Myocardial Infarction Risk After Discontinuation of Thienopyridine Therapy in the Randomized DAPT Study (Dual Antiplatelet Therapy)

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BACKGROUND: Thienopyridine plus aspirin beyond 1 year after coronary stenting reduces myocardial infarction (MI) risk and increases bleeding risk in comparison with aspirin alone. The hazard associated with late thienopyridine discontinuation and risk factors for MI after discontinuation are poorly defined.

METHODS: In the DAPT Study (Dual Antiplatelet Therapy), after percutaneous coronary intervention and 12 months of thienopyridine (clopidogrel or prasugrel) plus aspirin, eligible patients remained on aspirin and were randomly assigned to continued thienopyridine versus placebo for 18 months. At 30 months, patients stopped the study drug and were observed for 3 months. Cumulative incidence of MI was assessed over 3 months after randomization (months 12–15) and 3 months after study drug discontinuation (months 30–33). The MI hazard for each of these periods was assessed across randomized treatment arms and by DAPT score values <2 or ≥2.

RESULTS: Among the 11 648 randomly assigned patients, the monthly cumulative incidence of MI was lower with continued thienopyridine versus placebo at 12 to 15 months (0.12% versus 0.37%, $P<0.001$, in all patients; 0.13% versus 0.27%, $P=0.02$, in patients not treated with paclitaxel-eluting stents), and higher at 30 to 33 months (0.30% versus 0.15%, $P=0.013$, in all patients; in patients without paclitaxel-eluting stents, 0.18% versus 0.17%, $P=0.91$). The majority of MIs in both time periods (74% and 76%) were not related to stent thrombosis. After multivariable adjustment, treatment arm independently predicted MI at months 12 to 15 ($P<0.001$) and 30 to 33 ($P=0.011$). During months 12 to 15, patients with DAPT scores <2 or ≥2 both had lower rates of MI with continued thienopyridine (MI monthly incidence 0.16% versus 0.51%, $P<0.001$, for scores ≥2; 0.08% versus 0.24%, $P=0.012$, for scores<2, interaction $P=0.064$).

CONCLUSIONS: Discontinuing thienopyridine after either 12 or 30 months is associated with an early increase in MI risk, mainly unrelated to stent thrombosis; the magnitude of risk is highest in the earlier time frame, and lower in patients not treated with paclitaxel-eluting stents. Although higher DAPT scores identify patients with greater absolute ischemic benefit (relative to bleeding harm) with continued thienopyridine therapy, discontinuation at 12 months increases MI hazard regardless of DAPT score group.

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Clinical Perspective

What Is New?

- This analysis is the first to assess the risk of myocardial infarction (MI) in the first 3 months after randomized discontinuation of thienopyridine in a large trial.
- We show an increase in the incidence of MI in that period, in patients randomly assigned to discontinue thienopyridine 1 year after percutaneous coronary intervention.
- The majority of MIs were not related to stent thrombosis.
- An increased incidence of MI of lesser magnitude was also observed in patients discontinuing thienopyridine per protocol 30 months after their percutaneous coronary intervention.

What Are the Clinical Implications?

- Our analysis suggests that patients who discontinue thienopyridine, either 12 months or 30 months after a percutaneous coronary intervention, are at an increased risk of an MI in the subsequent months.
- Assessment of the individualized balance between ischemic benefit and bleeding risk, with tools such as the DAPT score (Dual Antiplatelet Therapy), is important. In patients in whom discontinuation of thienopyridine is recommended, counseling and clinical follow-up is important because they remain at risk.

Prior observational studies suggest that the incidence of myocardial infarction (MI) is higher immediately after discontinuation of clopidogrel[1,2] than in subsequent months. This apparent MI risk has not been evident in some randomized trials and may be confounded by the underlying reason(s) that treatment was discontinued.[3,4] In the DAPT Study (Dual Antiplatelet Therapy), patients randomly assigned to continue thienopyridine plus aspirin 1 year after percutaneous coronary intervention (PCI) had a reduced cumulative risk of MI over the next 18 months in comparison with patients randomly assigned to placebo plus aspirin.[5,6] For patients randomly assigned to placebo, discontinuation of thienopyridine after 12 months of treatment with thienopyridine plus aspirin appeared to be associated with an early risk of MI. However, the change in hazard of MI over subsequent months and risk factors for MI early after thienopyridine discontinuation have not been described in detail. In addition to a randomized treatment period of 12 to 30 months, the DAPT Study protocol also included a 3-month observational period to prospectively evaluate the impact of planned discontinuation on ischemic hazard. The effect of thienopyridine discontinuation during this later period (months 30–33) has not previously been described.

In this context, we evaluated the impact of thienopyridine discontinuation in the DAPT Study on the occurrence of MI at both 12 to 15 and 30 to 33 months, and attempted to identify risk factors for MI during these time periods as well.

METHODS

Study Design

The DAPT Study was a randomized, double-blind, placebo-controlled, international trial designed to evaluate the benefits and risks of 30 versus 12 months of dual antiplatelet therapy after an index PCI with bare metal (BMS) or drug-eluting stents (DES). Patients with either stable angina or an acute coronary syndrome (ACS) were enrolled within 72 hours of PCI. Patients were treated with open-label thienopyridine (clopidogrel or prasugrel) plus aspirin for 12 months. Those who were adherent to therapy for that period, and who had not had a major bleeding or ischemic event, were then randomly assigned to continued thienopyridine therapy or to placebo for the next 18 months. At the end of this period, patients in both arms stopped the study drug and were followed for 3 more months. All patients remained on aspirin for the entire duration of the trial. Full details of the study protocol have been previously published.[5,7]

Study Population and Procedures

Patients aged ≥18 years who had received a coronary stent and were candidates for treatment with dual antiplatelet therapy were enrolled. Details of the inclusion and exclusion criteria have been previously published.[7] The study was approved by the institutional review board of each site, and the subjects gave informed consent. In this analysis, both DES- and BMS-treated patients were included.

Study End Points

The coprimary effectiveness end points of the DAPT Study were the incidence of stent thrombosis (ST) and major adverse cardiovascular or cerebrovascular events.[5,7] For this current analysis, the end point of interest was the cumulative incidence of MI, assessed over the 3 months after randomization (months 12–15 after the index PCI), the subsequent 15 months, and the 3 months after randomized study drug discontinuation (months 30–33 after PCI). MIs were further classified as related to ST, defined according to the Academic Research Consortium definition of definite or probable ST,[8] or not related to ST. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO) moderate or severe bleeding was also analyzed.[9]

DAPT Score

The DAPT score was developed from DAPT Study data to predict the benefit/risk balance (reduction in ST and MI versus increase in bleeding risk) associated with continued thienopyridine therapy beyond 12 months after PCI for individual patients.[10] We have previously described that patients with a DAPT score ≥2 experienced a reduced rate of ischemic events (MI or ST), without a significant increase in GUSTO

moderate/severe bleeding during the randomized treatment period (months 12–30) when receiving continued thienopyridine therapy in comparison with placebo. Conversely, patients with DAPT scores <2 experienced an increased risk of bleeding without significant ischemic benefit when treated with continued thienopyridine (versus placebo) during the same time period. Variables used to calculate the DAPT score are: age (–2 points for age ≥75, –1 for age 65–75, 0 for age <65), smoking (+1 point), diabetes mellitus (+1 point), MI at index PCI (+1 point), prior PCI or prior MI (+1 point), stent diameter <3 mm (+1 point), paclitaxel-eluting stents (PES) (+1 point), congestive heart failure or ejection fraction<30% (+2 points), and index PCI to a vein graft (+1 point).

Statistical Analysis

The Kaplan-Meier method was used to estimate the cumulative incidence of MI in each randomized treatment arm over the 12- to 15-month, 15- to 30-month, and 30- to 33-month periods. For each period, all patients who had not been lost to follow-up were considered at risk for events, regardless of events experienced in a prior period. The log-rank test was used to compare time-to-MI between randomized groups, stratifying by thienopyridine type at randomization, region (North America, Europe, or Australia and New Zealand) and complexity. Patients were categorized as complex if they had at least 1 prespecified criterion at enrollment/index PCI, including ACS, renal insufficiency (creatinine level ≥2 mg/dL or dialysis), left ventricular ejection fraction <30%, >2 vessels stented, treatment of in-stent restenosis of a DES, prior brachytherapy to a target lesion, or an anatomically complex target lesion (unprotected left main lesion, >2 lesions per vessel, lesion length ≥30 mm, bifurcation lesion with side branch ≥2.5 mm, vein bypass graft, or a thrombus-containing lesion).[7]

Stepwise Cox proportional hazard regression models were used to identify predictors of MI in the 12- to 15-month, 15- to 30-month, and 30- to 33-month periods. Candidate demographic and procedural variables, established at the time of index PCI, were entered in the model with a criterion of P=0.20 and kept with a stay criterion of P=0.10. Candidate variables were randomized group, thienopyridine type (clopidogrel versus prasugrel), aspirin dose at randomization, ACS within 72 hours of enrollment, renal insufficiency (defined as creatinine ≥2 mg/dL or dialysis), left ventricular ejection fraction <30%, PCI characteristics, age ≥75 years, race (white versus nonwhite), sex, body mass index (below or above the median), diabetes mellitus, tobacco use at enrollment, history of prior MI, prior PCI, or prior coronary artery bypass. PCI characteristics included were the number of vessels treated (≤2 versus >2), target lesion being in-stent restenosis of a DES, target lesion previously treated with intracoronary brachytherapy, unprotected left main target lesion, >2 lesions per vessel, target lesion length ≥30 mm, bifurcation lesion with a side branch with diameter ≥2.5 mm, saphenous vein bypass graft target vessel, and thrombus in the target lesion. Stent type (BMS versus non-PES DES versus PES) was forced in the model.

The monthly cumulative incidence of MI was also compared between the continued thienopyridine and placebo groups within DAPT score groups (<2 versus ≥2) over each period. The consistency of absolute risk difference of MI in randomized treatment arms across DAPT score groups was assessed by using a Z test for additive interaction.

Sensitivity analyses were performed in the subset of patients who did not receive a PES, because these stents have been associated with a higher risk of thrombosis than newer DES in previous randomized trials.[11] The majority of the patients treated with a PES in the DAPT Study were part of TL-PAS (Taxus Liberté Post Approval Study), which was designed to assess outcomes in patients receiving open-label PES and treated with prasugrel.[12] The patients enrolled in TL-PAS and eligible to participate in the DAPT Study were randomly assigned at 12 months after index PCI to blinded study drug, either a continuation of prasugrel for another 18 months or placebo. The TL-PAS Data Monitoring Committee reviewed interim data, and, on the basis of the observation of an increased incidence of MI after discontinuation of thienopyridine at 12 and 30 months, recommended in mid-2013 that patients who had not reached their 30-month follow-up should be unblinded and given the opportunity to continue open-label prasugrel beyond 30 months after PCI (thus, 1.1% of patients in the placebo group and 1.4% of patients in the prasugrel group had their treatment unblinded).[13]

Statistical analyses were conducted at the Baim Institute for Clinical Research, with SAS software version 9.4 (SAS Institute Inc). A 2-sided P value of ≤0.05 was considered significant for all analyses. The authors (L.M., J.M.M.) had full access to all the data in the study and take responsibility for its integrity and the data analysis.

RESULTS

Study Population

Between August 13, 2009, and July 1, 2011, 25 682 patients were enrolled at 452 sites in 11 countries and 11 648 patients underwent randomization at 12 months post-PCI. Randomly assigned patients had a mean age of 61.3 years; 25.1% were women, 29.2% had diabetes mellitus, 73.4% had hypertension, 27.4% were current or recent smokers (within the past year), and 30.7% had an MI as their indication for the index PCI (Table 1). During the index PCI, 9961 of 11 648 (85.5%) patients had received a DES, and 1687 of 11 648 (14.5%) had received a BMS. The most commonly implanted DESs were everolimus-eluting stents (40.4% of patients overall); 22.9% of patients overall received PES. Prasugrel was used in the majority (81.9%) of patients treated with PES, whereas clopidogrel was used in the majority not treated with PES (84.1%, P<0.001). Patients treated with PES were younger (mean age, 59.9±9.7 versus 61.8±10.4 in those not treated with PES, P<0.001), had a higher prevalence of diabetes mellitus (33.0% versus 28.0%, P<0.001), smaller stent diameter (50.4% with minimum stent diameter <3 mm versus 41.1%, P<0.001), a higher DAPT score (78.1% versus 42.2% with score ≥2, P<0.001), and were less likely to have been enrolled after a PCI for stable angina than those treated with other DES or BMS. Other baseline characteristics are presented in online-only Data Supplement Table I.

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Table 1. Baseline and Procedural Characteristics of All Randomly Assigned Patients

Characteristic	All Randomized Patients (n=11 648)
Age, y	61.33±10.29
Female sex, n (%)	2925/11 648 (25.1)
Nonwhite race, n (%)*	980/11 430 (8.6)
Hispanic or Latino ethnic group, n (%)	406/11 432 (3.6)
Body mass index, kg/m^2	30.40±5.73
Diabetes mellitus, n (%)	3391/11 601 (29.2)
Hypertension, n (%)	8522/11 614 (73.4)
Cigarette smoker, current or in the past year, n (%)	3142/11 478 (27.4)
Prior myocardial infarction, n (%)	2456/11 476 (21.4)
Prior PCI, n (%)	3368/11 603 (29.0)
Prior CABG, n (%)	1249/11 624 (10.8)
Stroke or transient ischemic attack, n (%)	401/11 618 (3.5)
Congestive heart failure, n (%)	524/11 608 (4.5)
Peripheral artery disease, n (%)	649/11 464 (5.7)
Indication for index procedure, n (%)	
Acute coronary syndrome	3576/11 648 (30.7)
STEMI	1680/11 648 (14.4)
NSTEMI	1896/11 648 (16.3)
Unstable angina	1821/11 648 (15.6)
Stable angina	4149/11 648 (35.6)
Other	2102/11 648 (18.1)
Region	
North America	9946/11 648 (85.4)
Europe	1411/11 648 (12.1)
Australia and New Zealand	291/11 648 (2.5)
Thienopyridine at randomization, n (%)	
Clopidogrel	7962/11 648 (68.4)
Prasugrel	3686/11 648 (31.6)
Type of DES or BMS, n (%)	
Everolimus	4703/11 648 (40.4)
Paclitaxel	2666/11 648 (22.9)
Zotarolimus	1264/11 648 (10.9)
Sirolimus	1118/11 648 (9.6)
BMS	1687/11 648 (14.5)
>1 DES type	210/11 648 (1.8)
No. of treated lesions	1.28±0.53
No. of treated vessels	1.11±0.32
No. of stents	1.44±0.73
Minimum stent diameter, n (%)	
<3 mm	5041/11 648 (43.3)
≥3 mm	6607/11 648 (56.7)
Total stent length, mm	27.0±16.4
Native coronary artery lesions, n (%)	14517/14 959 (97.1)
Left main	111/14 959 (0.74)
Left anterior descending	5915/14 959 (39.5)
Right	5099/14 959 (34.1)
Circumflex	3392/14 959 (22.7)
Venous graft, n (%)	376/14 959 (2.5)
Arterial graft, n (%)	66/14 959 (0.44)
In-stent restenosis, n (%)	516/14 969 (3.5)
Extreme tortuosity, n (%)	582/14 838 (3.9)
Heavy calcification, n (%)	1164/14 837 (7.9)
Modified ACC or AHA lesion class B2 or C, n (%)	6287/14 338 (43.9)
DAPT score group, n (%)	
<2	5731/11 648 (49.2)
≥2	5917/11 648 (50.8)

Values are mean±SD when appropriate. ACC indicates American College of Cardiology; AHA, American Heart Association; BMS, bare metal stent; CABG, coronary artery bypass graft; DAPT, Dual Antiplatelet Therapy; DES, drug-eluting stent; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stents; NSTEMI, non–ST-segment–elevation myocardial infarction; and STEMI, ST-segment–elevation myocardial infarction.

*Race and ethnic group were self-reported.

Incidence of MI During Months 12 to 15, After Discontinuation of Thienopyridine in the Group Randomly Assigned to Placebo

Over the first 3 months after randomization (months 12–15), the monthly cumulative incidence of MI was lower in patients randomly assigned to continued thienopyridine than in those randomly assigned to placebo (0.12% versus 0.37%, $P<0.001$; Figure 1A). The monthly cumulative incidence of MI remained lower in patients randomly assigned to continued thienopyridine through the entire randomization period (0.12% versus 0.20%, $P<0.001$ in months 15–30). The monthly cumulative incidence of GUSTO moderate or severe bleeding was, however, higher in patients randomly assigned to continue thienopyridine in comparison with placebo in both the 12- to 15-month period (0.17% versus 0.05%, $P=0.001$, Table 2), and the 15- to 30-month period, as well (0.13% versus 0.085%, $P=0.01$).

Among the subset of patients not treated with PES (n=8864), the monthly cumulative incidence of MI was lower in patients randomly assigned to continued thieno-

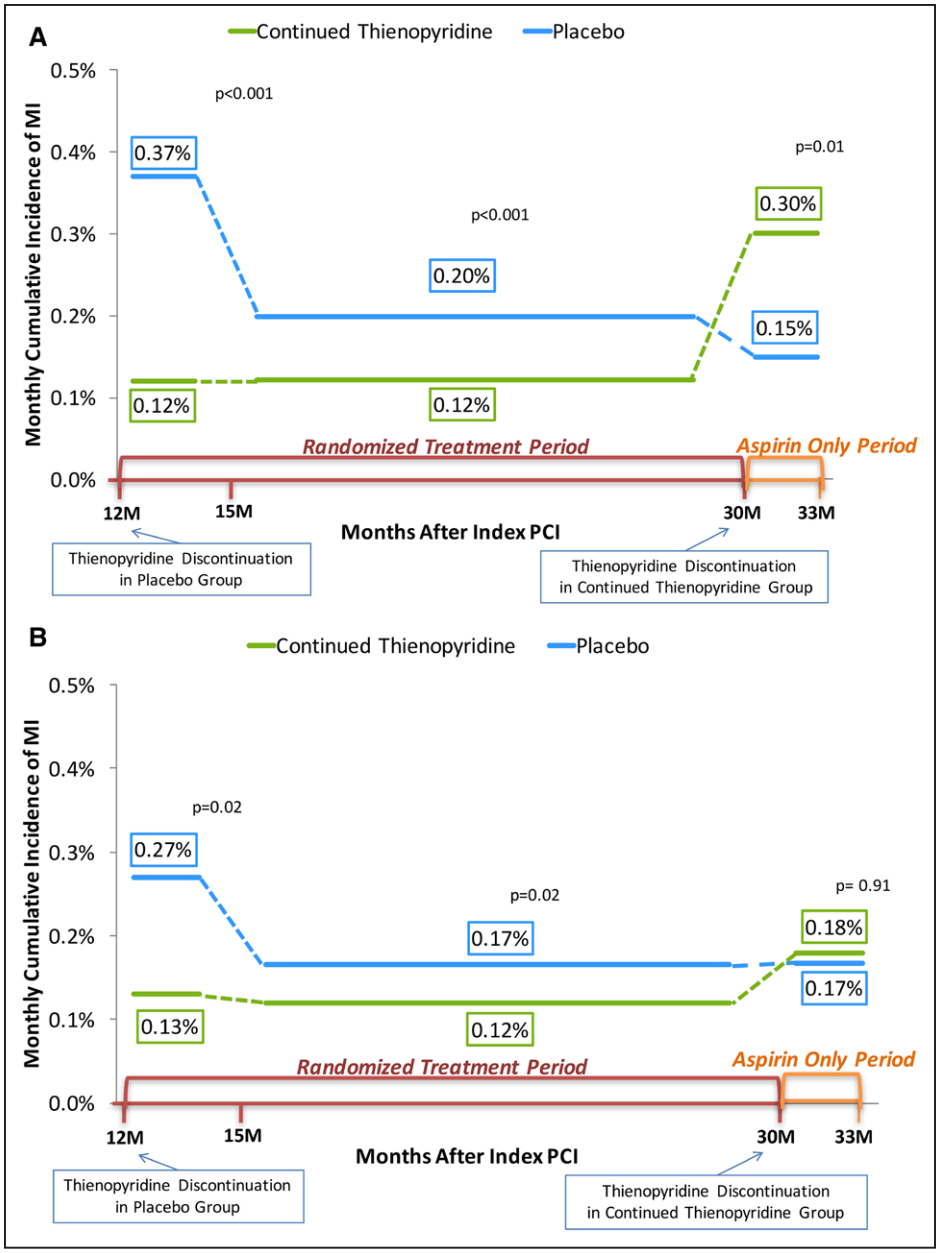

Figure 1. Monthly cumulative incidence of MI by period (12–15, 15–30, and 30–33 months after PCI) and randomized treatment arm.

A, In all randomly assigned patients (n=11 648). **B,** In patients without PES at index PCI (n=8864). M indicates month; MI, myocardial infarction; PCI, percutaneous coronary intervention, and PES, paclitaxel-eluting stents.

pyridine versus placebo at 12 to 15 months (0.13% versus 0.27%, *P*=0.02, Figure 1B) and at 15 to 30 months (0.12% versus 0.17%, *P*=0.02, Table 3).

Incidence of MI During Months 30 to 33, After Per-Protocol Discontinuation of Study Drug in the Group Randomly Assigned to Continued Thienopyridine

At 30 months, patients stopped randomized study drug and were followed for an additional 3 months on aspirin alone. The monthly cumulative incidence of MI was similar between 15 to 30 and 30 to 33 months in the placebo group, whereas, in the continued thienopyridine group, MI incidence increased at 30 to 33 months (following discontinuation of active therapy) (Figure 1A). Patients in the continued thienopyridine group had a higher incidence of MI over months 30 to 33 (following discontinuation) than did those in the placebo group (cumulative monthly incidence 0.30% versus 0.15%, *P*=0.01, Figure 1A). This difference between treatment arms was not evident when patients treated with PES were excluded (0.18% versus 0.17%, *P*=0.91, Figure 1B).

Table 2. Monthly Rates of Ischemic and Bleeding End Points, by Time Period, in All Randomly Assigned Patients

	12–15 mo				15–30 mo				30–33 mo			
	Continued Thienopyridine (n=5862) n (%)	Placebo (n=5786) n (%)	HR	*P* Value	Continued Thienopyridine n (%)	Placebo n (%)	HR	*P* Value	Continued Thienopyridine n (%)	Placebo n (%)	HR	*P* Value
Ischemic events												
MACCE (death, MI, stroke)	12.7 (0.22)	26 (0.45)	0.48 (0.33–0.72)	<0.001	14 (0.25)	16.9 (0.30)	0.81 (0.67–0.97)	0.024	23.7 (0.47)	13.3 (0.26)	1.74 (1.17–2.57)	0.005
MI	7 (0.12)	21.3 (0.37)	0.32 (0.19–0.53)	<0.001	6.8 (0.12)	11 (0.20)	0.59 (0.46–0.76)	<0.001	14.7 (0.30)	7.7 (0.15)	1.91 (1.14–3.19)	0.013
ST-related MI	0.7 (0.01)	6.7 (0.12)	0.10 (0.02–0.44)	<0.001	1.3 (0.02)	3.5 (0.06)	0.36 (0.21–0.62)	<0.001	4 (0.08)	1.3 (0.03)	3.97 (1.12–14.07)	0.021
Non–ST-related MI	6.3 (0.11)	14.7 (0.26)	0.42 (0.24–0.73)	0.002	5.8 (0.10)	7.7 (0.14)	0.72 (0.54–0.96)	0.024	10.7 (0.22)	6.7 (0.13)	1.50 (0.85–2.64)	0.16
Death	4 (0.07)	3.3 (0.06)	1.31 (0.55–3.11)	0.54	6.3 (0.11)	4.9 (0.09)	1.31 (0.96–1.79)	0.094	6.3 (0.12)	4.3 (0.09)	1.38 (0.67–2.81)	0.38
Stroke	2.3 (0.04)	2 (0.03)	1.15 (0.39–3.42)	0.80	2.4 (0.04)	2.8 (0.05)	0.79 (0.50–1.26)	0.32	3.7 (0.07)	3.3 (0.07)	1.10 (0.47–2.58)	0.83
Bleeding events												
GUSTO severe or moderate	9.7 (0.17)	3 (0.05)	3.47 (1.58–7.62)	<0.001	7.2 (0.13)	4.7 (0.09)	1.50 (1.10–2.05)	0.010	2.3 (0.05)	5 (0.10)	0.50 (0.20–1.24)	0.13

GUSTO indicates Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; HR, hazard ratio; MACCE, major adverse cardiac and cardiovascular events; MI, myocardial infarction; and ST, stent thrombosis.

The monthly cumulative incidence of GUSTO moderate or severe bleeding in the 30- to 33-month period was similar between randomized treatment groups (0.05% versus 0.10%, continued thienopyridine versus placebo, respectively, *P*=0.13 in all randomly assigned patients; 0.04% versus 0.10%, *P*=0.11 in patients not treated with PES, Tables 2 and 3).

Relationship of MI and ST

The majority of MIs occurring in each study period were not related to ST (74% in the 12- to 15-month period and 76% in the 30- to 33-month period, Figure 2A). Similarly, in the subset of patients not treated with PES, the majority of MIs were not related to ST (Figure 2B). Risks of MI not related to ST and of MI related to ST were both lower in the continued thienopyridine group than in the placebo group in the 12- to 15-month period (0.11% versus 0.26%, *P*=0.002; 0.010% versus 0.12%, *P*<0.001, respectively, Figure 2A). During the 30- to 33-month period, monthly rates of MI not related to ST were numerically, but not significantly higher with continued thienopyridine in comparison with placebo (0.22% versus 0.13%, *P*=0.16), whereas those related to ST were significantly higher in the continued thienopyridine group (0.08% versus 0.03%, *P*=0.02, Figure 2A).

Predictors of MI After Thienopyridine Discontinuation

Randomization to continued thienopyridine was an independent predictor of MI risk in both discontinuation time periods, being protective during the early time frame (12–15 months after PCI) and a hazard when discontinuation occurred later (30–33 months; see Table 4). Markers of coronary artery disease severity (MI or PCI before index admission), renal insufficiency, and PES use were risk factors for MI in both discontinuation time periods.

DAPT Score and Risk of MI After Thienopyridine Discontinuation

At 12 to 15 months, patients with either a DAPT score ≥2 or <2 had a reduction in the risk of MI with continued thienopyridine therapy in comparison with placebo (cumulative monthly incidence of 0.16% versus 0.51%, *P*<0.001 for a score ≥2; 0.08% versus 0.24%, *P*=0.01, for a score <2; online-only Data Supplement Table II), albeit with a trend toward greater magnitude in those with a score ≥2 (absolute risk reduction 0.35%), in comparison with a score <2 (absolute risk reduction 0.15%, interaction *P*=0.06, Figure 3A). At 30 to 33 months, the continued thienopyridine group had a higher risk of MI than the placebo group in patients with a DAPT score

Table 3. Monthly Rates of Ischemic and Bleeding End Points, by Time Period, in Randomly Assigned Patients Not Treated With Paclitaxel-Eluting Stents

	12–15 mo				15–30 mo				30–33 mo			
	Continued Thienopyridine (n=4447) n (%)	Placebo (n=4417) n (%)	HR	*P* Value	Continued Thienopyridine n (%)	Placebo n (%)	HR	*P* Value	Continued Thienopyridine n (%)	Placebo n (%)	HR	*P* Value
Ischemic events												
MACCE (death, MI, stroke)	9.3 (0.21)	14.7 (0.33)	0.66 (0.40–1.07)	0.087	10.5 (0.25)	11.4 (0.27)	0.91 (0.73–1.14)	0.43	13.7 (0.37)	10 (0.26)	1.33 (0.82–2.15)	0.25
MI	5.7 (0.13)	11.7 (0.27)	0.50 (0.27–0.91)	0.020	5.0 (0.12)	7 (0.17)	0.70 (0.52–0.95)	0.022	6.3 (0.18)	6.3 (0.17)	0.96 (0.50–1.87)	0.91
ST-related MI	0.3 (0.01)	3.0 (0.07)	0.13 (0.02–1.01)	0.020	0.7 (0.02)	1.6 (0.04)	0.42 (0.20–0.88)	0.018	0.7 (0.02)	1.3 (0.04)	0.66 (0.11–3.96)	0.65
Non–ST-related MI	5.3 (0.12)	8.7 (0.20)	0.62 (0.33–1.19)	0.15	4.4 (0.10)	5.6 (0.13)	0.77 (0.55–1.08)	0.13	5.7 (0.16)	5.3 (0.14)	0.96 (0.47–1.94)	0.91
Death	2.3 (0.05)	2.3 (0.05)	1.17 (0.39–3.48)	0.78	4.9 (0.11)	3.5 (0.08)	1.45 (1.01–2.10)	0.045	5.0 (0.13)	3.0 (0.08)	1.55 (0.67–3.58)	0.30
Stroke	2 (0.05)	1.3 (0.03)	1.49 (0.42–5.28)	0.53	1.8 (0.04)	2.3 (0.06)	0.70 (0.42–1.18)	0.18	3.0 (0.08)	2.3 (0.06)	1.31 (0.49–3.51)	0.60
Bleeding events												
GUSTO severe or moderate	7.7 (0.17)	2.3 (0.05)	3.67 (1.49–9.05)	0.002	5.6 (0.13)	3.7 (0.09)	1.54 (1.08–2.20)	0.017	1.3 (0.04)	3.7 (0.10)	0.40 (0.13–1.28)	0.11

GUSTO indicates Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; HR, hazard ratio; MACCE, major adverse cardiac and cardiovascular events; MI, myocardial infarction; and ST, stent thrombosis.

≥2 (cumulative monthly incidence 0.43% versus 0.18%, *P*=0.008), with a similar incidence between randomly assigned groups in patients with a DAPT score <2 (0.16% versus 0.13% respectively, *P*=0.61; interaction *P*=0.05 across DAPT score strata).

Among patients not treated with PES, over the 12- to 15-month period, the same direction of effect in cumulative monthly incidence of MI was seen among patients with a DAPT score <2 (0.09% in the thienopyridine group versus 0.22% in placebo, *P*=0.04), and in those with a DAPT score ≥2 (0.18% versus 0.33%, respectively, *P*=0.11; interaction *P*=0.86, Figure 3B). Over the 30- to 33-month period, patients in both DAPT score groups had a similar incidence of MI regardless of randomized treatment group (0.15% in the thienopyridine group versus 0.13% in the placebo group with a DAPT score <2, *P*=0.74, and 0.22% versus 0.23% in DAPT score ≥2, *P*=0.75, Figure 3B).

In both the full randomized cohort and after exclusion of those treated with PES, over the 15- to 30-month period, patients with a DAPT score <2 had a similar risk of MI in both randomly assigned groups, whereas patients with a DAPT score ≥2 had a reduced risk of MI with continued thienopyridine (Figure 3A and 3B).

DISCUSSION

In this analysis of >11 000 DAPT Study patients, we observed an increased risk of MI after discontinuation of thienopyridine at 12 months (placebo group) and at 30 months (following later discontinuation of randomly assigned thienopyridine therapy). The majority of MIs that occurred in the setting of discontinuation were not related to ST. Furthermore, even though patients were required to be free from major ischemic events during the 12-month open-label treatment period between enrollment and randomization, an increased risk of MI followed thienopyridine discontinuation at 12 months, in both patients with lower and higher predicted overall benefit-risk profile for continuation of dual antiplatelet therapy beyond 12 months (as reflected by DAPT scores <2 versus ≥2). Similar findings were observed within the cohort that excluded PES. This observation suggests that, even among a group of patients who are stable for 1 year after PCI, there is an ongoing risk of MI, mainly unrelated to the stent that is exposed following antiplatelet therapy discontinuation. The increased risk of MI is evident even for patients in whom discontinuation at 12 months may be reasonable on the basis of risk profile (DAPT score). Overall, there was an increased risk of MI in the 30- to 33-month period for patients discontinuing thienopyridine in comparison with those discontinuing placebo, but this risk was no longer evident within the larger subset of patients not treated with PES. This observation may suggest that the risk associated with discontinuation declines over time for non-PES patients, among both those with high and low DAPT scores.

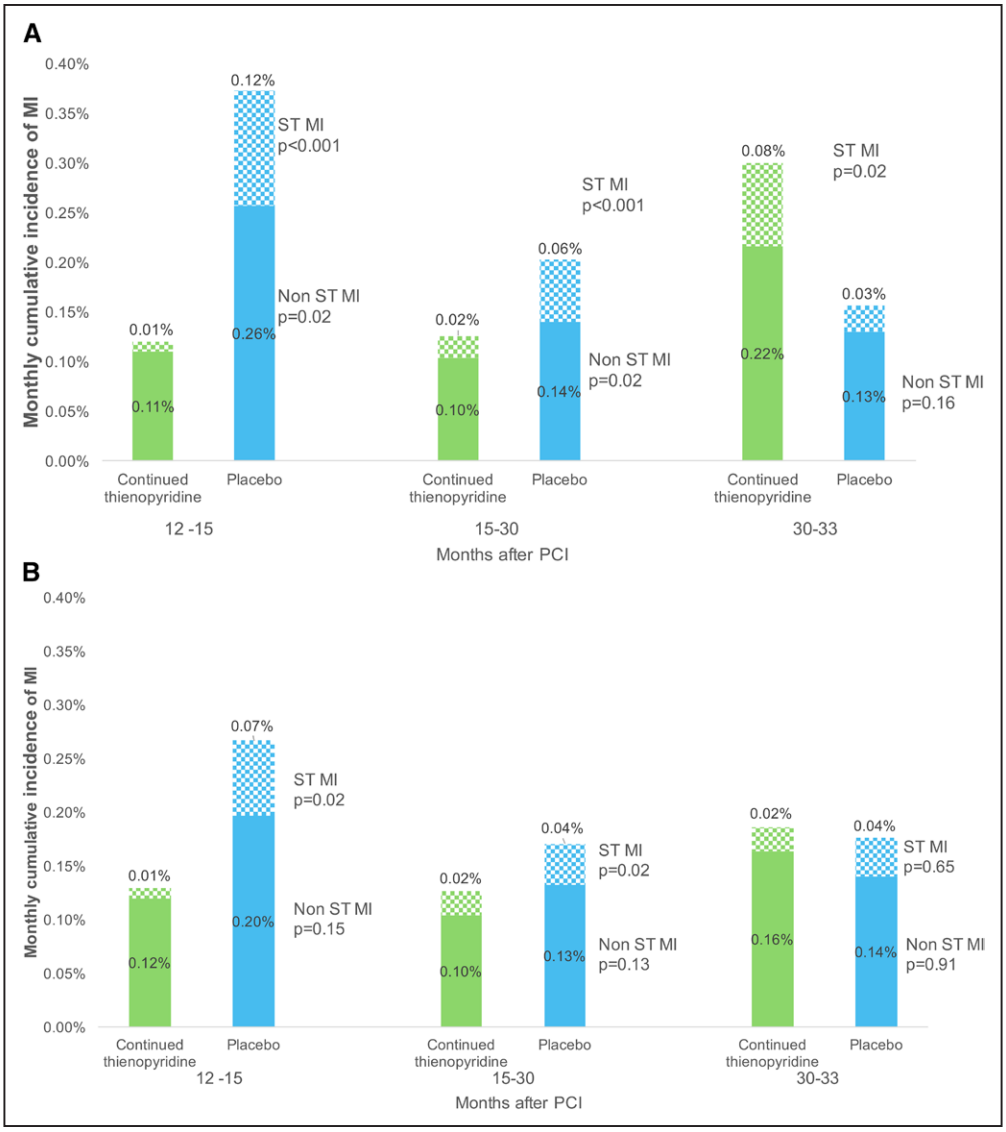

Figure 2. Monthly cumulative incidence of MI not related to ST, and MI related to ST, by study period and randomized treatment arm.

A, In all randomly assigned patients (n=11 648). **B,** In patients without PES at index PCI (n=8864). Log-rank *P* values are for comparison between randomized treatment arms for each MI etiology. MI indicates myocardial infarction; non–ST MI, non-stent thrombosis–related myocardial infarction; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stents; and ST MI, stent thrombosis–related myocardial infarction.

The increase in incidence of MI after discontinuing thienopyridine has not previously been shown in a randomized trial setting. Although this risk has been suggested by prior observational studies,[1,2,14] it has not been reported in some recent randomized clinical trials[15] or registries,[16] although many of these studies have been underpowered to detect a difference in rates of MI or had shorter observational periods. The current observation provides evidence of the protective effect of thienopyridine continuation as demonstrated in the primary results of the DAPT Study,[5] and also demonstrates that the highest risk of MI is within the first 3 months after discontinuation of thienopyridine, with persistence of risk difference over the ensuing 15 months. The mechanism for this increase in risk may be attributable to withdrawal of the protective antithrombotic effect of thienopyridine or other etiologies (such as a hypothesized, but as yet unproven, rebound phenomenon); further biological studies are warranted.

Although the MI risk associated with discontinuation of thienopyridine at 12 months after PCI remains present after excluding patients who had received PES, the MI risk associated with discontinuation at 30 months appears to be confined to patients treated with PES. However, stent type was not randomized in this study, and differences in baseline characteristics, and treatment,

Table 4. Multivariate Predictors of Myocardial Infarction, by Time Period

Risk Factors	HR (95% CI)	*P* Value
12–15 mo after index PCI		
Randomly assigned to continued thienopyridine	0.32 (0.19–0.52)	<0.001
Prior MI	2.12 (1.37–3.31)	<0.001
Stent type		
PES vs non-PES DES	2.11 (1.34–3.32)	0.001
BMS vs non-PES DES	0.88 (0.43–1.82)	0.74
Renal insufficiency	2.91 (1.46–5.82)	0.003
Body mass index ≥ median (30.4 kg/m^2)	0.57 (0.37–0.89)	0.012
30–33 mo after index PCI		
Prior PCI (in addition to index PCI)	2.25 (1.39–3.64)	<0.001
Stent type		
PES vs non-PES DES	2.09 (1.27–3.45)	0.004
BMS vs non-PES DES	0.66 (0.26–1.71)	0.39
Randomly assigned to continued thienopyridine	1.93 (1.16–3.19)	0.011
Renal insufficiency	2.39 (1.03–5.56)	0.043
Tobacco use at index PCI	1.61 (0.97–2.67)	0.068

BMS indicates bare metal stent; DES, drug-eluting stent; MI, myocardial infarction; PCI, percutaneous coronary intervention; and PES, paclitaxel-eluting stents.

as well, exist between patients for whom a PES was chosen at the index PCI and those for whom another stent type was used. The majority of PES-treated patients received prasugrel, half had an ACS presentation before their index PCI, they had a higher prevalence of diabetes mellitus, and they had a smaller minimum stent diameter at index PCI than patients not treated with PES. Although an association between PES and late ST has been observed in other trials,[11] the independent contributions of stent type, thienopyridine type, ACS at presentation, and baseline coronary risk factors confound any conclusion in the present analysis. It is notable that the largest portion of MI risk after discontinuation of prasugrel (12- to 15-month time period) following PES implantation in the TAXUS Liberté DAPT substudy was not related to ST (cumulative MI incidence of 1.5% in the placebo group versus 0.4% for continued prasugrel, *P*=0.007, in comparison with incidence of MI related to ST of 0.7% versus 0%, respectively, *P*=0.005),[13] which suggests a significant contribution of patient-related factors unrelated to the stent, including ACS at presentation.[17]

Paclitaxel stents are no longer available for coronary use, and in the non–PES-treated cohort in the present study, the increased risk of MI that was present at 12 to 15 months was no longer evident at 30 to 33 months. These findings suggest that, among more current DES, the benefit of continuing thienopyridine in the 30- to 33-month window appears to be small. Nevertheless, an increase in the magnitude of MI risk was observed when thienopyridine treatment was stopped at 30 months. Although the study did not provide follow-up beyond 33 months to definitively determine whether even longer courses of therapy would be beneficial in some subset of patients, we identified several factors associated with MI risk following thienopyridine discontinuation at 30 months, including renal insufficiency and history of prior PCI (other than the index procedure). These findings suggest that the consideration of how long to continue thienopyridine therapy depends on an ongoing assessment of balance between bleeding and ischemic risk over time.

In the entire randomized cohort, the majority of MIs occurring 12 to 33 months after PCI were not related to ST. These findings suggest that the benefit of thienopyridine, beyond 12 months after PCI, is in large part attributable to prevention of MI unrelated to the stent. Similar results were reported in the PEGASUS Trial (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin),[18] which randomly assigned stable patients 1 to 3 years after a qualifying MI to ticagrelor or placebo, with all patients continuing aspirin. In the patients with a prior PCI, 95% of which had been performed at least a year before study enrollment, ST represented 17% of MI.[19] Patients randomly assigned to the ticagrelor arm had a lower cumulative incidence of MI during the study period, and a lower incidence of ST in the on-treatment analysis. In contrast to the DAPT Study and the PEGASUS Trial, most other studies reporting ST have either focused on risks of ST within the first year after PCI, or have been

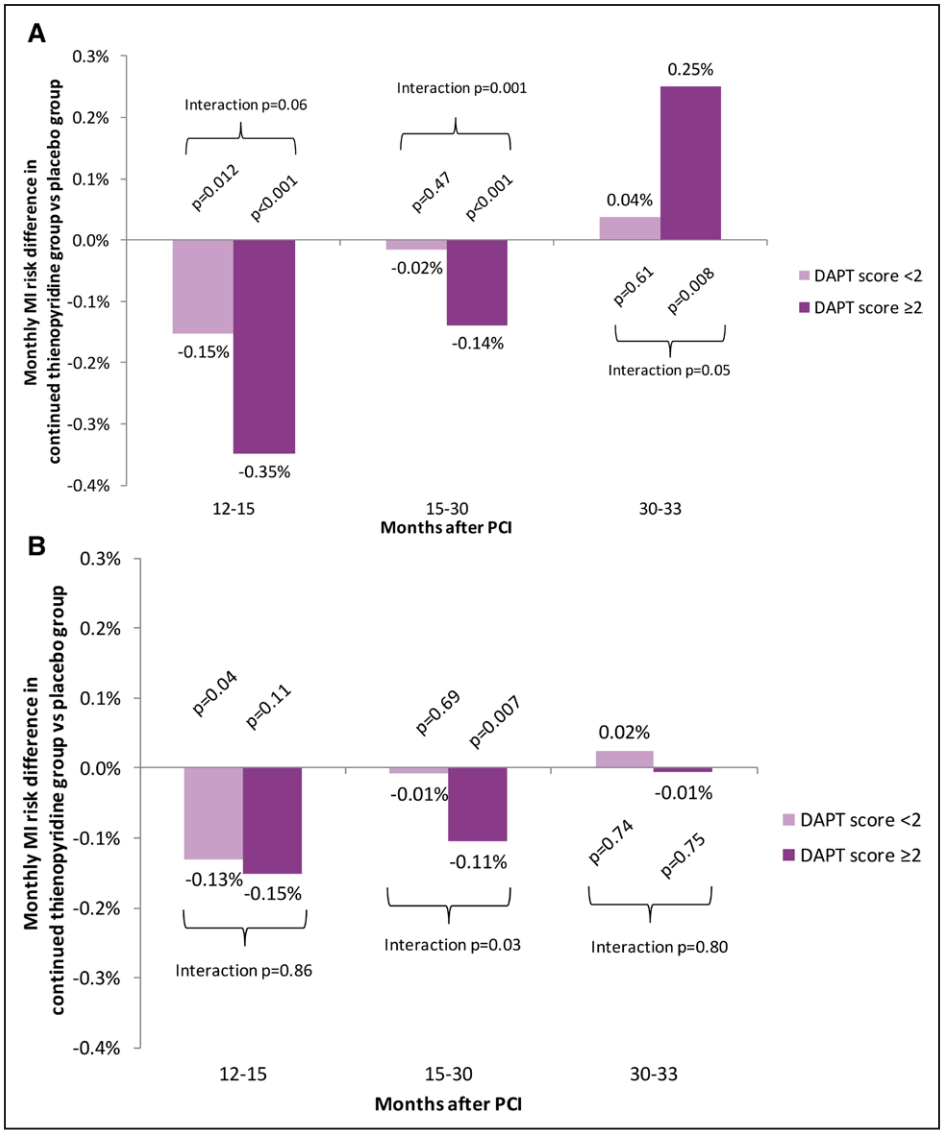

Figure 3. Difference in monthly incidence of MI between randomized treatment arms, by DAPT score group. **A,** In all randomly assigned patients (n=11 648). **B,** In patients without PES at index PCI (n=8864). Log-rank *P* values for treatment effect in each DAPT score category are presented according to time interval, and interaction *P* values on the additive scale are presented for each time period. See online-only Data Supplement Table II. DAPT indicates Dual Antiplatelet Therapy; MI, myocardial infarction; PCI, percutaneous coronary intervention; and PES, paclitaxel-eluting stents.

driven by results within the first year of follow-up, when the risks of ST are higher than beyond 1 year,[20] and also relatively greater than risks of MI not related to ST, likely because of proximity to the procedure. The 2016 update to the American College of Cardiology/American Heart Association guidelines on duration of dual antiplatelet therapy in patients with coronary artery disease[21] and the 2014 European Society of Cardiology guidelines on myocardial revascularization[22] recommend a shorter duration of dual antiplatelet therapy after PCI for patients with stable ischemic heart disease, on the basis of the lower thrombotic risk seen with new-generation DES, and state that continuation of therapy beyond 6 months may be reasonable on the basis of assessment of bleeding risks. However, our findings after discontinuation of thienopyridine at 12 to 15 months indicate that the risks associated with discontinuation of thienopyridine after 1 year of uncomplicated therapy are chiefly unrelated to the stent. Furthermore, previous results from the DAPT Study do not indicate a different degree of benefit for late thienopyridine therapy between BMS and DES.[6,23] Although use of PES (no longer available) was associated with higher risks, in the remainder of patients, a significant risk of discontinuation was present at 12 months that was not dependent on stent type. Thus, the choice of whether to continue thienopyridine therapy with aspirin beyond the 6- to 12-month time frame should include a thorough assessment of the balance between the potentials for MI risk

reduction versus increased risk of bleeding.[21] The DAPT score has previously been shown to stratify patients into categories of higher ischemic benefit/lower bleeding risk versus lower ischemic benefit/higher bleeding risk over the 12- to 30-month randomized study period.[10,24] It is important to note that the current analysis demonstrates an increase in early ischemic risk following thienopyridine discontinuation at 12 months, regardless of stent type or DAPT score risk profile (albeit with greater magnitude of risk in those with DAPT score ≥2 in comparison with <2). Therefore, patients in whom thienopyridine discontinuation is clinically advised on the basis of an increased risk of bleeding should be followed closely in this early at-risk period. Similarly, although DAPT scores <2 may predict decreased ischemic benefit and a greater risk of bleeding, thus prompting discontinuation of thienopyridine, the 3-month period after discontinuation carries increased ischemic hazard.

Limitations

This analysis was performed as intention-to-treat and may thus underestimate the risk of MI associated with discontinuing thienopyridine, because it does not account for patients randomly assigned to continued therapy who discontinued thienopyridine earlier than indicated by the protocol, nor patients randomly assigned to placebo who were then treated with thienopyridine as a result of ischemic events that occurred during the treatment period. The monthly cumulative incidence of MI by time period, and by subgroups of stent type and DAPT score, were not prespecified end points and may be underpowered. Although there may be a benefit to continuation beyond 30 months in certain patients with higher-risk features who have tolerated therapy without bleeding, a smaller absolute risk of MI, and deviations from randomized treatment as a result of intercurrent events, as well, affect both the power and reliability of conclusions regarding the risks of thienopyridine discontinuation beyond 30 months.

CONCLUSION

In conclusion, MI risk was elevated after thienopyridine discontinuation, appeared highest during the first 3 months after discontinuation in the group randomly assigned to placebo, and remained present to the extent of follow-up (33 months). This hazard was evident at 12 months in the entire randomized cohort, including patients not treated with PES. At 30 months, the increased MI risk associated with thienopyridine discontinuation was less evident overall and was limited to patients with specific risk factors. Although continued thienopyridine was protective against MI (both with and without ST), the majority of MIs that occurred during periods of thienopyridine discontinuation were not related to ST.

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FOOTNOTES

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Myocardial Infarction Risk After Discontinuation of Thienopyridine Therapy in the Randomized DAPT Study (Dual Antiplatelet Therapy)

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On behalf of the DAPT Investigators

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SUPPLEMENTAL MATERIAL

Myocardial Infarction Risk after Discontinuation of Thienopyridine Therapy in the Randomized DAPT Study

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Supplemental Table 1: Baseline and procedural characteristics of all randomized patients, stratified by PES use

Characteristic	Excluding patients treated with PES (n= 8864)	Patients treated with PES (n= 2784)	p-value
Age, years	61.77±10.43	59.94±9.70	<0.001
Female sex, n (%)	2223/8864 (25.1%)	702/2784 (25.2%)	0.88
Non white race, n (%)*	738/8727 (8.5%)	242/2703 (9.0%)	0.43
Hispanic or Latino ethnic group, n (%)	300/8656 (3.5%)	106/2776 (3.8%)	0.38
Body-mass index, kg/m^2	30.22±5.7	30.96±5.9	<0.001
Diabetes mellitus, n (%)	2472/8819 (28.0%)	919/2782 (33.0%)	<0.001
Hypertension, n (%)	6507/8832 (73.7%)	2015/2782 (72.4%)	0.20
Cigarette smoker, current or in the past year, n (%)	2352/8706 (27.0%)	790/2772 (28.5%)	0.13
Prior myocardial infarction, n (%)	1895/8703 (21.8%)	561/2773 (20.2%)	0.089
Prior PCI, n (%)	2524/8823 (28.6%)	844/2780 (30.4%)	0.076
Prior CABG, n (%)	892/8841 (10.1%)	357/2783 (12.8%)	<0.001
Stroke or transient ischemic attack, n (%)	382/8837 (4.3%)	19/2781 (0.68%)	<0.001
Congestive heart failure, n (%)	390/8827 (4.4%)	134/2781 (4.82%)	0.37
Peripheral arterial disease, n (%)	484/8690 (5.6%)	165/2774 (6.0%)	0.45
Indication for index procedure, n (%)			
STEMI	1324/8864 (14.9%)	356/2784 (12.8%)	0.005
NSTEMI	1466/8864 (16.5%)	430/2784 (15.5%)	0.18
Unstable Angina	1195/8864 (13.5%)	626/2784 (22.5%)	<0.001
Stable Angina	3307/8864 (37.3%)	842/2784 (30.2%)	<0.001
Other			

	1572/8864 (17.7%)	530/2784 (19.0%)	0.12
Region, n (%)			<0.001
North America	7294/8864 (82.3%)	2652/2784(95.3%)	
Europe	1279/8864 (14.4%)	132/2784 (4.7%)	
Australia and New Zealand	291/8864 (3.3%)	0/2784 (0%)	
Thienopyridine at randomization, n(%)			<0.001
Clopidogrel	7457/8864 (84.1%)	505/2784 (18.1%)	
Prasugrel	1407/8864 (15.9%)	2279/2784(81.9%)	
PCI characteristics			
Type of DES or BMS, n(%)			
Everolimus	4703/8864 (53.1%)	0/2784 (0%)	--
Paclitaxel	0/8864 (0%)	2666/2784 (95.8%)	<0.001
Zotarolimus	1264/8864 (14.3%)	0/2784 (0%)	<0.001
Sirolimus	1118/8864 (12.6%)	0/2784 (0%)	<0.001
BMS	1687/8864 (19.0%)	0/2784 (0%)	<0.001
>1 type	92/8864 (1.0%)	118/2784 (4.2%)	<0.001
No. of treated lesions	1.27±0.52 (8864)	1.31±0.56 (2784)	0.001
No. of treated vessels	1.10±0.31 (9947)	1.12±0.35 (2784)	<0.001
No. of stents	1.44±0.73 (8864)	1.45±0.74 (2784)	0.46
Minimum stent diameter, n (%)			<0.001
<3mm	3639/8864 (41.1%)	1402/2784(50.4%)	
≥3mm	5225/8864 (60.0%)	1382/2784(49.6%)	
Total stent length, mm	26.68±16.09	28.16±17.46	<0.001
Treated vessel			
	n=11296	n=3663	
Native coronary artery lesions, n (%)	10982/11296 (97.2%)	3535/3663(96.5%)	0.029

Left main			
Left anterior descending	77/11296 (0.68%)	34/3663(0.93%)	0.15
Right	4489/11296(39.7%)	1426/3663(38.9%)	0.39
Circumflex	3880/11296(34.4%)	1219/3663(33.3%)	0.24
	2536/11296(22.5%)	856/3663 (23.4%)	0.26
Venous graft, n (%)	256/11296 (2.3%)	120/3663 (3.3%)	0.001
Arterial graft, n (%)	58/11296 (0.51%)	8/3663 (0.22%)	0.021
In-stent restenosis, n (%)	404/11306 (3.6 %)	112/3663 (3.1%)	0.15
Extreme tortuosity, n (%)	507/11194 (4.5%)	75/3644 (2.1%)	<0.001
Heavy calcification, n (%)	1021/11194 (9.1%)	143/3643 (3.9%)	<0.001
Modified ACC or AHA lesion class B2 or C, n (%)	4794/10714 (44.8%)	1493/3624 (41.2%)	<0.001
DAPT score group, n (%)			<0.001
<2	5122/8864 (57.8%)	609/2784 (21.9%)	
≥ 2	3742/8864 (42.2%)	2175/2784(78.1%)	

Values are mean±SD when appropriate.

*Race and ethnic group were self-reported.

ACC indicates American College of Cardiology; AHA: American Heart Association; BMS: Bare metal stent; CABG: coronary artery bypass graft; DES: Drug-eluting stent;

PCI: percutaneous coronary intervention; PES: paclitaxel-eluting stents. STEMI: ST-segment elevation myocardial infarction; NSTEMI: Non-ST-segment elevation myocardial infarction.

Supplemental Table 2: Cumulative Incidence of myocardial infarction stratified by Dual Antiplatelet Therapy (DAPT) Score group

All Randomized Patients					
Cumulative incidence of MI	Continued thienopyridine (N = 5862)	Placebo (N = 5786)	Risk Difference, Continued thienopyridine group vs. placebo group	P-value	P-value for interaction
12-15 month period, n(%)					0.06
DAPT Score <2 (N=5731)	7 (0.25%)	20 (0.70%)	-0.46% [-0.82%, -0.10%]	0.012	
DAPT Score ≥2 (N=5917)	14 (0.47%)	44 (1.5%)	-1.05% [-1.56%, -0.53%]	<0.001	
15-30 month period					0.001
DAPT Score <2	39 (1.4%)	46 (1.7%)	-0.24% [-0.89%, 0.42%]	0.47	
DAPT Score ≥2	63 (2.2%)	119 (4.3%)	-2.08% [-3.02%, -1.14%]	<0.001	
30-33 month period					0.052
DAPT Score <2	11 (0.49%)	9 (0.38%)	0.11% [-0.34%, 0.56%]	0.61	
DAPT Score ≥2	33 (1.3%)	14 (0.53%)	0.75% [0.16%, 1.34%]	0.008	

Excluding patients treated with PES					
Cumulative incidence of MI	Continued thienopyridine (N = 5862)	Placebo (N = 5786)	Risk Difference, Continued thienopyridine group vs. placebo group	P-value	P-value for interaction
12-15 month period, n(%)					0.86
DAPT Score <2 (N=5122)	7 (0.28%)	17 (0.67%)	-0.39% [-0.77%, -0.01%]	0.043	
DAPT Score ≥2 (N=3742)	10 (0.53%)	18 (0.99%)	-0.45% [-1.02%, 0.11%]	0.11	
15-30 month period					0.03
DAPT Score <2	33 (1.4%)	37 (1.5%)	-0.13% [-0.80%, 0.54%]	0.69	
DAPT Score ≥2	42 (2.3%)	68 (3.9%)	-1.58% [-2.74%, -0.41%]	0.007	
30-33 month period					0.80
DAPT Score <2	9 (0.46%)	8 (0.39%)	0.07% [-0.41%, 0.55%]	0.74	
DAPT Score ≥2	10 (0.66%)	11 (0.68%)	-0.02% [-0.71%, 0.68%]	0.75	

DAPT indicates Dual Antiplatelet Therapy; MI, myocardial infarction; PES, paclitaxel-eluting stents. Risk difference data presented as % [95% confidence interval]