)	1445 (12.5%)	0.003
Death	125 (1.1%)	169 (1.5%)	0.02
Myocardial infarction	332 (2.9%)	275 (2.4%)	0.01
Stroke	97 (0.9%)	96 (0.8%)	0.82
Stent thrombosis	35 (0.3%)	73 (0.6%)	<.001
Revascularization	725 (6.4%)	906 (7.8%)	<.001
Severe/Moderate bleeding (GUSTO)	309 (2.7%)	336 (2.9%)	0.43
Non-Compliance or interruption >14 days**	668 (5.9%)	712 (6.2%)	0.42

Event rates are expressed as absolute percentages.

*Subjects may have more than 1 event.

**Includes non-compliance with prescribed thienopyridine (<80% or >120%) or an interruption of >14 days of prescribed thienopyridine.

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

Table 2. Baseline characteristics of all randomized subjects treated with everolimus-eluting stents versus other drug-eluting stents.

Measure*	Everolimus-Eluting Stents N=4703	Other Drug-Eluting Stents N=5258	P Value
Demographics			
Age (years)	62.3±10.2	61.2±10.1	<.001
Female	1142 (24.3%)	1384 (26.3%)	0.02
Non-White race**	399 (8.7%)	458 (8.9%)	0.75
Hispanic or Latino ethnic group**	117 (2.5%)	201 (3.9%)	<.001
Weight (kg)	91.1±19.0	91.9±20.1	0.03
BMI (Kg/m^2)	30.3±5.6	30.8±5.9	<.001
Medical History			
Diabetes mellitus	1341 (28.6%)	1696 (32.3%)	<.001
Hypertension	3439 (73.4%)	4006 (76.3%)	<.001
Cigarette smoker	1050 (22.7%)	1382 (26.5%)	<.001
Stroke/Transient ischemic attack	192 (4.1%)	132 (2.5%)	<.001
History of major bleeding	30 (0.6%)	39 (0.7%)	0.63
Congestive heart failure	174 (3.7%)	287 (5.5%)	<.001
Peripheral arterial disease	226 (4.9%)	342 (6.6%)	<.001
Prior percutaneous coronary intervention	1365 (29.2%)	1682 (32.1%)	0.002
Prior Coronary artery bypass graft	506 (10.8%)	643 (12.2%)	0.03
History of cancer	499 (10.8%)	455 (8.7%)	<.001
Prior Myocardial Infarction	962 (20.9%1)	1156 (22.1%)	0.14
Indication for Index Procedure			
Acute coronary syndromes	1272 (27.1%)	1316 (25.0%)	0.02
STEMI	499 (10.6%)	546 (10.4%)	0.72
Non-STEMI	773 (16.4%)	770 (14.6%)	0.02
Unstable angina†	583 (12.4%)	1080 (20.5%)	<.001
Stable angina	1914 (40.7%)	1838 (35.0%)	<.001
Other	934 (19.9%)	1024 (19.5%)	0.63
Region			<.001
North American	3854 (82.0%)	5064 (96.3%)	
Europe	617 (13.1%)	190 (3.6%)	
Australia/New Zealand	232 (4.9%)	4 (0.08%)	
Thienopyridine at Randomization			
Clopidogrel	3968 (84.4%)	2532 (48.2%)	<.001
Prasugrel	735 (15.6%)	2726 (51.8%)	<.001

*Plus–minus values are means ±SD; all other numbers are N (%). Less than 2.5% of patients had missing values.

** Race and ethnic group were self-reported.

† This category included unstable angina without reported elevation of cardiac enzymes.

STEMI denotes ST-elevation myocardial infarction.