Original Investigation

Development and Validation of a Prediction Rule for Benefit and Harm of Dual Antiplatelet Therapy Beyond 1 Year After Percutaneous Coronary Intervention

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IMPORTANCE Dual antiplatelet therapy after percutaneous coronary intervention (PCI) reduces ischemia but increases bleeding.

OBJECTIVE To develop a clinical decision tool to identify patients expected to derive benefit vs harm from continuing thienopyridine beyond 1 year after PCI.

DESIGN, SETTING, AND PARTICIPANTS Among 11 648 randomized DAPT Study patients from 11 countries (August 2009-May 2014), a prediction rule was derived stratifying patients into groups to distinguish ischemic and bleeding risk 12 to 30 months after PCI. Validation was internal via bootstrap resampling and external among 8136 patients from 36 countries randomized in the PROTECT trial (June 2007-July 2014).

EXPOSURES Twelve months of open-label thienopyridine plus aspirin, then randomized to 18 months of continued thienopyridine plus aspirin vs placebo plus aspirin.

MAIN OUTCOMES AND MEASURES Ischemia (myocardial infarction or stent thrombosis) and bleeding (moderate or severe) 12 to 30 months after PCI.

RESULTS Among DAPT Study patients (derivation cohort; mean age, 61.3 years; women, 25.1%), ischemia occurred in 348 patients (3.0%) and bleeding in 215 (1.8%). Derivation cohort models predicting ischemia and bleeding had *c* statistics of 0.70 and 0.68, respectively. The prediction rule assigned 1 point each for myocardial infarction at presentation, prior myocardial infarction or PCI, diabetes, stent diameter less than 3 mm, smoking, and paclitaxel-eluting stent; 2 points each for history of congestive heart failure/low ejection fraction and vein graft intervention; −1 point for age 65 to younger than 75 years; and −2 points for age 75 years or older. Among the high score group (score ≥2, n = 5917), continued thienopyridine vs placebo was associated with reduced ischemic events (2.7% vs 5.7%; risk difference [RD], −3.0% [95% CI, −4.1% to −2.0%], $P < .001$) compared with the low score group (score <2, n = 5731; 1.7% vs 2.3%; RD, −0.7% [95% CI, −1.4% to 0.09%], $P = .07$; interaction $P < .001$). Conversely, continued thienopyridine was associated with smaller increases in bleeding among the high score group (1.8% vs 1.4%; RD, 0.4% [95% CI, −0.3% to 1.0%], $P = .26$) compared with the low score group (3.0% vs 1.4%; RD, 1.5% [95% CI, 0.8% to 2.3%], $P < .001$; interaction $P = .02$). Among PROTECT patients (validation cohort; mean age, 62 years; women, 23.7%), ischemia occurred in 79 patients (1.0%) and bleeding in 37 (0.5%), with a *c* statistic of 0.64 for ischemia and 0.64 for bleeding. In this cohort, the high-score patients (n = 2848) had increased ischemic events compared with the low-score patients and no significant difference in bleeding.

CONCLUSION AND RELEVANCE Among patients not sustaining major bleeding or ischemic events 1 year after PCI, a prediction rule assessing late ischemic and bleeding risks to inform dual antiplatelet therapy duration showed modest accuracy in derivation and validation cohorts. This rule requires further prospective evaluation to assess potential effects on patient care, as well as validation in other cohorts.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00977938.

JAMA. 2016;315(16):1735-1749. doi:10.1001/jama.2016.3775
Published online March 29, 2016. Corrected on May 24, 2016.

Supplemental content at jama.com

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The optimal duration of dual antiplatelet therapy with aspirin and thienopyridine after percutaneous coronary intervention (PCI) with stents is the subject of debate. Among patients who complete 1 year of dual antiplatelet therapy after PCI without an ischemic or bleeding event, continuing therapy decreases stent thrombosis and myocardial infarction but increases bleeding.[1,2] Continuing dual antiplatelet therapy thus involves a careful assessment of the trade-offs between reduced ischemia and increased bleeding for individual patients.

However, assessing the balance between ischemia and bleeding risks can be challenging for clinicians and patients. Factors related to recurrent ischemic events and bleeding in patients undergoing PCI overlap substantially, making it difficult to determine optimal treatment.[3] Although subgroup analyses have been helpful in determining groups with larger absolute benefits from continuing therapy (eg, patients presenting with myocardial infarction),[4,5] there remain patients within these broad categories who may also experience serious bleeding events. Most data estimating ischemia and bleeding risk following PCI have focused on early risks, including periprocedural events.[6,7] It remains unclear which patients are at high risk for late ischemic events and may thus benefit most from longer-term dual antiplatelet therapy vs those who are at high risk for late bleeding events and may thus be harmed.

BMS *bare metal stent*

CHF *congestive heart failure*

DES *drug-eluting stent*

EES *everolimus-eluting stent*

PCI *percutaneous coronary intervention*

SES *sirolimus-eluting stent*

ZES *zotarolimus-eluting stent*

The goal of this study was to identify factors predicting whether the expected benefit of reduced ischemia would outweigh the expected increase in bleeding associated with continued dual antiplatelet therapy beyond 1 year for individual patients, using data from the Dual Antiplatelet Therapy (DAPT) Study. These factors were used to develop a decision tool to help select the duration of therapy for individual patients being evaluated 1 year after stenting.

Methods

This secondary analysis of the DAPT Study was approved by the institutional review board of Partners HealthCare. The Patient-Related Outcomes With Endeavor vs Cypher Stenting (PROTECT) protocol was approved by ethical boards in accordance with local regulations. All patients in both studies provided written informed consent. The DAPT Study, conducted from August 2009 to May 2014 in 11 countries, enrolled patients after PCI with either drug-eluting stents (DES) or bare metal stents (BMS) and treated them with open-label thienopyridine plus aspirin for 12 months; at 12 months, eligible patients who were free from major bleeding and ischemic events and adherent to therapy remained taking aspirin and were randomized to continued thienopyridine vs placebo for 18 months.[8] The full enrollment and randomization criteria are listed in the eAppendix in the Supplement. Patients receiving long-term anticoagulation therapy, those with planned surgical procedures necessitating discontinuation of antiplatelet therapy for more than 14 days, and those with a life expectancy of less than 3 years were excluded from enrollment. At 12 months, only those patients who were adherent with thienopyridine therapy and free from myocardial infarction, stroke, repeat coronary revascularization, stent thrombosis, and moderate or severe bleeding by the GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries) criteria[9] during the first 12 months after enrollment were randomized.

As permitted by regulatory authorities, race and ethnicity data were collected via patient self-report. Race categories were prespecified as American Indian or Alaska Native, Asian, black or African American, Native Hawaiian or other Pacific Islander, white, and other. Ethnicity was collected as Hispanic or Latino and not Hispanic or Latino. This information was collected to assess potential heterogeneous treatment effects among different subgroups.

The primary follow-up period of the study was 12 to 30 months after the index procedure (or 18 months after randomization). Details of the study design and results have been described previously.[1,2,8] As the results of the study were consistent across DES- and BMS-treated cohorts,[2] all randomized patients were included in this analysis.

Study Goals

The goal of this study was to distinguish patients within the DAPT Study who derived the greatest benefit from those who experienced the most harm from continuation of dual antiplatelet therapy more than 1 year after PCI, considering individual patient characteristics and their independent associations with ischemic and bleeding events. This study sought to stratify outcomes based on a single multivariable risk score.[10] This entailed (1) identifying factors associated with ischemic and bleeding risks, (2) choosing those that selectively predicted either ischemic or bleeding risk to generate a simplified risk score, and (3) assessing the randomized treatment results observed in the trial, stratified by the new risk score. An ideal score would identify patients with simultaneous high ischemic risk (and corresponding high benefit with continued thienopyridine) and low bleeding risk (and corresponding low risk of harm with continued therapy), and vice versa. In addition, the ability of the score to stratify ischemic and bleeding risk within an external sample was assessed.

Ischemic and Bleeding End Points

The primary ischemic end point was a composite of myocardial infarction or definite or probable stent thrombosis (as defined by the Academic Research Consortium),[11] and the primary bleeding end point was moderate or severe bleeding (as defined by the GUSTO criteria).[9]

Predictors

A total of 37 candidate variables potentially associated with ischemic or bleeding events based on a comprehensive literature review and clinical plausibility were identified. Variables included sociodemographic variables, cardiovascular history, noncardiovascular medical comorbidities, anatomical and procedural factors, and concomitant medical therapy. (Candidate Variables for Model Building in the eAppendix in the Supplement).

Statistical Analysis

Development of Ischemic and Bleeding Event Models

Clinical and procedural characteristics were compared between patients experiencing events from 12 through 30 months and those without events, using Fisher exact or *t* tests as appropriate. Cox regression was used to develop 2 separate models within the DAPT randomized study population (derivation cohort), the first to predict ischemic events and the second to predict bleeding events after randomization. Data were censored at the time of a myocardial infarction or stent thrombosis for the ischemia model; a moderate or severe bleed for the bleeding model; or at the time of death, last known contact, or 30 months, whichever was earliest. Candidate variables that differed in bivariable comparisons at a significance level of less than .30 were incorporated. Stepwise selection was then performed, using the .05 significance level. To identify possible heterogeneous treatment effects, simple Cox regression models were developed for each outcome including treatment group, variable of interest, and their interaction term. Interactions terms significant at a *P* value less than .15 were entered into the stepwise selection process with other candidate variables.

Proportionality was evaluated for all variables in the models. Model discrimination was assessed using the *c* statistic. Calibration was assessed through the examination of calibration plots and using the corrected Nam and D'Agostino goodness-of-fit test.[12,13] The primary models were internally validated using bootstrap resampling for 200 iterations.[14] For each resampling, the stepwise selection process was rerun, and the discrimination of the bootstrap model was assessed in the bootstrap sample and the full data set. The mean difference between these bootstrap model values was defined as the "optimism," and was subtracted from the final reported discrimination of the models.[15]

Development of a Simplified Clinical Prediction Score

For each patient, the predicted risk (cumulative incidence) of an ischemic event from 12 through 30 months was estimated, assuming treatment with continued thienopyridine plus aspirin beyond 12 months and separately assuming treatment with aspirin alone beyond 12 months; similarly, bleeding event risks were predicted under these 2 assumptions. The difference between these 2 predicted values represented the predicted absolute risk reduction in combined myocardial infarction or stent thrombosis anticipated with continued thienopyridine from the ischemic model, and the predicted absolute risk increase in moderate or severe bleeding anticipated with continued thienopyridine from the bleeding model. The absolute difference between the predicted ischemic reduction and bleeding increase was defined as the "benefit-risk difference," and estimated for each patient.

A linear regression model was created, using benefit-risk difference as the outcome and all predictors that were selected in the ischemia and bleeding models. Variables that statistically accounted for more than 1% of the observed variation in estimated benefit-risk difference were included in a simplified clinical prediction score. To facilitate ease of use, continuous variables (such as age and stent diameter) were categorized based on reference to prior studies or at median values and confirmation that the gradient of effect was maintained when transformed, and all variables were assigned an integer score of 1 or 2 (or −1 to −2) based on β coefficients (Development of a Predictive Score in the eAppendix in the Supplement). The range of potential scores was between −2 and 10.

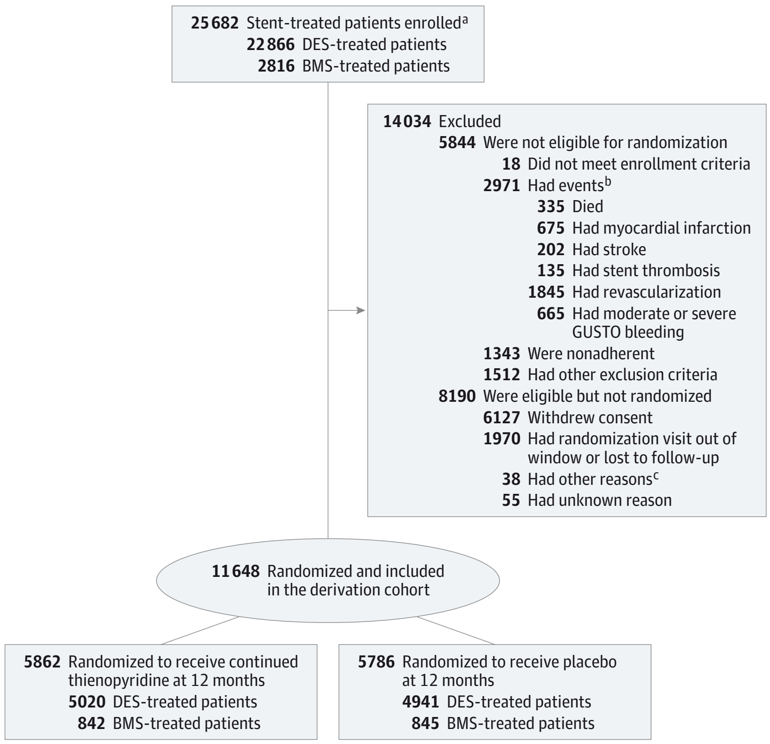
Evaluation of Randomized Treatment Effect Stratified by Clinical Prediction Score

The derivation cohort was divided into approximate quartiles based on the score, and Kaplan-Meier event rates from 12 through 30 months were compared within each score quartile by randomized treatment group. Additionally, event rates were examined among patients receiving only everolimus-eluting stents (EES). Based on these results, clinically relevant score groupings were created, defining patients more likely to benefit from thienopyridine continuation (high score group) vs those more likely to be harmed (low score group). The absolute risk differences in ischemic and bleeding event rates associated with continued thienopyridine vs placebo across high vs low score groups were compared using a *Z* test for interaction.

External Validation

The risk models and the clinical prediction score were externally validated within the PROTECT trial, conducted from June 2007 through July 2014 in 36 countries, in which patients undergoing PCI were randomized to receive sirolimus-eluting (SES) vs zotarolimus-eluting stents (ZES) and were followed up for 5 years.[16] This trial was selected for validation due to its large inclusive population of stent-treated patients, with similar definitions and adjudicated outcomes as those used in the DAPT Study. Those patients not sustaining myocardial infarction, stent thrombosis, or a moderate/severe bleeding event within the first 12 months in the PROTECT trial served as the validation cohort (n = 8136). Two forms of validation were conducted: (1) evaluation of the DAPT Study–derived ischemic and bleeding models and (2) evaluation of prediction score performance in stratifying risks of ischemic and bleeding events. First, for the validation of the models, because PROTECT trial patients were not randomized to different durations of dual antiplatelet therapy, dual antiplatelet therapy duration was likely confounded by treatment indication and was therefore not included in the validation. The anticipated statistical effect of omitting this variable in the validation would be to yield a conservative estimate of each model's performance, given that randomized treatment group is strongly associated with both bleeding and ischemic events. Models were validated via the estimation of *c* statistics and goodness-of-fit tests by applying the function derived in the DAPT Study to PROTECT patients from 12 through 30 months after PCI, limited to patients not sustaining myocardial infarction, stent thrombosis, or a moderate/severe bleeding event within the first 12 months.

Figure 1. Flow of Patients Through the Dual Antiplatelet Therapy Study



BMS indicates bare metal stent; DES, drug-eluting stent; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries. A total of 11 648 randomized patients comprised the cohort used to derive a clinical prediction score to stratify individual risk of benefit and harm with continuation of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention.

[a] Screening for eligibility data are not available to report.

[b] Patients may have had more than 1 event.

[c] Other reasons include site terminated participation, randomization target met prior to patient follow-up, or patient not recognized as eligible by site.

Because PROTECT had lower overall ischemic and bleeding event rates than the DAPT Study, the calibration of the models was assessed after accounting for this difference in baseline hazard,[17] and then the goodness of fit of the recalibrated model was assessed.

Second, the ability of the clinical prediction score to stratify ischemic and bleeding risk was evaluated by comparing overall rates of myocardial infarction, stent thrombosis, and moderate or severe bleeding among patients with a high vs low score in the validation cohort.

A 2-tailed α of .05 was used to define the significance threshold for all comparisons. All analyses were performed at the Harvard Clinical Research Institute, using SAS (SAS Institute), version 9.4.

Results

Study Population

A total of 11 648 patients undergoing PCI with coronary stents were randomized in the DAPT Study and included in this analysis (derivation cohort) (**Figure 1**). Of these, patients receiving EES were 40.3%; paclitaxel-eluting stents, 22.9%; ZES, 10.9%; SES, 9.6%; BMS, 14.4%; receiving more than 1 stent type, 1.8%. From 12 through 30 months after their index procedure, 348 patients (3.0%) developed myocardial infarction or stent thrombosis (myocardial infarction without stent thrombosis, 251; stent thrombosis, 97) and 215 patients (1.8%) developed moderate or severe bleeding (moderate, 142; severe, 72; 2 different events adjudicated as moderate and severe, 1). Thirty-three patients had both an ischemic and bleeding event in follow-up. Patients who had an ischemic event in follow-up had higher rates of cardiovascular risk factors (including diabetes, hypertension, peripheral arterial disease, renal insufficiency/failure, and smoking), had higher rates of cardiovascular disease (including history of congestive heart failure [CHF], low ejection fraction, prior myocardial infarction, and prior PCI), and were more likely to have been randomized to placebo compared with patients without an ischemic event (**Table 1**). Patients with a bleeding event were older, had a lower prevalence of smoking, had a higher prevalence of hypertension, prior CHF, renal insufficiency/failure, peripheral arterial disease, atrial fibrillation, prior stroke/transient ischemic attack, prior PCI, and history of cancer, and were more likely to have been randomized to continued thienopyridine compared with patients without a bleeding event.

Risk Prediction Models

In multivariable Cox regression, significant predictors of both ischemic and bleeding events included randomized treatment group, peripheral arterial disease, hypertension, and renal insufficiency/failure. Variables that predicted only the risk of ischemic events included history of PCI or myocardial infarction prior to the index procedure, stent diameter less than 3 mm, myocardial infarction at presentation, history of CHF or left ventricular ejection fraction lower than 30%, paclitaxel-eluting stent, vein graft stent, cigarette smoking within the year prior to index procedure, and diabetes mellitus (**Table 2**). No tested interactions between covariates and randomized treatment for ischemic events were retained in

Table 1. Baseline Characteristics of Patients With vs Without Ischemic or Bleeding Events From 12 to 30 Months in the Derivation Cohort (N = 11 648)[a]

Measure	Myocardial Infarction or Stent Thrombosis Events, No. (%)			Moderate or Severe Bleeding Events, No. (%)[b]		
	Event (n = 348 Patients)	No Event (n = 11 300 Patients)	*P* Value	Event (n = 215 Patients)	No Event (n = 11 433 Patients)	*P* Value
Demographics						
Age, mean (SD), y	61.7 (10.8)	61.3 (10.3)	.47	66.4 (10.3)	61.2 (10.3)	<.001
Median (IQR)	62.0 (54.0-69.0)	62.0 (54.0-68.6)		67.8 (60.0-74.0)	61.0 (54.0-68.0)	
Women	92 (26.4)	2833 (25.1)	.57	63 (29.3)	2862 (25.0)	.15
Race/ethnicity						
Hispanic or Latino ethnic group	17 (4.9)	389 (3.5)	.18	8 (3.8)	398 (3.6)	.85
Nonwhite race[c]	35 (10.3)	950 (8.6)	.28	17 (8.0)	968 (8.6)	.90
BMI, mean (SD)	30.1 (5.6)	30.4 (5.7)	.28	29.5 (5.1)	30.4 (5.8)	.01
Medical History						
Diabetes mellitus	138 (39.9)	3253 (28.9)	<.001	67 (31.3)	3324 (29.2)	.50
Hypertension	282 (81.0)	8240 (73.1)	<.001	181 (84.2)	8341 (73.2)	<.001
Cigarette smoker	113 (33.0)	3029 (27.2)	.02	39 (18.2)	3103 (27.6)	.002
Stroke or TIA	20 (5.8)	381 (3.4)	.02	16 (7.6)	385 (3.4)	.003
Congestive heart failure	36 (10.4)	488 (4.3)	<.001	17 (8.0)	507 (4.5)	.02
LVEF <30%	15 (4.6)	192 (1.9)	.002	6 (3.1)	201 (1.9)	.28
Renal insufficiency/failure	27 (7.9)	441 (3.9)	.001	20 (9.4)	448 (3.9)	<.001
Peripheral arterial disease	37 (10.9)	612 (5.5)	<.001	30 (14.3)	619 (5.5)	<.001
Prior PCI	147 (42.4)	3221 (28.6)	<.001	81 (37.7)	3287 (28.9)	.01
Prior CABG	61 (17.5)	1188 (10.5)	<.001	31 (14.4)	1218 (10.7)	.09
Atrial fibrillation	13 (3.8)	327 (2.9)	.33	12 (5.6)	328 (2.9)	.04
Prior myocardial infarction	112 (32.7)	2344 (21.1)	<.001	47 (22.2)	2409 (21.4)	.80
History of cancer	36 (10.5)	1034 (9.2)	.39	34 (16.0)	1036 (9.1)	.002
Cancer reported prior to randomization (0-12 mo)	2 (0.6)	48 (0.4)	.66	3 (1.4)	47 (0.4)	.07
Indication for Index Procedure						
STEMI	50 (14.4)	1630 (14.4)	>.99	22 (10.2)	1658 (14.5)	.08
NSTEMI	77 (22.1)	1819 (16.1)	.004	26 (12.1)	1870 (16.4)	.11
Stable angina	110 (31.6)	4039 (35.7)	.13	74 (34.4)	4075 (35.6)	.77
Unstable angina	57 (16.4)	1764 (15.6)	.71	37 (17.2)	1784 (15.6)	.51
Other	54 (15.5)	2048 (18.1)	.23	56 (26.1)	2046 (17.9)	.003
Lesion and Procedure Characteristics						
In-stent restenosis	30 (8.6)	513 (4.5)	.001	13 (6.1)	530 (4.6)	.33
No. of treated vessels per patient, mean (SD)	1.1 (0.3)	1.1 (0.3)	.84	1.1 (0.3)	1.1 (0.3)	.87
No. of stents per patient, mean (SD)	1.5 (0.8)	1.4 (0.7)	.11	1.4 (0.7)	1.4 (0.7)	.58
>2 vessels stented	0	49 (0.43)	.41	0	49 (0.4)	>.99
Reference vessel diameter, mean (SD), mm[d]	2.9 (0.5)	3.0 (0.5)	<.001	3.1 (0.6)	3.0 (0.5)	.09
Modified ACC lesion class B2 or C1	168 (50.8)	5128 (47.1)	.20	97 (45.8)	5199 (47.3)	.68
Vein bypass graft stented	22 (6.3)	300 (2.7)	<.001	8 (3.7)	314 (2.81)	.40
Thrombus-containing lesion	50 (15.3)	1482 (14.2)	.57	19 (9.6)	1513 (14.3)	.06
Stent type						
Drug-eluting	301 (86.5)	9960 (85.5)	<.001	192 (89.3)	9769 (85.4)	.16
Sirolimus-eluting	28 (8.1)	1090 (9.7)		28 (13.0)	1090 (9.5)	
Zotarolimus-eluting	27 (7.8)	1237 (11.0)		25 (11.6)	1239 (10.8)	
Paclitaxel-eluting	114 (32.8)	2552 (22.6)		45 (20.9)	2621 (22.9)	
Everolimus-eluting	122 (35.1)	4581 (40.5)		87 (40.5)	4616 (40.4)	
>1 type	10 (2.9)	200 (1.8)		7 (3.3)	203 (1.8)	
Bare metal	47 (13.5)	1640 (14.5)		23 (10.7)	1664 (14.6)	
Minimum stent diameter, mm						
<3	193 (55.5)	4848 (42.9)	<.001	95 (44.2)	4946 (43.3)	.78
≥3	155 (44.5)	6452 (57.1)		120 (55.8)	6487 (56.7)	

(continued)

Table 1. Baseline Characteristics of Patients With vs Without Ischemic or Bleeding Events From 12 to 30 Months in the Derivation Cohort (N = 11 648)[a] (continued)

Measure	Myocardial Infarction or Stent Thrombosis Events, No. (%)			Moderate or Severe Bleeding Events, No. (%)[b]		
	Event (n = 348 Patients)	No Event (n = 11 300 Patients)	P Value	Event (n = 215 Patients)	No Event (n = 11 433 Patients)	P Value
Total stent length, mean (SD), mm	28.1 (16.8)	27.0 (16.4)	.21	26.1 (15.0)	27.1 (16.5)	.39
Thienopyridine at randomization						
Prasugrel	138 (39.7)	3548 (31.4)	.002	63 (29.3)	3623 (31.7)	.51
Clopidogrel	210 (60.3)	7752 (68.6)		152 (70.7)	7810 (68.3)	
Aspirin at randomization, mg						
>100	127 (41.2)	4424 (43.7)	.41	78 (40.8)	4473 (43.7)	.46
≤100	181 (58.8)	5698 (56.3)		113 (59.2)	5766 (56.3)	
Statin use at randomization	300 (86.2)	10 098 (89.4)	.06	185 (86.1)	10 213 (89.4)	.12
Randomization group						
Placebo	225 (64.7)	5561 (49.2)	<.001	80 (37.2)	5706 (49.9)	<.001
Continued thienopyridine	123 (35.3)	5739 (50.8)		135 (62.8)	5727 (50.1)	

Abbreviations: ACC, American College of Cardiology; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BMS, bare metal stent; CABG, coronary bypass artery graft; DES, drug-eluting stent; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack.

[a] Zero to 2.3% of patients had missing values, except for the following variables, for which up to 11.5% of the patients had missing values: LVEF <30%, modified ACC lesion class B2 or C1, thrombus-containing lesion, and aspirin at randomization.

[b] As defined by Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries criteria.

[c] Race was self-reported.

[d] Reference vessel diameter indicates the diameter of the unaffected vessel immediately adjacent to coronary lesion.

Table 2. Myocardial Infarction or Stent Thrombosis Prediction Model and Moderate or Severe Bleeding Prediction Model

Predictors of Events[a]	Predictors of Myocardial Infarction or Stent Thrombosis[b]		Predictors of Moderate or Severe Bleeding[c]	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Continued thienopyridine vs placebo	0.52 (0.42-0.65)	<.001	1.66 (1.26-2.19)	<.001
Myocardial infarction at presentation	1.65 (1.31-2.07)	<.001		
Prior PCI or prior myocardial infarction	1.79 (1.43-2.23)	<.001		
History of CHF or LVEF <30%	1.88 (1.35-2.62)	<.001		
Vein graft stent	1.75 (1.13-2.73)	.01		
Stent diameter <3 mm	1.61 (1.30-1.99)	<.001		
Paclitaxel-eluting stent	1.57 (1.26-1.97)	<.001		
Cigarette smoking	1.40 (1.11-1.76)	.01		
Diabetes mellitus	1.38 (1.10-1.72)	.01		
Age, per 10 y			1.54 (1.34-1.78)	<.001
Peripheral arterial disease	1.49 (1.05-2.13)	.03	2.16 (1.46-3.20)	<.001
Hypertension	1.37 (1.03-1.82)	.03	1.45 (1.00-2.11)	.05
Renal insufficiency/failure	1.55 (1.03-2.32)	.04	1.66 (1.04-2.66)	.03

Abbreviations: CHF, congestive heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

[a] Predictors of events from 12 through 30 months after coronary stenting.

[b] The ischemia model had a *c* -statistic of 0.70 within the DAPT Study randomized population, and goodness-of-fit *P* = .81.

[c] The bleeding model had a *c* statistic of 0.68 within the DAPT Study randomized population, and a goodness-of-fit *P* = .34. Moderate or severe bleeding was defined by Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries criteria. Blank table cells indicate no significant association.

the model. The ischemic model had moderate discrimination (*c* statistic, 0.70 [95% CI, 0.68-0.73]) and was well calibrated (goodness-of-fit *P* = .81).

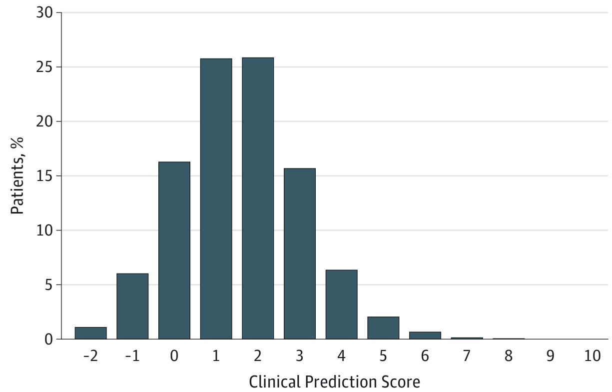
Increasing age was a significant independent predictor of bleeding, but not of ischemic events (Table 2). No tested interactions between covariates and randomized treatment for bleeding were retained in the model. The bleeding model showed similar discrimination to the ischemia model (*c* statistic, 0.68 [95% CI, 0.65-0.72]) and was well calibrated (goodness-of-fit *P* = .34). After bootstrap internal validation, optimism-corrected *c* statistics for both the ischemia (0.68 [95% CI, 0.65-0.70]) and bleeding models (0.66 [95% CI, 0.62-0.70]) were similar.

Clinical Prediction Score

A simplified risk score was generated to predict the difference between the anticipated reduction in ischemic events and the anticipated increase in bleeding events with continued thienopyridine (ie, the benefit-risk difference) (Development of a Predictive Score in the eAppendix in the Supplement). The score, ranging from −2 to 10, assigned points as follows: for patients younger than 65 years, 0 points; for age 65 to younger than 75 years, −1; for patients 75 years or older, −2; for vein graft stent, 2; for current cigarette smoker or within past year, 1; for diabetes mellitus, 1; for myocardial infarction at presentation, 1; for stent diameter less than 3 mm, 1; for history of CHF or left ventricular ejection fraction lower than 30%, 2; for prior

Figure 2. Elements of Clinical Prediction Score and Distribution of Score Among Randomized DAPT Study Patients (Derivation Cohort, 11 648 Patients)

Clinical Prediction Score Variable	Points
Age, y	
≥75	−2
65-<75	−1
<65	0
Cigarette smoking	1
Diabetes mellitus	1
MI at presentation	1
Prior PCI or prior MI	1
Paclitaxel-eluting stent	1
Stent diameter <3 mm	1
CHF or LVEF <30%	2
Vein graft stent	2
Total score range: −2 to 10	



CHF indicates congestive heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention. Variables reflect characteristics at the time of the index procedure. Cigarette smoking was defined as smoking within 1 year prior to index procedure.

PCI or prior myocardial infarction, 1; and for paclitaxel-eluting stent, 1 (**Figure 2**). Among the derivation cohort, a higher score quartile was associated with higher rates of myocardial infarction or stent thrombosis (interaction *P* < .001), whereas lower score quartiles were associated with higher rates of moderate or severe bleeding (interaction *P* = .006). In addition, higher score quartiles were associated with larger observed risk reductions in myocardial infarction or stent thrombosis with randomization to continued thienopyridine (*P* = .001), and lower score quartiles were associated with greater observed risk increases in bleeding (*P* = .04, **Table 3**).

When separated into groups (high score group [score, ≥2] vs low score group [score, <2]), among patients in the high score group (n = 5917), randomization to continued thienopyridine was associated with larger reductions in myocardial infarction or stent thrombosis (2.7% for continued thienopyridine vs 5.7% for placebo; risk difference [RD], −3.0% [95% CI, −4.1% to −2.0%], *P* < .001) compared with those in the low score group (n = 5731; 1.7% for continued thienopyridine vs 2.3% for placebo; RD, −0.7% [95% CI, −1.4% to 0.09%], *P* = .07; interaction *P* < .001). Conversely, randomization to continued thienopyridine was associated with smaller increases in bleeding among the high score group (1.8% for continued thienopyridine vs 1.4% for placebo; RD, 0.4% [95% CI, −0.3% to 1.0%], *P* = .26) compared with the low score group (3.0% for continued thienopyridine vs 1.4% for placebo; RD, 1.5% [95% CI, 0.8% to 2.3%], *P* < .001; interaction *P* = .02) (**Figure 3**; eTable 3 in the Supplement).

The risk reduction in major adverse cardiovascular and cerebrovascular events (defined as the composite of death, myocardial infarction, and stroke) with continued thienopyridine was significantly greater among the high score group (4.9% for continued thienopyridine vs 7.6% for placebo; RD, −2.7% [95% CI, −4.0% to −1.5%]; *P* < .001) vs the low score group (3.7% for continued thienopyridine vs 3.8% for placebo; RD, −0.2% [95% CI, −1.2% to 0.86%]; *P* = .73; interaction *P* = .001). The all-cause mortality rate was 2.1% for continued thienopyridine vs 2.1% for placebo for the high score group (RD, 0.01% [95% CI, −0.73% to 0.76%]; *P* = .99) compared with 1.7% for continued thienopyridine vs 0.9% for placebo for the low score group (RD, 0.73% [95% CI, 0.13% to 1.33%], *P* = .02; interaction *P* = .14 [nonsignificant]) .

Outcomes in Patients Treated With EES

After restricting the population to those treated with EES (n = 4703), the rates of myocardial infarction or stent thrombosis were 2.9% for continued thienopyridine vs 4.7% for placebo (RD, −1.89% [95% CI, −3.70% to −0.08%], *P* = .04) among the high score group (n = 1869) and were 1.7% for continued thienopyridine vs 2.2% for placebo (RD, −0.50% [95% CI, −1.55% to 0.56%], *P* = .33; interaction *P* = .18 [non-significant]) among the low score group (n = 2834). The corresponding rates of bleeding were 1.8% for continued thienopyridine vs 1.2% for placebo (RD, 0.52% [95% CI, −0.63% to 1.67%], *P* = .38) for the high score group and 3.0% for continued thienopyridine vs 1.4% for placebo in the low score group (RD, 1.67% [95% CI, 0.55% to 2.78%], *P* = .003; interaction *P* = .15 [nonsignificant]). (**Figure 4**, eTable 4 in the Supplement). All-cause mortality occurred in 2.5% for continued thienopyridine vs 1.8% for placebo (*P* = .31) among the high score group, and 1.9% for continued thienopyridine vs 0.7% for placebo (*P* = .01, interaction *P* = .54 [nonsignificant]) among the low score group.

External Validation

Among 8136 patients who did not have a myocardial infarction, stent thrombosis, or moderate/severe bleeding within the first 12 months after PCI in the PROTECT trial (validation cohort), the models used to derive the predictive score (excluding the variable reflecting randomization to continued thienopyridine vs placebo) showed modestly reduced discrimination (*c* statistic: ischemic model, 0.64 [95% CI, 0.58 to 0.70]; bleeding model, 0.64 [95% CI, 0.55 to 0.73]). These results were overall similar within the ZES and SES populations of the validation cohort (*c* statistic: ischemic model, 0.62 [95% CI, 0.52 to 0.72] in the ZES group and 0.64 [95% CI, 0.57 to 0.72] in the SES group; bleeding model, 0.63 [95% CI, 0.51 to 0.76] in the ZES group and 0.65 [95% CI, 0.53 to 0.76]in the SES group). Because the PROTECT trial enrolled a lower-risk population than the DAPT Study, both ischemic and bleeding event rates were overestimated. After recalibration to the baseline event

Table 3. Observed Outcomes by Treatment Group From 12 Through 30 Months After Index Procedure Stratified by Prediction Score Quartile for the Derivation Cohort

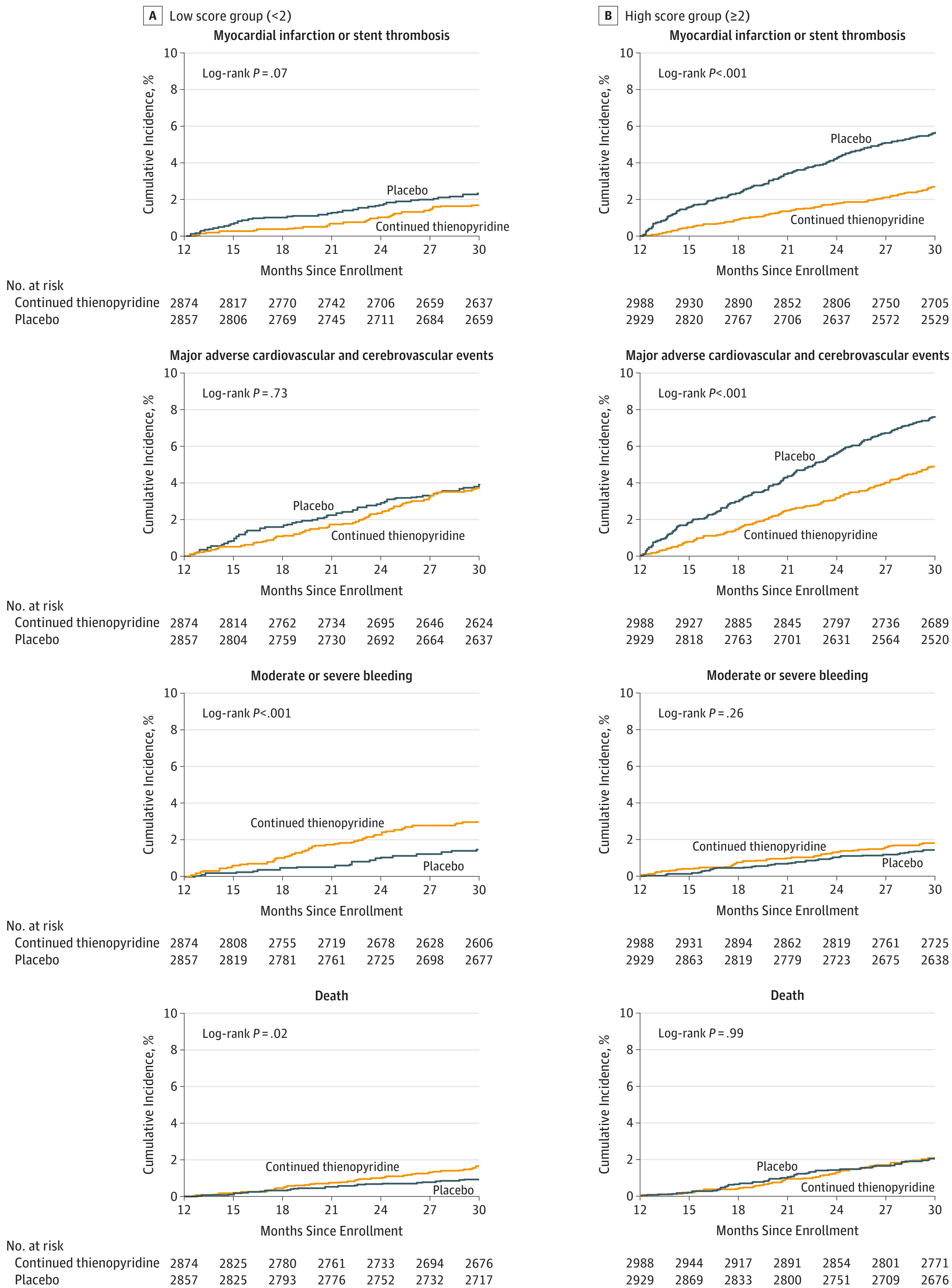
	No. of Patients		No. of Events (%)				
Event	Continued Thienopyridine	Placebo	All Patients (n = 11 648)	Continued Thienopyridine (n = 5862)	Placebo (n = 5786)	Risk Difference, % (95% CI)	Interaction *P* Value[a]
Myocardial Infarction							
Score							
−2 to 0	1373	1356	40 (1.5)	15 (1.2)	25 (1.9)	−0.73 (−1.68 to 0.21)	.001
1	1501	1501	71 (2.4)	31 (2.1)	40 (2.7)	−0.59 (−1.72 to 0.55)	
2	1525	1486	82 (2.8)	23 (1.6)	59 (4.1)	−2.56 (−3.80 to −1.33)	
≥3	1463	1443	151 (5.4)	52 (3.7)	99 (7.2)	−3.48 (−5.20 to −1.76)	
Stent Thrombosis							
Score							
−2 to 0	1373	1356	3 (0.1)	1 (0.1)	2 (0.2)	−0.07 (−0.33 to 0.19)	<.001
1	1501	1501	11 (0.4)	5 (0.3)	6 (0.4)	−0.06 (−0.51 to 0.39)	
2	1525	1486	29 (1.0)	5 (0.3)	24 (1.7)	−1.34 (−2.08 to −0.59)	
≥3	1463	1443	54 (1.9)	12 (0.9)	42 (3.0)	−2.18 (−3.23 to −1.12)	
Myocardial Infarction or Stent Thrombosis							
Score							
−2 to 0	1373	1356	40 (1.5)	15 (1.2)	25 (1.9)	−0.73 (−1.68 to 0.21)	.001
1	1501	1501	71 (2.4)	31 (2.1)	40 (2.7)	−0.59 (−1.72 to 0.55)	
2	1525	1486	85 (2.9)	24 (1.6)	61 (4.3)	−2.63 (−3.88 to −1.38)	
≥3	1463	1443	152 (5.4)	53 (3.8)	99 (7.2)	−3.41 (−5.13 to −1.68)	
Major Adverse Cardiovascular and Cerebrovascular Events[b]							
Score							
−2 to 0	1373	1356	99 (3.7)	52 (3.9)	47 (3.5)	0.40 (−1.06 to 1.86)	.02
1	1501	1501	110 (3.8)	50 (3.4)	60 (4.1)	−0.65 (−2.04 to 0.75)	
2	1525	1486	137 (4.7)	51 (3.4)	86 (6.0)	−2.54 (−4.10 to −0.98)	
≥3	1463	1443	221 (7.9)	91 (6.4)	130 (9.3)	−2.95 (−4.97 to −0.92)	
Death							
Score							
−2 to 0	1373	1356	43 (1.6)	28 (2.1)	15 (1.1)	0.99 (0.02 to 1.96)	.33
1	1501	1501	29 (1.0)	18 (1.2)	11 (0.7)	0.49 (−0.24 to 1.22)	
2	1525	1486	48 (1.6)	25 (1.7)	23 (1.6)	0.09 (−0.85 to 1.02)	
≥3	1463	1443	70 (2.5)	35 (2.5)	35 (2.5)	−0.06 (−1.24 to 1.11)	
Moderate or Severe Bleed[c]							
Score							
−2 to 0	1373	1356	72 (2.7)	49 (3.7)	23 (1.7)	1.97 (0.71 to 3.23)	.04
1	1501	1501	51 (1.8)	34 (2.3)	17 (1.2)	1.17 (0.20 to 2.14)	
2	1525	1486	45 (1.5)	28 (1.9)	17 (1.2)	0.69 (−0.22 to 1.60)	
≥3	1463	1443	47 (1.7)	24 (1.7)	23 (1.7)	0.03 (−0.95 to 1.01)	
Moderate Bleed[c]							
Score							
−2 to 0	1373	1356	45 (1.7)	28 (2.1)	17 (1.3)	0.83 (−0.17 to 1.84)	.33
1	1501	1501	37 (1.3)	26 (1.8)	11 (0.8)	1.03 (0.21 to 1.86)	
2	1525	1486	26 (0.9)	18 (1.2)	8 (0.6)	0.66 (−0.04 to 1.35)	
≥3	1463	1443	35 (1.3)	19 (1.3)	16 (1.2)	0.18 (−0.66 to 1.03)	
Severe Bleed[c]							
Score							
−2 to 0	1373	1356	28 (1.1)	21 (1.6)	7 (0.5)	1.07 (0.27 to 1.86)	.08
1	1501	1501	14 (0.5)	8 (0.6)	6 (0.4)	0.14 (−0.37 to 0.65)	
2	1525	1486	19 (0.7)	10 (0.7)	9 (0.6)	0.04 (−0.56 to 0.63)	
≥3	1463	1443	12 (0.4)	5 (0.4)	7 (0.5)	−0.15 (−0.66 to 0.35)	

[a] *P* value for interaction assesses whether the absolute risk reduction observed between randomized treatment groups differs across quartiles of the clinical prediction score, as assessed by the *Q* statistic for heterogeneity.

[b] Major adverse cardiovascular and cerebrovascular events were defined by the composite of death, myocardial infarction, or stroke.

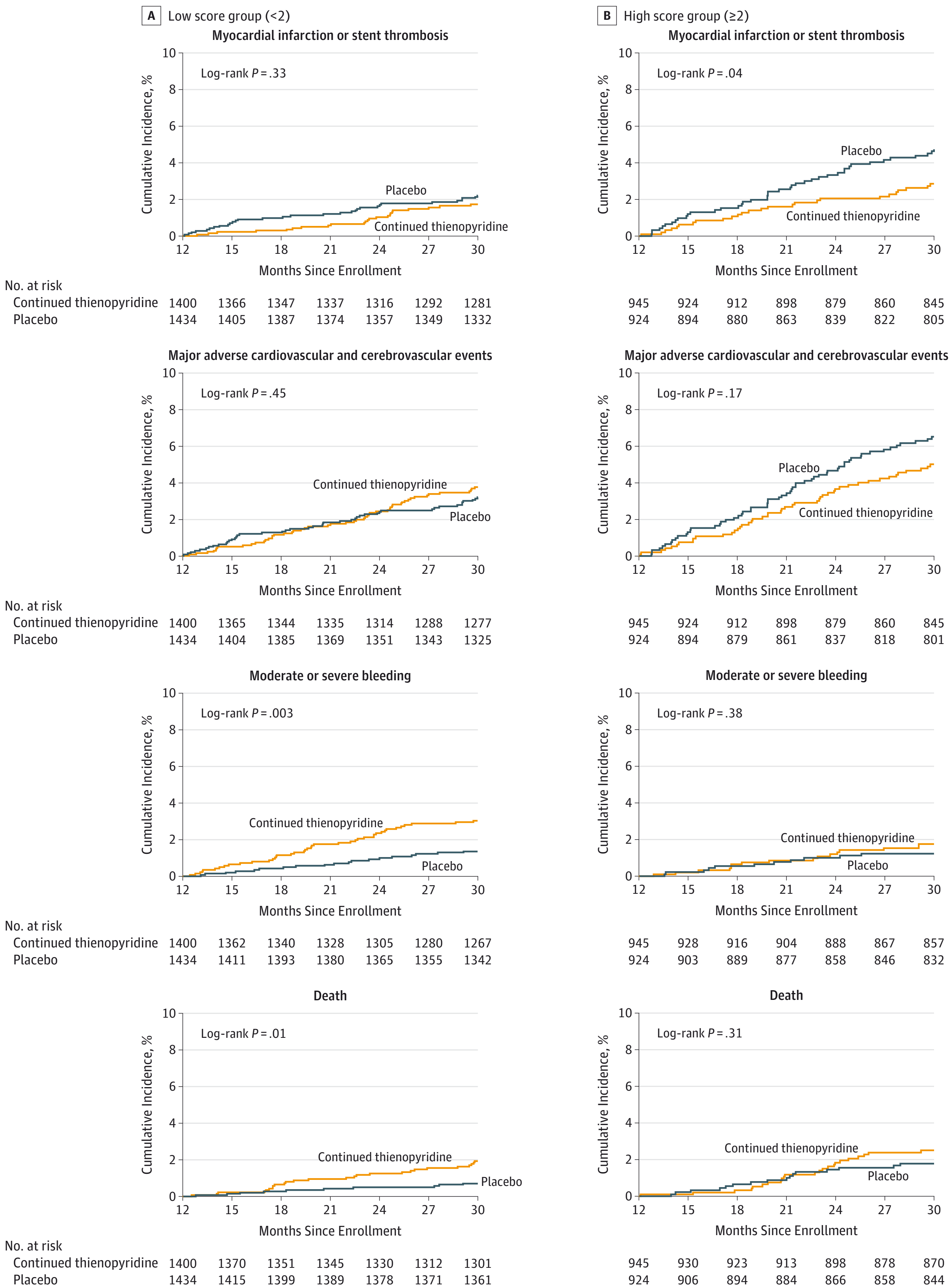
[c] As defined by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries criteria.

Figure 3. Observed Rates of Outcomes From 12 Through 30 Months After Percutaneous Coronary Intervention Among Randomized Patients by Clinical Prediction Score Group in the Derivation Cohort



Moderate or severe bleeding was defined by Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries criteria. 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.

Figure 4. Observed Rates of Outcomes From 12 Through 30 Months After Percutaneous Coronary Intervention Among Patients Treated With Everolimus-Eluting Stents Only by Clinical Prediction Score Group in the Derivation Cohort



Moderate or severe bleeding was defined by Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries criteria. 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.

rates observed in the PROTECT trial, the models were well fit (*P* = .81 for the ischemia model, *P* = .91 for the bleeding model) (eAppendix in the Supplement).

Within the validation cohort, the rate of myocardial infarction or stent thrombosis from 12 through 30 months after PCI was greater among the high-score patients (n = 2848) compared with the low-score patients (n = 5288; 1.5% high-score patients vs 0.7% low-score patients; hazard ratio [HR], 2.01 [95% CI, 1.29 to 3.13], *P* = .002). Rates of moderate or severe bleeding were not significantly different by score (0.4% in the high-score patients vs 0.5% in the low-score patients; HR, 0.69 [95% CI, 0.33 to 1.42], *P* = .31).

Discussion

This study developed a clinical prediction score based on ischemic and bleeding risk factors to help identify patients with greater expected benefit vs greater expected harm from continuation of dual antiplatelet therapy from among patients who had completed 1 year of dual antiplatelet therapy after coronary stent treatment without a major ischemic or bleeding event. For patients randomized in the DAPT Study (derivation cohort) with clinical predictive scores of 2 or higher (high score group; 50.8%), continued thienopyridine was associated with an absolute risk reduction in myocardial infarction or stent thrombosis that was 8.2 times greater than the absolute risk increase in moderate or severe bleeding. Conversely, among patients with scores lower than 2 (low score group; 49.2%), randomization to continued thienopyridine was associated with an absolute increase in bleeding that was 2.4 times the absolute reduction in myocardial infarction or stent thrombosis. Within the PROTECT trial (validation cohort), the high score group was observed to have significantly greater ischemic risk and no significant difference in bleeding risk, compared with the low score group. Despite prior evidence suggesting that ischemic and bleeding risk are strongly correlated,[3,18] these results suggest that it may be possible to identify individual patients with discordant ischemic risks and bleeding risks.

Numerous randomized trials evaluating duration of dual antiplatelet therapy after coronary stenting have demonstrated a trade-off between reductions in ischemia and increases in bleeding associated with longer durations of treatment.[19-23] Although clinical trial results are expected to be applied to the population represented by enrollment criteria, in the setting of discordant risks and benefits of treatment, tailoring therapies to individual patient profiles to maximize benefits and minimize harms affords an opportunity to further optimize outcomes.

A number of limitations should be considered in interpreting these findings. The results of this study should be interpreted with the understanding that patients enrolled in clinical trials may not represent those cared for in routine practice on the basis of the inclusion and exclusion criteria of the trial, as well as other unmeasured differences between study participants and nonparticipants. Patients taking oral anticoagulants were not enrolled in the DAPT Study, and they make up 4% to 7% of all PCI patients.[24-26] Patients who interrupted therapy for more than 14 days or sustained a major bleeding or ischemic event in the first year after PCI were also not randomized in the DAPT Study, and represented 22.7% of enrolled patients. Similarly, in a recent large registry of patients undergoing coronary stenting, discontinuation of antiplatelet therapy for more than 14 days occurred in 11.5% of patients; cessation due to a clinical event or nonadherence in 9.7%; and major bleeding in 1.4%; whereas myocardial infarction occurred in 2.2% and target-vessel revascularization in 5.1%—altogether representing approximately 30% of all PCI patients.[26] Although there remains a sizable proportion of patients undergoing PCI who do not have events that would have disqualified them from randomization in the DAPT Study, the patients used to derive the clinical prediction score make up a group of patients that may not be representative of those seen in clinical practice.

Variables in the predictive score included patient and procedural characteristics that have demonstrated an association with either ischemic or bleeding events after PCI in prior studies. For instance, prior PCI, presentation with myocardial infarction, current smoking, and diabetes have each been predictive of stent thrombosis occurring within the first year after PCI.[27] Similarly, advanced age, renal disease and history of peripheral arterial disease have correlated with both in-hospital and 30-day bleeding after PCI.[28,29] In this study, peripheral arterial disease, renal insufficiency, and hypertension were predictive of both ischemic and bleeding events. Because these factors did not help identify discordant bleeding and ischemic risk, they were not included in the predictive score.

On the other hand, certain variables uniquely predicted either bleeding risk or anti-ischemic benefit: advanced age was predictive of increased bleeding only, whereas presentation with myocardial infarction, history of CHF, and prior PCI were predictive of myocardial infarction or stent thrombosis but not bleeding. Deaths not preceded by myocardial infarction or stent thrombosis were not considered in the creation of the prediction model because such deaths may not be directly modified by dual antiplatelet therapy. This may explain why age was not a significant predictor of the composite ischemia end point.

The median predictive score was 2, and patients with a score of 2 or higher (the high score group) had a clinically meaningful reduction in ischemic events (number needed to treat to benefit [NNTB], 34) with a smaller effect on bleeding events when randomized to continued thienopyridine (number needed to treat to harm [NNTH], 272), whereas those with scores less than 2 (the low score group) had a larger increase in bleeding events (NNTH, 64) and a smaller reduction in ischemic events (NNTB, 153). Nonetheless, scores ranging from −2 to 10 likely define a continuous gradient of risk and benefit. The model used to derive the point values for variables required an assumption that bleeding and ischemic events were of equal weight. However, examination of the results stratified by score quartile allows assessment of different score cutoffs with varied weighting of bleeding and ischemic events, as well as examination of the association of the score with other relevant end points, including bleeding events not classified as moderate or severe. The ischemic and bleeding events as defined in this analysis may not have an equivalent effect on patient outcomes, including mortality, and the results may have been different had other ischemic and bleeding end points been chosen.

Although the statistical test for interaction did not show a difference in the effect of continuation of long-term dual antiplatelet therapy on mortality in high vs low score groups, it is of interest that the numerical difference in all-cause mortality was concentrated among patients in the low score group. After analyzing the results of 12 randomized trials enrolling 56 799 patients, the US Food and Drug Administration recently concluded that there was no evidence of an increase in either cancer or mortality with extended thienopyridine treatment.[30] Whether different subgroups of patients may in fact have greater mortality with continuation of long-term dual antiplatelet therapy has been suggested[31] and may be a topic of future inquiry.

Paclitaxel-eluting stents were found to be associated with higher risk of myocardial infarction or stent thrombosis. Although these results are consistent with those of other studies,[32] stent type was not randomized in the DAPT Study. As these stents are rarely used, the use of this predictive score going forward is unlikely to utilize this variable. In addition, among the stents used in the DAPT Study, only EES are widely used today. Among the EES subgroup (n = 4703), tests for interaction comparing treatment effect among high vs low score groups were not significant. However, interaction testing is generally underpowered in clinical trials and more underpowered when performed within a subset of patients. Approximately half of the risk reduction for myocardial infarction attributed to continued thienopyridine therapy in the DAPT Study was not attributable to stent thrombosis,[1] and bleeding risk should not be influenced by stent type. Therefore, the ability of the prediction rule to stratify patient risks for myocardial infarction unrelated to stent thrombosis and for bleeding should not vary by stent type.

The incorporation of more variables into the individual bleeding and ischemia models may have improved discrimination, at the expense of parsimony. In addition, the estimation of risks based on the use of the separate ischemic and bleeding model coefficients rather than use of the simplified score could improve the ability to predict such events, and provide the opportunity for clinicians to identify patients with concordantly high ischemic and bleeding risks, in addition to those with discordant risks (Estimation of Ischemic and Bleeding Risk in the eAppendix in the Supplement).

Although the development of the score was prespecified, the analysis should be considered exploratory. Thus, use of this prediction score should be cautious until further validation is performed, and optimal clinical and procedural care to reduce overall bleeding and ischemic risks should be practiced independent of a patient's score. Preexisting anemia, prior bleeding, and granular measures of atherosclerosis extent and severity were not available and may in part explain the modest discrimination of the ischemia and bleeding prediction. In addition, patients receiving ticagrelor or other antiplatelet combinations could have a different risk-benefit relationship. The score is relevant to patients with characteristics similar to those enrolled in the DAPT Study, and its generalizability to other patient populations not studied in the trial may be limited. Although BMS-treated patients were included, the score is not applicable to patients for whom a BMS is selected due to high risk of bleeding or nonadherence. The end points considered in developing the score, although well defined and adjudicated, are heterogeneous in severity. Although the PROTECT trial served as an external population for validation, it was not a randomized trial of dual antiplatelet therapy duration, and the observed duration of therapy was likely influenced by patient risk factors. Therefore, these data could only be used to evaluate whether the score stratified patient ischemic or bleeding risk, and not actual benefit or harm with long-term dual antiplatelet therapy. These results would ideally be replicated in a similarly designed, large randomized trial of different durations of dual antiplatelet therapy among PCI patients. Use of the clinical score has not been demonstrated to improve patient outcomes.

Conclusions

Among patients not sustaining major bleeding or ischemic events 1 year after PCI, a prediction rule assessing late ischemic and bleeding risks to inform dual antiplatelet therapy duration showed modest accuracy in derivation and validation cohorts. This rule requires further prospective evaluation to assess potential effects on patient care, as well as validation in other cohorts.

ARTICLE INFORMATION

Published Online: March 29, 2016. doi:10.1001/jama.2016.3775.

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Correction: This article was corrected for an update to the conflict of interest disclosures for Drs Yeh and Mauri and corrected for errors in the Supplement and the bar graph of Figure 2 on May 24, 2016.

Author Contributions: Drs Yeh and Mauri had full access to all of the data in the study and take

responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Yeh, Secemsky, Kereiakes, Cohen, Mauri.
Acquisition, analysis, or interpretation of data: Yeh, Secemsky, Kereiakes, Normand, Gershlick, Spertus, Steg, Cutlip, Rinaldi, Camenzind, Wijns, Apruzzese, Song, Massaro, Mauri.
Drafting of the manuscript: Yeh, Secemsky, Kereiakes, Apruzzese, Mauri.
Critical revision of the manuscript for important intellectual content: Kereiakes, Normand, Gershlick, Cohen, Spertus, Steg, Cutlip, Rinaldi, Camenzind, Wijns, Song, Massaro.
Statistical analysis: Yeh, Secemsky, Kereiakes, Normand, Apruzzese, Song, Massaro, Mauri.
Obtained funding: Yeh, Normand, Mauri.
Administrative, technical, or material support: Cutlip, Mauri.
Study supervision: Yeh, Kereiakes, Mauri.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Yeh reports receiving personal fees from Abbott Vascular, Boston Scientific, and Merck; research salary from Harvard Clinical Research Institute. Dr Kereiakes reports receiving personal fees from Abbott Vascular, Boston Scientific, and sanofi-aventis. Dr Gershlick reports receiving personal fees from AstraZeneca, Eli Lilly, Daiichi-Sankyo, Medtronic, Abbott Vascular, and Boston Scientific. Dr Cohen reports receiving grant funding and personal fees from Abbott Vascular, Medtronic, AstraZeneca, and Eli Lilly, and grant funding from Daiichi-Sankyo. Dr Spertus reports ownership of equity interest in Health Outcomes Sciences and having a patent for ePRISM. Dr Steg reports receiving personal fees from Amarin, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, GlaxoSmithKline, Eli Lilly, Merck Sharpe and Dohme, Novartis, Regeneron, Janssen, Pfizer, Regado, and Roche; grants and personal fees from Sanofi and Servier; personal fees and nonfinancial support from The Medicines Company; and serving on the steering committee for CSL Behring. Dr Cutlip reports receiving grant funding from Medtronic and Boston Scientific and Celonova. Dr Rinaldi reports serving on the advisory boards of Abbott Vascular, Boston Scientific, and Volcano. Dr Wijns reports receiving grant funding from Medtronic, Boston Scientific, Terumo, MiCell, Microport, St Jude Medical, Stentys, AstraZeneca, Biotronik, and Abbott Vascular; and serving as a nonexecutive board member and shareholder of Argonauts Partners, Celyad, and Genae. Dr Massaro reports receiving personal fees from Harvard Clinical Research Institute. Dr Mauri reports receiving grant funding from Abbott Vascular, Boston Scientific, Cordis, Bristol-Myers Squibb, and Daiichi Sankyo; grants and personal fees from Medtronic, Eli Lilly, sanofi-aventis, Boehringer Ingelheim, Biotronik; personal fees from Amgen, Recor, AstraZeneca, and St Jude Medical. No other disclosures were reported.

Funder/Sponsor: This article was sponsored by Harvard Clinical Research Institute, grant K23 HL 118138 from the National Heart, Lung, and Blood Institute (Dr Yeh); grant 1RO1FD003870-01 from the US Department of Health and Human Services. The 8 stent and pharmaceutical manufacturers who contributed to the funding of the DAPT study included Abbott Vascular (Xience everolimus-eluting stent), Boston Scientific (TAXUS paclitaxel-eluting and PROMUS everolimus-eluting stents), Cordis (Cypher sirolimus-eluting stent), Medtronic (Endeavor zotarolimus-eluting stent), Bristol-Myers Squibb, Sanofi, Eli Lilly, and Daiichi Sankyo.

Role of the Funder/Sponsor: The stent manufacturers who funded the DAPT Study were participating members in the design of the trial, the conduct of the study, and in the collection of the data. Specifically, the DAPT Study included patients contributed from each of 4 industry-designed and conducted postmarket studies. The funders had no role in the management, analysis, and interpretation of the data. Harvard Clinical Research Institute was responsible for the scientific conduct of the DAPT Study and independent analysis of the data. For this substudy, the funders had no role in study design or the decision to submit the manuscript for publication, but were given the opportunity to review and approve the manuscript prior to submission.

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Additional Contributions: We thank Joanna Suomi, MSC (Harvard Clinical Research Institute), for her assistance with the preparation of this article. She was compensated for her contribution.

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