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Impact of Bleeding on Mortality After Percutaneous Coronary Intervention

Results From a Patient-Level Pooled Analysis of the REPLACE-2 (Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events), ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy), and HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) Trials

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Objectives This study sought to develop a risk score predictive of bleeding in patients undergoing percutaneous coronary intervention (PCI) and to investigate the impact of bleeding on subsequent mortality.

Background Bleeding complications after PCI have been independently associated with early and late mortality.

Methods This study represents a patient-level pooled analysis including 17,034 patients undergoing PCI from 3 large, randomized trials of bivalirudin versus heparin plus glycoprotein IIb/IIIa inhibitors, including the REPLACE-2 (Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events), ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy), and HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trials. We developed a risk score to predict noncoronary artery bypass graft (CABG)–related TIMI (Thrombolysis In Myocardial Infarction) major bleeding and evaluated the impact of various types of bleeding on 1-year mortality.

Results A non-CABG–related TIMI major bleed occurred within 30 days in 267 patients (1.6%), and death occurred in 497 patients (2.9%) within 1 year. A risk score was developed to predict the bleeding risk of patients undergoing PCI, consisting of 7 variables (serum creatinine, age, sex, presentation, white blood cell count, cigarette smoking, and randomized treatment). The TIMI major bleeding rates increased by bleeding risk score groups: from 0.4% for those in the lowest to 5.8% for those in the highest risk group. Non-CABG–related TIMI major bleeding and the occurrence of myocardial infarction within 30 days were independent predictors of subsequent mortality, with respective hazard ratios of 4.2 and 2.9, each $p < 0.001$. Ranked in order of severity, TIMI major bleeding, blood transfusion without TIMI bleed, TIMI minor bleeding requiring blood transfusion, and TIMI minor bleeding not requiring blood transfusion were independent predictors of subsequent mortality with hazard ratios of 4.89, 2.91, 2.73, and 1.66, respectively. Isolated hematomas were not predictive of subsequent mortality.

Conclusions Non-CABG–related bleeding within 30 days is strongly associated with an increased risk of subsequent mortality at 1 year in patients undergoing PCI for all indications. A risk score was established to calculate the bleeding risk for patients undergoing PCI, allowing therapeutic decision making to minimize the incidence of bleeding. (J Am Coll Cardiol Intv 2011;4:654–64) © 2011 by the American College of Cardiology Foundation

The use of multiple antithrombotic drugs along with early invasive strategies has increased the risk of bleeding in patients with acute coronary syndrome (ACS) and in those undergoing percutaneous coronary intervention (PCI) (1–4). Recent studies have shown that bleeding complications have been consistently and independently associated with adverse clinical outcomes, including myocardial infarction (MI), stroke, and death (4–10). Major bleeding is associated with a 2- to 8-fold increase in subsequent mortality in ACS (5–7) and PCI (4–6,8–10). The increase in hazard of death among patients who develop major bleeding is equivalent to or greater than that for those who develop MI (11,12). Notably, the association between bleeding and mortality appears to have a monotonic relationship, that is, increasing severity of bleeding is associated with an increased risk of death (5,13,14).

We recently developed a risk score to predict the rate of noncoronary artery bypass graft (CABG)–related bleeding in ACS patients based upon a pooled analysis of the large-scale multicenter ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy Trial) (15) and HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) (16) trials (13). However, this previous analysis had 2 major limitations that limit its applicability to predict bleeding after PCI: 1) only ACS patients were included; and 2) a large proportion of patients were treated medically or surgically.

To develop a simple-to-use risk score to identify patients undergoing PCI who are at increased risk for bleeding, we now report an analysis from a pooled database of 17,034 patients undergoing PCI in the ACUITY, HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction), and REPLACE-2 (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events) (17) trials. The latter trial principally enrolled patients with stable ischemic heart disease undergoing PCI. We sought to develop a risk score applicable across the spectrum of coronary artery disease risk (i.e., stable angina, unstable angina, ST-segment elevation myocardial infarction [STEMI], and non-STEMI), which may allow personalized decision making to select therapies and subsequently improve clinical outcomes in a broad cross section of patients.

Methods

This study represents a patient-level pooled analysis of PCI patients from 3 large, randomized trials of bivalirudin versus heparin plus glycoprotein IIb/IIIa inhibitors (GPI): the REPLACE-2 trial in stable and unstable ischemic syndromes, the ACUITY trial in unstable angina and non-STEMI, and HORIZONS-AMI trial in patients with STEMI. The design and principal results of each trial have been published previously (15–19). In brief, in the REPLACE-2 trial, 6,010 patients undergoing elective or urgent PCI were randomized to heparin plus a GPI (abciximab or eptifibatide) or bivalirudin with provisional GPI use. Provisional GPI with either abciximab or eptifibatide could be administered for procedural or angiographic complications in the bivalirudin group. All patients received aspirin, and pretreatment with clopidogrel with daily administration for at least 30 days after intervention was strongly encouraged.

In ACUITY, 13,819 patients with moderate- and high-risk ACS were randomly assigned to 1 of 3 antithrombotic regimens before cardiac catheterization: a heparin (unfractionated or enoxaparin) plus a GPI, bivalirudin plus a GPI, or bivalirudin monotherapy, in which GPI administration was

Abbreviations and Acronyms

ACS = acute coronary syndrome(s)
CABG = coronary artery bypass graft
GPI = glycoprotein IIb/IIIa inhibitor
HR = hazard ratio
MI = myocardial infarction
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction

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permitted only for bail-out indications (15,18). All patients received aspirin, and timing and dosing of clopidogrel was left to the discretion of investigators and treating physicians. The details of the dosing and timing of the study medications has been previously described (15,18).

In HORIZONS-AMI, 3,602 patients with STEMI who presented within 12 h after symptom onset in whom primary PCI was planned were randomly assigned to treatment with unfractionated heparin plus a GPI or to bivalirudin monotherapy (16,19). Aspirin and clopidogrel (either 300 mg or 600 mg, at the discretion of the investigator), or ticlopidine (500 mg in the case of allergy to clopidogrel) was administered before catheterization (16,19).

For the purpose of the current analysis, only those patients were selected who actually underwent PCI as their primary treatment and who did not have a TIMI (Thrombolysis In Myocardial Infarction) major bleed before the index PCI (REPLACE-2: n = 5,902, ACUITY: n = 7,783, HORIZONS-AMI: n = 3,349, combined: n = 17,034). All primary and secondary endpoints of the 3 trials including major bleeding were adjudicated by a blinded clinical events committee. Bleeding was adjudicated as related or not related to the performance of CABG. Only major bleeding complications adjudicated as unrelated to CABG are included in the current analysis. In the REPLACE-2 trial, major bleeding was defined as intracranial, intraocular, or retroperitoneal hemorrhage; clinically overt blood loss resulting in a decrease in hemoglobin of more than 3 g/dl; any decrease in hemoglobin of more than 4 g/dl; or transfusion of 2 or more units of packed red blood cells or whole blood. In HORIZONS-AMI and ACUITY, the definition of major bleeding included all the above, plus access site hemorrhage requiring intervention and hematoma ≥5 cm at the puncture site. Moreover, any blood product transfusion was regarded as a major bleeding. For the purpose of the current analysis, using detailed clinical and laboratory data, overall major bleeding was classified in a hierarchy from severe to mild as TIMI major bleeding, blood transfusion with no TIMI bleed, TIMI minor bleeding with blood transfusion, TIMI minor bleeding without blood transfusion, or isolated large hematoma (≥5 cm). The TIMI bleeding definition has been published in detail previously (20). Likewise, the definition of MI in the REPLACE-2, ACUITY, and HORIZONS-AMI trials have been published in detail previously (15–17).

The REPLACE-2, 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. For each study, all patients provided written informed consent.

Statistical analysis. The databases of the REPLACE-2, ACUITY, and HORIZONS-AMI trials were combined, and from these, the univariate associations of 20 baseline variables and randomized treatment with non-CABG–related TIMI major bleeding within 30 days and death within 1 year were determined. A forward stepwise logistic regression model was used to identify the independent predictor TIMI major bleeding within 30 days; $p < 0.1$ was the criterion for inclusion in the final model. The logistic model predictor was converted to a more user-friendly integer score predicting an individual's probability of bleeding within 30 days. Having grouped each quantitative factor 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. A 0 score indicates a person at very low risk: for example, a man under 50 years of age 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.

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 TIMI major bleeding 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 TIMI 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 (21). To estimate the time-dependent risk on mortality of TIMI major bleeding and MI, the Cox models were extended to have different time-updated binary covariates for different time intervals, that is, days 0 to 1, days 2 to 7, days 8 to 30, and days 31+ post-event. Further models then introduced covariates for 5 different types of bleeding: TIMI major bleeding, TIMI minor bleeding with blood transfusion, blood transfusion with no TIMI bleed, TIMI minor bleeding without blood transfusion, and large hematoma only (≥5 cm). Each bleeding was assigned to its most severe category. All analyses were carried out using 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 the 3 trials. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Incidence and predictors of non-CABG–related bleeding. Among 17,041 patients undergoing PCI in the 3 trials, 7 patients were excluded for the current analysis as they experienced a TIMI major bleed before their index PCI. Among the

Table 1. Baseline Characteristics

		Total Number of Patients	TIMI Major Bleeding Within 30 Days	Death Within 1 Year
Total*		17,034	267 (1.6%)	497 (2.9%)
Study	REPLACE-2	5,902	43 (0.7%)	124 (2.1%)
	ACUITY	7,783	137 (1.8%)	239 (3.1%)
	HORIZONS-AMI	3,349	87 (2.6%)	134 (4.0%)
Presentation†	Normal biomarkers (Elective/ACS)	6,626	69 (1.0%)	144 (2.2%)
	Raised biomarkers (NSTEMI)	5,206	102 (2.0%)	175 (3.4%)
	STEMI	3,349	87 (2.6%)	134 (4.0%)
ACS‡	No ACS	4,551	33 (0.7%)	102 (2.2%)
	ACS	9,134	147 (1.6%)	261 (2.9%)
	STEMI	3,349	87 (2.6%)	134 (4.0%)
Treatment	UFH/Enox + GPI	7,178	135 (1.9%)	225 (3.1%)
	Bivalirudin alone	7,249	71 (1.0%)	189 (2.6%)
	Bivalirudin + GPI	2,607	61 (2.3%)	83 (3.2%)
Age, yrs		62.2 ± 11.4	66.6 ± 12.1	70.5 ± 10.7
Sex	Male	12,668	168 (1.3%)	337 (2.7%)
	Female	4,366	99 (2.3%)	160 (3.7%)
Weight, kg		85.6 ± 17.8	81.5 ± 18.2	80.1 ± 18.3
Ethnic groups	Caucasian	15,587	239 (1.5%)	448 (2.9%)
	Other	1,439	28 (1.9%)	49 (3.4%)
Diabetic status	Any	4,283	82 (1.9%)	187 (4.4%)
	None	12,691	184 (1.4%)	308 (2.4%)
	Noninsulin diabetes	3,073	56 (1.8%)	116 (3.8%)
	Insulin-requiring diabetes	1,210	26 (2.1%)	71 (5.9%)
Current cigarette smoker		5,450	98 (1.8%)	128 (2.3%)
Hypertension		10,771	173 (1.6%)	356 (3.3%)
Previous MI		4,829	71 (1.5%)	170 (3.5%)
Previous PCI		5,391	65 (1.2%)	158 (2.9%)
Previous CABG		2,538	34 (1.3%)	112 (4.4%)
Serum creatinine, mg/dl		1.00 (0.84–1.14)	1.10 (0.90–1.30)	1.10 (0.90–1.40)
	n >2.5 mg/dl	73 (0.4)	4 (1.6)	14 (3.0)
CrCl, ml/min		89 (67–114)	74 (49–99)	64 (47–82)
	n >250 ml/min	45 (0.3)	0 (0.0)	1 (0.2)
Hematocrit, %		41 ± 5	41 ± 7	39 ± 6
Hemoglobin, g/dl		14.0 ± 1.6	13.8 ± 2.0	13.3 ± 2.0
Anemia§		2,818	64 (2.3%)	154 (5.5%)
Platelet count, g/dl		237 ± 67	250 ± 82	245 ± 90
White blood cell count, 10^9/l		8.1 (6.5–10.3)	9.2 (7.3–12.0)	9.3 (7.3–12.6)
	n >20 10^9/l	115 (0.7)	10 (3.8)	14 (3.0)

Values are n, mean ± SD, n (%), or median (interquartile range). *Excludes 7 patients (0 deaths) undergoing PCI who experienced a TIMI major bleed before the procedure. †Biomarkers in non-STEMI patients. ‡ACS in non-STEMI patients. Note all HORIZONS-AMI patients were included as STEMI presentation. §Men: hemoglobin <13 g/dl; Women: hemoglobin <12 g/dl.

ACS = acute coronary syndrome(s); ACUITY = Acute Catheterization and Urgent Intervention Triage Strategy Trial; CABG = coronary artery bypass graft; CrCl = creatinine clearance; Enox = enoxaparin; GPI = glycoprotein IIb/IIIa inhibitor; HORIZONS-AMI = Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; REPLACE-2 = Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction; UFH= unfractionated heparin; UFH/Enox + GPI = unfractionated heparin or enoxaparin plus a glycoprotein IIb/IIIa inhibitor.

remaining 17,034 patients, a TIMI major bleed occurred within 30 days of randomization in 43 of 5,902 (0.7%) REPLACE-2 patients, 137 of 7,783 (1.8%) ACUITY patients, and 87 of 3,349 (2.6%) HORIZONS-AMI patients. Within 1 year after randomization, death had occurred in 124 (2.1%) REPLACE-2 patients, 239 (3.1%) ACUITY patients, and 134 (4.0%) HORIZONS-AMI patients. Table 1 displays baseline characteristics for all patients included in the current analysis, those with 30-day TIMI major bleeding, and those with 1-year mortality in the combined REPLACE-2, ACUITY, and HORIZONS-AMI trials.

Multivariable analysis selected 6 baseline demographic and laboratory variables and 1 treatment-related variable as

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Table 2. Independent Predictors of Non-CABG–Related TIMI Major Bleeding Within 30 Days, Using Multiple Logistic Regressions

Risk Factor		Odds Ratio	95% CI	Coefficient*	z Score†
Serum creatinine	Per 0.1 mg/dl	1.12	1.09–1.16	0.117	6.87
Age	Per 5 yrs	1.21	1.14–1.29	0.190	5.92
Sex	Male	1.00	—	—	—
	Female	1.77	1.36–2.31	0.57	4.23
Presentation	Normal biomarkers (Elective/ACS)	1.00	—	—	—
	NSTEMI – raised biomarkers	1.49	1.08–2.05	0.40	2.40
	STEMI	2.16	1.50–3.12	0.77	4.15
White blood cell count	Per 10^9/l	1.08	1.03–1.12	0.073	3.64
Current cigarette smoker	No	1.00	—	—	—
	Yes	1.67	1.25–2.24	0.51	3.43
Randomized treatment	UFH/Enox + GPI	1.00	—	—	—
	Bivalirudin alone	0.50	0.37–0.67	−0.70	−4.70
	Bivalirudin + GPI	1.34	0.96–1.88	0.29	1.70

*Intercept = −8.97. †Absolute value of z score >1.96, 2.58, 3.29, 3.89, 4.42 corresponds to p value <0.05, 0.01, 0.001, 0.0001, 0.00001, respectively.
CI = confidence interval; other abbreviations as in Table 1.

independent predictors of TIMI major bleeding within 30 days (Table 2): elevated serum creatinine, advanced age, female sex, presentation (by normal biomarkers [elective/ACS], raised biomarkers [non-STEMI], and STEMI), elevated white blood cell count, current cigarette smoking, and randomized treatment (heparin + GPI as compared with bivalirudin monotherapy [in REPLACE-2, 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) that represent the individual risk of bleeding if the patient received heparin + a GPI. If bivalirudin is administered instead, 6 points are subtracted from the integer score. Figure 2 shows the risk distribution and the predicted probability of a bleeding in all 17,034 patients for each integer score assuming they were on heparin + a GPI. From observation of these data, 4 categories for bleeding risk may arbitrarily be defined: low, moderate, high, and very high corresponding to integer scores <10, 10 to 14, 15 to 19, and ≥20, respectively. Table 3 shows the observed incidence of 30-day TIMI major bleeding, overall major bleeding, and its individual components in these 4 risk categories. When compared with heparin + a GPI, bivalirudin monotherapy resulted in less 30-day TIMI major bleeding in patients with moderate (0.5% vs. 1.3%), high (1.2% vs. 2.6%), and very high risk (2.8% vs. 5.8%).

Non-CABG–related bleeding and mortality. Table 4 presents the multivariable Cox model relating deaths within 1 year (n = 497 [2.9%] of 17,034 patients) in the combined REPLACE-2/ACUITY/HORIZONS-AMI database to independent baseline predictors. We identified 9 independent predictors of 1-year mortality, of which advanced age, elevated white blood cell count and serum creatinine, reduced hemoglobin, and diabetes were the most strongly related. In this model, bivalirudin monotherapy as compared with unfractionated heparin + GPI was associated with a decreased risk of mortality (hazard ratio [HR]: 0.82), whereas bivalirudin + GPI therapy and unfractionated heparin + GPI had an identical risk (HR: 1.00).

When added to this multivariate model as time-updated covariates, both the occurrence of TIMI major bleeding and the occurrence of MI within 30 days were independent predictors of subsequent mortality, with respective HRs of 4.2 and 2.9, each $p < 0.001$ (Fig. 3). A difference in the temporal relationship between the impact of these variables on mortality was noted, however. Following occurrence of MI, the mortality risk declined over time, whereas following a TIMI major bleeding, the associated mortality increase remained significantly elevated even beyond 30 days.

Table 5 displays the hierarchical incidence of 5 types of non-CABG–related bleeding within 30 days, ranked in order of severity (from greatest to least) as TIMI-defined major bleeding, transfusion with no TIMI bleed, TIMI minor bleeding with transfusion, TIMI minor bleeding without transfusion, and large hematoma only. Figure 4 shows the relationship between the severity of 5 types of non-CABG–related bleeding and subsequent mortality. TIMI major bleeding was an independent predictor of subsequent mortality with an HR of 4.89. TIMI minor bleeding requiring a blood transfusion or a transfusion with no TIMI bleed had an almost 3-fold increased hazard of mortality, whereas TIMI minor bleeding not requiring transfusion nearly 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.

								Add to score
Serum creatinine (mg/dl)	<1.0 0	1.0-<1.2 +2	1.2-<1.4 +4	1.4-<1.6 +6	1.6-<1.8 +8	1.8-<2.0 +10	≥2.0 +12	
Age (years)	<50 0	50-59 +3	60-69 +6	70-79 +9	≥80 +13			
Gender	Male 0	Female +5						
White blood cell count (giga/l)	<10 0	10-<12 +1	12-<14 +2	14-<16 +4	16-<18 +5	18-<20 +6	≥20 +8	
Presentation	Normal biomarkers (elective and NSTEMI) 0	NSTEMI - Raised biomarkers +3	STEMI +6					
Current cigarette smoker	No 0	Yes +4						
Antithrombotic medications	Heparin or Bivalirudin plus a GPI 0	Bivalirudin monotherapy -6						
		Total Score*						

Figure 1. Integer-Based Risk Score for Non-CABG–Related TIMI Major Bleeding Within 30 Days of PCI

For a patient who has a creatinine of 1.3 mg/dl, is 72 years of age, is female, has a white cell count of 11 10^9/l, has non–ST-segment elevation myocardial infarction (NSTEMI) without raised biomarkers, and is a nonsmoker, her risk score would be: 4 + 9 + 5 + 1 + 0 + 0 = 19 total score, signifying a 2.7% chance of a noncoronary artery bypass graft (CABG)–related TIMI (Thrombolysis In Myocardial Infarction) major bleed within 30 days (see Fig. 2). If the patient is treated with bivalirudin alone rather than heparin + a glycoprotein IIa/IIIb inhibitor (GPI), the total score should be reduced by 6 to 13 points, indicating a 1.4% chance of a non-CABG–related TIMI major bleed within 30 days. PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Discussion

This patient-level pooled analysis demonstrates that across a broad spectrum of patients with coronary artery disease undergoing PCI: 1) the occurrence of TIMI major bleeding within 30 days is strongly associated with an increased risk of subsequent mortality at 1 year, even more so than the risk arising from a periprocedural MI; 2) a simple risk model can be created from 6 baseline demographic and laboratory variables and 1 treatment-related variable that is strongly predictive of TIMI major bleeding within 30 days in patients undergoing PCI; and 3) the risk of subsequent mortality depends on the type of bleeding, which ranked in decreasing order of severity—TIMI major bleeding, transfusion with no TIMI bleed, TIMI minor bleeding with transfusion, and TIMI minor bleeding without transfusion—are associated with an increased risk of mortality at 1-year follow-up, whereas an isolated large hematoma was not.

Quantifying risk in relation to clinically meaningful events has always been a challenge for clinical research studies. Our initial observations that have compared the relative prognostic impact of MI and periprocedural bleeding have shown that both events are associated with an increased risk for mortality (11,22). In the present study, we increased the sample size by merging 3 datasets of large-sized contemporary multicenter randomized clinical trials and used individual patient data elements to construct a risk score for bleeding for patients undergoing PCI, either elective or emergent. Our current analysis has shown that the risk conveyed by a bleeding event indeed pertains to early as well as late mortality (Fig. 3). Additionally, it appears that the risk for subsequent mortality conferred by a MI event is much stronger in the peri-MI period, but fades over time, more quickly than the risk conferred by bleeding.

We then sought to determine what type of bleeding would best correlate with mortality. We subdivided all

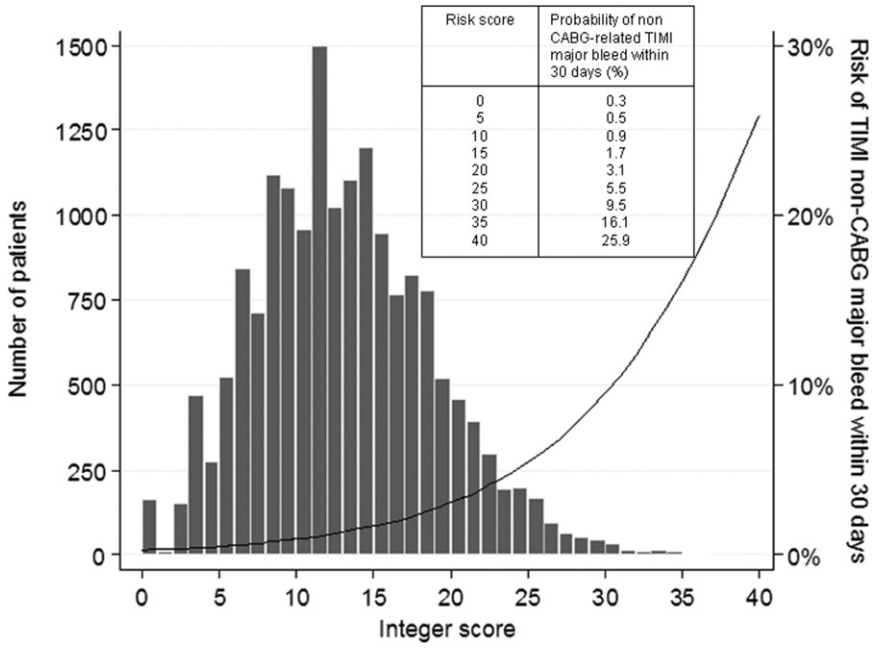

Figure 2. Distribution of the Integer Risk Score and Consequent Probability of a Non-CABG–Related TIMI Major Bleed Within 30 Days of PCI

Distribution of the integer risk score and consequent probability of a non-CABG–related TIMI major bleed within 30 days of PCI (assuming treatment with heparin + GPI). For patients treated with bivalirudin monotherapy, 6 points should be subtracted from the score. Assuming treatment with heparin + a GPI. For patients treated with bivalirudin monotherapy, 6 points should be subtracted from the score. Abbreviations as in Figure 1.

non-CABG–related bleeding into 5 bleeding types and documented that short of an isolated hematoma (even when large-sized), all other types of bleeding were independent predictors of subsequent mortality. Interestingly, bleeding that required transfusion, but did not meet the criteria for a TIMI bleed (HR: 2.91), conferred a similar risk of subsequent mortality as a TIMI minor bleed requiring transfusion (HR: 2.73). Recently, an analysis by the STEEPLE (Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention patients: An International Randomized Evaluation) investigators also showed no relationship between hematomas ≥5 cm and clinical outcome after elective PCI, which is consistent with the observations in the current analysis (14). Previous studies have also suggested that bleeding is associated with an increased risk of recurrent ischemic events, longer hospital stay, and increased cost (11,23,24). Although a causal link between bleeding and adverse outcome has not been established, there are several potential mechanisms linking bleeding with an increased risk of ischemic events (1,3,10), including discontinuation

Table 3. Incidence of Bleeding by 30 Days Stratified by Risk Category

	Risk Category				
Type of Bleed*	<10 (n = 5,346)	10–14 (n = 5,790)	15–19 (n = 3,835)	≥20 (n = 2,063)	Total†
TIMI major	33 (0.6)	57 (1.0)	78 (2.0)	99 (4.8)	267/17,034 (1.6)
TIMI minor with blood transfusion	29 (0.5)	49 (0.8)	53 (1.4)	84 (4.1)	215/17,001 (1.3)
Blood transfusion without TIMI bleed	14 (0.3)	38 (0.7)	60 (1.6)	83 (4.0)	195/17,001 (1.1)
TIMI minor without blood transfusion	88 (1.6)	162 (2.8)	151 (3.9)	108 (5.3)	509/17,001 (3.0)
Large hematoma only	59 (1.1)	89 (1.5)	45 (1.2)	31 (1.5)	224/17,020 (1.3)
Overall major bleeding including hematoma	166 (3.1)	251 (4.3)	253 (6.6)	282 (13.8)	952/16,996 (5.6)
Overall major bleeding without hematoma	108 (2.0)	175 (3.0)	215 (5.6)	258 (12.6)	756/17,009 (4.4)

Values are n (%) or n/N (%). *TIMI bleed with/without transfusion relates to the event status at 30 days. Large hematoma only relates to whether the patient experienced the event in the absence of a TIMI bleed or transfusion at 30 days. †The denominator excludes those with each type of bleed before percutaneous coronary intervention.

TIMI = Thrombolysis In Myocardial Infarction.

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

Risk Factor		Hazard Ratio	95% CI	Coefficient	z Score*
Age	Per 5 yrs	1.40	1.33–1.47	0.335	13.37
White blood cell count	Per 10^9/l	1.16	1.13–1.19	0.145	10.87
Serum creatinine	Per 0.1 mg/dl	1.09	1.06–1.11	0.082	6.82
Hemoglobin	Per g/dl	0.84	0.79–0.88	−0.179	−6.39
Diabetic status	No diabetes	1.00	—	—	—
	Noninsulin dependent	1.38	1.11–1.72	0.32	2.94
	Insulin dependent	1.70	1.30–2.23	0.53	3.86
Presentation	Normal biomarkers (elective/ACS)	1.00	—	—	—
	Raised biomarkers (NSTEMI)	1.31	1.04–1.66	0.27	2.32
	STEMI	1.63	1.24–2.15	0.49	3.50
Current smoker	No	1.00	—	—	—
	Yes	1.43	1.14–1.80	0.36	3.04
Previous CABG	No	1.00	—	—	—
	Yes	1.40	1.11–1.76	0.33	2.86
Previous MI	No	1.00	—	—	—
	Yes	1.32	1.08–1.61	0.28	2.75
Randomized treatment	UFH/Enox + GPI	1.00	—	—	—
	Bivalirudin alone	0.82	0.67–0.99	−0.20	−2.02
	Bivalirudin + GPI	1.00	0.77–1.31	0.00	0.00

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

of antithrombotic drugs in patients who suffer bleeding complications (25,26), the direct effects of blood transfusion with stored red cells used to treat bleeding (3,27), or greater prevalence of comorbidities in patients who bleed (25). Other unknown factors such as intraplaque hemorrhage due to long-term use of dual antiplatelet therapy may also be involved. Balancing the anti-ischemic benefits against the potential bleeding risk of long-term use (>1 year) of dual antiplatelet therapy also warrants further study.

When determining which patients undergoing PCI will benefit the most from more aggressive antiplatelet and antithrombotic therapy, it is important to assess the risk of bleeding complications. Currently, several bleeding risk models have been proposed. The CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) bleeding score was developed and validated in >89,000 community-treated non-STEMI patients that included those undergoing initial invasive strategy and revascularization and those conservatively managed without catheterization (28). Similar to the CRUSADE bleeding score, the present study found that female sex and lower creatinine clearance were independent predictors of bleeding. The other variables identified in this report to increase bleeding differ from the CRUSADE analysis. However, the CRUSADE investigators limited their analysis to non-STEMI patients, of whom almost half did not undergo PCI. Moreover, because a large number of variables were missing in the CRUSADE database, the patients with a complete dataset, upon which the CRUSADE risk score was derived, represent a highly selected sample. Furthermore, follow-up of CRUSADE patients was limited to in-hospital events.

Mehta et al. (2) recently proposed a bleeding risk score based upon an analysis of 302,152 PCI procedures from the NCDR (National Cardiovascular Data Registry). Although they investigated a very large number of patients who underwent PCI for a broad range of indications, the NCDR bleeding definition differs from the most commonly used bleeding definitions, such as the TIMI definition used in the current paper. Moreover, no analysis was performed to identify whether bleeding according to the NCDR definition is associated with a higher mortality rate.

The current bleeding risk score for patients undergoing PCI is similar but not identical to the risk score we recently proposed for ACS patients based upon an analysis from the pooled ACUITY and HORIZONS-AMI trials (13). In this previous analysis, only ACS patients were included, and a large proportion of these patients were not treated with PCI, but rather were managed medically or surgically. The current risk score is designed to predict the risk of a non-CABG–related TIMI major bleed, whereas the previous model predicted for a broader range of bleeding definitions (TIMI major bleed, transfusion without TIMI bleed, and TIMI minor bleed). We decided to focus on TIMI major bleeding, because this bleeding definition has the most significant clinical impact. Moreover, we showed that even in

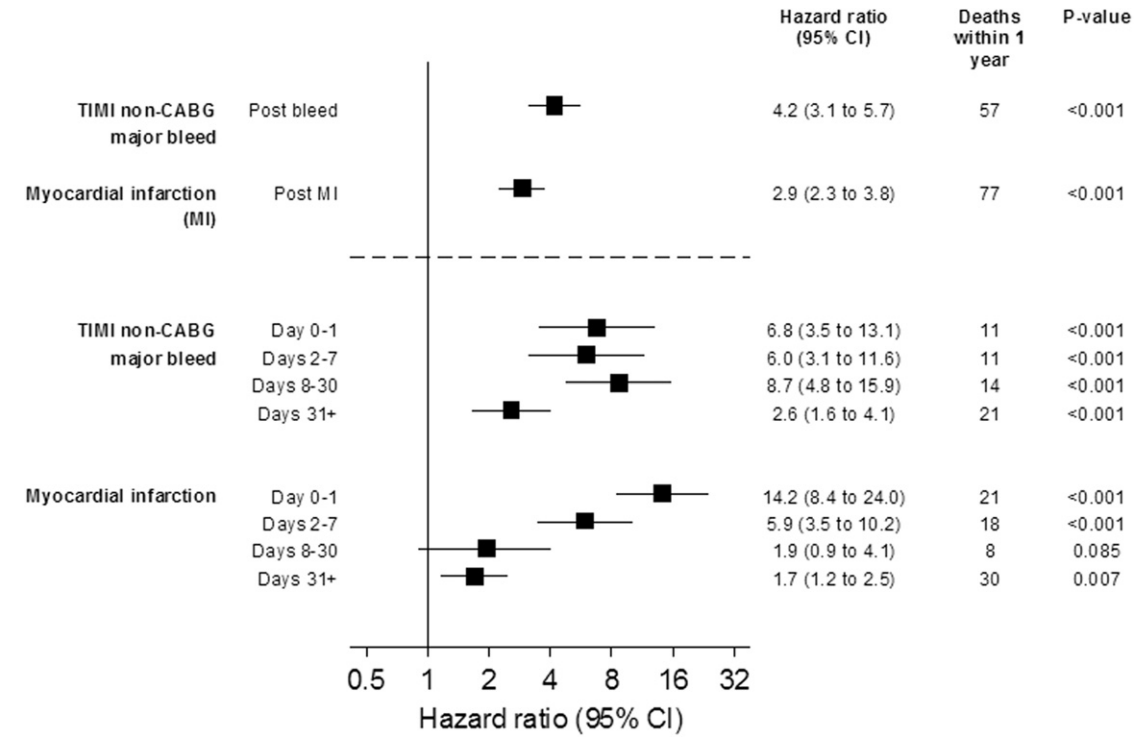

Figure 3. Independent Hazard of the Occurrence of TIMI Non-CABG–Related Major Bleed and of MI Within 30 Days on Subsequent Mortality Within 1 Year

Independent hazard of the occurrence of TIMI non-CABG–related major bleed and of MI within 30 days on subsequent mortality within 1 year, adjusted for baseline predictors. Note that 45 patients had both a TIMI major bleed and an MI within 30 days, and 11 of those patients died within 1 year. For such patients, the models in Figure 3 have time-updated covariates for both events. Adjusted for baseline predictors. CI = confidence interval; MI = myocardial infarction; other abbreviations as in Figure 1.

patients with a modest risk of TIMI major bleeding (risk scores: 10 to 14), there was an important risk for other types of clinically significant bleeding (transfusion without TIMI bleed, TIMI minor bleed). In the previous, but not in the current risk score, baseline anemia was a predictor of bleeding, whereas current smoking is a predictor of bleeding in the current model. Moreover, the integer values for the individual components of the risk score have been updated in the current model to accurately predict the bleeding risk for patients undergoing PCI.

We believe that the current risk score is practical (variables are readily available) and has documented prognostic importance. We showed that bivalirudin monotherapy was associated with lower bleeding rates and mortality. The greatest absolute reduction in bleeding with bivalirudin was seen among patients in the highest bleeding risk category. Therefore, the use of bivalirudin in patients at high risk of

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

	REPLACE-2 (n = 5,894)	ACUITY (n = 7,746)	HORIZONS-AMI (n = 3,349)	Total (n = 16,989*)
TIMI major bleed	43 (0.7)	133 (1.7)	87 (2.6)	263 (1.5)
Transfusion with no TIMI bleed	49 (0.8)	46 (0.6)	20 (0.6)	115 (0.7)
Transfusion with TIMI minor bleed	30 (0.5)	73 (0.9)	23 (0.7)	126 (0.7)
TIMI minor bleed without blood transfusion	92 (1.6)	300 (3.9)	91 (2.7)	483 (2.8)
Large hematoma only†	100 (1.7)	76 (1.0)	14 (0.4)	190 (1.1)
Total	314 (5.3)	628 (8.1)	235 (7.0)	1,177 (6.9)

Values are n (%). Patients are represented only once according to their most severe bleed. *Excluding patients with any bleed before the PCI. †Large hematoma refers to a patient without a TIMI bleed, transfusion or other component of study defined major bleed.

Abbreviations as in Table 1.

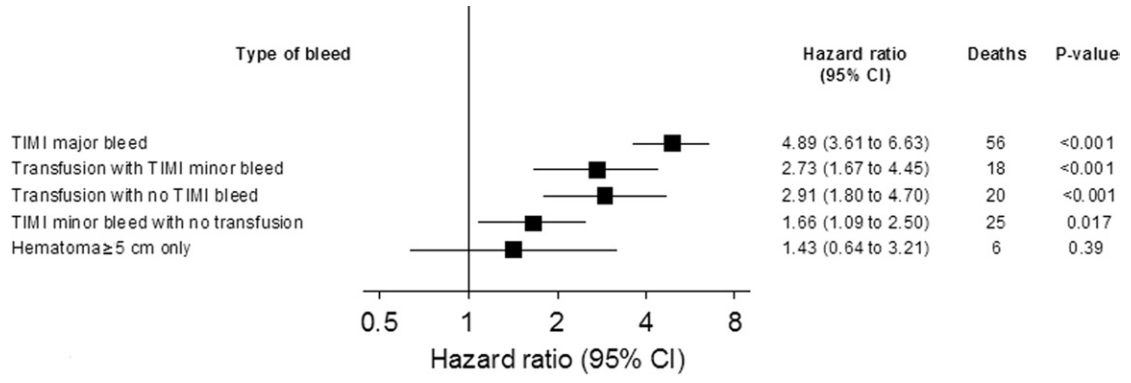

Figure 4. Independent Hazard of the Occurrence of Different Types of Major Bleed Within 30 Days on Subsequent Mortality Within 1 Year

Independent hazard of the occurrence of different types of major bleed within 30 days on subsequent mortality within 1 year, adjusted for baseline predictors. Abbreviations as in Figures 1 and 3.

bleeding would be expected to have the greatest impact on survival. A recent cost-effectiveness study by Amin et al. (29) suggested that bivalirudin, as opposed to unfractionated heparin, would be cost-effective in patients with a bleeding risk of ≥5%. Furthermore, several studies suggest that radial as opposed to femoral arterial access is associated with reduced rates of bleeding and vascular complications, with similar rates of procedural success when performed by experienced operators (30,31). As the greatest absolute effect of radial versus femoral access, however, is to decrease hematomas, these 2 approaches may have comparable survival.

Study limitations. This is a post hoc analysis of a pooled dataset of randomized controlled trials and, therefore, should be considered hypothesis-generating. Despite adjustment for potential confounders, unmeasured variables may not have been controlled for, and data to prove a causal relation between bleeding events, MI, and death cannot be established. The results of the current analysis may only be applied to PCI patients. Thus, our results and proposed risk model of bleeding cannot be extrapolated to patients managed either medically or surgically. None of the patients in this large pooled dataset was treated with heparin monotherapy; therefore, this risk score is not applicable to patients undergoing PCI with heparin monotherapy. Moreover, the use of novel antiplatelet agents such as prasugrel and ticagrelor may affect the bleeding risk of patients undergoing PCI. Despite the large sample size of the present study, given the wide confidence interval around the hazard for isolated hematomas (HR: 1.43, 95% confidence interval: 0.64 to 3.21), an effect of hematomas on subsequent survival cannot be totally excluded. Only a very small proportion of patients in the current pooled dataset were treated with radial access; therefore, we were unable to assess the influence of the radial approach on the incidence of bleeding or survival. Finally, external validation of this risk score in another dataset is warranted. Nonetheless, the present study represents a very robust, patient-based analysis across a broad spectrum of patients undergoing PCI, for whom data were prospectively collected and all adverse events were adjudicated by independent observers blinded to treatment group.

Conclusions

The present analysis demonstrates that the occurrence of a non-CABG–related bleed occurring within 30 days after PCI is associated with an increased risk of subsequent mortality through 1 year of follow-up. In order of severity, TIMI major bleeding, transfusion without TIMI bleed, TIMI minor bleeding with transfusion, and TIMI minor bleeding without transfusion were all independent predictors of mortality. The strength of the current risk score, derived from this large-scale patient-level pooled database lies in its applicability to patients undergoing PCI for all indications and can guide medical decision making to prevent bleeding.

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Key Words: bleeding ■ mortality ■ myocardial infarction ■ risk score.