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Twelve or 30 Months of Dual Antiplatelet Therapy After Drug-eluting Stents

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Abstract

Background—Dual antiplatelet therapy is recommended after coronary stenting to prevent thrombotic complications, yet the benefits and risks of treatment beyond 1 year are uncertain.

Methods—Subjects were enrolled after a drug-eluting coronary stent procedure. After 12 months of thienopyridine (clopidogrel bisulfate [Plavix] or prasugrel [Effient/Efient]) with aspirin, subjects were randomized to continued thienopyridine or placebo for another 18 months; all continued aspirin. The co-primary effectiveness end points were stent thrombosis and major adverse cardiovascular and cerebrovascular events (a composite of death, myocardial infarction, or stroke) at 12 to 30 months. The primary safety end point was moderate or severe bleeding.

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*The full list of study investigators and study committee members is available in the Appendix

Results—Subjects (N=9,961) were randomized to continued thienopyridine or placebo. Continued thienopyridine reduced stent thrombosis (0.4% vs. 1.4%, hazard ratio 0.29, 95% confidence interval [CI] 0.17-0.48, P<0.001) and major adverse cardiovascular and cerebrovascular events (4.3% vs. 5.9%, hazard ratio 0.71, 95% CI 0.59-0.85, P<0.001). Myocardial infarction was reduced (2.1% vs. 4.1%, hazard ratio 0.47, P<0.001). Rates of all-cause mortality in the continued thienopyridine and placebo groups were 2.0 and 1.5%, respectively (hazard ratio 1.36, 95% CI 1.00-1.85, P=0.052). Moderate or severe bleeding was increased with continued thienopyridine (2.5% vs. 1.6%, P=0.001). An elevated hazard for stent thrombosis and myocardial infarction was observed in both groups during the 3 months following thienopyridine discontinuation.

Conclusion—Dual antiplatelet therapy beyond one year after drug-eluting stent placement significantly reduced the risks of stent thrombosis and major adverse cardiovascular and cerebrovascular events compared with aspirin alone, but was associated with increased bleeding.

Introduction

Millions of patients worldwide receive coronary stents each year for the treatment of ischemic heart disease.[1,2] Although drug-eluting stents reduce restenosis compared with bare metal stents, there is concern that drug-eluting stents may be associated with risks of stent thrombosis occurring beyond one year after treatment.[3] Stent thrombosis, while rare, is frequently associated with myocardial infarction, and may be fatal.[3] Furthermore, ischemic events such as myocardial infarction, stroke, or cardiovascular death, unrelated to the treated coronary lesion, also occur beyond one year.[4,5]

The use of dual antiplatelet therapy combining a P2Y12 receptor inhibitor with aspirin is critically important to prevent coronary stent thrombosis, and is currently recommended for 6 to 12 months after implantation of a drug-eluting stent.[6,7] While some observational studies suggest that extending dual antiplatelet therapy beyond one year is associated with a lower risk of myocardial infarction following drug-eluting stent treatment[8], several trials have also demonstrated increased risk of bleeding without lowering myocardial infarction incidence with longer therapy.[9-12] Whether treatment with dual antiplatelet therapy beyond one year reduces either coronary stent thrombosis or ischemic events remote to the stent has not been determined by an adequately powered randomized trial.

The Dual Antiplatelet Therapy (DAPT) Study was an international, multicenter, randomized placebo-controlled trial to determine the benefits and risks of continuing dual antiplatelet therapy beyond one year after treatment with coronary stents.

Methods

Study Design

The DAPT Study design has been described previously.[13] The trial was designed in response to a request from the United States Food and Drug Administration (FDA) to manufacturers of coronary stents, and was conducted under an investigational-device exemption through a public-private collaboration involving the FDA, eight funding stent and pharmaceutical manufacturers (see Supplementary Appendix), and Harvard Clinical

Research Institute (HCRI). The stent manufacturers who contributed to the funding of the trial had contributing roles in trial design and in data collection as detailed in the Supplementary Appendix. HCRI was responsible for the scientific conduct and independent analysis of the trial.

A single uniform randomized trial was designed incorporating five individual component studies to facilitate enrollment (Supplementary Appendix). Subjects were enrolled into the trial either by HCRI or from one of four post-marketing surveillance studies designed to collect similar clinical data in similar patient populations. Each contributing study followed uniform randomization criteria and follow-up as specified by the overall DAPT Study protocol. A single clinical events committee blinded to the randomized treatment assignment adjudicated events, and an unblinded independent central data monitoring committee oversaw the safety of all subjects. All participating institutions received institutional review board approval.

The first three authors and the last author, who wrote the manuscript under the coordination of HCRI, had full access to the data; they vouch for the integrity of the analyses presented and for the fidelity of this report to the trial protocol, which is available with the full text of this article at NEJM.org. The manuscript was provided to the funding manufacturers for review in advance of publication; however, they did not have the right of refusal except with regard to individual manufacturer confidential information.

Study Population

Adults who were candidates for dual antiplatelet therapy following treatment with FDA-approved drug-eluting or bare metal stents were enrolled. Detailed inclusion and exclusion criteria are listed in the Supplementary Appendix. Each subject provided written informed consent at enrollment.

The primary analytic population and focus of this report is subjects treated with drug-eluting stents only (results in subjects treated with bare metal stents will be reported in a separate publication; see Figure 1). Drug-eluting stents included sirolimus-eluting stents (Cypher, Cordis), zotarolimus-eluting stents (Endeavor, Medtronic), paclitaxel-eluting stents (TAXUS, Boston Scientific), and everolimus-eluting stents (Xience, Abbott Vascular and PROMUS, Boston Scientific). It was recommended that all subjects receive either clopidogrel at a maintenance dose of 75 mg daily or prasugrel at a maintenance dose of 10 mg daily (a dose of 5 mg daily was recommended in subjects weighing less than 60 kg).[13] The recommended maintenance aspirin dosage was 75 to 162 mg daily, continued indefinitely.

Study Procedures

Subjects were enrolled within 72 hours of stent placement and were given open-label aspirin and thienopyridine for 12 months. At 12 months, subjects who were both event-free (from major adverse cardiovascular and cerebrovascular events, repeat revascularization, or moderate or severe bleeding) and compliant with thienopyridine (defined as having taken 80% to 120% of the drug without an interruption of longer than 14 days) were eligible for randomization (see Figure 1).

Eligible subjects continued aspirin and were randomized in a 1:1 ratio to continued thienopyridine or placebo for an additional 18 months (months 12 to 30 after enrollment). A computer-generated randomization schedule stratified subjects by stent type (drug-eluting versus bare metal stent), hospital site, thienopyridine type, and presence or absence of at least one prospectively-defined clinical or lesion-related risk factor for stent thrombosis (risk factors listed in Table S1 of the Supplementary Appendix).[13] After completing the randomized treatment period, subjects were followed for a 3-month observational period on aspirin alone (months 30 to 33 after enrollment) to assess the effect of thienopyridine discontinuation on end point event rates.

End Points

The co-primary effectiveness end points were the cumulative incidence of definite or probable stent thrombosis[14] and major adverse cardiovascular and cerebrovascular events (defined as the composite of death, myocardial infarction or stroke) during the randomized treatment period (months 12 to 30). The primary safety end point was the incidence of moderate or severe bleeding during this same period (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries [GUSTO] classification).[15] Bleeding was also evaluated according to the Bleeding Academic Research Consortium [BARC] definitions.[16] End point definitions are provided in the Supplementary Appendix. After the primary analysis had been completed, a second blinded clinical events committee was convened to adjudicate non-cardiovascular causes of death.

Statistical Analysis

The primary efficacy analysis was a superiority analysis performed using the log-rank test, stratified by geographic region (North America, Europe, or Australia and New Zealand), thienopyridine type at randomization, and presence or absence of stent thrombosis risk factors, controlling the two-sided family-wise error rate of 0.05 across the two co-primary end points using the Benjamini-Hochberg method.[17] Using this method, the null hypothesis of randomized treatment equivalence is rejected if significance is achieved on both end points at a two-sided alpha = 0.05, or on one end point at a two-sided alpha = 0.025. We assumed annual placebo event rates of 0.5% for stent thrombosis and 2.9% for major adverse cardiovascular and cerebrovascular events; hazard ratios of 0.45 for stent thrombosis and 0.75 for major adverse cardiovascular and cerebrovascular events for continued thienopyridine vs. placebo; and up to 3% annual loss to follow-up. Given these assumptions, a sample size of 9,800 randomized subjects receiving drug-eluting stents yielded at least 85% power. This sample size was reduced from the 12,196 specified in the original protocol based on changes made in statistical parameters before enrollment was completed and without inspection of the study data (as described in the Supplementary Appendix).

The primary safety analysis was a non-inferiority analysis performed using the Farrington-Manning risk difference approach[18]. Assuming an annualized moderate or severe bleeding rate of 1.9%, and an absolute non-inferiority margin (δ) of 0.8%, at an alpha = 0.025 (1-sided) significance, a sample size of 9,960 subjects provided 80% power to detect non-inferiority.

For major adverse cardiovascular and cerebrovascular events and stent thrombosis, the primary analyses were performed on all randomized subjects treated with drug-eluting stents (the intention-to-treat principle). Kaplan-Meier estimates of the cumulative incidence of each end point are presented by treatment group, with 2-sided 95% confidence intervals (CI) of stratified hazard ratios. Subjects not experiencing an end point were censored for the analysis on that end point at the time of last known contact or 30 months, whichever was earlier. Secondary analyses included examining these same outcomes on all randomized subjects over the 21-month post-randomization period, the last three months of which subjects were not receiving randomized treatment, and hazards before and after study drug-discontinuation were assessed for qualitative differences.

For bleeding, the primary non-inferiority assessment was performed on randomized subjects treated with drug-eluting stents who completed at least 17 months of follow-up (the minimum allowable visit window for the 18 month post-randomization visit) or experienced a moderate or severe bleeding event. Bleeding event rates are presented as percentages. The moderate or severe bleeding hazard ratio is also presented as a *post hoc* descriptive analysis.

To account for missing data, we repeated the treatment comparisons including all randomized subjects using multiple imputation[19] logistic regression modeling with baseline covariates (50 imputations) for missing data regarding the primary end points. We also assessed the consistency of the treatment effect on the primary end points for 14 pre-specified factors assessed at baseline.

Results

Study Population

Between Aug 13, 2009 and July 1, 2011, a total of 25,682 subjects from 452 sites in 11 countries were enrolled in the DAPT Study, of whom 22,866 received a drug-eluting stent. Among these subjects, 5,261 (23.0%) were not eligible for randomization after 12 months of follow-up, 7,644 (33.4%) were eligible but not randomized (Supplementary Appendix Table S2), and 9,961 (43.6%) were randomized (Figure 1). Among those who were eligible but not randomized, the most common reason was withdrawal of consent during the year between enrollment and randomization (76%).

Baseline characteristics of randomized subjects treated with drug-eluting stents were similar between treatment groups (Table 1). Overall, 26% presented with acute myocardial infarction, and 50.9% had at least one clinical or lesion-related risk factor for stent thrombosis (Supplementary Appendix Table S1). Rates of discontinuation of study drug were not different for the continued thienopyridine and placebo groups at 30 months (21.4% vs. 20.3%, respectively, P=0.18).

Stent Thrombosis and Major Adverse Cardiovascular and Cerebrovascular Events

Over the primary analysis period for all randomized subjects, the continued thienopyridine group experienced a significantly lower cumulative incidence of stent thrombosis (0.4% vs. 1.4%, hazard ratio 0.29, 95% CI 0.17-0.48, P<0.001) and major adverse cardiovascular and cerebrovascular events (4.3% vs. 5.9%, hazard ratio 0.71, 95% CI 0.59-0.85, P<0.001),

compared with the placebo group (Table 2a and Figures 2 and 3). Continued thienopyridine was associated with a lower cumulative incidence of myocardial infarction than placebo (2.1% vs. 4.1%, hazard ratio 0.47, P<0.001, Supplementary Appendix Figure S1), of which non-stent thrombosis-related myocardial infarction comprised 55% of the treatment benefit (1.8% vs. 2.9% hazard ratio 0.59, P<0.001). Rates of cardiac mortality (0.9% vs. 1.0%, P=0.98), vascular mortality (0.1% vs. 0.1%, P=0.98), and stroke (0.8% vs 0.9%, P=0.32) were similar between groups. Total mortality rates were 2.0% and 1.5%, respectively (hazard ratio 1.36, 95% CI 1.00-1.85, P=0.052, Supplementary Appendix Figure S2). The results using multiple imputation were consistent (hazard ratio for stent thrombosis 0.27, P<0.001; hazard ratio for major adverse cardiovascular and cerebrovascular events 0.77, P=0.002, Supplementary Appendix Table S3a), as were the findings when the analysis period included the three months after study drug discontinuation (Supplementary Appendix Table S4).

Bleeding

Rates of moderate or severe bleeding for the primary analysis period were significantly higher in the continued thienopyridine group (2.53% vs. 1.57%, hazard ratio 1.61, 95% CI 1.21-2.16, P=0.001), and did not meet the pre-specified definition of non-inferiority versus placebo (P=0.70, Table 2b). There was not a significant difference between randomized treatments in GUSTO severe bleeding (0.81% vs. 0.56%, P=0.15) or in BARC fatal bleeding (type 5, 0.15% vs. 0.09%, P=0.38), in the continued thienopyridine vs. placebo groups, respectively. More details of bleeding results by BARC subtype are shown in Supplementary Appendix Table S5. The results using multiple imputation were consistent (risk difference for moderate or severe bleeding 0.98%, P=0.73 for non-inferiority, Supplementary Appendix Table S3b), as were the findings when the analysis period included the three months after study drug discontinuation (Supplementary Appendix Table S6).

Mortality

Over the primary analysis period of 12 to 30 months, the rates of all-cause mortality in the continued thienopyridine and placebo groups were 2.0% and 1.5%, respectively (hazard ratio 1.36, P=0.052). During the secondary analysis period of 12 to 33 months, all-cause mortality was 2.3% vs. 1.8% (hazard ratio 1.36, P=0.04, Supplementary Appendix Figure S2 and Table S4), the difference accounted for by non-cardiovascular death (1.1% vs. 0.6%, hazard ratio 1.80, P=0.01). Among these non-cardiovascular deaths, bleeding-related death (N=11 vs. 3, P=0.057) was mainly related to fatal trauma (N=7 vs. N=2, P=0.07). Cancer-related death differed between groups (N=31 vs. 14, P=0.02), and was mediated by bleeding in a few cases (N=3 vs. 0, Supplementary Appendix Table S7).

There were 22 more subjects with a history of cancer at baseline in the thienopyridine group (Supplementary Appendix Table S8), and blinded review of cancer-related deaths identified an imbalance in the number of randomized subjects where the cancer had been diagnosed prior to enrollment (8 vs. 1, Supplementary Appendix Table S9). When these subjects were excluded in a *post hoc* sensitivity analysis, differences in mortality were no longer significant (Supplementary Appendix Table S10).

Additional Analyses

The effect of continued thienopyridine versus placebo on the primary endpoints and on myocardial infarction was consistent across most subgroups (Supplementary Appendix Figure S3). Hazards after thienopyridine discontinuation are presented in the Supplementary Appendix.

Discussion

Among patients receiving drug-eluting coronary stents, continued thienopyridine and aspirin beyond one year reduced the risk of stent thrombosis and major adverse cardiovascular and cerebrovascular events compared with aspirin alone. This treatment benefit was driven by concurrent reductions in stent thrombosis and in myocardial infarction. Longer thienopyridine administration was also associated with more bleeding, although severe or fatal bleeding was uncommon and not significantly different between study groups.

The DAPT Study included a large proportion of subjects with stent thrombosis risk factors, including many with preceding myocardial infarction. Across almost all subjects and lesion types, continued thienopyridine was associated with reductions in the risk of both co-primary end points. Different stents[20,21] and P2Y12 inhibitors[22] have been associated with varied rates of stent thrombosis and myocardial infarction in previous reports, yet in this study, thienopyridine use beyond one year reduced the risks of both outcomes across all stent and drug types. Although results from prior studies vary with regard to risk of thienopyridine discontinuation after 6 months, [10-13,23,24] the current study detected an increased risk of myocardial infarction (both stent- and non-stent related) during the first three months after discontinuation in both treatment groups. Future evaluation of thienopyridine therapy to suppress risks of cardiovascular events beyond the duration of this study may be warranted.

An unexpected finding was that all-cause mortality during the treatment period was numerically higher for the continued thienopyridine group, driven by an increase in non-cardiovascular deaths. While the diagnosis of cancer did not differ after randomization, cancer-related death was more frequent in subjects treated with continued thienopyridine and may reflect a chance imbalance in subjects with known cancer prior to enrollment. While one study comparing long-term thienopyridine therapy to placebo in subjects with lacunar stroke identified an unexpected increase in mortality,[25] other large randomized studies in subjects with coronary artery disease have not identified either increased or decreased risks of mortality.[26-28]

Several limitations of the study should be considered. First, only drug-compliant subjects who did not have major adverse cardiovascular and cerebrovascular events, stent thrombosis or moderate or severe bleeding in the first year were randomized, which may have selected for subjects at lower risk for late adverse events. Second, while we did not quantify the net impact of ischemic and bleeding events; decision analysis suggests that small absolute differences in cardiovascular event rates may be sufficient[29] to counterbalance bleeding risks. Third, while four different metal platform durable polymer drug-eluting stents and two platelet P2Y12 inhibitors were included, whether the treatment benefits observed will be

generalizable to other stent types[30,31] or non-thienopyridine P2Y12 inhibitors[32,33] is unknown. Additionally, since stent and drug type were not randomized, direct comparisons of different stent or drug types may be confounded, and within-subgroup estimates of treatment effect may be underpowered.

In conclusion, in patients treated with drug-eluting stents, continuation of thienopyridine plus aspirin beyond one year reduced the risks of ischemic events compared with aspirin alone. Reduction in risk of ischemic events was consistent across drug and stent types, and was evident regardless of risk of stent thrombosis. The clinical benefit of extended thienopyridine treatment was tempered by an increase in bleeding events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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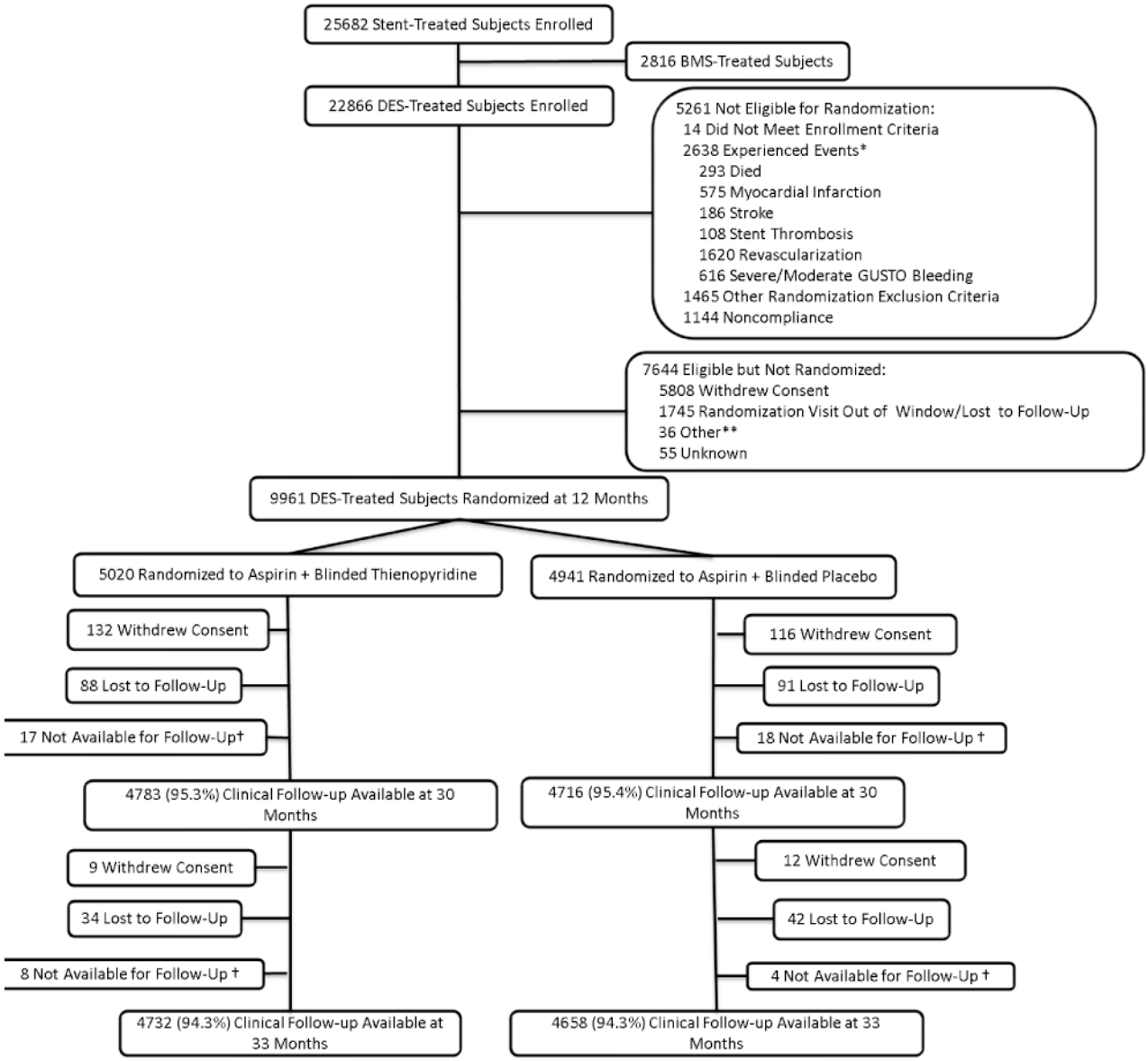


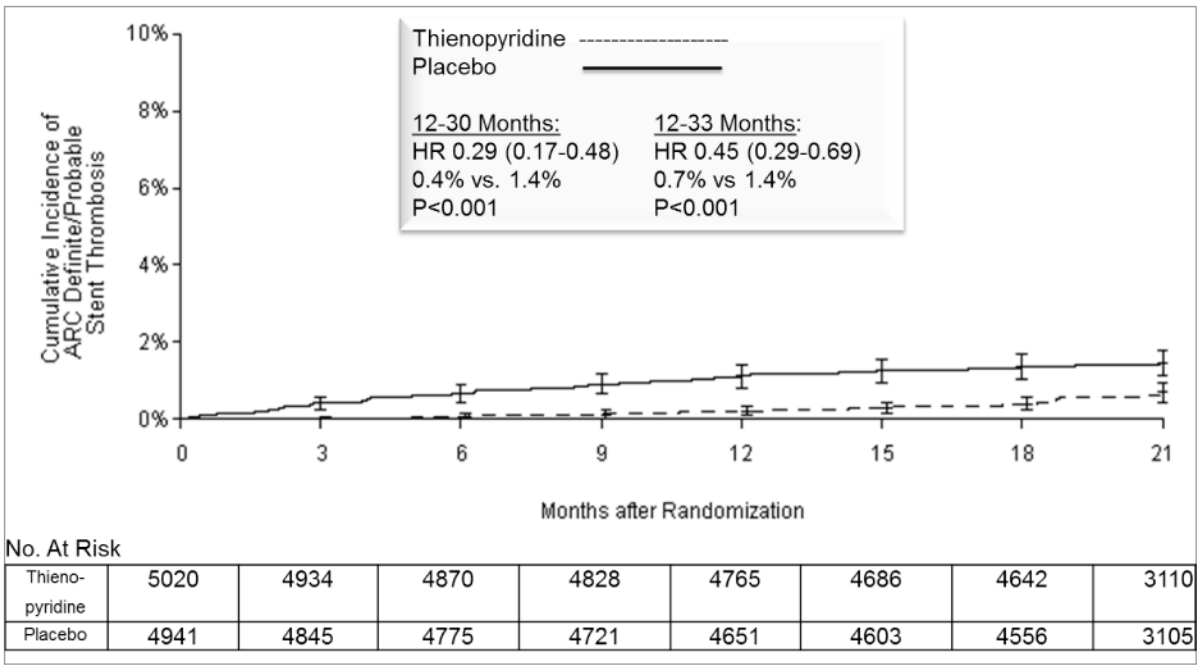
Figure 1. Subject Randomization and Follow-Up

Subjects were enrolled within 72 hours of stent placement, followed for 12 months on open-label thienopyridine plus aspirin, then randomized to 18 months of thienopyridine or placebo (each in addition to aspirin). Randomized treatment ended at 30 months and subjects remained on aspirin only and were followed for another 3 months. While the number of subjects with clinical follow-up available is reported in each arm, the co-primary efficacy endpoints were analyzed according to the principle of intention to treat, including all randomized subjects and last available follow-up information.

*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

Thieno-pyridine	5020	4934	4870	4828	4765	4686	4642	3110
Placebo	4941	4845	4775	4721	4651	4603	4556	3105

Figure 2. Cumulative Incidence of Stent Thrombosis, According to Treatment Group

Cumulative incidence curve is shown for the primary effectiveness outcome of stent thrombosis in the intention-to-treat analysis population. Randomization occurred at 12 months after stenting. The primary analysis period was 12-30 months after percutaneous coronary intervention, i.e. the 18 months after randomization over which subjects were treated with study drug. Subjects were followed for an observational period of an additional three months, off study drug and off open label thienopyridine treatment, to a total of 33 months, i.e. 21 months post randomization. P values were calculated with stratified log-rank test. The number at risk is defined as the number of subjects without the event of interest and available for subsequent follow-up. The numbers at risk at the start of final 33 month visit (i.e. 20 months post randomization) were 4,438 vs. 4,362 for continued thienopyridine vs. placebo, respectively.

Abbreviations: ARC, Academic Research Consortium; HR, hazard ratio; MACCE, major adverse cerebral and cardiovascular events.

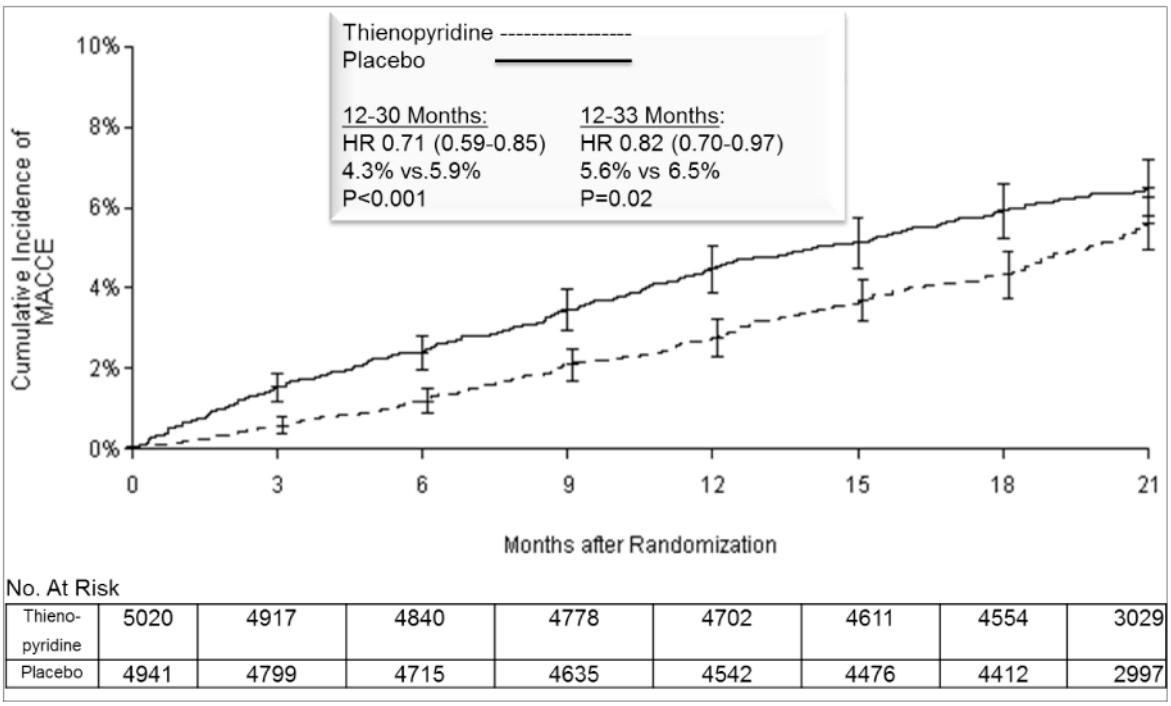


Figure 3. Cumulative Incidence of Major Adverse Cardiovascular and Cerebrovascular Events (MACCE) According to Treatment Group

Cumulative incidence curve is shown for the primary effectiveness outcome of MACCE in the intention-to-treat analysis population. Randomization occurred at 12 months after stenting. The primary analysis period was 12-30 months after percutaneous coronary intervention, i.e. the 18 months after randomization over which subjects were treated with study drug. Subjects were followed for an observational period of an additional three months, off study drug and off open label thienopyridine treatment, to a total of 33 months, i.e. 21 months post randomization. P values were calculated with stratified log-rank test. Error The number at risk is defined as the number of subjects without the event of interest and available for subsequent follow-up. The numbers at risk at the start of final 33-month visit (i.e. 20 months post randomization) were 4,336 vs. 4,217 for continued thienopyridine vs. placebo, respectively.

Abbreviations: ARC, Academic Research Consortium; HR, hazard ratio; MACCE, major adverse cerebral and cardiovascular events.

Table 1

Characteristics of Randomized Subjects Treated with Drug-Eluting Stents*

Measure	Continued Thienopyridine N=5020 Subjects	Placebo N=4941 Subjects
Subject Characteristics		
Age (years)	61.8± 10.2	61.6 ± 10.1
Female	1242 (24.7%)	1284 (26.0%)
Race-Non- White	438/4918 (8.9%)	419/4847 (8.6%)
Hispanic or Latino	159/4924 (3.2%)	159/4847 (3.3%)
Weight (kg)	91.5± 19.7 (5009)	91.5±19.4 (4931)
BMI (Kg/m^2)	30.5± 5.8 (4973)	30.6±5.8 (4901)
Diabetes mellitus	1556/5006 (31.1%)	1481/4927 (30.1%)
Hypertension	3796/5006 (75.8%)	3649/4934 (74.0%)
Current cigarette smoker or within past year	1222/4965 (24.6%)	1210/4893 (24.7%)
Stroke/TIA	155/5006 (3.1%)	169/4931 (3.4%)
Congestive heart failure	238/5001 (4.8%)	223/4926 (4.5%)
Peripheral arterial disease	284/4937 (5.8%)	284/4857 (5.8%)
Prior PCI	1518/4995 (30.4%)	1529/4928 (31.0%)
Prior CABG	568/5012 (11.3%)	581/4930 (11.8%)
Prior MI	1092/4953 (22.0%)	1026/4870 (21.1%)
Positive stress test**	1487/3916 (38.0%)	1485/3843 (38.6%)
Indication for PCI		
STEMI	534 (10.6%)	511 (10.3%)
NSTEMI	776 (15.5%)	767 (15.5%)
Unstable angina***	838 (16.7%)	825 (16.7%)
Stable angina	1882 (37.5%)	1870 (37.8%)
Other	990 (19.7%)	968 (19.6%)
Region		
North America	4502 (89.7%)	4416 (89.4%)
Europe	402 (8.0%)	405 (8.2%)
Australia/New Zealand	116 (2.3%)	120 (2.4%)
Treatment Characteristics		
Clopidogrel	3275 (65.24%)	3230 (65.37%)
Prasugrel	1745 (34.76%)	1711 (34.63%)
DES type at index procedure		
Everolimus-eluting	2345 (46.71%)	2358 (47.72%)
Paclitaxel-eluting	1350 (26.89%)	1316 (26.63%)
Zotarolimus-eluting†	642 (12.79%)	622 (12.59%)
Sirolimus-eluting	577 (11.49%)	541 (10.95%)
>1 DES type	106 (2.11%)	104 (2.10%)

Measure	Continued Thienopyridine N=5020 Subjects	Placebo N=4941 Subjects
Number of treated lesions	1.30±0.55	1.29±0.54
Number of treated vessels	1.11±0.33	1.12±0.34
Number of stents	1.47±0.75	1.45±0.75
Minimum stent diameter		
<3	2341 (46.63%)	2293 (46.41%)
=3	1593 (31.73%)	1595 (32.28%)
>3	1086 (21.63%)	1053 (21.31%)
Total stent length	27.70±16.77	27.43±17.02
Lesion Characteristics	**N=6594 Lesions**	**N=6413 Lesions**
Treated vessel(s)		
Native coronary	6396/6586 (97.12%)	6204/6407 (96.83%)
Left main	55/6586 (0.84%)	55/6407 (0.86%)
LAD	2715/6586 (41.22%)	2586/6407 (40.36%)
RCA	2153/6586 (32.69%)	2057/6407 (32.11%)
Circumflex	1473/6586 (22.37%)	1506/6407 (23.51%)
Venous graft	154/6586 (2.34%)	173/6407 (2.70%)
Arterial graft	36/6586 (0.55%)	30/6407 (0.47%)
Modified ACC/AHA lesion class B2 or C‡	2754/6335 (43.47%)	2643/6137 (43.07%)

* There were no significant differences between the two groups except for hypertension (P=0.03).

Denominators are shown when they differed from the total number in the treatment group.

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; BMI, body mass index; CABG, coronary artery bypass graft; LAD, left anterior descending; MI, myocardial infarction; NSTEMI, non-ST elevation MI; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-elevation MI; TIA, transient ischemic attack.

** For most variables, 0-3% of patients had missing values; 6% of patients were missing lesion class; 22% of patients were missing positive stress test due to not being collected in one contributing study.

*** Without reported cardiac enzyme elevation.

† Endeavor stent.

Table 2a

Stent Thrombosis and Major Adverse Cardiovascular and Cerebrovascular Events (MACCE)

Subjects were randomized to 18 months of either continued thienopyridine or placebo plus aspirin 12 months after receiving a drug-eluting stent. Data are presented according to intention-to-treat. The primary analysis period was 12-30 months after enrollment, and the study co-primary effectiveness end points were stent thrombosis and MACCE. Hazard ratios are presented as continued thienopyridine vs. placebo.

Outcome	Continued Thienopyridine N=5020	Placebo N=4941	Stratified Hazard Ratio (95% CI)	Stratified Log-rank P Value
Stent thrombosis	19 (0.4%)	65 (1.4%)	0.29 (0.17, 0.48)	<0.001
ARC definite	15 (0.3%)	58 (1.2%)	0.26 (0.14, 0.45)	<0.001
ARC probable	5 (0.1%)	7 (0.1%)	0.71 (0.22, 2.23)	0.55
MACCE (death, MI, or stroke)	211 (4.3%)	285 (5.9%)	0.71(0.59, 0.85)	<0.001
Death	98 (2.0%)	74 (1.5%)	1.36 (1.00, 1.85)	0.052
Cardiac	45 (0.9%)	47 (1.0%)	1.00 (0.66, 1.52)	0.98
Vascular	5 (0.1%)	5 (0.1%)	0.98 (0.28, 3.39)	0.98
Non-cardiovascular	48 (1.0%)	22 (0.5%)	2.23 (1.32, 3.78)	0.002
MI	99 (2.1%)	198 (4.1%)	0.47 (0.37, 0.61)	<0.001
Stroke	37 (0.8%)	43 (0.9%)	0.80 (0.51, 1.25)	0.32
Ischemic	24 (0.5%)	34 (0.7%)	0.68 (0.40, 1.17)	0.16
Hemorrhagic	13 (0.3%)	9 (0.2%)	1.20 (0.50, 2.91)	0.68
Type uncertain	0 (0.0%)	1 (0.0%)	0 (--, --)	0.32

Abbreviations: ARC, Academic Research Consortium; ASA, aspirin; MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction; ST, stent thrombosis.

Table 2b

Bleeding Outcomes at 12-30 Months

The primary safety end point was GUSTO Moderate or Severe bleeding. The one-sided test of non-inferiority (based on a delta of 0.8%) was calculated according to the Farrington-Manning approach. Only evaluable subjects were included in this analysis, e.g. subjects whose last contact date was ≥ 510 days post randomization or who experienced any adjudicated bleeding outcome at or before 540 days. The secondary analysis of BARC results by subtype are shown in Supplementary Appendix Table S5.

Bleeding Complications	Continued Thienopyridine N=4713	Placebo N=4650	Risk Difference (95% CI)	Two-sided P Value for Difference	One-sided P Value for Non-Inferiority
GUSTO Severe/Moderate	119 (2.53%)	73 (1.57%)	0.96% (0.38%, 1.53%)	0.001	0.70
GUSTO Severe	38 (0.81%)	26 (0.56%)	0.25% (-0.09%, 0.58%)	0.15	
GUSTO Moderate	81 (1.72%)	48 (1.03%)	0.69% (0.22%, 1.16%)	0.004	
BARC Types 2, 3, or 5	263 (5.58%)	137 (2.95%)	2.64% (1.82%, 3.45%)	<0.001	
BARC Type 2	145 (3.08%)	72 (1.55%)	1.53% (0.92%, 2.14%)	<0.001	
BARC Type 3	122 (2.59%)	68 (1.46%)	1.13% (0.56%, 1.70%)	<0.001	
BARC Type 5	7 (0.15%)	4 (0.09%)	0.06% (-0.08%, 0.20%)	0.38	

Abbreviations: BARC, Bleeding Academic Research Consortium; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries.