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A Risk Score to Predict Bleeding in Patients With Acute Coronary Syndromes

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Objectives The aim of this study was to develop a practical risk score to predict the risk and implications of major bleeding in acute coronary syndromes (ACS).

Background Hemorrhagic complications have been strongly linked with subsequent mortality in patients with ACS.

Methods A total of 17,421 patients with ACS (including non–ST-segment elevation myocardial infarction [MI], ST-segment elevation MI, and biomarker negative ACS) were studied in the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) and the HORIZONS-AMI (Harmonizing Outcomes with RevascularizatiON and Stents in Acute Myocardial Infarction) trials. An integer risk score for major bleeding within 30 days was developed from a multivariable logistic regression model.

Results Non-coronary artery bypass graft surgery (CABG)-related major bleeding within 30 days occurred in 744 patients (7.3%) and had 6 independent baseline predictors (female sex, advanced age, elevated serum creatinine and white blood cell count, anemia, non–ST-segment elevation MI, or ST-segment elevation MI) and 1 treatment-related variable (use of heparin + a glycoprotein IIb/IIIa inhibitor rather than bivalirudin alone) (model c-statistic = 0.74). The integer risk score differentiated patients with a 30-day rate of non–CABG-related major bleeding ranging from 1% to over 40%. In a time-updated covariate-adjusted Cox proportional hazards regression model, major bleeding was an independent predictor of a 3.2-fold increase in mortality. The link to mortality risk was strongest for non–CABG-related Thrombolysis In Myocardial Infarction (TIMI)-defined major bleeding followed by non-TIMI major bleeding with or without blood transfusions, whereas isolated large hematomas and CABG-related bleeding were not significantly associated with subsequent mortality.

Conclusions Patients with ACS have marked variation in their risk of major bleeding. A simple risk score based on 6 baseline measures plus anticoagulation regimen identifies patients at increased risk for non–CABG-related bleeding and subsequent 1-year mortality, for whom appropriate treatment strategies can be implemented. (J Am Coll Cardiol 2010;55:2556–66) © 2010 by the American College of Cardiology Foundation

Hemorrhagic complications have emerged as an independent risk factor for subsequent mortality in patients with acute coronary syndromes (ACS) and in those undergoing percutaneous coronary intervention (PCI), representing a hazard equivalent to or greater than that for myocardial infarction (MI) (1–7). Major bleeding also considerably prolongs the hospital stay and increases resource consumption, representing an important source of excess expenditures (8). Minimizing bleeding complications (most of which are iatrogenic, attributable to femoral arterial access in concert with use of potent antiplatelet and antithrombin

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medications) is therefore an important objective in the management of patients with ACS.

Current strategies to reduce hemorrhagic complications include the use of newer antithrombotic medications with reduced potential for bleeding, avoidance of overdosing, and identifying patients at risk for major bleeding events (for whom radial artery access or other approaches might be indicated) (9–13). Contemporary large-scale studies have consistently identified elderly patients, women, and patients with impaired renal function and/or baseline anemia to be at increased risk for bleeding (5,6,12). The relative hazard of these factors and their interaction have been incompletely characterized, and large databases are required to identify the independent correlates of bleeding. Identifying the patient at risk for hemorrhagic complications is especially important, given the introduction of newer, more potent antiplatelet and antithrombin agents, which might increase bleeding complications (14,15). The development of a simple-to-use risk score for bleeding could standardize quality of care and patient outcomes. Risk stratification could also be employed to compare outcomes across clinical studies and institutions. Therefore, we pooled the databases from the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) and HORIZONS-AMI (Harmonizing Outcomes with RevascularizatiON and Stents in Acute Myocardial Infarction) trials to develop and test the performance of a practical risk score to predict the risk and implications of major bleeding in ACS.

Methods

Study design. The design and principal results of the ACUITY and HORIZONS-AMI trials have been published (11,16–19). In brief, in the ACUITY trial, 13,819 patients with moderate- and high-risk ACS (unstable angina or non–ST-segment elevation myocardial infarction [NSTEMI]) were randomly assigned in an open-label fashion to 1 of 3 antithrombotic regimens before cardiac catheterization: heparin (unfractionated or enoxaparin) plus a glycoprotein IIb/IIIa inhibitor (GPI), bivalirudin plus a GPI, or bivalirudin monotherapy, in which GPI administration was permitted only for bail-out indications (11,16,17). Patients assigned to a GPI arm were randomized again in a 2 × 2 factorial design to either upstream GPI initiation in all patients immediately after randomization or to deferred GPI initiation for selective use in PCI patients only, starting in the catheterization laboratory. Either eptifibatide or tirofiban was permitted, per Food and Drug Administration-approved labeling, for upstream use, and either eptifibatide or abciximab was permitted for deferred selective use. The details of the dosing and timing of the study medications have been previously described (11,16,17).

Coronary angiography was required within 72 h of randomization with subsequent triage to PCI, coronary artery bypass graft surgery (CABG), or medical management as per standard of care. Aspirin was administered before angiography. A loading dose of 300 mg of clopidogrel was required in all cases no later than 2 h after PCI. Blood product transfusions were performed at the discretion of the treating physician for clinical indications.

In HORIZONS-AMI, 3,602 patients with ST-segment elevation myocardial infarction (STEMI) who presented within 12 h after symptom onset in whom primary PCI was planned were randomly assigned in an open-label fashion in a 1:1 ratio to treatment with unfractionated heparin plus a GPI or to bivalirudin monotherapy (18,19). 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) was administered before catheterization. The details of the study medication dosing and timing have been previously described (18,19). After patency was restored in the infarct-related vessel, 3,006 eligible patients were randomly assigned again—in a 3:1 ratio—to either TAXUS paclitaxel-eluting stents or uncoated but otherwise identical bare-metal stents (Boston Scientific, Natick, Massachusetts).

Abbreviations and Acronyms

ACS = acute coronary syndromes
CABG = coronary artery bypass graft surgery
CI = confidence interval
GPI = glycoprotein IIb/IIIa inhibitor
HR = hazard ratio
MI = myocardial infarction
NSTEMI = non–ST-segment elevation myocardial infarction
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction

Major bleeding was defined in both trials as the composite of intracranial or intraocular bleeding, access site hemorrhage requiring intervention, reduction in hemoglobin of ≥4 g/dl without or ≥3 g/dl with an overt bleeding source, reoperation for bleeding, or blood product transfusion (11,16–19). For the purpose of this analysis, isolated hematomas have been excluded from the criteria for a major bleed and were analyzed separately. Bleeding was adjudicated as whether related or not related to the performance of CABG. All primary and secondary end points of the 2 trials including major bleeding were adjudicated by a blinded Clinical Events Committee under the same supervision and using the same definitions (11,16–19). The ACUITY and HORIZONS-AMI trials were conducted according to the Declaration of Helsinki and were approved by the institutional review board or ethics committee at each participating center, and all patients provided written informed consent.

Statistical analysis. The databases of the ACUITY and HORIZONS-AMI trials were combined, from which the univariate associations of 20 baseline variables and randomized treatment with major bleeding within 30 days and death within 1 year were determined. A forward stepwise logistic regression model was used to identify the independent predictors of non–CABG-related major bleeding within 30 days; a p value <0.01 was the criterion for inclusion in the final model. The logistic model predictor was converted to a more user-friendly integer score, pre-

dicting an individual's probability of major bleeding within 30 days. With each quantitative factor grouped into convenient categories (e.g., 10-year age-group), an individual's score increases by an integer amount for each level above the lowest category. Each integer amount is a rounding of the exact figure obtained from the logistic model. We determined that a 0 score should mean that a person is at very low risk (e.g., a man under age 50 years with the lowest-risk category of each other predictor). Because the effect of randomized treatment is assessed subsequently, the integer risk score first assumes the patient received heparin plus a GPI. If instead they received bivalirudin monotherapy, one can subtract 5 from the integer score.

The model's goodness of fit was assessed by calculating the risk score for every patient and categorizing these scores into 4 categories from low risk to very high risk. The actual observed percentage with a major bleed in each category was compared with the expected percentage, the latter being the sum of the individual predicted probabilities from the logistic model.

To investigate the impact of the occurrence of major bleeding and MI on the occurrence and timing of subsequent mortality, baseline and randomized treatment adjusted Cox models were fitted with each adverse event as a time-updated binary covariate (20). To estimate the time-dependent risk on mortality of major bleeding and MI, the Cox models were extended to have different time-updated binary covariates for different time intervals (i.e., days 0 to 1, days 2 to 7, days 8 to 30, and days 31+ after the event). Further models then introduced time-updated covariates for 4 different types of protocol-defined major bleed in increasing order of severity: large hematoma only, other major bleed without blood transfusion, bleeding with blood transfusion, and Thrombolysis In Myocardial Infarction (TIMI)-defined major bleed. Each bleed was assigned to its most severe category.

All analyses were carried out with STATA version 10.1 (StataCorp, College Station, Texas). All significance levels are 2-sided. All statistical data analyses were performed at an independent data coordinating center, separate from the clinical coordinating and data coordinating centers of these 2 trials.

Results

Incidence and predictors of non–CABG-related major bleeding. A non–CABG-related major bleed occurred within 30 days of randomization in 520 (3.8%) of the 13,819 ACUITY patients and in 224 (6.2%) of the 3,602 HORIZONS-AMI patients. Within 1-year after randomization, death had occurred in 514 (3.7%) ACUITY patients and 146 (4.1%) HORIZONS-AMI patients. Table 1 displays the univariate associations of 20 baseline characteristics with 30-day major bleeding and with 1-year mortality in the combined ACUITY and HORIZONS-AMI trials.

Multivariable analysis selected 6 baseline demographic and laboratory variables and 1 treatment-related variable as independent predictors of non–CABG-related major bleeding within 30 days (Table 2): female sex, advanced age, elevated serum creatinine and white blood cell count, anemia, presentation (STEMI and raised biomarkers [NSTEMI]), and randomized treatment (heparin + GPI as compared with bivalirudin monotherapy [in ACUITY and HORIZONS-AMI] and bivalirudin + GPI as compared with bivalirudin monotherapy [in ACUITY]) (model *c*-statistic = 0.74). The integer risk score derived from this model appears in Figure 1. It consists of the summation of 6 integers (1 from each baseline variable), representing the individual risk of bleeding if the patent received heparin + a GPI. If bivalirudin is administered instead, 5 points are subtracted from the integer score. Figure 2 shows the risk distribution and the predicted probability of a major bleed in all 17,421 patients for each integer score, assuming they were taking heparin plus a GPI. From observation of these data, 4 categories of bleeding might arbitrarily be defined: low, moderate, high, and very high, corresponding to integer scores <10, 10 to 14, 15 to 19, and ≥ 20, respectively (with 30-day non–CABG-related bleeding rates of 1.9%, 3.3%, 6.9%, and 12.4%, respectively, in patients treated with a heparin plus a GPI and 0.7%, 2.0%, 3.7%, and 8.4%, respectively, in patients treated with bivalirudin monotherapy).

Table 3 shows the observed incidence of 30-day non–CABG-related major bleeding by randomized treatment for patients in these 4 risk categories as well as the expected incidence, on the basis of each individual patient's predicted risk calculated from the logistic model in Table 2. Close agreement between the observed and expected bleeding rates were present. In all 4 risk categories the incidence of major bleeding was higher in patients treated with heparin plus a GPI compared with bivalirudin alone, although the absolute risk difference was greatest in those at very high risk (12.4% vs. 8.4%, representing 4 major bleeds prevented for every 100 patients treated with bivalirudin monotherapy rather than heparin plus a GPI).

Non–CABG-related major bleeding and mortality risk. Table 4 presents the multivariable Cox model relating deaths within 1 year (n = 660 [3.8%] of 17,421 patients) in the combined ACUITY/HORIZONS-AMI database to independent baseline predictors. A total of 9 independent predictors of 1-year mortality were identified, of which advanced age, elevated white blood cell count and serum creatinine, diabetes, and reduced hemoglobin were the most highly significant. Randomized treatment assignment was not an independent predictor of mortality in this model.

Both the occurrence of non–CABG-related major bleeding and MI within 30 days were independent predictors of subsequent mortality, when added to this multivariate model as time-updated covariates, with comparable hazard ratios (HRs) of 3.2 and 3.0, respectively, each $p < 0.001$ (Fig. 3). A difference in the temporal relationship between

Table 1 Baseline Characteristics by Non–CABG-Related Protocol-Defined Major Bleeding Within 30 Days and Mortality Within 1 Year

	Total	Major Bleeding Within 30 Days	Death Within 1 Year
Total	17,421	744 (4.3%)	660 (3.8%)
Study			
ACUITY	13,819	520 (3.8%)	514 (3.7%)
HORIZONS-AMI	3,602	224 (6.2%)	146 (4.1%)
Presentation*			
Biomarker-negative ACS	5,160	163 (3.2%)	128 (2.5%)
NSTEMI-raised biomarkers	7,552	330 (4.4%)	341 (4.5%)
STEMI	3,602	224 (6.2%)	146 (4.1%)
Treatment			
UFH/Enox + GPI	6,405	348 (5.4%)	258 (4.0%)
Bivalirudin monotherapy	6,412	209 (3.3%)	229 (3.6%)
Bivalirudin + GPI	4,604	187 (4.1%)	173 (3.8%)
Age, yrs	62.1 ± 11.7	67.4 ± 12.1	70.6 ± 10.9
Sex			
Male	12,422	395 (3.2%)	461 (3.7%)
Female	4,999	349 (7.0%)	199 (4.0%)
Weight, kg	84.6 ± 18.0	79.8 ± 19.0	80.3 ± 18.6
Ethnic group			
Caucasian	15,605	656 (4.2%)	595 (3.8%)
Other	1,805	88 (4.9%)	65 (3.6%)
Diabetic status			
Any	4,445	234 (5.3%)	251 (5.6%)
None	12,863	506 (3.9%)	404 (3.1%)
Noninsulin diabetes	3,093	149 (4.8%)	148 (4.8%)
Insulin-requiring diabetes	1,352	85 (6.3%)	103 (7.6%)
Current cigarette smoker	5,595	211 (3.8%)	171 (3.1%)
Hypertension	11,136	513 (4.6%)	480 (4.3%)
Previous MI	4,614	180 (3.9%)	210 (4.6%)
Previous PCI	5,706	182 (3.2%)	201 (3.5%)
Previous CABG	2,570	104 (4.0%)	137 (5.3%)
Serum creatinine, mg/dl			
Median (IQR)	1.00 (0.82–1.14)	1.06 (0.87–1.30)	1.10 (0.90–1.39)
n >2.5 mg/dl	108 (0.7%)	11 (1.6%)	12 (2.0%)
Creatinine clearance, ml/min			
Median (IQR)	87 (66–112)	68 (49–92)	64 (47–83)
n >250 ml/min	41 (0.3%)	1 (0.1%)	1 (0.2%)
Hematocrit, %	41 ± 5	40 ± 6	40 ± 6
Hemoglobin, g/dl	14.1 ± 1.6	13.5 ± 2.1	13.5 ± 1.9
Anemia†	2,525	209 (8.3%)	178 (7.0%)
Platelet count, g/dl	240 ± 69	252 ± 85	241 ± 87
White blood cell count, giga/l			
Median (IQR)	8.5 (6.8–10.7)	9.4 (7.5–12.1)	9.6 (7.6–12.7)
n >20 giga/l	136 (0.8%)	22 (3.1%)	19 (3.1%)

Values are n, n (%), or mean ± SD unless otherwise indicated. *Biomarkers in non–ST-segment elevation myocardial infarction (NSTEMI) patients; HORIZONS-AMI (Harmonizing Outcomes with RevascularizatiON and Stents in Acute Myocardial Infarction) patients were all ST-segment elevation myocardial infarction (STEMI) presentation. †Men: hemoglobin <13 g/dl; women: hemoglobin <12 g/dl.

ACUITY = Acute Catheterization and Urgent Intervention Triage strategy; CABG = coronary artery bypass grafting; IQR = interquartile range; MI = myocardial infarction; PCI = percutaneous coronary intervention; UFH/Enox + GPI = unfractionated heparin or enoxaparin plus a glycoprotein IIb/IIIa inhibitor.

the impact of these variables on mortality was noted, however. After an MI the mortality risk declined over time, such that there is no evidence of excess mortality risk beyond 30 days after the event, whereas after a non–CABG-related major bleed the associated mortality increase remained significantly elevated even >30 days later.

Table 5 displays the hierarchical incidence of non–CABG-related major bleeding within 30 days, ranked in order of severity (from greatest to least) as TIMI-defined major bleed, non-TIMI major bleed with transfusion, major bleed without transfusion, and large hematoma only. Figure 4 shows the relationship between the severity of non–

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Table 2 Independent Predictors of Non–CABG-Related Major Bleeding Within 30 Days, With Multiple Logistic Regression

Risk Factor	Odds Ratio	95% CI	Coefficient*	z Value†
Sex				
Male	1.00	—	—	
Female	2.32	1.98–2.72	0.84	10.36
Age, per 5 yrs	1.17	1.13–1.21	0.157	8.79
Serum creatinine, per 0.1 mg/dl	1.09	1.07–1.12	0.088	7.91
White blood cell count, giga/l	1.10	1.07–1.12	0.094	7.83
Anemia				
No	1.00	—	—	
Yes	1.98	1.65–2.37	0.68	7.47
Presentation				
Biomarker-negative ACS	1.00	—	—	
NSTEMI-raised biomarkers	1.26	1.04–1.54	0.23	2.30
STEMI	1.92	1.52–2.44	0.65	5.38
Randomized treatment				
UFH/Enox + GPI	1.00	—	—	
Bivalirudin monotherapy	0.56	0.47–0.67	−0.58	−6.38
Bivalirudin + GPI	0.89	0.73–1.08	−0.12	−1.21

*Intercept = −7.46; †Absolute value of z >1.96, 2.58, 3.29, 3.89, and 4.42 corresponds to p value <0.05, 0.01, 0.001, 0.0001, and 0.00001, respectively.
CI = confidence interval; other abbreviations as in Table 1.

CABG-related major bleeding and subsequent mortality. Non–CABG-related bleeding meeting the TIMI major criteria was an independent predictor of subsequent mortality with an HR of 4.45. Non–CABG-related major bleeding requiring a blood transfusion but otherwise not meeting the TIMI major criteria had a 3-fold increased hazard of mortality, whereas non-TIMI major bleeding not requiring transfusion doubled the risk of subsequent mortality. In contrast, development of a hematoma ≥5 cm without more severe bleeding indexes was not a statistically significant predictor of subsequent mortality.

CABG-related major bleeding. Among 1,600 patients who underwent a planned CABG within 30 days (1,539 and 61 patients in ACUITY and HORIZONS-AMI trials, respectively), 857 (53.6%) experienced a CABG-related major bleed (822 [53.4%] and 35 [57.4%] patients in the ACUITY and HORIZONS-AMI trials, respectively). In a time-updated baseline covariate-adjusted Cox model for mortality, CABG-related major bleeding was not a significant predictor of subsequent mortality in these patients (HR: 1.21, 95% confidence interval [CI]: 0.81 to 1.80, p = 0.34).

Discussion

The main results of the present analysis based on the combined databases from 2 of the largest contemporary

							Add to score
Gender	Male 0				Female +8		
Age (years)	<50 0	50-59 +3		60-69 +6	70-79 +9	≥80 +12	
Serum creatinine (mg/dl)	<1.0 0	1.0- +2	1.2- +3	1.4- +5	1.6- +6	1.8- +8	≥2.0 +10
White blood cell count (giga/l)	<10 0	10- +2	12- +3	14- +5	16- +6	18- +8	≥20 +10
Anemia	No 0				Yes +6		
Presentation	STEMI +6		NSTEMI - Raised biomarkers +2			NSTEMI - Normal biomarkers 0	
Antithrombotic medications	Heparin plus a GPI 0				Bivalirudin monotherapy -5		
	Total Score*						

Figure 1 Integer-Based Risk Score for Non–CABG-Related Major Bleeding Within 30 Days of Patient Presentation With Acute Coronary Syndrome

Example: For a patient who is female, 72 years of age, creatinine 1.3 mg/dl, white cell count 11 giga/l, not anemic, and non–ST-segment elevation myocardial infarction (NSTEMI) without raised biomarkers, her risk score is: 8 + 9 + 3 + 2 + 0 + 0 = 22 total score, signifying a 9.6% chance of a non–coronary artery bypass graft (CABG)-related major bleed within 30 days (Fig. 2). *If patient is on bivalirudin alone rather than heparin plus glycoprotein IIb/IIIa inhibitor (GPI), the total score should be reduced by 5. STEMI = ST-segment elevation myocardial infarction.

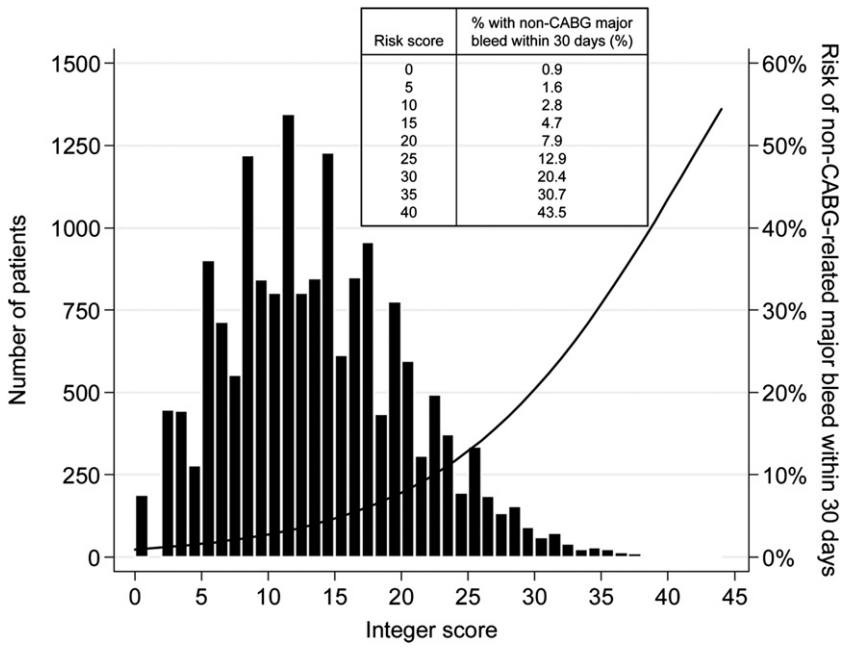

Figure 2 Distribution of the Integer Risk Score and Consequent Probability of a Major Non–CABG-Related Bleed Within 30 Days

Assuming treatment with heparin + glycoprotein IIb/IIIa inhibitor. For patients treated with bivalirudin monotherapy, 5 points should be subtracted from the score. CABG = coronary artery bypass grafting.

randomized trials of patients with NSTEMI and STEMI undergoing an invasive management strategy are as follows: 1) the risk of experiencing a non–CABG-related major bleed within 30 days of presentation varies greatly, depending to a large extent on baseline clinical characteristics, laboratory results, and choice of anticoagulation regimen; 2) a simple integer-based scoring system incorporating 7 variables demonstrated good performance in identifying patients with different risks for major bleeding; 3) the use of bivalirudin as compared with heparin plus a GPI was beneficial among patients with any degree of risk for non–CABG-related major bleeding; 4) after accounting for baseline predictors and therapies, both non–CABG-related major bleeding and MI have a significant impact on subsequent mortality within 1-year; and 5) isolated large hematoma was not a significant independent predictor of mortality, whereas more severe forms of non–CABG-related major bleeding with or without blood transfusion significantly predicted an increase in subsequent mortality. CABG-related major bleeding, however, was not a significant predictor of subsequent death.

As more potent antithrombotic and antiplatelet agents are being introduced to further reduce the incidence of ischemic events in patients with ACS, safety issues—principally hemorrhagic complications—are emerging as a major focus of attention (14,15). Understanding the predictive factors for bleeding is especially important in light of the multiple studies that have firmly established the strong linkage between hemorrhagic complications of drugs and procedures and subsequent mortality in patients with ACS and in those treated with PCI (1–7). The present study confirms and extends these observations. In a time-updated, covariate-adjusted multivariable model, non–CABG-related major bleeding was an independent predictor of subsequent mortality, with an HR of 3.2 (95% CI: 2.6 to 3.9), comparable in prognostic impact to MI after treatment.

Table 3 Incidence of Non–CABG-Related Major Bleeding Within 30 Days According to Risk Score Category (%)

		Heparin + GPI			Bivalirudin Alone		
Risk Category	Integer Score	n	Observed	Expected	n	Observed	Expected
Low	<10	1,969	38 (1.9%)	38.2 (1.9%)	1,876	14 (0.7%)	20.3 (1.1%)
Moderate	10–14	1,795	60 (3.3%)	65.3 (3.6%)	1,907	38 (2.0%)	39.0 (2.0%)
High	15–19	1,406	97 (6.9%)	84.1 (6.0%)	1,362	51 (3.7%)	47.2 (3.5%)
Very high	≥20	1,235	153 (12.4%)	160.4 (13.0%)	1,267	106 (8.4%)	102.5 (8.1%)
Total		6,405	348 (5.4%)		6,412	209 (3.3%)	

Abbreviations as in Table 1.

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Table 4 Independent Predictors of 1-Year Mortality From Multivariable Cox Regression

Risk Factor	Hazard Ratio	95% CI	Coefficient	z Value*
Age, per 5 yrs	1.43	1.37–1.49	0.359	16.45
White blood cell count, giga/l	1.14	1.12–1.17	0.135	11.99
Serum creatinine, per 0.1 mg/dl	1.07	1.05–1.09	0.067	6.04
Diabetic status				
No diabetes	1.00	—	—	
Noninsulin dependent	1.36	1.13–1.65	0.31	3.18
Insulin-dependent	1.92	1.53–2.41	0.65	5.61
Hemoglobin, g/dl	0.87	0.83–0.92	−0.134	−5.19
Presentation				
Normal biomarkers	1.00	—	—	
Raised biomarkers	1.53	1.24–1.88	0.42	3.99
STEMI	1.39	1.07–1.82	0.33	2.43
Current smoker				
No	1.00	—	—	
Yes	1.48	1.22–1.80	0.39	3.90
Sex				
Male	1.00	—	—	
Female	0.76	0.63–0.91	−0.27	−2.93
Previous MI				
No	1.00	—	—	
Yes	1.27	1.07–1.51	0.24	2.70
Randomized treatment				
UFH/Enox + GPI	1.00	—	—	
Bivalirudin monotherapy	0.89	0.74–1.06	−0.12	−1.34
Bivalirudin + GPI	0.97	0.79–1.18	−0.04	−0.34

*Absolute value of $z > 1.96$, 2.58, 3.29, 3.89, and 4.42 corresponds to p value < 0.05, 0.01, 0.001, 0.0001, and 0.00001, respectively.
Abbreviations as in Tables 1 and 2.

The present study has documented an enormous variation in the likelihood for individual patients to develop a non–CABG-related major bleed within 30 days of presentation with ACS, ranging from 1% to over 40%, depending on the patient's risk profile. Non–CABG-related major bleeding was independently predicted by 6 baseline clinical and laboratory-based variables (female sex, advanced age, increased serum creatinine and white blood cell count, anemia, and admission for STEMI or NSTEMI). Several of these factors have been previously described (5,6,21–24). The finding of a higher white blood count predicting major bleeding, perhaps reflecting the influence of systemic inflammation, is novel and deserves future investigation. Of note, the rates of non–CABG-related major bleeding were higher in patients enrolled with STEMI than with NSTEMI (6.2% vs. 3.8%, respectively), although among the latter major bleeding was increased in those with raised biomarkers at baseline. The increased rate of bleeding in patients with STEMI compared with NSTEMI might reflect the urgency of care provided, more frequent use of venous sheaths, unadjusted patient comorbidities, and the more frequent use of a 600-mg loading dose of clopidogrel (25–28). Furthermore, the GPI regimens used were somewhat different in STEMI and NSTEMI in these studies. In NSTEMI patients, approximately 60% of patients received eptifibatide, followed by tirofiban (19%) and abciximab (17%), whereas STEMI patients received primarily abciximab (52%) or eptifibatide (46%) but rarely tirofiban (0.2%). In the Blue Cross Blue Shield of Michigan Cardiovascular Consortium regional registry of contemporary PCI among 3,541 patients undergoing primary PCI, gastrointestinal bleeding was more common in patients treated with abciximab compared with eptifibatide, although the blood transfusion rate was comparable (29). In the randomized, double-blind TARGET (Do Tirofiban and ReoPro Give Similar Efficacy Trial), assignment to abciximab versus tirofiban resulted in similar rates of TIMI major bleeding but higher rates of TIMI minor bleeding with abciximab (30). Abciximab might also be associated with rates of thrombocytopenia higher than other GPIs (31,32).

The frequency of major bleeding rose steadily with an increasing risk score in patients treated with heparin plus a GPI or with bivalirudin monotherapy. However, use of bivalirudin monotherapy rather than heparin plus a GPI resulted in a significant reduction in non–CABG-related major bleeding in both trials (a 39% reduction in the pooled database) as well as across the spectrum of patients with low, moderate, high, and very high risk score for major bleeding (relative reductions 63%, 39%, 46%, and 32%, respectively, representing absolute reductions 1.2%, 1.3%, 3.2%, and 4.0%, respectively). The choice of anticoagulant regimen with low bleeding potential is thus an important option to increase the safety margin when managing patients with ACS. Several scoring systems have been developed to predict major bleeding in patients treated with PCI. In patients undergoing elective PCI in the STEEPLE (Safety and Efficacy of Enoxaparin in PCI Patients, an International Randomized Evaluation) trial, there were only 3 predictors of major bleeding, including female sex, the use of unfractionated heparin versus enoxaparin, and the use of GPI versus no GPI (33). From the REPLACE (Randomized Evaluation in Percutaneous Coronary Intervention Linking Angiomax to Reduced Clinical Events)-1 and -2 randomized trials of patients undergoing PCI with principally stable ischemic heart disease, independent predictors of major bleeding included age >73 years, female sex, chronic renal insufficiency, baseline anemia, systolic blood pressure >150 mm Hg, weight <70 kg, administration of low molecular weight heparin within 48 h before procedure, use of intra-aortic balloon pump, and administration of GPI (34). In the OASIS-5 (Organization to Assess Strategies in Ischemic Syndromes-5) trial of patients with ACS without ST-segment elevation, the GRACE (Global Registry of Acute Coronary Events) risk score (which is known to predict in-hospital and 6-month mortality in patients with ACS) also had a modest ability to predict major bleeding (*c*-statistic 0.63) (28,35). Among community-treated NSTEMI patients enrolled in the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the

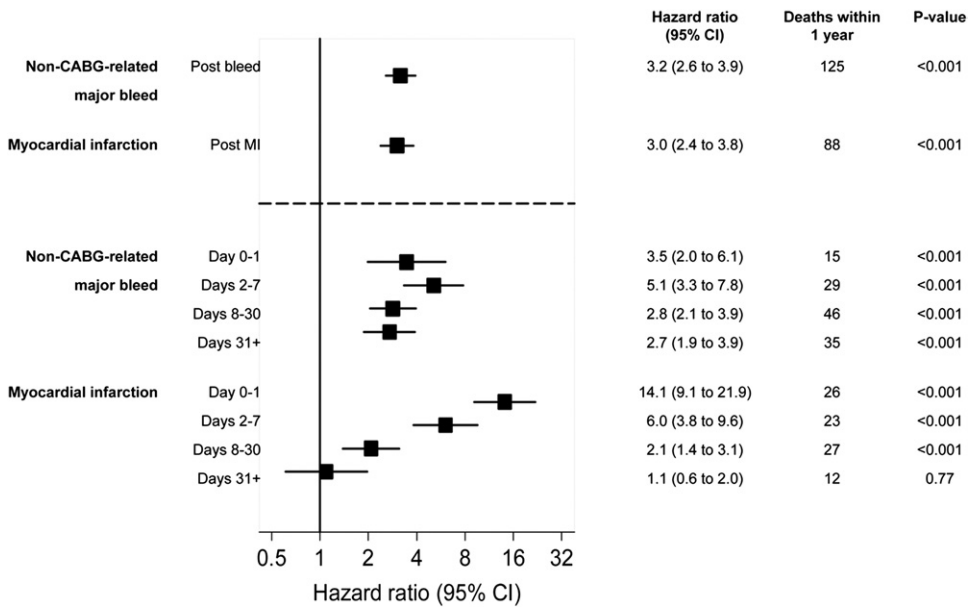

Figure 3 **Independent Hazard of the Occurrence of Major Non–CABG-Related Bleed and of MI Within 30 Days on Subsequent Mortality Within 1 Year**

Adjusted for baseline predictors. Note: 98 patients had both a major bleed and a myocardial infarction (MI) within 30 days, of whom 24 died within 1 year. For such patients, the models in Figure 3 have time-updated covariates for both events. CABG = coronary artery bypass grafting; CI = confidence interval.

ACC/AHA guidelines) Quality Improvement Initiative, the factors independently associated with in-hospital major bleeding included baseline hematocrit, estimated creatinine clearance, baseline heart rate, baseline systolic blood pressure, female sex, signs of congestive heart failure on presentation, prior vascular disease, and diabetes mellitus (*c*-statistic 0.71) (36). The *c*-statistic from the ACUITY/HORIZONS-AMI model (0.74) is slightly higher than these previous models, suggesting better discrimination.

Of note, whereas both non–CABG-related bleeding and MI were independent predictors of mortality in our analysis, the timing of the maximal impact of these adverse events was different. This was previously reported by our group in the population with NSTEMI (37) and now might be extended to the patients with STEMI. Specifically, the hazard of dying after an MI was sharply elevated within the first 24 h after the event, with a steep decline in prognostic impact beyond the first day, such that no significant increase in the risk of death after the 30th day was present. In contrast, the impact of major bleeding on subsequent mortality was significant both within and after 30 days. The possible mechanisms as to how bleeding might affect mortality include hypovolemia and platelet activation that might provoke or exacerbate ischemia and arrhythmias, premature discontinuation of drugs known to improve outcomes after ACS, and the detrimental effects of blood product transfusions (38–42). A potentially important finding from the present analysis is that the prognostic impact of bleeding was found to directly correlate with the severity of the bleeding event, with all classes of non–CABG-related bleeding except isolated large (≥5 cm) hematomas having a statistically significant impact on 1-year mortality. In contrast, a femoral hematoma >4 cm in diameter was an independent predictor of 30-day mortality from a study of 17,901 consecutive patients undergoing PCI from the Mayo Clinic (43). However, in this study the hematoma had to be accompanied by a blood transfusion, surgery, or prolonged hospital stay. The present study is, to our knowledge, the first to examine the impact of isolated hematomas and found that this adverse event, although uncomfortable and disruptive to the patient's recovery, does not significantly affect mortality and thus, in the absence of corrective intervention or transfusion, should not be included in future risk scores to predict mortality.

Table 5 **Hierarchical Incidence of Non–CABG-Related Major Bleeding Within 30 Days**

	ACUITY (n = 13,819)	HORIZONS (n = 3,602)	Total (n = 17,421)
TIMI-defined major bleed	204 (1.5%)	84 (2.3%)	288 (1.7%)
Non-TIMI major bleed with blood transfusion	190 (1.4%)	42 (1.2%)	232 (1.3%)
Non-TIMI major bleed without blood transfusion	172 (1.2%)	98 (2.7%)	270 (1.5%)
Large hematoma only*	124 (0.9%)	14 (0.4%)	138 (0.8%)
Total	690 (5.0%)	238 (6.6%)	928 (5.3%)

Each patient is represented only once according to their most severe bleed. In the ACUITY trial, 46 Thrombolysis In Myocardial Infarction (TIMI) bleeds were not included under the definition for major bleed. *Hematomas are not included in earlier analysis of major bleeds.
Abbreviations as in Table 1.

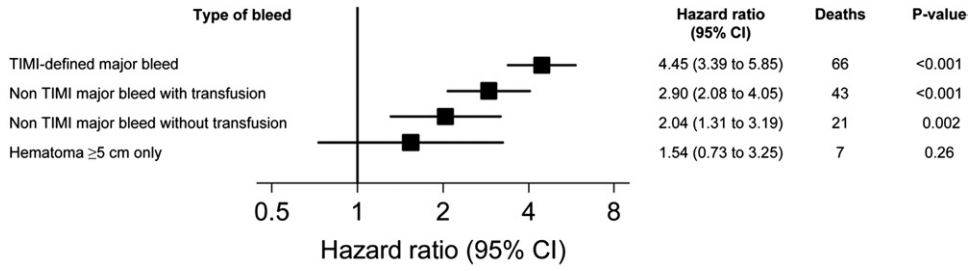

Figure 4 **Independent Hazard of the Occurrence of Different Types of Major Bleed Within 30 Days on Subsequent Mortality Within 1 Year**

Adjusted for baseline predictors. CI = confidence interval; TIMI = Thrombolysis In Myocardial Infarction.

Finally, a novel finding from the present analysis is that CABG-related major bleeding, which occurred in 54% of patients undergoing planned CABG, did not significantly predict subsequent mortality, with an HR of 1.21 (95% CI: 0.81 to 1.80). This is potentially important, because medications that might decrease PCI-related ischemic complications but increase surgical bleeding (e.g., thienopyridines) are often withheld from patients with ACS until angiography confirms a likely nonsurgical management strategy. Moreover, 2 studies have now shown that thienopyridine agents when administered before CABG in patients with ACS might decrease peri-surgical MI rates (44,45). This fact, coupled with the lack of effect of CABG-related bleeding on mortality after surgery in patients with ACS, suggests that thienopyridine agents should be administered as early as possible before cardiac catheterization (i.e., in the ambulance or emergency room), so they might reach their maximal effect in patients undergoing PCI, which represents the majority of the patients with both NSTEMI and STEMI. Nonetheless, the relationship between the severity of CABG-related bleeding and nonfatal clinical outcomes should be further assessed in future studies.

Study limitations. Although the data were collected prospectively, this was a post hoc analysis. Not all variables of potential interest were available in both databases to allow incorporation into the risk model. Although the proposed risk scoring system had adequate performance as assessed by comparison of actual and predicted rates of major bleeding, external validation in another dataset is desirable, especially because the present model was created from randomized clinical trial data.

Conclusions

These limitations notwithstanding, we can conclude that for individuals with ACS there is marked variation in the risk of non–CABG-related major bleeding. A practical ACUITY/HORIZONS-AMI scoring system with 6 readily available baseline clinical and laboratory variables plus the anticoagulation regimen used provides a rapid and reliable tool to predict the rate of non–CABG-related major bleeding in patients with ACS and its impact on subsequent mortality within 1 year. Such knowledge will aid the accurate prognostication of patients with ACS, facilitating appropriate personalized decision-making for the patient at high risk of bleeding and mortality.

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