Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

Enrollment and Randomization Criteria for the DAPT Study

Enrollment Inclusion Criteria

Subject must have met all of the following criteria to be eligible for treatment in the study:

1. Subject was > 18 years of age.
2. Subjects undergoing percutaneous intervention with stent deployment (or had within 3 calendar days).
3. Subjects without known contraindication to dual antiplatelet therapy for at least 30 months after enrollment and stent implantation.
4. The subject had consented to participate and had authorized the collection and release of his medical information by signing the "Patient Informed Consent Form". The informed consent was valid for the duration of the trial or until the subject withdrew.

Enrollment Exclusion Criteria

Subjects were to be excluded from the study if any of the following criteria were met:

1. Index procedure stent placement with stent diameter <2.25 mm or >4.0 mm.
2. Pregnant women.
3. Planned surgery necessitating discontinuation of antiplatelet therapy (>14 days) within the 30 months following enrollment.
4. Concurrent medical condition with a life expectancy of less than 3 years.
5. Concurrent enrollment in another device or drug study where the primary endpoint had not yet been reached or the device/drug could affect major endpoint outcomes in either open label or randomized phases of the DAPT study. A subject could only be enrolled in the DAPT Study once.
6. Subjects on long-term warfarin (or similar anticoagulant) therapy who were anticipated to still be on warfarin at the time of randomization.
7. Subjects with hypersensitivity or allergies to one of the drugs or components indicated in the Instructions for Use for the device implanted.
8. Subject was unable to give informed consent.
9. Subject treated with both drug-eluting stent (DES) and bare metal stent (BMS) during the index procedure.

Randomization Inclusion Criterion at 12 months

Subject must have met the following criterion to be eligible for randomization in the study:

1. Subject was "12-Month Clear", defined as subjects who were treated with 12 months of dual antiplatelet therapy post index procedure and who were event free (from all death, myocardial infarction, stroke, repeat coronary revascularization, stent thrombosis, and major bleeding – "severe" or "moderate" by GUSTO classification) during that time. During the open label portion of this study (time 0-12 months post-index procedure), a subject was considered compliant with the thienopyridine therapy for the purposes of eligibility if they took between 80% and 120% of the prescribed drug in the 0-6 month and 6-12 month periods without an interruption of therapy longer than 14 days.

Randomization Exclusion Criteria at 12 months

Subjects were to be excluded from randomization if any of the following criteria were met:

1. Pregnant women.

2. Subject switched thienopyridine type or dose within 6 months prior to randomization.
   NOTE: thienopyridine switching during the open-label portion of this study was discouraged.
3. Percutaneous coronary intervention or cardiac surgery between 6 weeks post index procedure and randomization.
4. Planned surgery necessitating discontinuation of antiplatelet therapy (>14 days) within the 21 months following randomization.
5. Concurrent medical condition with a life expectancy of less than 3 years.
6. Subjects on warfarin or similar anticoagulant therapy.

Endpoint Definitions

Ischemia Endpoint

The composite of myocardial infarction (MI) or stent thrombosis within the 12-30 month period following stent implantation:

Academic Research Consortium (ARC) Stent Thrombosis:[1]

Definite stent thrombosis*

Angiographic confirmation of stent thrombosis**

The presence of a thrombus† that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:

Acute onset of ischemic symptoms at rest

New ischemic ECG changes that suggest acute ischemia

Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI)

Nonocclusive thrombus

Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.

Occlusive thrombus

TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch).

Pathological confirmation of stent thrombosis

Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

Probable stent thrombosis

Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

Any unexplained death within the first 30 days§

Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

*Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation.
**The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion).
†Intracoronary thrombus.
§For studies with ST-elevation MI population, one may consider the exclusion of unexplained death within 30 days as evidence of probable stent thrombosis.

Myocardial Infarction*:

Classification	**Biomarker Criteria†**	**Additional Criteria**
Peri-procedural PCI *(within 48h after PCI**) or*	Troponin >3 times URL or CKMB > 3 times UR, Sites were instructed to use CKMB instead of troponin when possible for peri-procedural events. Routine assessment of peri-procedural biomarkers was not mandated.	Baseline value <URL
Peri-Procedural CABG *(within 72h after CABG)*	Troponin >5 times URL or CKMB >5 times URL	Baseline value <URL AND Any of the following: • New pathologic‡ Q waves or LBBB • New native or graft vessel occlusion • Imaging evidence of loss of viable myocardium
Spontaneous *(>48h following PCI, >72h following CABG)*	Troponin >URL or CKMB >URL	*Baseline value <URL* AND Any of the following: • symptoms of ischemia, • ECG changes indicative of new ischemia (new ST-T changes or new LBBB), • development of pathological Q waves, or • imaging evidence of a new loss of viable myocardium or a new regional wall motion abnormality
Silent	*No biomarker data available*	*New pathologic‡ Q waves or LBBB*

Sudden Death	Death before biomarkers obtained or before expected to be elevated	Symptoms suggestive of ischemia AND Any of the following: • New ST elevation or LBBB • Documented thrombus by angiography or autopsy

*Adapted from Global Task Force [Universal Definition of Myocardial Infarction (Thygesen et al.)][2]
**The assessment of CKMB is preferred over the assessment of troponin for the diagnosis of peri-procedural MI, if possible.
† Baseline biomarker value required before study procedure and presumes a typical rise and fall
‡Pathologic Q waves may be defined according to the Global Task Force, Minnesota code, or Novacode
URL = upper reference limit, defined as 99th percentile of normal reference range
LBBB = left bundle branch block; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft

Bleeding Endpoints

Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO) classification of severe and moderate bleeding:[3]

Severe or life-threatening: Either intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention.

Moderate: Bleeding that requires blood transfusion but does not result in hemodynamic compromise.

Bleeding Academic Research Consortium (BARC) definition for bleeding:[4]

Type 2: Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation

Type 3

Type 3a: Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed)
Any transfusion with overt bleeding

Type 3b: Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed)
Cardiac tamponade
Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
Bleeding requiring intravenous vasoactive agents

Type 3c: Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
Subcategories confirmed by autopsy or imaging or lumbar puncture
Intraocular bleed compromising vision

Type 5: fatal bleeding

Type 5a: Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

Type 5b: Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

*Corrected for transfusion (1 U packed red blood cells or 1 U whole blood=1 g/dL hemoglobin).

Candidate Variables for Model Building

Variables were considered for model building if they demonstrated *a priori* associations with stent thrombosis, major adverse cardiovascular and cerebrovascular events (MACCE) or bleeding in previously published literature and were thought to have a clinically plausible relationship with both ischemia and bleeding outcomes.

eTable 1. Candidate Predictors

Sociodemographic Variables
Age
Sex
Race
Cardiovascular History Variables
Congestive heart failure or left ventricular ejection fraction < 30%
Prior percutaneous coronary intervention
Prior coronary artery bypass graft
Prior myocardial infarction
Peripheral arterial disease
Stroke/Transient ischemic attack
Atrial fibrillation
Comorbidity Variables
Diabetes mellitus
Renal insufficiency (Cr > 2)
Cancer at time of randomization
History of major bleeding
Hypertension
Current smoking
Body mass index
Procedural Variables
Presentation with myocardial infarction
Stenting of a vein graft
Stent diameter
Stent type
Prior in-stent restenosis
Number of stents
Severe coronary calcification
Coronary lesion class C
Total stent length
> 2 Lesions per vessel
Number of treated vessels
Pre-procedural stenosis
TIMI grade flow post procedure
Unprotected left main stenting
Bifurcation stenting
Thrombus-containing lesion
Prior brachytherapy

Sociodemographic Variables
Medical Therapy Variables
Randomization arm (continued thienopyridine vs. placebo)
Treatment with clopidogrel vs. prasugrel
Treatment with statin at time of randomization

Note: Tested interaction terms for the ischemia model included (all with randomized treatment arm): age, sex, diabetes, smoking, prior PCI, presentation with myocardial infarction, stent type (DES vs. BMS), renal insufficiency, total stent length, reference vessel diameter, and the presence of any anatomical risk factor for stent thrombosis.

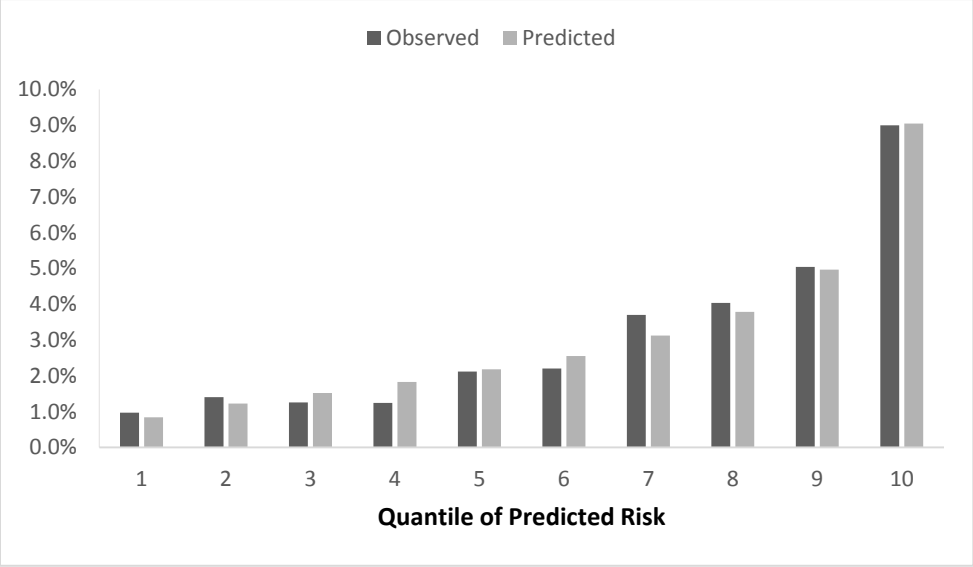
Tested interaction terms for the bleeding model including (all with randomized treatment arm): age, sex, body mass index, history of major bleeding, history of cancer, renal insufficiency, peripheral arterial disease, proton pump inhibitor use at randomization, aspirin dose, non-steroidal anti-inflammatory use and smoking. After testing, no interaction terms were ultimately retained in the final.

Continuous variables such as age, stent diameter, and stent length were initially incorporated as multilevel categorical variables. Age demonstrated a continuous relationship with bleeding, but was converted to a categorical variable for incorporation into the prediction score to facilitate ease of use. Stent diameter was found to have a threshold effect on ischemia and was dichotomized. Stent length was not associated with either outcome.

Calibration of Ischemic and Bleeding Risk Models

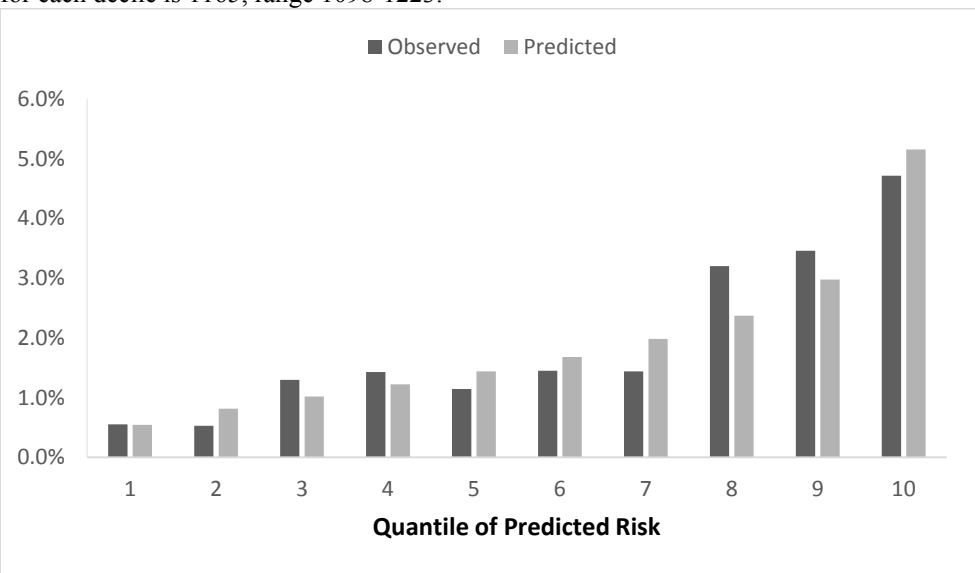
Calibration plots for the ischemia and bleeding risk models are shown in 1) the DAPT Study population (eFigure 1 and 2) and 2) the PROTECT population (eFigure 3 and 4).

eFigure 1. Observed vs. Expected Kaplan-Meier Rates of Myocardial Infarction or Stent Thrombosis within the DAPT Study population, by Quantile of Increasing Risk. The total sample size is 11,648; the mean sample size for each quantile is 1165, range 1092-1218.



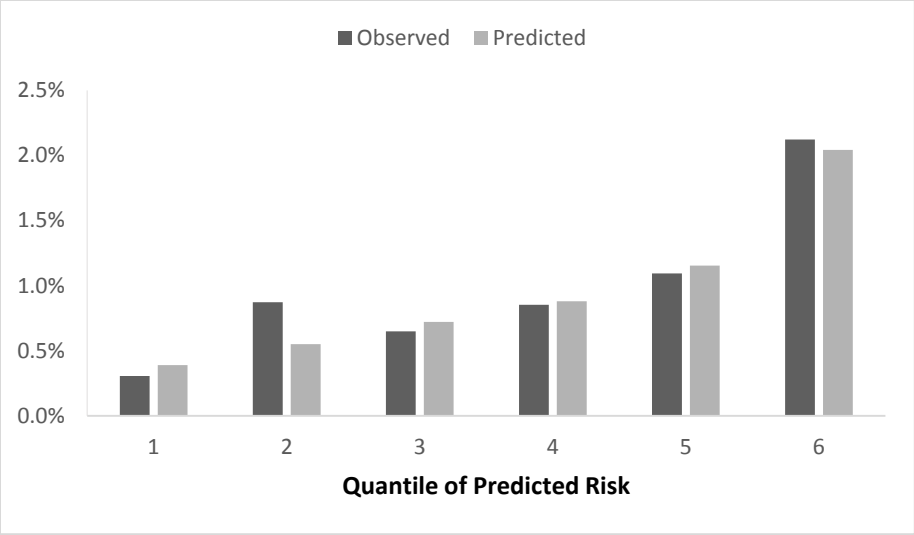
Goodness-of-fit = 5.257, P-value = 0.811.

eFigure 2. Observed vs. Expected Kaplan-Meier Rates of GUSTO Moderate or Severe Bleeding within the DAPT Study population, by Quantile of Increasing Risk. The total sample size is 11,648; the mean sample size for each decile is 1165, range 1098-1223.



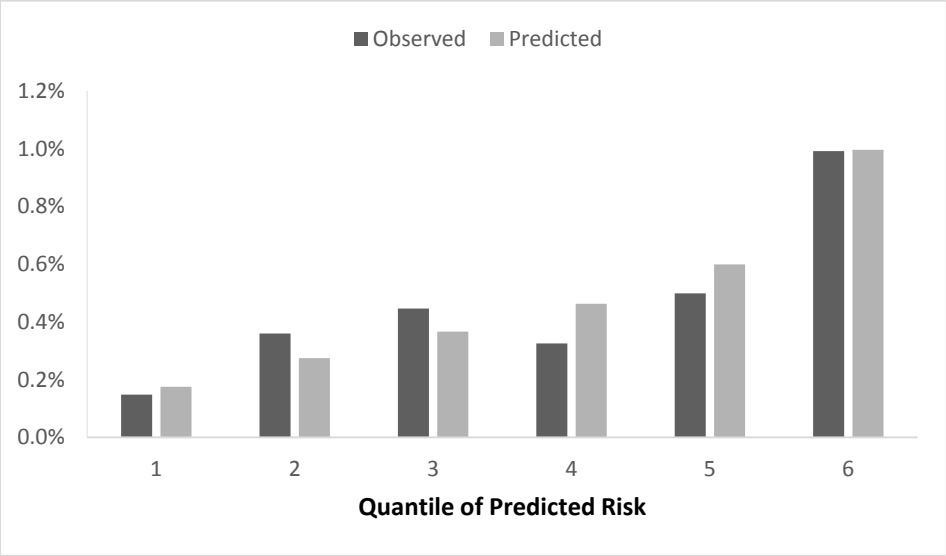
Goodness-of-fit = 10.145, P-value = 0.339.

eFigure 3. Observed vs. Expected Kaplan-Meier Rates of Myocardial Infarction or Stent Thrombosis within the PROTECT Population, by Quantile of Increasing Risk.
Predicted events rates were calculated using the original model coefficients and recalibrated accounting for the overall lower event rate in the PROTECT population. The total sample size is 8,136; the mean sample size for each quantile is 1356, range 1243-1514.



Goodness-of-fit = 2.28, P-value = 0.81.

eFigure 4. Observed vs. Expected Kaplan-Meier Rates of GUSTO Moderate or Severe Bleeding within the PROTECT Population, by Quantile of Increasing Risk. The total sample size is 8,136; the mean sample size for each quantile is 1356, range 1242-1422.

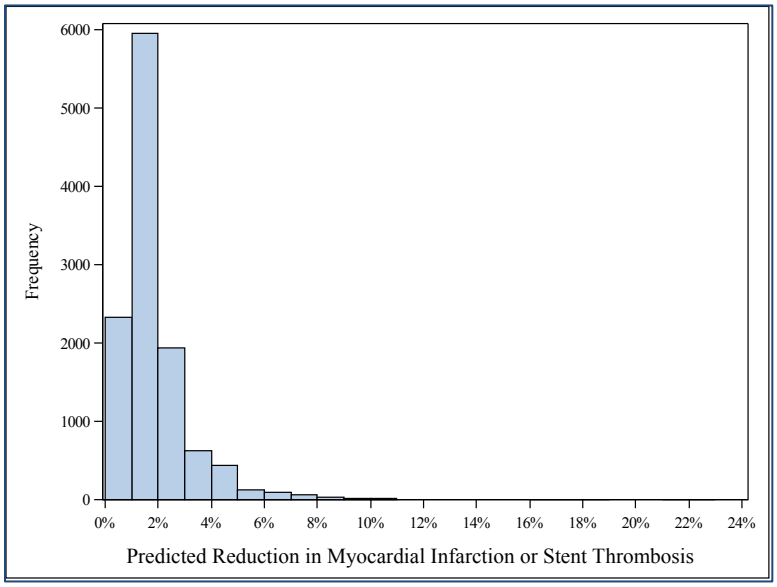


Goodness-of-fit = 1.55, P-value = 0.908.

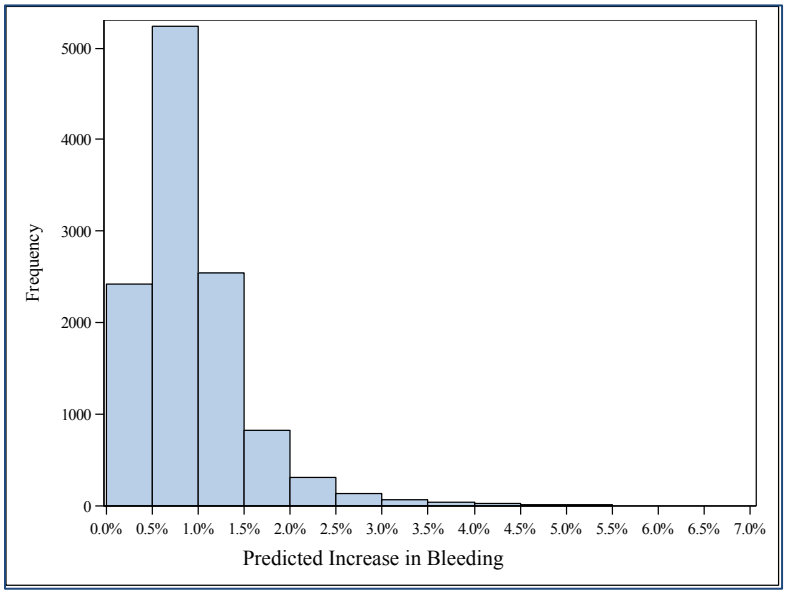
Distribution of Ischemic and Bleeding Risk

eFigure 5. Distribution of Predicted Reduction in Ischemic Events (A) and Bleeding (B) with Continuation of Dual Antiplatelet Therapy from 12-30 Months among Randomized DAPT Study Patients, Based on Ischemic and Bleeding Models.

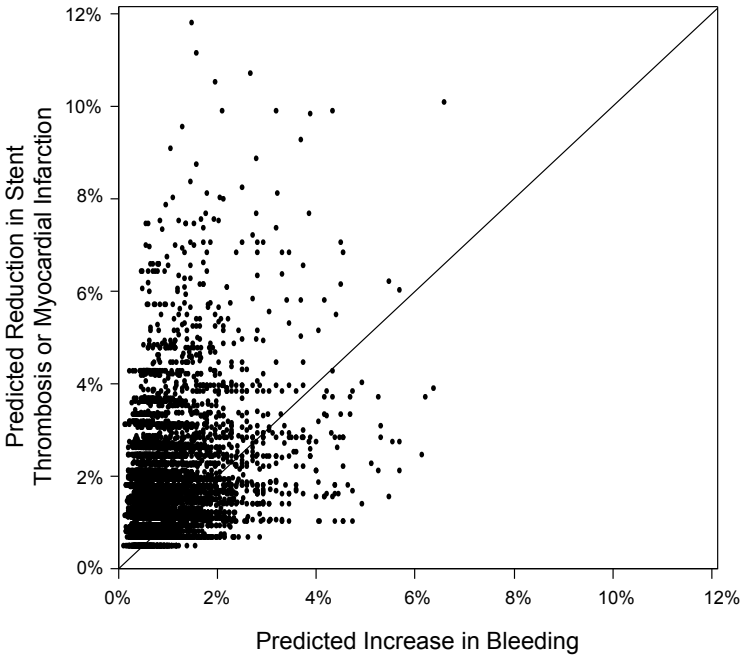
A.



B.



eFigure 6. Scatter Plot of Predicted Benefit vs. Harm with Continued Thienopyridine between 12-30 Months among Randomized DAPT Study Patients, Based on Ischemic and Bleeding Models.



The diagonal line represents the equivalent predicted increase in bleeding and predicted reduction in ischemia (myocardial infarction or stent thrombosis) for patients in the DAPT Study.

Development of a Predictive Score

We aimed to create single score that could accurately balance the benefit and risk of continued thienopyridine therapy and be used at the bedside. For each patient, the ischemia model was used to predict the probability of myocardial infarction or stent thrombosis between 12-30 months assuming continued treatment with thienopyridine, and then again assuming treatment with placebo. The difference in these values represented the predicted ischemic reduction with continued thienopyridine therapy, and was estimated for each patient. The predicted increase in bleeding with continued therapy was similarly estimated for each patient.

Modeling Benefit-Risk Difference

The absolute difference between the predicted ischemic reduction and predicted bleeding increase was defined as the "benefit-risk difference." A greater benefit-risk difference corresponded to a greater overall benefit of continued thienopyridine therapy, where as those with lesser benefit risk differences, including those with values in the negative range, corresponded to lesser benefit or harm. We estimated this number for each patient.
We then created a linear regression model, using benefit-risk difference as the outcome, and all predictors that were selected in the ischemia and bleeding models. The coefficients of these predictors can be understood as the predicted absolute change in benefit-risk difference of continued thienopyridine therapy imparted by each variable.
Model results were as follows

Root MSE	0.00583	R-Square	0.8200
Dependent Mean	0.00984	Adj R-Square	0.8198
Coefficent of Variation	59.27823		

	Estimate	Standard Error	P-value	Squared Semi-partial Corr Type II	Squared Partial Corr Type II
1 Intercept	-0.00767	0.00014878	<0.0001	.	.
2 Peripheral arterial disease	-0.00129	0.00024042	<0.0001	0.00044732	0.00248
3 Renal insufficiency/failure	0.00409	0.00028005	<0.0001	0.00330	0.01801
4 Hypertension	0.00211	0.00013021	<0.0001	0.00405	0.02202
5 Age 65-<75 vs. Age <65	-0.00478	0.00012825	<0.0001	0.02148	0.10659
6 Vein bypass graft stented	0.01634	0.00033402	<0.0001	0.03704	0.17062
7 Diabetes mellitus	0.00647	0.00012338	<0.0001	0.04259	0.19131
8 Current cigarette smoker or within past year	0.00679	0.00012947	<0.0001	0.04262	0.19143
9 Age ≥75 vs. Age <65	-0.01192	0.00019131	<0.0001	0.06009	0.25026
10 TAXUS stent vs. Non-TAXUS stent	0.00963	0.00012803	<0.0001	0.08751	0.32711
11 STEMI/Non-STEMI vs. other indication for PCI	0.00983	0.00012470	<0.0001	0.09608	0.34798
12 History of CHF or LVEF<30%	0.01919	0.00023963	<0.0001	0.09921	0.35530
13 Stent diameter: <3mm vs. ≥3mm	0.00891	0.00011028	<0.0001	0.10107	0.35955
14 Prior PCI or prior MI	0.01133	0.00011673	<0.0001	0.14583	0.44752

Abbreviations: CHF, congestive heart failure; LVEF, left-ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

The squared semi-partial correlations represent the percentage that each variable contributed to explaining the overall variation in benefit-risk differences in the study population. As expected, variables that predicted and increased risk of both ischemia and bleeding (peripheral arterial disease, renal insufficiency and hypertension) each explained less than 1% of the variation in benefit risk difference. Coefficients were then rounded to the nearest percentage point and points ranging from -2 to 2 were assigned. Because paclitaxel-eluting stents are no longer commonly used in clinical practice, this variable was not included in the point score.

Assessment of Predictive Score Fidelity versus Ischemia and Bleeding Models

In order to assess the loss of fidelity in the estimation of benefit-risk difference vs. the use of the predictive score, patients were separated into quartiles for the predicted benefit risk difference based on the applications of the ischemia and bleeding models as well as quartiles of the score. Reclassification tables were then constructed to examine the concordance of the score to the model-based benefit-risk difference calculations.

			Model-Based Benefit Risk Difference Quartile			
			Harm	Harm	Benefit	Benefit
			1st	2nd	3rd	4th
Point Score Quartile	Harm	1st	2354	375	0	0
	Harm	2nd	480	2154	368	0
	Benefit	3rd	0	423	2411	177
	Benefit	4th	0	0	141	2765

A total of 83% of patients were classified into the same quartile by both methods. After examining the impact of continued thienopyridine on outcomes based on the score (Manuscript Table 3 and Appendix eTable 2), patients in the highest 2 quartiles were considered to have scores indicating overall benefit, while those in the lowest 2 quartiles were considered to have low scores indicating overall harm. 6.8% of patients were classified differently into groups of benefit vs. harm using the model-based benefit-risk difference compared with the point score.

Validation of the Predictive Score in the PROTECT Trial

Because the score is meant to predict the discordance of ischemic and bleeding risk by simultaneously integrating the results of two models, validation using the typical metrics of discrimination and calibration would not be appropriate since they are only performed for one endpoint at a time.

As a measure of the ability of the score to identify a high ischemic/low bleeding risk group as well as a low ischemic/high bleeding risk group, we compared the rates of MI or stent thrombosis as well as GUSTO moderate or severe bleeding for high (≥ 2) versus low (< 2) score groups within the PROTECT study.

In PROTECT, high score patients had a higher rate of MI or stent thrombosis between 12 to 30 months after index procedure compared to low score patients (HR 2.01, 95% CI 1.29 - 3.13, p = 0.002). The hazard ratio for GUSTO moderate or severe bleeding for high vs. low score patients was 0.69 (95% CI 0.33 - 1.42, p = 0.31). The predictive score was thus able to define a group of patients at higher ischemic and nominally lower bleeding risk, who could benefit from treatment with a longer duration of thienopyridine, and a group with lower ischemic and nominally higher bleeding risk, who might be better served with discontinuation at 1 year after index PCI. The divergent directions of the HRs for ischemia and bleeding for high vs. low score groups reflect the ability of the score to simultaneously account for ischemic and bleeding risk, in contrast to models which might identify a high ischemic risk population that was also at high bleeding risk.

Estimation of Ischemic and Bleeding Risk

Predicting Ischemic Risk (Risk of Myocardial Infarction or Stent thrombosis)

The Cox proportional hazards ischemia model estimated from the randomized DAPT Study sample can be used to estimate an individual's ischemic risk (i.e., probability of MI or stent thrombosis) between 12-30 months post PCI, assuming the individual has been treated with thienopyridine in the first 12 months post PCI and has not had a major ischemic or bleeding event during that time. This can be carried out as described below.

The table below contains the DAPT study-estimated Cox regression coefficients for the significant risk factors that entered the ischemia model. Also shown is an example of an individual for whom the predicted risk of MI or stent thrombosis is calculated.

	Risk Factor	Cox Regression Coefficient	Individual Example Values	Coefficient x Value
	Example individual: Smoker undergoing stenting with paclitaxel-eluting stent <3mm in diameter, with hypertension but no other risk factors, continued DAPT 12-30 months post PCI			
1	Continuing DAPT 12-30 months post PCI (No=0, Yes=1)	-0.653	1	-0.653
2	Myocardial infarction at presentation (0=No, 1=Yes)	0.499	0	0
3	Prior PCI or prior MI (0=No, 1=Yes)	0.580	0	0
4	History of CHF or LVEF<30% (0=No, 1=Yes)	0.633	0	0
5	Vein graft PCI (0=No, 1=Yes)	0.562	0	0
6	Stent diameter <3mm (0=No, 1=Yes)	0.475	1	0.475
7	Paclitaxel-eluting stent (0=No, 1=Yes)	0.454	1	0.454
8	Cigarette smoker (0=No, 1=Yes)	0.333	1	0.333
9	Diabetes (0=No, 1=Yes)	0.320	0	0
10	Peripheral arterial disease (0=No, 1=Yes)	0.401	0	0
11	Hypertension (0=No, 1=Yes)	0.315	1	0.315
12	Renal insufficiency (0=No, 1=Yes)	0.435	0	0

The predicted risk for a given individual is calculated as follows:

1. For each risk factor, multiply the above Cox regression coefficient by the individual's value of the risk factor.
2. Sum the coefficient x values across the risk factors for the individual. For the example individual above, this sum is 0.924 (= -0.653 + 0 + 0 + 0 + 0 + 0 + 0.475 + 0.454 + 0.333 + 0 +0 + 0.315 + 0).
3. The estimated risk of MI/stent thrombosis in the 12-30 month period post PCI is calculated as:

$$1 - S(18)^{\exp(\text{Sum of [Coefficient x Individual Risk Factor Values]} - \text{Sum of [Coefficient} * \text{Mean Risk Factor Values])}}$$

where $S(18)$ is the overall baseline Kaplan-Meier rate of freedom from MI/stent thrombosis in the 18 month period that includes the 12-30 months follow-up post PCI.

The sum of the coefficient x mean risk factor values estimated from the DAPT Study sample can be used and can be shown to equal 0.790. $S(18)$, also estimated from the DAPT Study, can be used here as well and is equal to 0.9691.

The estimated 18-month risk of MI/stent thrombosis for the example individual is thus:

$$1 - S(18)^{\exp(\text{Sum of [Coefficient x Individual Values]} - \text{Sumof [Coefficient} * \text{Mean Values])}}$$
$$= 1 - 0.9691^{\exp(0.924 - 0.790)} = 0.035 \text{ or } 3.5\%$$

Note that if the patient did not continue thienopyridine in the 12-30 month period, the predicted risk would increase to 0.067 or 6.7%, and the ischemic risk reduction with continuing thienopyridine at 12-30 months versus not continuing thienopyridine is predicted to be 3.2%.

Predicting Risk of GUSTO Moderate or Severe Bleeding

The Cox proportional hazards bleeding model estimated from the randomized DAPT Study sample can be used to estimate an individual's probability of GUSTO moderate or severe bleeding between 12-30 months post PCI, assuming the individual has been treated with thienopyridine in the first 12 months post PCI and has not had a major ischemic or bleeding event during that time. This can be carried out as described below.

The table below contains the DAPT Study-estimated GUSTO moderate or severe bleeding Cox regression coefficients for the significant risk factors that entered the model. Also shown is an example of an individual for whom the predicted risk of GUSTO moderate or severe bleeding is calculated (same individual as above).

	Risk Factor	Cox Regression Coefficient	Individual Example Values	Coefficient x Value
	Example individual: 60 year old with hypertension and without peripheral arterial disease and without renal insufficiency failure, continued DAPT 12-30 months post PCI			
1	Continuing DAPT 12-30 months post PCI (No=0, Yes=1)	0.506	1	0.506
2	Age	0.043	60	2.580
3	Peripheral arterial disease (No=0, Yes=1)	0.769	0	0.000
4	Hypertension (No=0, Yes=1)	0.374	1	0.374
5	Renal insufficiency (No=0, Yes=1)	0.509	0	0.000

The predicted risk for a given individual is calculated as follows:

1. For each risk factor, multiply the above Cox regression coefficient by the individual's value of the risk factor.
2. Sum the coefficient x values across the risk factors for the individual. For the example individual above, this sum is 3.46 (= 0.506 + 2.580 + 0 + 0.374 + 0).
3. The estimated risk of GUSTO moderate or severe bleeding in the 12-30 month period post PCI is calculated as:

$$1 - S(18)^{\exp(\text{Sum of [Coefficient x Individual Risk Factor Values]} - \text{Sum of [Coefficient} * \text{Mean Risk Factor Values])}}$$

where *S*(18) is the overall baseline Kaplan-Meier rate of freedom from GUSTO moderate or severe bleeding in the 18 month period that includes the 12-30 months follow-up post PCI.

The sum of the coefficient x mean risk factor values estimated from the DAPT Study sample can be used and can be shown to equal 3.23. *S*(18), also estimated from the DAPT Study, can be used here as well and is equal to 0.9809.

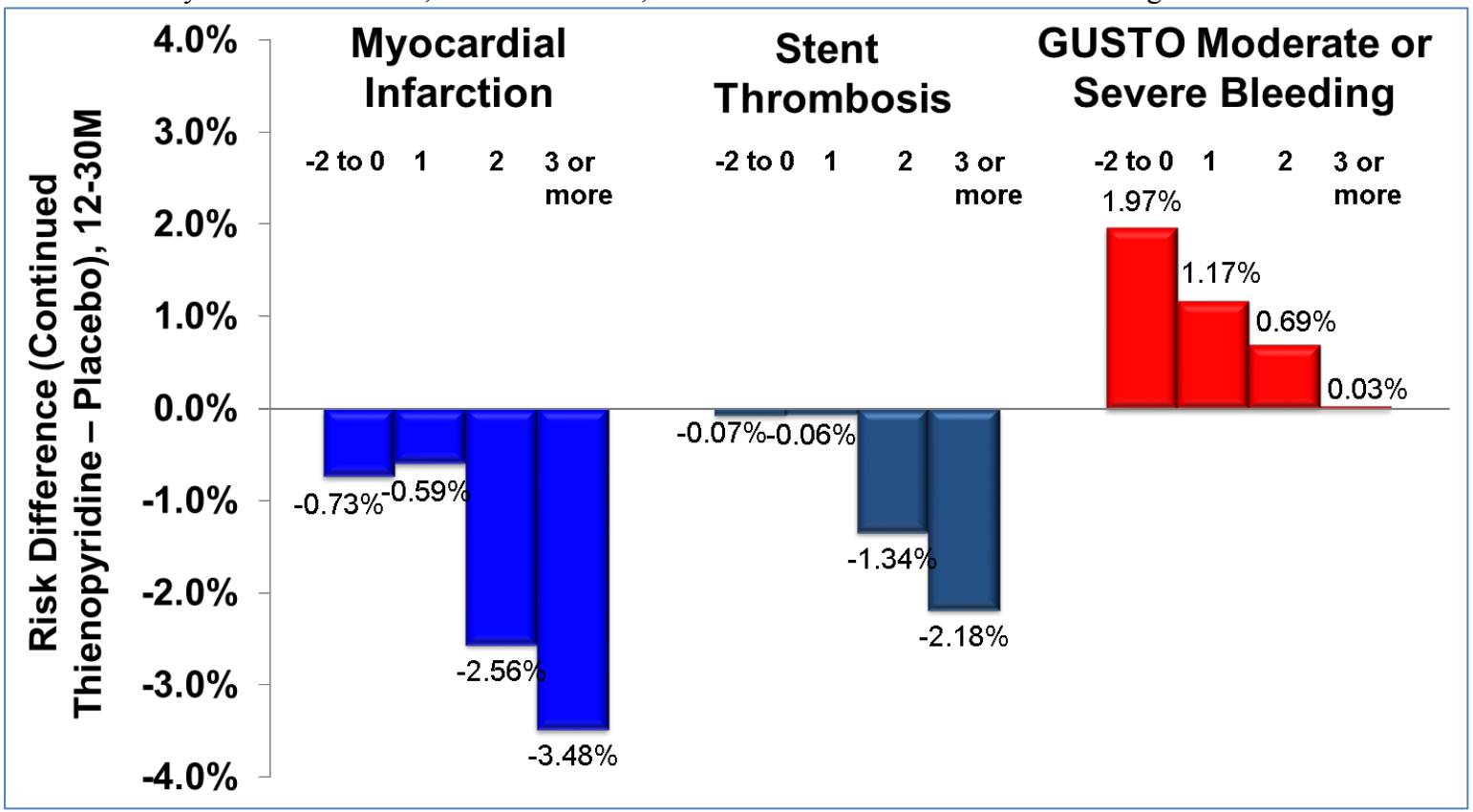
The estimated 18-month risk of GUSTO Moderate/severe bleeding for the example individual is thus:

$$1 - S(18)^{\exp(\text{Sum of [Coefficient x Individual Values]} - \text{Sum of [Coefficient} * \text{Mean Values])}}$$
$$= 1 - 0.9809^{\exp(3.46 - 3.23)} = 0.024 \text{ or } 2.4\%$$

Note that if the patient did not continue thienopyridine in the 12-30 month period, the predicted risk would decrease to 0.015 or 1.5%, and the predicted reduction in bleeding risk of 0.9%.

Other Tables and Figures

eFigure 7. Continued Thienopyridine vs. Placebo Treatment Effect by Prediction Score Group. Risk difference of continued thienopyridine minus placebo at 12-30 months in all randomized patients (N=11,648), stratified by prediction score quartile, for the outcomes of myocardial infarction, stent thrombosis, and GUSTO moderate or severe bleeding.



eTable 2. Additional outcomes between 12-30 months since enrollment stratified by prediction score quartile.

Event	N (Continued Thienopyridine)	N (Placebo)	All Patients N = 11648	Continued Thienopyridine N = 5862	Placebo N = 5786	Risk Difference Continued Thienopyridine – Placebo (95% CI)	Interaction P Value*
Cardiovascular Death							
Score -2 to 0	1373	1356	19 (0.7%)	9 (0.7%)	10 (0.8%)	-0.06% [-0.72%,0.59%]	0.74
Score 1	1501	1501	17 (0.6%)	11 (0.8%)	6 (0.4%)	0.35% [-0.21%,0.91%]	
Score 2	1525	1486	26 (0.9%)	12 (0.8%)	14 (1.0%)	-0.16% [-0.85%,0.54%]	
Score ≥ 3	1463	1443	49 (1.7%)	22 (1.6%)	27 (2.0%)	-0.40% [-1.39%,0.59%]	
Non-Cardiovascular Death							
Score -2 to 0	1373	1356	24 (0.9%)	19 (1.4%)	5 (0.4%)	1.06% [0.33%,1.79%]	0.10
Score 1	1501	1501	12 (0.4%)	7 (0.5%)	5 (0.3%)	0.14% [-0.33%,0.62%]	
Score 2	1525	1486	22 (0.8%)	13 (0.9%)	9 (0.6%)	0.25% [-0.39%,0.89%]	
Score ≥ 3	1463	1443	21 (0.8%)	13 (0.9%)	8 (0.6%)	0.34% [-0.32%,0.99%]	
BARC 3,5 Bleed							
Score -2 to 0	1373	1356	79 (3.0%)	52 (3.9%)	27 (2.0%)	1.89% [0.57%,3.21%]	0.052
Score 1	1501	1501	50 (1.7%)	37 (2.5%)	13 (0.9%)	1.65% [0.69%,2.61%]	
Score 2	1525	1486	45 (1.5%)	29 (2.0%)	16 (1.1%)	0.83% [-0.08%,1.74%]	
Score ≥ 3	1463	1443	50 (1.8%)	27 (1.9%)	23 (1.7%)	0.25% [-0.76%,1.26%]	
BARC 2,3,5 Bleed							
Score -2 to 0	1373	1356	133 (5.0%)	91 (6.9%)	42 (3.2%)	3.71% [2.03%,5.40%]	0.02
Score 1	1501	1501	113 (3.9%)	81 (5.6%)	32 (2.2%)	3.36% [1.95%,4.78%]	
Score 2	1525	1486	102 (3.5%)	68 (4.6%)	34 (2.3%)	2.20% [0.85%,3.56%]	
Score ≥ 3	1463	1443	102 (3.7%)	59 (4.2%)	43 (3.1%)	1.06% [-0.37%,2.48%]	
BARC 2 Bleed							
Score -2 to 0	1373	1356	62 (2.3%)	43 (3.3%)	19 (1.4%)	1.83% [0.66%,3.00%]	0.47
Score 1	1501	1501	67 (2.3%)	47 (3.2%)	20 (1.4%)	1.86% [0.76%,2.96%]	
Score = 2	1525	1486	58 (2.0%)	40 (2.7%)	18 (1.3%)	1.45% [0.41%,2.48%]	
Score ≥ 3	1463	1443	59 (2.1%)	37 (2.6%)	22 (1.6%)	1.02% [-0.07%,2.11%]	

Table continued on next page

BARC 3 Bleed							
Score -2 to 0	1373	1356	74 (2.8%)	48 (3.6%)	26 (2.0%)	1.67% [0.39%,2.95%]	0.13
Score 1	1501	1501	49 (1.7%)	36 (2.5%)	13 (0.9%)	1.58% [0.63%,2.53%]	
Score 2	1525	1486	42 (1.4%)	27 (1.8%)	15 (1.1%)	0.77% [-0.12%,1.65%]	
Score ≥ 3	1463	1443	47 (1.7%)	27 (1.9%)	20 (1.5%)	0.47% [-0.51%,1.45%]	
BARC 5 Bleed							
Score -2 to 0	1373	1356	5 (0.2%)	4 (0.3%)	1 (0.08%)	0.23% [-0.11%,0.56%]	0.42
Score 1	1501	1501	1 (0.03%)	1 (0.07%)	0 (0.0%)	0.07% [-0.07%,0.21%]	
Score 2	1525	1486	3 (0.11%)	2 (0.1%)	1 (0.07%)	0.06% [-0.18%,0.30%]	
Score ≥ 3	1463	1443	3 (0.11%)	0 (0.0%)	3 (0.2%)	-0.22% [-0.48%,0.03%]	

Abbreviations: BARC, Bleeding Academic Research Consortium; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction. * P-value for interaction assesses whether the absolute risk reduction observed between randomized treatment groups differs across quartiles of Prediction score, as assessed by the Q-statistic for heterogeneity.

eTable 3. Observed Outcomes between 12-30 months since enrollment stratified by prediction score group for all randomized patients (N=11,648).

Event	N (Continued Thienopyridine)	N (Placebo)	Continued Thienopyridine N = 5862	Placebo N = 5786	Risk Difference [95% CI] Continued Thienopyridine - Placebo	Log Rank P Value	Interaction P Value*
Stent Thrombosis							<0.001
Prediction Score < 2	2874	2857	6 (0.2%)	8 (0.3%)	-0.06% [-0.33%, 0.20%]	0.60	
Prediction Score ≥ 2	2988	2929	17 (0.6%)	66 (2.3%)	-1.75% [-2.39%, -1.11%]	<0.001	
MI							<0.001
Prediction Score < 2	2874	2857	46 (1.7%)	65 (2.3%)	-0.66% [-1.40%, 0.09%]	0.07	
Prediction Score ≥ 2	2988	2929	75 (2.6%)	158 (5.6%)	-3.02% [-4.07%, -1.96%]	<0.001	
MI or Stent Thrombosis							<0.001
Prediction Score < 2	2874	2857	46 (1.7%)	65 (2.3%)	-0.66% [-1.40%, 0.09%]	0.07	
Prediction Score ≥ 2	2988	2929	77 (2.7%)	160 (5.7%)	-3.02% [-4.08%, -1.95%]	<0.001	
MACCE							0.001
Prediction Score < 2	2874	2857	102 (3.7%)	107 (3.8%)	-0.15% [-1.16%, 0.86%]	0.73	
Prediction Score ≥ 2	2988	2929	142 (4.9%)	216 (7.6%)	-2.75% [-4.02%, -1.47%]	<0.001	
Death							0.14
Prediction Score < 2	2874	2857	46 (1.7%)	26 (0.9%)	0.73% [0.13%, 1.33%]	0.02	
Prediction Score ≥ 2	2988	2929	60 (2.1%)	58 (2.1%)	0.01% [-0.73%, 0.76%]	0.99	
Cardiovascular Death							0.25
Prediction Score < 2	2874	2857	20 (0.7%)	16 (0.6%)	0.15% [-0.28%, 0.58%]	0.49	
Prediction Score ≥ 2	2988	2929	34 (1.2%)	41 (1.5%)	-0.28% [-0.88%, 0.33%]	0.35	
Non-Cardiovascular Death							0.36
Prediction Score < 2	2874	2857	26 (0.9%)	10 (0.4%)	0.58% [0.15%, 1.01%]	0.01	
Prediction Score ≥ 2	2988	2929	26 (0.9%)	17 (0.6%)	0.29% [-0.17%, 0.75%]	0.21	

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Event	N (Continued Thienopyridine)	N (Placebo)	Continued Thienopyridine N = 5862	Placebo N = 5786	Risk Difference [95% CI] Continued Thienopyridine - Placebo	Log Rank P Value	Interaction P Value*
GUSTO Moderate or Severe Bleed							0.02
Prediction Score < 2	2874	2857	83 (3.0%)	40 (1.4%)	1.55% [0.76%, 2.33%]	<0.001	
Prediction Score ≥ 2	2988	2929	52 (1.8%)	40 (1.4%)	0.37% [-0.30%, 1.04%]	0.26	
GUSTO Moderate Bleed							0.22
Prediction Score < 2	2874	2857	54 (1.9%)	28 (1.0%)	0.94% [0.29%, 1.58%]	0.004	
Prediction Score ≥ 2	2988	2929	37 (1.3%)	24 (0.9%)	0.42% [-0.12%, 0.97%]	0.12	
GUSTO Severe Bleed							0.04
Prediction Score < 2	2874	2857	29 (1.0%)	13 (0.5%)	0.58% [0.12%, 1.04%]	0.01	
Prediction Score ≥ 2	2988	2929	15 (0.5%)	16 (0.6%)	-0.06% [-0.45%, 0.34%]	0.79	
BARC 3,5 Bleed							0.02
Prediction Score < 2	2874	2857	89 (3.2%)	40 (1.4%)	1.76% [0.96%, 2.57%]	<0.001	
Prediction Score ≥ 2	2988	2929	56 (1.9%)	39 (1.4%)	0.54% [-0.13%, 1.22%]	0.11	
BARC 2,3,5 Bleed							0.01
Prediction Score < 2	2874	2857	172 (6.2%)	74 (2.7%)	3.53% [2.43%, 4.62%]	<0.001	
Prediction Score ≥ 2	2988	2929	127 (4.4%)	77 (2.8%)	1.64% [0.66%, 2.63%]	<0.001	
BARC 2 Bleed							0.27
Prediction Score < 2	2874	2857	90 (3.2%)	39 (1.4%)	1.84% [1.04%, 2.65%]	<0.001	
Prediction Score ≥ 2	2988	2929	77 (2.7%)	40 (1.4%)	1.24% [0.49%, 1.99%]	<0.001	
BARC 3 Bleed							0. 051
Prediction Score < 2	2874	2857	84 (3.0%)	39 (1.4%)	1.62% [0.84%, 2.41%]	<0.001	
Prediction Score ≥ 2	2988	2929	54 (1.9%)	35 (1.3%)	0.62% [-0.04%, 1.28%]	0.06	
BARC 5 Bleed							0. 08
Prediction Score < 2	2874	2857	5 (0.2%)	1 (0.04%)	0.14% [-0.03%, 0.32%]	0.10	
Prediction Score ≥ 2	2988	2929	2 (0.07%)	4 (0.15%)	-0.08% [-0.25%, 0.10%]	0.39	

Abbreviations: BARC, Bleeding Academic Research Consortium; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction. *P-value for interaction assesses whether the observed risk difference in event rates between randomized treatment groups differs between high vs. low Prediction score groups.

eTable 4. Observed outcomes between 12-30 months since enrollment when divided into two prediction score groups among patients treated with everolimus-eluting stents (N=4703).

Event	N (Continued Thienopyridine)	N (Placebo)	Continued Thienopyridine N = 2345	Placebo N = 2358	Risk Difference [95% CI] Continued Thienopyridine - Placebo	Log Rank P Value	Interaction P Value*
Stent Thrombosis							0.10
Prediction Score < 2	1400	1434	3 (0.2%)	5 (0.4%)	-0.13% [-0.53%,0.28%]	0.51	
Prediction Score ≥ 2	945	924	3 (0.3%)	11 (1.2%)	-0.91% [-1.75%,-0.07%]	0.03	
MI							0.18
Prediction Score < 2	1400	1434	23 (1.7%)	31 (2.2%)	-0.50% [-1.55%,0.56%]	0.33	
Prediction Score ≥ 2	945	924	25 (2.7%)	41 (4.6%)	-1.89% [-3.68%,-0.11%]	0.03	
MI or Stent Thrombosis							0.18
Prediction Score < 2	1400	1434	23 (1.7%)	31 (2.2%)	-0.50% [-1.55%,0.56%]	0.33	
Prediction Score ≥ 2	945	924	26 (2.9%)	42 (4.7%)	-1.89% [-3.70%,-0.08%]	0.04	
MACCE							0.11
Prediction Score < 2	1400	1434	51 (3.8%)	45 (3.2%)	0.56% [-0.83%,1.94%]	0.45	
Prediction Score ≥ 2	945	924	46 (5.0%)	58 (6.5%)	-1.50% [-3.69%,0.68%]	0.17	
Death							0.54
Prediction Score < 2	1400	1434	26 (1.9%)	10 (0.7%)	1.21% [0.35%,2.07%]	0.01	
Prediction Score ≥ 2	945	924	23 (2.5%)	16 (1.8%)	0.71% [-0.64%,2.07%]	0.31	
Cardiovascular Death							0.70
Prediction Score < 2	1400	1434	10 (0.7%)	6 (0.4%)	0.32% [-0.26%,0.90%]	0.28	
Prediction Score ≥ 2	945	924	13 (1.4%)	12 (1.3%)	0.08% [-1.02%,1.18%]	0.90	
Non-Cardiovascular Death							0.63
Prediction Score < 2	1400	1434	16 (1.2%)	4 (0.3%)	0.90% [0.25%,1.55%]	0.01	
Prediction Score ≥ 2	945	924	10 (1.1%)	4 (0.4%)	0.65% [-0.18%,1.47%]	0.12	

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Event	N (Continued Thienopyridine)	N (Placebo)	Continued Thienopyridine N = 2345	Placebo N = 2358	Risk Difference [95% CI] Continued Thienopyridine - Placebo	Log Rank P Value	Interaction P Value*
GUSTO Moderate or Severe Bleed							0.15
Prediction Score < 2	1400	1434	41 (3.0%)	19 (1.4%)	1.67% [0.55%,2.78%]	0.003	
Prediction Score ≥ 2	945	924	16 (1.8%)	11 (1.2%)	0.52% [-0.63%,1.67%]	0.38	
GUSTO Moderate Bleed							0.68
Prediction Score < 2	1400	1434	25 (1.9%)	16 (1.2%)	0.70% [-0.23%,1.63%]	0.13	
Prediction Score ≥ 2	945	924	11 (1.2%)	7 (0.8%)	0.43% [-0.51%,1.37%]	0.38	
GUSTO Severe Bleed							0.059
Prediction Score < 2	1400	1434	16 (1.2%)	3 (0.2%)	0.97% [0.33%,1.61%]	0.002	
Prediction Score ≥ 2	945	924	5 (0.6%)	4 (0.5%)	0.10% [-0.58%,0.77%]	0.78	
BARC 3,5 Bleed							0.09
Prediction Score < 2	1400	1434	42 (3.1%)	17 (1.2%)	1.88% [0.78%,2.99%]	<.001	
Prediction Score ≥ 2	945	924	16 (1.8%)	11 (1.2%)	0.53% [-0.62%,1.67%]	0.38	
BARC 2,3,5 Bleed							0.047
Prediction Score < 2	1400	1434	69 (5.1%)	26 (1.9%)	3.24% [1.84%,4.63%]	<.001	
Prediction Score ≥ 2	945	924	31 (3.4%)	20 (2.3%)	1.15% [-0.42%,2.72%]	0.15	
BARC 2 Bleed							0.39
Prediction Score < 2	1400	1434	29 (2.1%)	11 (0.8%)	1.36% [0.44%,2.28%]	0.003	
Prediction Score ≥ 2	945	924	17 (1.9%)	10 (1.1%)	0.73% [-0.42%,1.89%]	0.20	
BARC 3 Bleed							0.08
Prediction Score < 2	1400	1434	39 (2.9%)	16 (1.2%)	1.74% [0.67%,2.81%]	0.001	
Prediction Score ≥ 2	945	924	14 (1.5%)	10 (1.1%)	0.42% [-0.67%,1.50%]	0.46	
BARC 5 Bleed							0.87
Prediction Score < 2	1400	1434	3 (0.2%)	1 (0.07%)	0.15% [-0.14%,0.44%]	0.30	
Prediction Score ≥ 2	945	924	2 (0.2%)	1 (0.11%)	0.11% [-0.28%,0.50%]	0.59	

Abbreviations: BARC, Bleeding Academic Research Consortium; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction.

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