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CLINICAL RESEARCH

Development and Validation of a Stent Thrombosis Risk Score in Patients With Acute Coronary Syndromes

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Objectives This study sought to develop a practical risk score to predict the risk of stent thrombosis (ST) after percutaneous coronary intervention (PCI) for acute coronary syndromes (ACS).

Background ST is a rare, yet feared complication after PCI with stent implantation. A risk score for ST after PCI in ACS can be a helpful tool to personalize risk assessment.

Methods This study represents a patient-level pooled analysis of 6,139 patients undergoing PCI with stent implantation for ACS in the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) and ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trials who were randomized to treatment with bivalirudin versus heparin plus a glycoprotein IIb/IIIa inhibitor. The cohort was randomly divided into a risk score development cohort (n = 4,093) and a validation cohort (n = 2,046). Cox regression methods were used to identify clinical, angiographic, and procedural characteristics associated with Academic Research Consortium–defined definite/probable ST at 1 year. Each covariate in this model was assigned an integer score based on the regression coefficients.

Results Variables included in the risk score were type of ACS (ST-segment elevation myocardial infarction, non-ST-segment elevation ACS with ST deviation, or non–ST-segment elevation ACS without ST changes), current smoking, insulin-dependent diabetes mellitus, prior PCI, baseline platelet count, absence of early (pre-PCI) anticoagulant therapy, aneurysmal/ulcerated lesion, baseline TIMI (Thrombolysis In Myocardial Infarction) flow grade 0/1, final TIMI flow grade <3, and number of treated vessels. Risk scores 1 to 6 were considered low risk, 7 to 9 intermediate risk, and 10 or greater high risk for ST. Rates of ST at 1 year in low-, intermediate-, and high-risk categories were 1.36%, 3.06%, and 9.18%, respectively, in the development cohort (p for trend <0.001), and 1.65%, 2.77%, and 6.45% in the validation cohort (p for trend = 0.006). The C-statistic for this risk score was over 0.65 in both cohorts.

Conclusions The individual risk of ST can be predicted using a simple risk score based on clinical, angiographic, and procedural variables. (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction [HORIZONS-AMI]; NCT00433966) (Comparison of Angiomax Versus Heparin in Acute Coronary Syndromes [ACUITY]; NCT00093158) (J Am Coll Cardiol Intv 2012;5:1097–105) © 2012 by the American College of Cardiology Foundation

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JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 5, NO. 11, 2012
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Stent thrombosis (ST) is a rare, yet feared complication after percutaneous coronary intervention (PCI) that is associated with high rates of morbidity and mortality reported by several randomized clinical trials and registries (1–6). A large number of patient-related, lesion-related, procedural, and post-procedural factors have been associated with ST (1–4,6,7). Stenting in prothrombotic conditions in patients with acute coronary syndromes (ACS) is strongly associated with the occurrence of ST (7–9). However, due to the rarity of ST events, systematic ST risk assessment has not been realized at the individual patient level. A risk score for ST after PCI in ACS can be a helpful tool to personalize risk assessment.

See page 1106

In the present study, we aimed to develop and validate a practical risk score for ST based on a pooled analysis of patients undergoing PCI with stent implantation in 2 prospective randomized clinical trials of patients with ACS (10,11).

Abbreviations and Acronyms

ACS = acute coronary syndrome(s)

GPI = glycoprotein IIb/IIIa inhibitor

NSTE-ACS = non–ST-segment elevation acute coronary syndrome

PCI = percutaneous coronary intervention

ST = stent thrombosis

STEMI = ST-segment elevation myocardial infarction

Methods

This study represents a pooled analysis of patients undergoing PCI with stent implantation in 2 large randomized clinical trials of bivalirudin versus heparin plus a glycoprotein IIb/IIIa inhibitor (GPI): The HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial of patients with ST-segment elevation myocardial infarction (STEMI); and the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial of patients with unstable angina or non-STEMI (10,11).

The design and primary outcomes of these trials have been described in detail previously (11,12). Briefly, in HORIZONS-AMI, 3,602 patients admitted with STEMI presenting within 12 h after symptom onset were directed to therapy with primary angioplasty and were randomized (1:1) to receive either bivalirudin monotherapy (plus bailout GPI) or unfractionated heparin plus a GPI before PCI. Following angiography, 3,006 patients were randomized (3:1) to Taxus Express2 (Boston Scientific, Natick, Massachusetts) paclitaxel-eluting stents or otherwise identical metallic stents (Boston Scientific). Aspirin and clopidogrel (either 300 or 600 mg, at the discretion of the investigator) or ticlopidine (500 mg in the case of allergy to clopidogrel) were administered before catheterization.

In ACUITY, eligible patients with unstable angina or non-STEMI were randomly assigned to treatment with bivalirudin, versus bivalirudin plus a GPI, versus heparin (either unfractionated or low molecular weight) plus a GPI before performance of coronary angiography. All patients received aspirin, and timing and dosing of clopidogrel was left to the discretion of investigators and treating physicians. Clinical follow-up was prespecified at 30 days, 6 months, and 1 year in both trials. Extended follow-up of up to 3 years was only available in the HORIZONS-AMI trial.

The Academic Research Consortium definite or probable ST criteria were used (13), and all ST events were adjudicated using source documents by the independent clinical event committees of the 2 trials. In both trials, angiographic analysis was performed by an independent core laboratory using validated methods.

Risk score development. We randomly divided the pooled dataset in a 2:1 fashion into a development cohort and a validation cohort and considered the 1-year follow-up for the primary analysis because this was the longest common follow-up period for both datasets. Univariate and multivariate analyses for prediction of ST have previously been performed in both individual trials (14). A Cox proportional hazards model was used to calculate hazard ratios of clinical, angiographic, and procedural variables. Models were built using a stepwise variable selection procedure; a value of $p < 0.05$ was set as the level of significance for including variables in the model. To prevent overfitting, we included covariates that were independent predictors of ST in the individual trials in the model (14). Slight modifications were made to accommodate differences between the study databases. 1) ST-segment deviation was classified as STEMI, non-STEMI with ST-segment deviation ≥1 mm, or ACS

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Table 1. Rates of Definite Probable ST in Patients From the Individual Trials and in the Derivation and Validation Cohorts

	HORIZONS-AMI (n = 2,986)	ACUITY (n = 3,153)	Derivation (n = 4,093)	Validation (n = 2,046)
Acute	0.90	0.30	0.60	0.60
Subacute	1.50	1.00	0.90	1.40
Late	1.00	0.70	1.00	1.00
Overall 1 year	3.60	2.00	2.80	2.60
Very late	1.80	NA*	NA*	NA*
Overall 3 year	5.00	NA*	NA*	NA*

Values are %. *Maximum follow-up duration in ACUITY was 1 year.

ACUITY = Acute Catheterization and Urgent Intervention Triage Strategy; HORIZONS-AMI = Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; NA = not available; ST = stent thrombosis.

without ST-segment deviation. 2) Pre-randomization administration of antithrombotic medication was associated with ST in HORIZONS-AMI, and was generalized to early (pre-PCI) anticoagulant therapy in both trials. 3) Angiographic ulceration (according to the criteria for complex morphology as proposed by Ambrose et al. [15]) and aneurysm were independent predictors of ST in HORIZONS-AMI and were generalized to ulceration or aneurysm, instead of to 2 separate variables. The remaining variables included were baseline platelet count, current smoking, insulin-treated diabetes mellitus, prior PCI, number of treated vessels, baseline TIMI (Thrombolysis In Myocardial Infarction) flow grade 0/1, and final TIMI flow grade <3. Use of drug-eluting stents compared with bare-metal stents was not associated with ST. Each covariate in this model was assigned an integer score based on the regression coefficients. Integer scores were subsequently summed to give the risk score for each patient. The 1-year rate of ST within each score category was derived per integer score and then per low-, intermediate-, or high-risk classification. Additionally, separate models were created for early (0 to 30 days) definite/probable ST and late (1 month to 1 year) ST using the aforementioned methodology. A significant p value for trend was considered at the <0.05 level. Overall model performance was assessed with the C-statistic.

Score validation. To test the validity of these findings, we investigated the correlation of the derived risk score with the ST rate observed in the validation cohort. The rates of ST per risk score category were derived and compared for trend. Overall model performance was assessed by the C-statistic. A secondary analysis was performed with inclusion of the extended follow-up data of HORIZONS-AMI trial (beyond 1- and up to 3-year follow-up) in the validation dataset to provide information on prediction of very late ST.

Results

A total of 2,986 patients who received stent implantation after primary PCI in the HORIZONS-AMI trial, and a total of 3,153 patients who underwent PCI with stent placement in the ACUITY trial with complete datasets were included in this patient-pooled analysis (total cohort n = 6,139). Most patients were treated with at least 1 drug-eluting stent (n = 5,000, n = 81.4%). The cohort was then randomly split in a 2:1 fashion into development (n = 4,093) and validation (n = 2,046) cohorts. There were no differences in baseline clinical, angiographic, and procedural characteristics or in clinical outcomes between patients in the development and validation cohorts. The incidence of ST events in the individual trials and the development and validation cohorts according to the Academic Research Consortium's timing definitions is shown in Table 1.

Development dataset. Variables included in the risk score and their hazard ratios are shown in Table 2. Independent predictors of ST at 1-year follow-up were type of ACS (STEMI, non–ST-segment elevation acute coronary syndrome [NSTE-ACS] with ST-segment deviation, or NSTE-ACS without ST-segment changes), current smoking, insulin-dependent diabetes mellitus, prior PCI, baseline platelet count, absence of early (pre-PCI) anticoagulant therapy, ulceration or aneurysm of target lesion, baseline TIMI flow grade 0/1, final TIMI flow grade <3, and number of treated vessels.

Table 3 shows the corresponding integer assignments and calculation of the risk score. Each variable was assigned a +1 to +4 score according to the strength of the statistical association. The distribution of the integer risk score and consequent probability of ST at 1 year is shown in Figures 1A and 1B (p value for trend <0.0001). The C-statistic for the risk score was 0.67 in the development cohort. From observation of these data, 3 categories of ST risk might arbitrarily be defined: risk scores 1 to 6 were considered low risk, 7 to 9 intermediate risk, and 10 or greater high risk for ST. Rates of ST in low-, intermediate-,

Table 2. HR of Independent Predictors of Definite/Probable ST in the Development Cohort

Variables	HR	95% CI	p Value
Baseline platelet count	1.00	1.00–1.01	0.005
Current smoking	1.64	1.11–2.43	0.01
Insulin-treated diabetes mellitus	2.41	1.34–4.36	0.004
Final TIMI flow grade 3	0.49	0.29–0.83	0.008
History of PCI	1.70	1.06–2.72	0.03
Early (pre-PCI) heparin therapy*	0.63	0.43–0.93	0.02
Aneurysm or ulceration	2.18	1.21–3.93	0.01
Baseline TIMI flow grade 0/1	2.36	1.51–3.70	0.0002
Number of vessels treated	1.75	1.05–2.91	0.03
Type of acute coronary syndrome	1.39	1.08–1.80	0.01

*Includes parenteral heparin or low molecular weight heparin.

CI = confidence interval; HR = hazard ratio; PCI = percutaneous coronary intervention; ST = stent thrombosis; TIMI = Thrombolysis In Myocardial Infarction.

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 5, NO. 11, 2012
NOVEMBER 2012:1097–105

Table 3. Integer-Based Risk Score for 1-Year Definite/Probable ST in Patients With ACS

Variable	Integer Assignment for ST Risk Score Calculation			Add to Score
Type of ACS	NSTE-ACS w/o ST-segment changes: +1	NSTE-ACS with ST-segment deviation: +2	STEMI + 4	
Current smoking	Yes: +1	No: +0		
Insulin-treated diabetes mellitus	Yes: +2	No: +0		
History of PCI	Yes: +1	No: +0		
Baseline platelet count, K/μl	<250: +0	250–400: +1	>400: +2	
Absence of early (pre-PCI) heparin*	Yes: +1	No: 0		
Aneurysm or ulceration	Yes: +2	No: 0		
Baseline TIMI flow grade 0/1	Yes: +1	No: 0		
Final TIMI flow grade <3	Yes: +1	No: 0		
Number of vessels treated	1: +0	2: +1	3: +2	
ST risk score:				

*Includes parenteral heparin or low molecular weight heparin.

ACS = acute coronary syndrome (s); NSTE-ACS = Non–ST-segment elevation acute coronary syndrome; STEMI = ST-segment elevation myocardial infarction; other abbreviations as in Tables 1 and 2.

and high-risk groups are shown in Figures 1C and 1D (p value for trend <0.0001).

Independent predictors and corresponding risk models for definite/probable early (0 to 30 days) and late (1 month to 1 year) ST are shown in Tables 4 and 5, respectively. The C-statistics in the development cohort for the early ST model and the late ST model were 0.76 and 0.76, respectively.

Score validation. Figures 2A and 2B show the distribution of the integer risk score and consequent probability of definite/probable ST at 1 year in the validation cohort. The C-statistic for the ST risk score model in the validation cohort was 0.66. Figures 2C and 2D show the distribution of low-, intermediate-, and high-risk groups, as well as their corresponding ST rates at 1 year. The ST trends among the 3 risk categories remained significant ($p < 0.001$).

In a secondary analysis, we extended the preceding validation cohort to also include the data on the extended follow-up of the HORIZONS-AMI trial (beyond 1 year

Figure 1. Distribution of the Integer Risk Score and Consequent Probability of Definite/Probable ST Within 1 Year in the Derivation Cohort

Distribution of the integer risk score **(A);** incidence of definite/probable stent thrombosis (ST) by risk score integer **(B)**; distribution of low-, intermediate-, and high-risk categories **(C)**; and incidence of ST by risk category **(D)**.

Table 4. Early ST (0 to 30 Days) Predictors and Risk Score (Development Cohort)

	Early ST (0–30 Days) Predictors and Risk Score				
Outcome	**N**	**Events, n**	**Predictor**	**HR (95% CI)**	**p Value**
Definite/probable ST: ≤30 days	2,997	69	Baseline platelet count	1.00 (1.00–1.01)]	0.002
			History of IDDM	2.36 (1.25–4.46)	0.008
			Final TIMI flow grade 3 vs. 0/1/2	0.43 (0.24–0.75)	0.003
			Early anticoagulant therapy	0.61 (0.39–0.95)	0.03
			Aneurysm or ulceration	2.37 (1.25–4.50)	0.009
			Baseline TIMI flow grade 0/1 vs. 2/3	3.43 (2.08–5.66)	<0.0001
			Number of vessels treated	1.80 (1.05–3.08)	0.03

	Score Assignment		
Baseline platelet count, K/μl	<250:+0	250–400: +1	>400: +2
History of IDDM	Yes:+2	No: +0	
Final TIMI flow grade 3 vs. 0/1/2	Yes:+0	No: +2	
Early anticoagulant therapy	Yes:+0	No: +1	
Aneurysm or ulceration	Yes:+2	No: +0	
Baseline TIMI flow grade 0/1 vs. 2/3	Yes:+2	No: +0	
Number of vessels treated	2:+1	3: +2	

IDDM = insulin-dependent diabetes mellitus; other abbreviations as in Tables 1 and 2.

and until the 3-year study end) to also include a very late ST assessment. The ST rates in the low-, intermediate-, and high-risk categories were 2.52%, 4.70%, and 12.68% (p for trend <0.0001), respectively, and the C-statistic was 0.69 (Fig. 3). The performance of the ST risk score was similar when it was validated to exclusively predict very late ST in the HORIZONS-AMI trial; ST rates were 1.08%, 1.92%, and 2.75% in the low-, intermediate-, and high-risk groups, respectively (p = 0.04). The C-statistics in the validation cohort for the early ST model and the late ST model were 0.67 and 0.66, respectively.

Discussion

The current analysis in a patient-pooled dataset of 2 large randomized clinical trials that span the spectrum of ACS resulted in the development and validation of a convenient integer-based risk score consisting of 10 readily available variables. We believe that the development and initial validation of this ST risk score can be a useful tool for both clinical practice and future clinical investigation (future analyses of trials or registries), as it can be a simple way to risk stratify patients immediately following a procedure. The risk score could also be used in the informed consent process to better inform patients of their individual risk of ST (16).

In our analyses, we found that most patients were in the low-risk categories (Figs. 1C and 2C). This is in accordance with the rarity of ST events and with the great difficulties that smaller datasets with less prolonged follow-up would have had to perform such an analysis. In addition, we documented highly statistically significant incremental ST rates with increasing risk score integer values in both

Table 5. Late Stent Thrombosis (1 Month to 1 Year) Predictors and Risk Score (Development Cohort)

	Late Stent Thrombosis (1 Month to 1 Year) Predictors and Risk Score				
Outcome	**N**	**Events, n**	**Predictor**	**HR (95% CI)**	**p Value**
Definite/probable ST: >30 days	2,928	58	History of PCI	2.84 (1.17–6.89)	0.02
			STEMI vs. NSTE-ACS	3.72 (1.46–9.45)	0.006
			Current smoking	4.00 (1.66–9.64)	0.002

	Score Assignment	
Current smoking	Yes: +3	No: +0
History of PCI	Yes: +2	No: +0
STEMI vs. NSTE-ACS	NSTE-ACS: +0	STEMI: +3

Abbreviations as in Tables 1, 2, and 3.

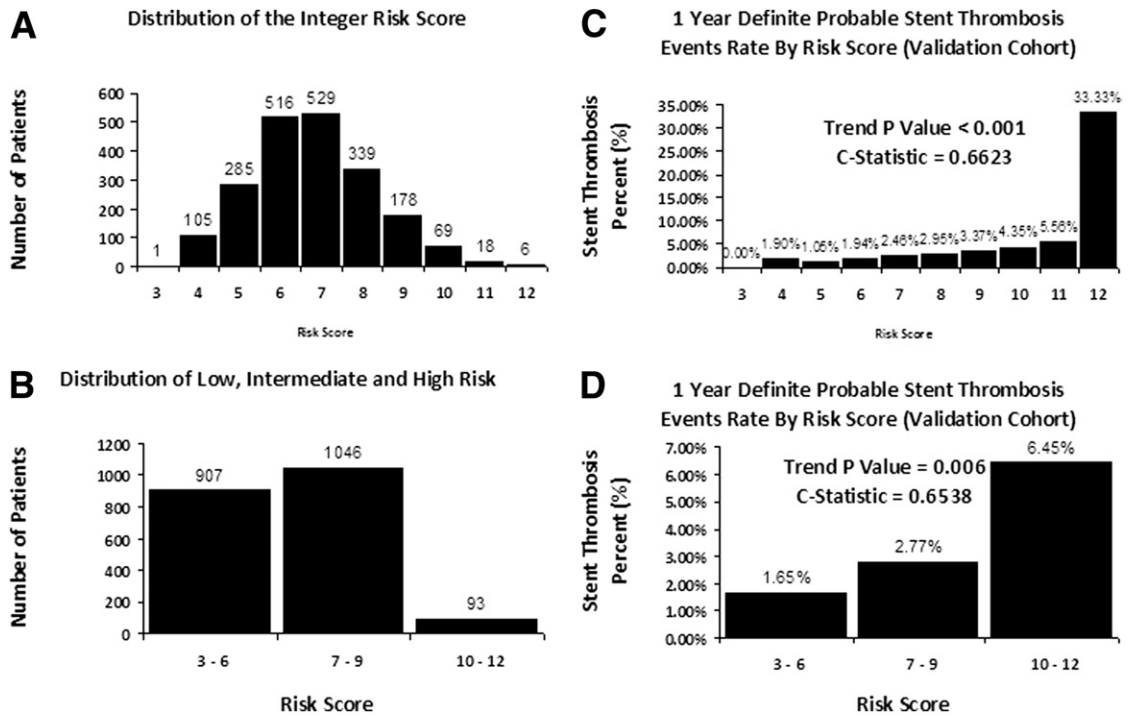

Figure 2. Distribution of the Integer Risk Score and Consequent Probability of Definite/Probable ST Within 1 Year in the Validation Cohort

Distribution of the integer risk score **(A)**; incidence of definite/probable stent thrombosis (ST) by risk score integer **(B)**; distribution of low-, intermediate-, and high-risk categories (**C**); and incidence of ST by risk category **(D)**.

the development and validation datasets. These trends paralleled each other in the derivation and validation cohorts.

Prior reports have suggested that predictors may differ for early (including acute and subacute) ST compared with late/very late ST (14,17). Late and very late ST may have a restenotic or neoatherosclerotic origin, whereas early ST may be more device- or pharmacology-related. Nonetheless, the present risk score was able to similarly predict the occurrence of ST not only within the first year, but also, including very late ST events.

The variables of the proposed risk score can be subcategorized into clinical and laboratory, pharmacological, and angiographic variables. Clinical variables include: type of ACS, prior studies have suggested higher ST rates in STEMI than in NSTE-ACS (7,14), moreover, the current investigation reported higher ST rates after NSTE-ACS with ST-segment deviation ≥1 mm compared with NSTE-ACS without ST-segment deviation; insulin-treated diabetes mellitus (previously described as a powerful predictor of subacute, late, and very late ST) (6,14); previous PCI, which might indicate prior stent placement and could also signify an index ACS because of ST of a previously implanted stent; current smoking, which has been associated with ST in multiple prior studies (6,14). Additionally, the laboratory value of thrombocytosis has been reported to be associated with ST in an earlier analysis in the HORIZONS-AMI trial (14).

We previously reported a protective effect of pre-randomization use of heparin in the HORIZONS-AMI trial (14). This important pharmacological variable was generalized as early (pre-PCI) administration of anticoagulant therapy to facilitate the clinical applicability of the current risk score. To be more specific, we mean any early use of a readily available parenteral heparin (either unfractionated or low molecular weight) therapy in the emergency department, ambulance, or medical floor well before the start of the PCI procedure. With respect to early use of GPI, the ACUITY timing substudy had already shown no difference with respect to clinical outcomes (including ST) of early versus during-PCI administration of these agents (18,19). With respect to early clopidogrel administration, an earlier report from the same trial found no major difference in outcomes with earlier administration as long as clopidogrel was administered before the procedure (20). Future investigation of different datasets that may include other potent antiplatelet agents administered at different times before PCI may be able to further identify whether such practices may be protective of ST (21–23). The present

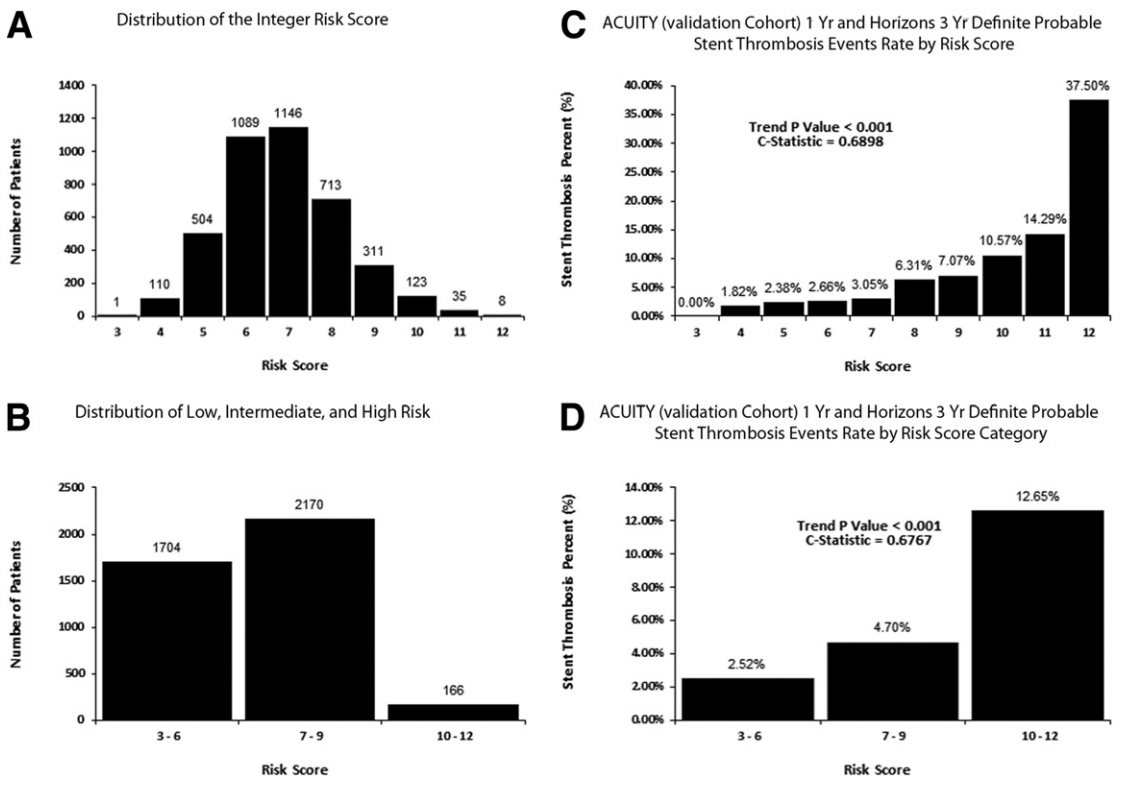

Figure 3. Distribution of the Integer Risk Score and Consequent Probability of Definite/Probable ST Within 1 Year in the Validation Cohort (Dataset) Enriched With 3-Year Follow-Up Data in HORIZONS-AMI

Distribution of the integer risk score **(A)**; incidence of definite/probable stent thrombosis (ST) by risk score integer **(B)**; distribution of low-, intermediate-, and high-risk categories **(C)**; and incidence of ST by risk category **(D)**. ACUITY = Acute Catheterization and Urgent Intervention Triage Strategy; HORIZONS-AMI = Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction.

study did not assess the discontinuation of antiplatelet therapy, which is a known important modifier of ST risk during the follow-up time (3), because we aimed to derive a risk score for ST based on information available solely at the time of stent implantation procedure.

Angiographic variables of this risk score largely reflect the thrombotic load. A baseline TIMI grade flow of 0 or 1 at the target lesion of an ACS patient signifies an occlusive thrombus at the time of PCI, and a final TIMI grade flow <3 during an ACS generally indicates distal embolization and microvascular impairment from microthrombi and vasoactive substances. Aneurysms or ulcerations at the target lesion site have also been used as indicators of thrombus (15). All of these parameters have also been associated with unfavorable outcomes in part due to possible misinterpretation of the true vessel size during stent implantation, possibly leading to malapposition (24,25). The number of treated vessels during the index PCI procedure during an ACS was also an important risk factor of ST. Finally, thrombus extraction before STEMI angioplasty has been associated with improved outcomes in a single large study (26). This study was completed after HORIZONS-AMI enrollment; the very low rate of aspiration thrombectomy in HORIZONS-AMI precluded the meaningful assessment of this variable in the present risk score.

We did not include the type of stent used, because no major difference in ST has been found between bare-metal stents and first-generation drug-eluting stent types within the trials we analyzed (19). This also has been reported by other research groups (27). Whether newer generation drug-eluting stents or future bioabsorbable or other stent designs may affect the incidence of ST, particularly very late ST, remains a question for further investigation. Recent evidence indeed suggests a suppression of ST with a widely studied second-generation drug-eluting stent (27).

The present risk score was developed and validated in patients with ACS; therefore, it may not be applicable to the large population of patients with elective or nonurgent PCI. It is also possible that other variables, such as multilesion/multistent PCI, SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score (28), bifurcation anatomy, and lesion or stent length may be preferable for inclusion in an ST risk score for use in an elective/nonurgent

PCI population. By contrast, the present risk score could also be validated in an elective/nonurgent PCI population with simple exclusion of the nonapplicable variables or in combination with an angiographic burden/jeopardy score (either for the entire coronary anatomy or of the target areas of the index PCI/stenting).

Risk factors associated with ST are multifactorial; in this respect, the present study has not been able to incorporate intravascular ultrasound imaging, genotyping information, and thienopyridine nonadherence or resistance data. Although each of these categories of risk factors has been indeed implicated in ST, very rarely are they taken under account at the time of PCI/stenting, especially in the urgent ACS setting. Very low rate of intravascular ultrasound use, almost nonexistent testing for genotypes and very scarce testing for platelet function have been documented in worldwide clinical practice for a variety of reasons. Even from a statistical point of view, the application of too many variables in the prediction model for such a rare clinical event would weaken the analysis methodology by overfitting the model. However, the aim of the current study was to provide a simple risk score that can be used to determine the risk of ST in ACS patients at the end of the procedure. Therefore, we opted to focus on a practical approach to assessing ST risk with use of readily available at time of PCI clinical and angiographic variables. Based on this risk assessment tool, practicing physicians could then triage the use of these additional risk factors in accordance to future studies and treatment guidelines.

Study limitations. This analysis of ST risk estimation was based on 2 clinical trials: 1 in patients with STEMI; 1 in patients with unstable angina or non-STEMI. In these trials, no data were collected on deployment pressure and CYP2C19 alleles. In addition, thrombus extraction before STEMI angioplasty has been associated with improved outcomes (26); only a small proportion of patients in the ACUITY and HORIZONS-AMI trials received this adjunctive treatment that limited our ability to investigate a potential protective effect. As HORIZONS-AMI and ACUITY were randomized clinical trials with specific inclusion and exclusion criteria, further validation of this risk score in different ACS trials and registries conducted by other research groups would be desirable. Finally, further validation in patients undergoing an elective or nonurgent PCI with stent implantation would be ideally done within other large trials or registries conducted in appropriately defined patient populations.

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