EDITORIAL

Dual Antiplatelet Therapy after Drug-Eluting Stents — How Long to Treat?

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The rationale behind dual antiplatelet therapy after successful stenting is based upon two indications. First, the stented segment requires protection from stent thrombosis that occurs as a result of inflammation during healing. Second, the areas inside and outside the stented section require protection from the development of progressive atherosclerosis and plaque rupture. The first of these two problems is of less concern with drug-eluting stents, especially second- and third-generation drug-eluting stents.[1,2] However, the second issue continues to be important. The most effective duration of dual antiplatelet therapy for preventing both stent thrombosis and spontaneous myocardial infarction, while limiting bleeding risk, remains unresolved.

Mauri et al. now report in the *Journal* the results of the Dual Antiplatelet Therapy (DAPT) study,[3] in which 9961 patients who had completed 12 months of dual antiplatelet therapy after implantation of a drug-eluting stent were randomly assigned to an additional 18 months of thienopyridine therapy (clopidogrel or prasugrel) or placebo; all the patients continued to take aspirin. The rates of the coprimary efficacy end points of stent thrombosis and major adverse cardiovascular and cerebrovascular events (a composite of death, myocardial infarction, or stroke) at 12 to 30 months were significantly reduced with continued thienopyridine therapy. There was a significant reduction in the rate of myocardial infarction in the group that continued to receive thienopyridine therapy; myocardial infarctions that were not related to stent thrombosis represented 55% of this benefit. On the other hand, the primary safety end point — moderate or severe bleeding — was increased with continued thienopyridine therapy. There was also an increase in overall mortality with continued thienopyridine treatment, although this increase may have been due, at least in part, to an imbalance in preexisting cancer (and subsequently in cancer-related mortality) in that group.

There has been a recent drive within the interventional cardiology community to shorten the duration of dual antiplatelet therapy after implantation of a drug-eluting stent from 12 months of therapy to 6 or even 3 months. Several previous trials and meta-analyses have shown this practice to be safe, at least in selected patients.[4-10] Therefore, the question of whether to continue dual antiplatelet therapy beyond 12 months may appear to be outdated. This apparent contradiction can be explained by separating the need for dual antiplatelet therapy after implantation of a drug-eluting stent into two phases: a period of "mandatory" dual antiplatelet therapy and a period of "possibly beneficial" dual antiplatelet therapy. The mandatory period is defined as the interval during which premature discontinuation of dual antiplatelet therapy would lead to an unacceptably high rate of stent thrombosis, whereas the possibly beneficial period is the subsequent interval during which the benefit versus risk of continued, uninterrupted therapy is more a matter of debate. The DAPT study addresses the possibly beneficial period rather than the mandatory period.[8] This study has clearly shown a reduction in both stent thrombosis and myocardial infarction when dual antiplatelet therapy is extended beyond 1 year after implantation of a drug-eluting stent. However, the observed increase in moderate or severe bleeding, as well as the possible increase in all-cause

mortality, leaves us with uncertainty regarding the incremental benefit from prolonging dual antiplatelet therapy.

Prolonged dual antiplatelet therapy is most likely to be of benefit in patients who are at high risk for stent thrombosis or myocardial infarction, but who are also at relatively low risk for bleeding. In this regard, the DAPT trial included only patients who had not had a major adverse cardiovascular or cerebrovascular event, repeat revascularization, or moderate or severe bleeding by the completion of 12 months of dual antiplatelet therapy and who were adherent to thienopyridine therapy. These and other criteria resulted in the exclusion from randomization of 23% of the patients who had initially been treated with a drug-eluting stent and were enrolled in the study. It is possible that the patients who were excluded from randomization because of a previous major adverse cardiovascular or cerebrovascular event are the very patients who would have benefited the most from prolonged treatment.

In addition, there was evidence suggesting that continued thienopyridine therapy had the greatest effect in reducing the rate of major adverse cardiovascular and cerebrovascular events among recipients of paclitaxel-eluting stents (hazard ratio, 0.52) and the least effect in reducing the rate among recipients of everolimus-eluting stents (hazard ratio, 0.89; P=0.05 for the interaction). This suggests that the potential benefits of prolonged dual antiplatelet therapy may depend on the type of stent that is implanted.

The key message of the DAPT study is the suggestion that some patients who have been treated with a drug-eluting stent may benefit from extending dual antiplatelet therapy beyond 1 year, but also that the potential harm with this approach should not be overlooked. Moreover, we do not know how long this benefit extends and which patients benefit most. The safest and most effective duration of dual antiplatelet therapy therefore remains uncertain and must be individualized for each patient; presumably in making this judgment, physicians should balance risk factors favoring atherothrombosis against the risk of bleeding.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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ORIGINAL ARTICLE

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

Patients were enrolled after they had undergone a coronary stent procedure in which a drug-eluting stent was placed. After 12 months of treatment with a thienopyridine drug (clopidogrel or prasugrel) and aspirin, patients were randomly assigned to continue receiving thienopyridine treatment or to receive placebo for another 18 months; all patients continued receiving aspirin. The coprimary efficacy end points were stent thrombosis and major adverse cardiovascular and cerebrovascular events (a composite of death, myocardial infarction, or stroke) during the period from 12 to 30 months. The primary safety end point was moderate or severe bleeding.

RESULTS

A total of 9961 patients were randomly assigned to continue thienopyridine treatment or to receive placebo. Continued treatment with thienopyridine, as compared with placebo, reduced the rates of stent thrombosis (0.4% vs. 1.4%; hazard ratio, 0.29 [95% confidence interval {CI}, 0.17 to 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 to 0.85]; P<0.001). The rate of myocardial infarction was lower with thienopyridine treatment than with placebo (2.1% vs. 4.1%; hazard ratio, 0.47; P<0.001). The rate of death from any cause was 2.0% in the group that continued thienopyridine therapy and 1.5% in the placebo group (hazard ratio, 1.36 [95% CI, 1.00 to 1.85]; P=0.05). The rate of moderate or severe bleeding was increased with continued thienopyridine treatment (2.5% vs. 1.6%, P=0.001). An elevated risk of stent thrombosis and myocardial infarction was observed in both groups during the 3 months after discontinuation of thienopyridine treatment.

CONCLUSIONS

Dual antiplatelet therapy beyond 1 year after placement of a drug-eluting stent, as compared with aspirin therapy alone, significantly reduced the risks of stent thrombosis and major adverse cardiovascular and cerebrovascular events but was associated with an increased risk of bleeding. (Funded by a consortium of eight device and drug manufacturers and others; DAPT ClinicalTrials.gov number, NCT00977938.)

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*A complete list of investigators and committee members in the Dual Antiplatelet Therapy (DAPT) study is provided in the Supplementary Appendix, available at NEJM.org.

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

A video summary is available at NEJM.org

The use of dual antiplatelet therapy in which a P2Y12-receptor inhibitor is combined with aspirin is critically important for the prevention of coronary stent thrombosis, and this therapy is currently recommended for 6 to 12 months after implantation of a drug-eluting stent.[6,7] Although some observational studies suggest that extending dual antiplatelet therapy beyond 1 year is associated with a reduced risk of myocardial infarction after the placement of a drug-eluting stent,[8] several trials have shown an increased risk of bleeding without a reduction in the incidence of myocardial infarction with longer therapy.[9-12] Whether treatment with dual antiplatelet therapy beyond 1 year reduces the rate of either coronary-stent thrombosis or ischemic events occurring in an area remote from 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 that was designed to determine the benefits and risks of continuing dual antiplatelet therapy beyond 1 year after the placement of a coronary stent.

Methods

Study Design

The design of the DAPT study has been described previously.[13] The trial was designed in response to a request from the 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 stent and pharmaceutical manufacturers who funded the study (see the Supplementary Appendix, available with the full text of this article at NEJM.org), and the Harvard Clinical Research Institute (HCRI). The stent manufacturers who funded the trial had contributing roles in the design of the trial and in the collection of the data, as detailed in the Supplementary Appendix. The HCRI was responsible for the scientific conduct of the trial and an independent analysis of the data.

To facilitate enrollment, a single, uniform randomized trial was designed that incorporated five individual component studies (see the Supplementary Appendix). Patients were enrolled in the trial either by the HCRI or through one of four postmarketing surveillance studies that were designed to collect similar clinical data in similar patient populations. Each contributing study followed uniform randomization criteria and the same follow-up schedule for assessments, as specified by the overall DAPT study protocol. A single clinical-events committee whose members were unaware of the group assignments adjudicated events, and an unblinded, independent, central data and safety monitoring committee oversaw the safety of all patients. The institutional review board at each participating institution approved the study.

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

Study Population

We enrolled patients older than 18 years of age who were candidates for dual antiplatelet therapy after treatment with FDA-approved drug-eluting or bare-metal stents. Details of the inclusion and exclusion criteria are provided in the Supplementary Appendix. Each patient provided written informed consent at the time of enrollment.

The population included in the primary analysis for this report comprised only patients who were treated with drug-eluting stents (results in patients who received bare-metal stents are not included in this analysis) (Fig. 1). Drug-eluting stents included sirolimus-eluting stents (Cypher, Cordis), zotarolimus-eluting stents (Endeavor, Medtronic), paclitaxel-eluting stents (TAXUS, Boston

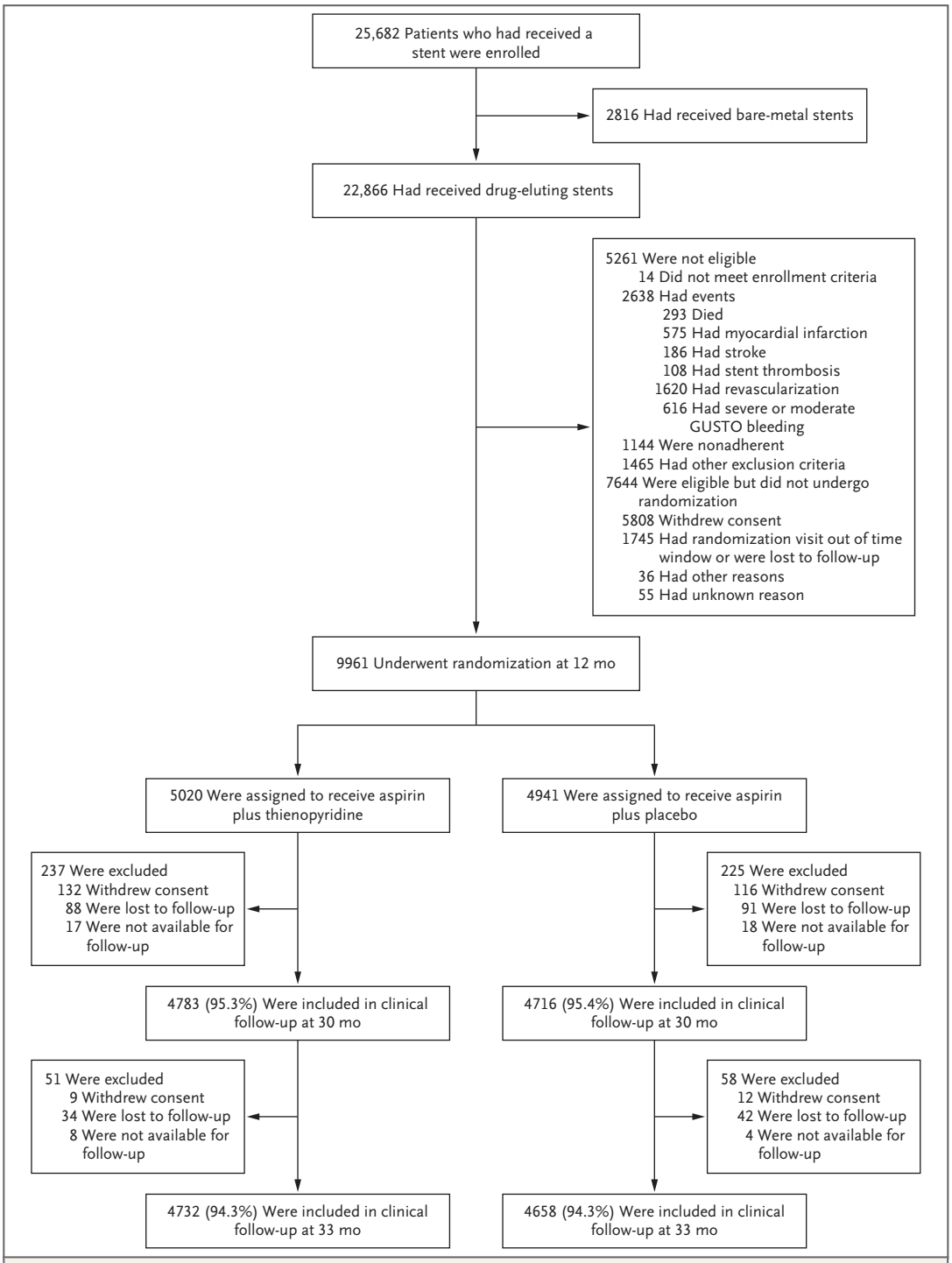

Figure 1. Enrollment, Randomization, and Follow-up.

Patients were enrolled within 72 hours after stent placement. They were followed for 12 months while they received open-label treatment with thienopyridine plus aspirin and were then randomly assigned to receive thienopyridine therapy or placebo (each in addition to aspirin) for an additional 18 months. The randomized treatment period ended at 30 months; thereafter, patients continued taking aspirin only and were followed for another 3 months. Although the number of patients with available data on clinical follow-up is reported in each group, the coprimary efficacy end points were analyzed with the last available follow-up information in the intention-to-treat population, which included all patients who underwent randomization. GUSTO denotes Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries.

Table 1. Characteristics of Patients Who Were Treated with Drug-Eluting Stents and Who Underwent Randomization.*

Characteristic	Continued Thienopyridine (N=5020)	Placebo (N=4941)
Patients		
Age — yr	61.8±10.2	61.6±10.1
Female sex — no. (%)	1242 (24.7)	1284 (26.0)
Nonwhite race — no./total no. (%)†	438/4918 (8.9)	419/4847 (8.6)
Hispanic or Latino ethnic group — no./total no. (%)†	159/4924 (3.2)	159/4847 (3.3)
Weight — kg‡	91.5±19.7	91.5±19.4
Body-mass index§	30.5±5.8	30.6±5.8
Diabetes mellitus — no./total no. (%)	1556/5006 (31.1)	1481/4927 (30.1)
Hypertension — no./total no. (%)	3796/5006 (75.8)	3649/4934 (74.0)
Current cigarette smoker or within past year — no./total no. (%)	1222/4965 (24.6)	1210/4893 (24.7)
Stroke or TIA — no./total no. (%)	155/5006 (3.1)	169/4931 (3.4)
Congestive heart failure — no./total no. (%)	238/5001 (4.8)	223/4926 (4.5)
Peripheral arterial disease — no./total no. (%)	284/4937 (5.8)	284/4857 (5.8)
Prior PCI — no./total no. (%)	1518/4995 (30.4)	1529/4928 (31.0)
Prior CABG — no./total no. (%)	568/5012 (11.3)	581/4930 (11.8)
Prior myocardial infarction — no./total no. (%)	1092/4953 (22.0)	1026/4870 (21.1)
Indication for PCI — no. (%)		
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)
Any risk factor for stent thrombosis — no./total no. (%)‖	2410/4751 (50.7)	2389/4685 (51.0)
Region — no. (%)		
North America	4502 (89.7)	4416 (89.4)
Europe	402 (8.0)	405 (8.2)
Australia or New Zealand	116 (2.3)	120 (2.4)
Thienopyridine drug at start of open-label period — no. (%)**		
Clopidogrel	3275 (65.2)	3230 (65.4)
Prasugrel	1745 (34.8)	1711 (34.6)
Type of drug-eluting stent at index procedure — no. (%)		
Everolimus-eluting	2345 (46.7)	2358 (47.7)
Paclitaxel-eluting	1350 (26.9)	1316 (26.6)
Zotarolimus-eluting	642 (12.8)	622 (12.6)
Sirolimus-eluting	577 (11.5)	541 (10.9)
>1 type	106 (2.1)	104 (2.1)
No. of treated lesions	1.30±0.55	1.29±0.54
No. of treated vessels	1.11±0.33	1.12±0.34
No. of stents	1.47±0.75	1.45±0.75
Minimum stent diameter — no. (%)		
<3 mm	2341 (46.6)	2293 (46.4)
≥3 mm	2679 (53.4)	2648 (53.6)
Total stent length — mm	27.70±16.77	27.43±17.02

Table 1. (Continued.)

Characteristic	Continued Thienopyridine (N=5020)	Placebo (N=4941)
Lesions		
Treated vessel††		
Native coronary-artery lesions	6396/6586 (97.1)	6204/6407 (96.8)
Left main	55/6586 (0.8)	55/6407 (0.9)
Left anterior descending	2715/6586 (41.2)	2586/6407 (40.4)
Right	2153/6586 (32.7)	2057/6407 (32.1)
Circumflex	1473/6586 (22.4)	1506/6407 (23.5)
Venous graft	154/6586 (2.3)	173/6407 (2.7)
Arterial graft	36/6586 (0.5)	30/6407 (0.5)
Modified ACC–AHA lesion class B2 or C — no./total no. (%)‡‡	2754/6335 (43.5)	2643/6137 (43.1)

* Plus–minus values are means ±SD. There were no significant differences between the two groups except with respect to hypertension (P=0.03). For most variables, 0 to 3% of the patients had missing values; however, 3.5% of the patients were missing data on lesion class. CABG denotes coronary-artery bypass grafting, NSTEMI non–ST-segment elevation myocardial infarction, PCI percutaneous coronary intervention, STEMI ST-segment elevation myocardial infarction, and TIA transient ischemic attack.
† Race and ethnic group were self-reported.
‡ Data on body weight were available for 5009 patients in the group that was randomly assigned to continued thienopyridine therapy and 4931 in the group that was assigned to placebo.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were available for 4973 in the group that was randomly assigned to continued thienopyridine therapy and 4901 in the group that was assigned to placebo.
¶ This category included unstable angina without reported elevation of cardiac enzymes.
‖ Risk factors for stent thrombosis are listed in Table S1 in the Supplementary Appendix.
** At the time of randomization (12 months after the start of the open-label period), 63.5% of the patients who were subsequently assigned to continue receiving thienopyridine were taking clopidogrel, and 34.7% were taking prasugrel; the corresponding rates among the patients who were subsequently assigned to the placebo group were 65.2% and 34.8%.
†† A total of 6594 lesions were treated in the thienopyridine group and 6413 in the placebo group.
‡‡ The definitions of class B2 and class C lesions according to the modified American College of Cardiology (ACC)–American Heart Association (AHA) criteria are provided in the Supplementary Appendix.

Scientific), and everolimus-eluting stents (Xience, Abbott Vascular; and Promus, Boston Scientific). It was recommended that all patients receive either clopidogrel at a maintenance dose of 75 mg daily or prasugrel at a maintenance dose of 10 mg daily (with a dose of 5 mg daily recommended in patients who weighed less than 60 kg).[13] The recommended maintenance dose of aspirin was 75 to 162 mg daily, to be taken indefinitely.

STUDY PROCEDURES

Patients were enrolled within 72 hours after placement of a stent and were given open-label aspirin and thienopyridine for 12 months. At 12 months, patients who had not had a major adverse cardiovascular or cerebrovascular event, repeat revascularization, or moderate or severe bleeding and had been adherent to thienopyridine therapy (defined as having taken 80 to 120% of the drug without an interruption of longer than 14 days) were eligible for randomization (Fig. 1).

Eligible patients continued taking aspirin and were randomly assigned, in a 1:1 ratio, to continued thienopyridine therapy or to placebo for an additional 18 months (months 12 to 30 after enrollment). A computer-generated randomization schedule stratified patients according to the type of stent they had received (drug-eluting vs. bare-metal), hospital site, type of thienopyridine drug, and presence or absence of at least one prespecified clinical or lesion-related risk factor for stent thrombosis (see Table S1 in the Supplementary Appendix).[13] After the end of the randomized treatment period, we followed patients for a 3-month observational period during which they took aspirin alone (months 30 to 33 after enrollment) so that we could assess the effect of discontinuation of thienopyridine on the rates of end-point events.

Table 2. Stent Thrombosis and Major Adverse Cardiovascular and Cerebrovascular Events.*

Outcome	Continued Thienopyridine (N=5020)	Placebo (N=4941)	Hazard Ratio, Thienopyridine vs. Placebo (95% CI)†	P Value†
	no. of patients (%)			
Stent thrombosis‡	19 (0.4)	65 (1.4)	0.29 (0.17–0.48)	<0.001
Definite	15 (0.3)	58 (1.2)	0.26 (0.14–0.45)	<0.001
Probable	5 (0.1)	7 (0.1)	0.71 (0.22–2.23)	0.55
Major adverse cardiovascular and cerebrovascular events§	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)	0.05
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
Noncardiovascular	48 (1.0)	22 (0.5)	2.23 (1.32–3.78)	0.002
Myocardial infarction	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	1 (<0.1)	—	0.32

* At 12 months after placement of a drug-eluting stent, patients were randomly assigned to receive either continued thienopyridine therapy plus aspirin or placebo plus aspirin for 18 months. Data are presented for the intention-to-treat population. The primary analysis was performed on data from the period of 12 to 30 months after enrollment, and the study coprimary efficacy end points were stent thrombosis and major adverse cardiovascular and cerebrovascular events. Percentages are Kaplan–Meier estimates.

† The hazard ratios and P values were stratified according to geographic region (North America, Europe, or Australia and New Zealand), thienopyridine drug received at the time of randomization, and presence or absence of risk factors for stent thrombosis. P values were calculated with the use of a log-rank test.

‡ Definite and probable stent thrombosis were determined according to the criteria of the Academic Research Consortium.

§ The end point of major adverse cardiovascular and cerebrovascular events was a composite of death, myocardial infarction, or stroke.

END POINTS

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

STATISTICAL ANALYSIS

The primary efficacy analysis was a superiority analysis performed with the use of the log-rank test, with stratification according to geographic region (North America, Europe, or Australia and New Zealand), thienopyridine drug received at the time of randomization, and presence or absence of risk factors for stent thrombosis. We controlled the two-sided family-wise error rate of 0.05 across the two coprimary end points using the Hochberg–Benjamini method.[17] With this method, the null hypothesis of randomized treatment equivalence is rejected if significance is achieved for both end points at a two-sided alpha level of 0.05 or for

one end point at a two-sided alpha level of 0.025. We assumed that the annual event rates with placebo would be 0.5% for stent thrombosis and 2.9% for major adverse cardiovascular and cerebrovascular events, that the hazard ratios with continued thienopyridine therapy versus placebo would be 0.45 for stent thrombosis and 0.75 for major adverse cardiovascular and cerebrovascular events, and that the annual loss to follow-up would be no more than 3%. Given these assumptions, we calculated that with a sample of 9800 patients undergoing randomization and receiving drug-eluting stents, the study would have at least 85% power for the superiority analysis. This sample size was reduced from the 12,196 specified in the original protocol because of 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 noninferiority analysis performed with the use of the Farrington–Manning risk-difference approach.[18] Assuming an annualized rate for moderate or severe bleeding of 1.9% and an absolute noninferiority margin of 0.8%, at a one-sided alpha level of significance of 0.025, we calculated that a sample size of 9960 patients would give the study 80% power to detect noninferiority.

The primary analyses of major adverse cardiovascular and cerebrovascular events and stent thrombosis were performed on data from all patients who underwent randomization and were treated with drug-eluting stents (the intention-to-treat population). Kaplan–Meier estimates of the cumulative incidence of each end point are presented according to study group, with two-sided 95% confidence intervals of stratified hazard ratios. Data for patients who did not have an end-point event were censored for the analysis of that end point at the time of the last known contact or at 30 months, whichever was earlier. Secondary analyses included an examination of the same end points in all the patients over the course of the 21-month postrandomization period, the last 3 months of which the patients were not receiving the randomized treatment, and hazards before and after discontinuation of the study drug were assessed for qualitative differences.

The primary noninferiority assessment of bleeding was performed on data from patients who underwent randomization, were treated with drug-eluting stents, and completed at least 17 months of follow-up (the minimum window allowed for the 18-month postrandomization visit) or had a moderate or severe bleeding event. Bleeding events are presented as binary rates. The hazard ratio for moderate or severe bleeding is also presented as a post hoc descriptive analysis.

To account for missing data, we repeated the treatment comparisons with data from all patients who underwent randomization using multiple-imputation[19] logistic-regression modeling, with baseline covariates (50 imputations) for missing

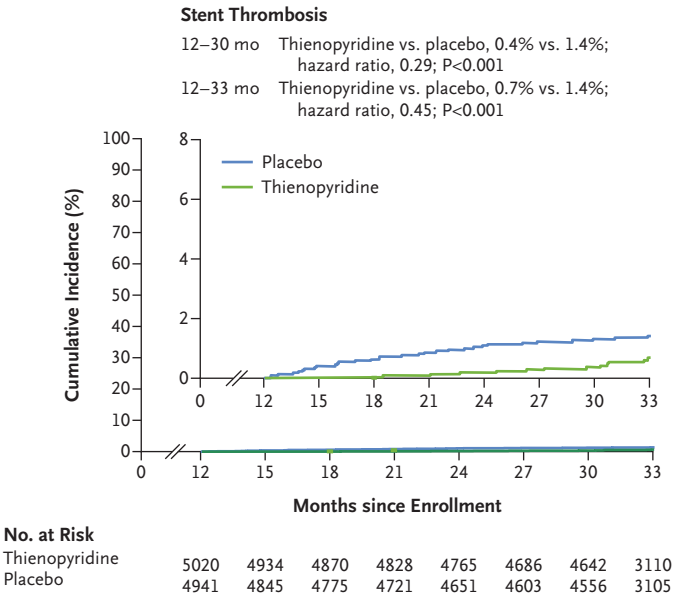

Figure 2. Cumulative Incidence of Stent Thrombosis, According to Study Group.

Cumulative incidence curves are shown for the primary efficacy end point of probable or definite stent thrombosis, as assessed according to the criteria of the Academic Research Consortium, in the intention-to-treat population. Randomization occurred at 12 months after stenting. The primary-analysis period was the period from month 12 to month 30 after percutaneous coronary intervention (i.e., the 18 months after randomization, during which subjects received the randomized study drug). Patients were followed for an observational period of an additional 3 months after discontinuation of the study drug (i.e., to 33 months after enrollment and 21 months after randomization). P values were calculated with the use of a stratified log-rank test. 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. The final 33-month assessment visit took place between 20 and 21 months after randomization. The figure shows the numbers at risk at the end of that period (i.e., 21 months after randomization). The numbers at risk at the start of that period (i.e., 20 months after randomization) were 4438 in the group that had been assigned to continued thienopyridine therapy versus 4362 in the group that had been assigned to placebo. The inset shows the same data on an enlarged y axis.

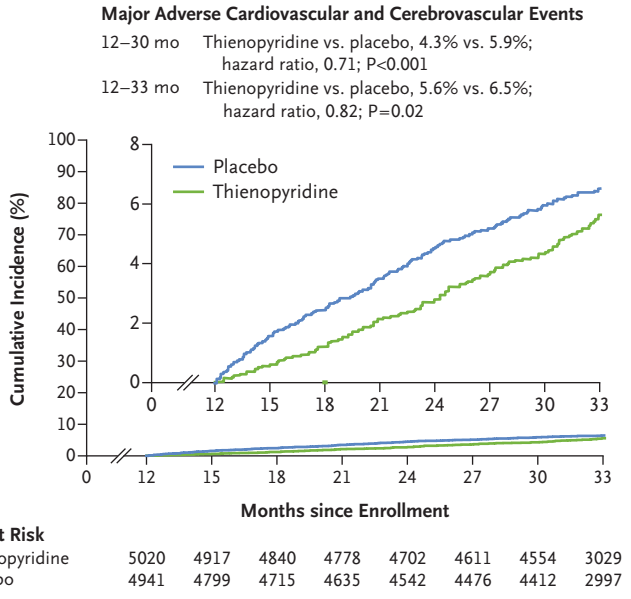

Figure 3. Cumulative Incidence of Major Adverse Cardiovascular and Cerebrovascular Events, According to Study Group.

Cumulative incidence curves are shown for the primary effectiveness outcome of major adverse cardiovascular and cerebrovascular events (a composite of death, myocardial infarction, or stroke) in the intention-to-treat population. P values were calculated with the use of the stratified log-rank test. The number at risk was defined as the number of subjects who had not had the event of interest and who were available for subsequent follow-up. The numbers at risk at the start of final 33-month visit (i.e., 20 months after randomization) were 4336 in the group that had been assigned to continued thienopyridine therapy and 4217 in the group that had been assigned to placebo. The inset shows the same data on an enlarged y axis.

data on the primary end points. We also assessed the consistency of the effect of treatment on the primary end points in subgroups defined according to 14 prespecified factors assessed at baseline.

RESULTS

STUDY POPULATION

Between August 13, 2009, and July 1, 2011, a total of 25,682 patients at 452 sites in 11 countries were enrolled in the DAPT study, of whom 22,866 received a drug-eluting stent. Among these patients, 5261 (23.0%) were not eligible for randomization after 12 months of follow-up, 7644 (33.4%) were eligible but did not undergo randomization (see Table S2 in the Supplementary Appendix), and 9961 (43.6%) underwent randomization (Fig. 1). Among those who were eligible but did not undergo randomization, the most common reason for not undergoing randomization was withdrawal of consent during the year between enrollment and randomization (76.0%).

The baseline characteristics of the patients who were treated with drug-eluting stents and underwent randomization were similar in the two study groups (Table 1). Overall, 26.0% presented with acute myocardial infarction, and 50.9% had at least one clinical or lesion-related risk factor for stent thrombosis (Table S1 in the Supplementary Appendix). The rates of discontinuation of the study drug did not differ significantly at 30 months between the group that continued thienopyridine therapy and the group that received placebo (21.4% and 20.3%, respectively; P=0.18).

EFFICACY END POINTS

During the period from month 12 to month 30 (the primary-analysis period), among all patients who underwent randomization, the group that continued thienopyridine, as compared with the group that received placebo, had a significantly lower cumulative incidence of stent thrombosis (0.4% vs. 1.4%; hazard ratio, 0.29 [95% confidence interval {CI}, 0.17 to 0.48]; P<0.001) and of major adverse cardiovascular and cerebrovascular events (4.3% vs. 5.9%; hazard ratio, 0.71 [95% CI, 0.59 to 0.85]; P<0.001) (Table 2 and Fig. 2 and 3). Continued thienopyridine therapy was associated with a lower cumulative incidence of myocardial infarction than was placebo (2.1% vs. 4.1%; hazard ratio, 0.47 [95% CI, 0.37 to 0.61]; P<0.001) (Fig. S1 in the Supplementary Appendix); myocardial infarction that was not related to stent thrombosis (1.8% vs. 2.9%; hazard ratio, 0.59; P<0.001) accounted for 55% of the treatment benefit. The two groups had similar rates of death from cardiac causes (0.9% and 1.0%, respectively; P=0.98), death from vascular causes (0.1% in each group, P=0.98), and stroke (0.8% and 0.9%, respectively; P=0.32). The rate of death from any cause was 2.0% with continued thienopyridine therapy and 1.5% with placebo (hazard ratio, 1.36 [95% CI, 1.00 to 1.85]; P=0.05) (Fig. S2 in the Supplementary Appendix). The results after multiple imputation were consistent with those from the primary analysis (hazard ratio for stent thrombosis, 0.27; P<0.001; and hazard ratio for major adverse cardiovascular and cerebrovascular events, 0.77; P=0.002) (Table S3a in the Sup-

Table 3. Bleeding End Point during Month 12 to Month 30.*

Bleeding Complications	Continued Thienopyridine (N=4710)	Placebo (N=4649)	Difference	Two-Sided P Value for Difference
	no. of patients (%)		*percentage points (95% CI)*	
GUSTO severe or moderate†	119 (2.5)	73 (1.6)	1.0 (0.4 to 1.5)	0.001
Severe	38 (0.8)	26 (0.6)	0.2 (–0.1 to 0.6)	0.15
Moderate	81 (1.7)	48 (1.0)	0.7 (0.2 to 1.2)	0.004
BARC type 2, 3, or 5	263 (5.6)	137 (2.9)	2.6 (1.8 to 3.5)	<0.001
Type 2	145 (3.1)	72 (1.5)	1.5 (0.9 to 2.1)	<0.001
Type 3	122 (2.6)	68 (1.5)	1.1 (0.6 to 1.7)	<0.001
Type 5	7 (0.1)	4 (0.1)	0.1 (–0.1 to 0.2)	0.38

* The primary safety end point was moderate or severe bleeding as assessed according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO) criteria. The one-sided test of noninferiority (based on a noninferiority margin of 0.8%) was calculated according to the Farrington–Manning approach. Only patients who could be evaluated were included in this analysis (i.e., patients whose last contact date was ≥510 days after randomization or who had any adjudicated bleeding event at or before 540 days). Patients could have had more than one bleeding episode. The secondary analysis of bleeding, as assessed according to the criteria of the Bleeding Academic Research Consortium (BARC), is shown according to subtype in Table S5 in the Supplementary Appendix.
† One-sided P=0.70 for noninferiority.

plementary Appendix), as were the findings when the analysis period included the 3 months after discontinuation of the study drug (Table S4 in the Supplementary Appendix).

SAFETY END POINTS

The rate of moderate or severe bleeding during the primary-analysis period was significantly higher in the group that continued to receive thienopyridine therapy than in the placebo group (2.5% vs. 1.6%; hazard ratio 1.61 [95% CI, 1.21 to 2.16]; P=0.001); treatment with thienopyridine did not meet the prespecified criterion for noninferiority to placebo (P=0.70) (Table 3). There was no significant difference between the randomized treatments with respect to severe bleeding according to the GUSTO criteria (0.81% with continued thienopyridine and 0.56% with placebo, P=0.15) or with respect to fatal bleeding (type 5 bleeding) according to the BARC criteria (0.15% and 0.09%, respectively; P=0.38). Additional details of the results regarding bleeding according to BARC subtype are provided in Table S5 in the Supplementary Appendix. The results after multiple imputation were consistent with those from the main analysis (between-group difference in the risk of moderate or severe bleeding, 0.98%; P=0.73 for noninferiority) (Table S3b in the Supplementary Appendix), as were the findings when the analysis period included the 3 months after study drug discontinuation (Table S6 in the Supplementary Appendix).

MORTALITY

During the primary-analysis period (month 12 to month 30), all-cause mortality was 2.0% in the group that continued to receive thienopyridine and 1.5% in the placebo group (hazard ratio, 1.36; P=0.05). During the secondary-analysis period (month 12 to month 33), all-cause mortality was 2.3% versus 1.8% (hazard ratio, 1.36; P=0.04) (Fig. S2 and Table S4 in the Supplementary Appendix), with the rate of death from noncardiovascular causes (1.1% vs. 0.6%; hazard ratio, 1.80; P=0.01) accounting for the difference in rates between the two analysis periods. Among the deaths from noncardiovascular causes, bleeding-related deaths (11 deaths in the group that continued to receive thienopyridine vs. 3 deaths in the placebo group, P=0.06) were related mainly to fatal trauma (7 deaths vs. 2 deaths, P=0.07). The number of cancer-related deaths differed significantly between the groups (31 vs. 14, P=0.02) and was mediated by bleeding in the case of three patients in the thienopyridine group (Table S7 in the Supplementary Appendix).

Among patients with a history of cancer at the time of enrollment in the study, 22 more patients were randomly assigned to the thienopyridine group than to the placebo group (Table S8 in the Supplementary Appendix), and a blinded review of cancer-related deaths identified a between-group imbalance in the number of patients who underwent randomization in whom cancer had been diagnosed before enrollment (8 vs. 1) (Table S9 in the Supplementary Appendix). When these patients were excluded in a post hoc sensitivity analysis, the differences in mortality were no longer significant (Table S10 in the Supplementary Appendix).

ADDITIONAL ANALYSES

The effect of continued thienopyridine therapy versus placebo on the rates of the primary end points and on the rate of myocardial infarction was consistent across most subgroups (Fig. S3 in the Supplementary Appendix). Hazards after discontinuation of thienopyridine therapy are provided in Table S11 in the Supplementary Appendix.

DISCUSSION

Among patients receiving drug-eluting coronary stents, continued treatment with thienopyridine and aspirin, as compared with aspirin alone, beyond 1 year reduced the risk of stent thrombosis and of major adverse cardiovascular and cerebrovascular events. This treatment benefit was driven by concurrent reductions in myocardial infarction related to the stent and occurring in other locations. A longer duration of thienopyridine treatment was associated with a greater risk of bleeding, although severe or fatal bleeding was uncommon and the rate did not differ significantly between the study groups.

The DAPT study included a large proportion of patients who had risk factors for stent thrombosis, including many who had received a stent for treatment of a myocardial infarction. Across almost all patients and lesion types, continued thienopyridine therapy was associated with reductions in the risk of both coprimary end points. In previous studies, different stents[20,21] and P2Y12 inhibitors[22] have been associated with varied rates of stent thrombosis and myocardial infarction; in this study, the use of thienopyridine beyond 1 year reduced the risks of both outcomes across all stent and drug types. Although the results of previous studies vary with respect to the risk of discontinuation of thienopyridine after 6 months,[10-13,23,24] the current study detected an increased risk of myocardial infarction (both stent-related and non–stent-related) in both study groups during the first 3 months after discontinuation. Future evaluation of thienopyridine therapy with an aim toward reducing the risks of cardiovascular events beyond the duration of this study may be warranted.

An unexpected finding was that the number of deaths from any cause during the treatment period was higher in the group that continued to receive thienopyridine than in the group that received placebo, a difference that was driven by an increase in the number of deaths from noncardiovascular causes in the thienopyridine group. The rate of diagnosis of cancer did not differ significantly after randomization; however, there were more cancer-related deaths among patients treated with continued thienopyridine than among those who received placebo, a finding that may have reflected a chance imbalance in patients with known cancer before enrollment. Although one study comparing long-term thienopyridine therapy with placebo in patients with lacunar stroke identified an unexpected increase in mortality,[25] other large, randomized studies involving patients with coronary artery disease have not identified either increased or decreased risks of death.[26-28]

Several limitations of the study should be considered. First, only patients who were adherent to therapy and who did not have a major adverse cardiovascular or cerebrovascular event, stent thrombosis, or moderate or severe bleeding in the first year underwent randomization, a study design that may have selected for patients who were at lower risk for late adverse events. Second, although we did not quantify the net effect of ischemic and bleeding events, a decision analysis suggests that small absolute differences in the rates of cardiovascular events may be sufficient[29] to counterbalance bleeding risks. Third, although the study included four different metal-platform, durable polymer, drug-eluting stents and two platelet P2Y12 inhibitors, whether the treatment benefits observed will be generalizable to other stent types[30,31] or non-thienopyridine P2Y12 inhibitors[32,33] is unknown. In addition, since patients were not randomly assigned to a specific thienopyridine drug or stent

type, direct comparisons between different stent types or drugs may be confounded, and within-subgroup estimates of treatment effect may be underpowered.

In conclusion, among patients treated with drug-eluting stents, continuation of thienopyridine-plus-aspirin therapy, as compared with aspirin therapy alone, beyond 1 year reduced the risks of ischemic events. The reduction in the risk of ischemic events was consistent across stent type and specific thienopyridine drug used and was evident regardless of the risk of stent thrombosis. The clinical benefit of extended thienopyridine treatment was tempered by an increase in bleeding events.

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APPENDIX

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