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Baseline Risk of Major Bleeding in Non–ST-Segment–Elevation Myocardial Infarction

The CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) Bleeding Score

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Background—Treatments for non–ST-segment–elevation myocardial infarction (NSTEMI) reduce ischemic events but increase bleeding. Baseline prediction of bleeding risk can complement ischemic risk prediction for optimization of NSTEMI care; however, existing models are not well suited for this purpose.

Methods and Results—We developed (n=71 277) and validated (n=17 857) a model that identifies 8 independent baseline predictors of in-hospital major bleeding among community-treated NSTEMI patients enrolled in the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) Quality Improvement Initiative. Model performance was tested by *c* statistics in the derivation and validation cohorts and according to postadmission treatment (ie, invasive and antithrombotic therapy). The CRUSADE bleeding score (range 1 to 100 points) was created by assignment of weighted integers that corresponded to the coefficient of each variable. The rate of major bleeding increased by bleeding risk score quintiles: 3.1% for those at very low risk (score ≤20); 5.5% for those at low risk (score 21–30); 8.6% for those at moderate risk (score 31–40); 11.9% for those at high risk (score 41–50); and 19.5% for those at very high risk (score >50; P_{trend} <0.001). The *c* statistics for the major bleeding model (derivation=0.72 and validation=0.71) and risk score (derivation=0.71 and validation=0.70) were similar. The *c* statistics for the model among treatment subgroups were as follows: ≥2 antithrombotics=0.72; <2 antithrombotics=0.73; invasive approach=0.73; conservative approach=0.68.

Conclusions—The CRUSADE bleeding score quantifies risk for in-hospital major bleeding across all postadmission treatments, which enhances baseline risk assessment for NSTEMI care. **(*Circulation*. 2009;119:1873-1882.)**

Key Words: myocardial infarction ■ bleeding ■ risk assessment

Treatment of non–ST-segment–elevation myocardial infarction (NSTEMI) traditionally has focused on prevention or minimization of ischemic complications with potent antithrombotic medications and catheter-based interventions.[1–3] Yet these reductions in recurrent ischemic events have come at the cost of increased major bleeding,[4–7] which is itself associated with worse clinical outcomes.[7–13] Bleeding complications have received attention recently, in part because newer antithrombotic agents for NSTEMI have unique ischemia and bleeding profiles. Some agents demonstrate low rates of major bleeding with similar efficacy,[5,14] whereas others demonstrate higher rates of major bleeding with superior efficacy.[15] Given the importance of safety and efficacy,[12] the recent American College of Cardiology/American Heart Association practice guidelines placed renewed emphasis on risk stratification to guide treatment for NSTEMI.[3] Although tools for ischemic risk stratification are well described (ie, TIMI [Thrombolysis In Myocardial Infarction], PURSUIT [Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using InTegrilin], and GRACE [Global Registry of Acute Coronary Events] risk scores),[16–18] bleeding risk stratification is more limited. The few bleeding risk stratification models in existence include treatments known to influence bleeding or are derived from

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subgroups or trial populations not representative of those at greatest risk.[10,13,19] Consequently, better estimation of baseline risk of bleeding in NSTEMI patients is needed to facilitate optimal treatment selection.

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Using data from the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) Quality Improvement Initiative, we developed and validated a scoring system to estimate baseline risk of in-hospital major bleeding in patients with NSTEMI. The CRUSADE bleeding score provides a tool that equips clinicians with the means to consider safety outcomes when making treatment decisions for patients with NSTEMI.

Methods

The CRUSADE Quality Improvement Initiative is a database of high-risk patients with non–ST-elevation acute coronary syndromes who were admitted to US hospitals from November 2001 through December 2006.[20] CRUSADE inclusion and exclusion criteria, data collection, and variables have been described previously.[21] Data on baseline and nadir hematocrit values were added to version 2 of the case report form, so the analysis in the present study was limited to patients enrolled from February 15, 2003, through December 31, 2006. The institutional review board of each center approved participation in CRUSADE. Because data were collected anonymously, informed consent was not required.

Population

The analysis population consisted of 89 134 patients enrolled across 485 US sites. Starting from the CRUSADE population that had recorded hematocrit values (n=118 252), patients with unstable angina (n=7173) and those taking warfarin at home (n=7752) were excluded owing to potential differences in treatment patterns that could influence bleeding risk. Patients transferred out of the CRUSADE hospital (n=12 000) were also excluded, because treatments and outcomes after transfer could not be collected owing to current US privacy regulations. Patients with improperly recorded baseline hematocrit (n=739) or missing data on major bleeding (n=143) were excluded. Additionally, patients who died within 48 hours of hospital arrival (n=1311) were excluded because they represent a censored population that has a truncated opportunity for both treatment and major bleeding events. The study population was then divided by use of simple random sampling into a derivation cohort (80%, n=71 277) and a validation cohort (20%, n=17 857) for model development. Patients with missing variables for age, sex, and race were excluded from the model development process (derivation n=1545 and validation n=375).

Data Definitions

Baseline and nadir (lowest recorded) hematocrit were abstracted on the data collection form. Blood transfusion was defined as any nonautologous transfusion of whole or packed red blood cells. Witnessed bleeding was a variable on the case report form that required evidence of a bleeding location. CRUSADE major bleeding was defined as intracranial hemorrhage, documented retroperitoneal bleed, hematocrit drop ≥12% (baseline to nadir), any red blood cell transfusion when baseline hematocrit was ≥28%, or any red blood cell transfusion when baseline hematocrit was <28% with witnessed bleed. The hematocrit cut point of 28% was chosen to prevent transfusions given for baseline anemia from being considered as bleeding events. Because the primary goal of the present analysis was to identify baseline risk of bleeding, bleeding in patients who underwent coronary artery bypass graft (CABG) surgery was included in the analysis only if it occurred before surgery. Bleeding during or after surgery was not considered. Creatinine clearance was estimated with the Cockcroft-Gault equation.[22] Congestive heart failure was defined as signs of congestive heart failure at presentation, indicated by exertional dyspnea, orthopnea, shortness of breath, labored breathing, fatigue at either rest or with exertion, rales heard over more than one third of the lung fields, elevated jugular venous pressure, S_3 gallop, or pulmonary congestion on x-ray believed to represent cardiac dysfunction. Prior vascular disease was defined as either prior stroke or peripheral arterial disease.

Statistical Analysis

The relationship between potential covariates and major bleeding was explored using Wilcoxon rank-sum test for continuous and ordinal categorical variables and χ^2 test stratified by hospital for nominal categorical variables. Continuous variables (such as age, weight, baseline hematocrit, creatinine clearance, heart rate, and systolic blood pressure) were investigated for nonlinearity, and plots of each continuous variable versus rates of major bleeding were reviewed to create dichotomous cut points when suitable. Systolic blood pressure cut-point values of <110 mm Hg or >180 mm Hg were chosen because the relationship between bleeding and systolic blood pressure increased linearly past these ranges but was flat in between. Similarly, a cut-point hematocrit of 36% was chosen because major bleeding only increased below this value. In addition, heart rate values ≤70 bpm were set to 70 bpm and creatinine clearance values ≥120 mL/min were set to 120 mL/min because the relationship between heart rate and creatinine clearance with major bleeding was flat beyond those values.

Variables with clinically and statistically significant univariate relationships with major bleeding were included in the multivariate model. The degree of missing data was approximately 2% across covariates. Missing values were set to the lower-risk group for discrete variables and replaced with sex-specific medians for continuous variables. To investigate the sensitivity of missing data imputation, 2 sensitivity analyses were performed in which the first analysis excluded all missing data of the covariates in the model (eg, complete case analysis, n=63 117) and the second analysis imputed missing data of the discrete variables to the higher-risk group. Because the *c* statistics of the sensitivity analyses were not remarkably different from the main analysis in which missing values were set to the lower-risk group for discrete variables, only the main analysis is presented. The logistic generalized estimating equations method was used to account for within-hospital clustering. This method produces estimates similar to those obtained from ordinary logistic regression, but the estimated variances of the estimates are adjusted for the correlation of outcomes within a hospital.[23] The predictive performance of the model was assessed with *c* statistics and observed versus plots of predicted probabilities.

The CRUSADE bleeding score was developed by assigning a weighted integer to each independent predictor on the basis of its coefficient in the final model. A point score for each patient was calculated by summing the weighted integers (range 1 to 100 points). The predicted rate of major bleeding was plotted as a continuous function of the score. The bleeding score was also divided into quintiles: Very low risk (≤20; n=19 486), low risk (21 to 30; n=12 545), moderate risk (31 to 40; 11 530), high risk (41 to 50; n=10 961), and very high risk (>50; n=15 210). The performance of the CRUSADE bleeding score was tested in derivation and validation cohorts, as well as in relevant postadmission treatment subgroups: Patients treated with ≥2 antithrombotic medications (antiplatelet [aspirin or clopidogrel], anticoagulant, or glycoprotein IIb/IIIa inhibitors; n=50 969); patients receiving <2 antithrombotic medications (n=5931); and, among patients receiving ≥2 antithrombotic medications, those who did not undergo cardiac catheterization (conservative strategy, n=3200) and those who underwent a cardiac catheterization (invasive strategy, n=43 492). In-hospital mortality was also determined for those who did and did not experience a major bleeding event in each risk group. In determining the association between in-hospital outcomes (major bleeding and mortality) and bleeding risk score groups, bleeding risk group was entered as an ordinal independent variable in the logistic generalized estimating

Table 1. Baseline Characteristics of Derivation and Validation Cohorts

Variable	Derivation Cohort (n=71 277)	Validation Cohort (n=17 857)
Demographics		
Age, y	67.0 (56.0, 79.0)	67.0 (56.0, 79.0)
Weight, kg	81.2 (68.0, 95.3)	81.1 (68.1, 95.3)
Male sex, %	60.2	60.3
White, %	80.1	79.6
Black, %	10.8	10.8
Asian, %	1.1	1.1
Hispanic, %	3.9	4.1
Medical history, %		
Family history of CAD	33.9	33.9
History of hypertension	70.5	70.6
Diabetes mellitus	32.7	32.5
Prior vascular disease*	18.4	18.1
Current/recent smoker	28.4	27.8
Hyperlipidemia	52.0	51.7
Prior myocardial infarction	28.1	27.9
Prior PCI	21.0	20.5
Prior CABG	18.2	18.5
Prior congestive heart failure	16.2	16.1
Signs and symptoms at presentation		
Signs of congestive heart failure, %	22.9	23.2
Heart rate, bpm	83 (70, 98)	83 (70, 98)
Systolic blood pressure, mm Hg	144 (124, 165)	144 (124, 165)
Baseline hematocrit, %	40.7 (36.5, 44.2)	40.7 (36.6, 44.1)
Creatinine clearance, mL/min†	70.3 (43,8, 101.9)	70.8 (44.0, 102.0)
ECG: % with ST depression	27.4	27.6
In-hospital events, %		
Death	2.7	2.6
Major bleeding	9.4	9.6

CAD indicates coronary artery disease; PCI, percutaneous coronary intervention.

Data are presented as median (25th, 75th percentile) for continuous variables and as percentage for categorical data.

*Prior vascular disease defined as peripheral artery disease or prior stroke.

†Creatinine clearance estimated by the Cockcroft-Gault formula.

equation models to test for a linear trend. All comparisons were 2-tailed, and $P < 0.05$ was considered statistically significant. All analyses were performed with SAS software (version 9.1, SAS Institute, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline characteristics and outcomes of the derivation and validation cohorts were similar (Table 1). CRUSADE patients had a median age of 67 years; 60% were male. A high prevalence of cardiovascular risk factors and of prior cardiovascular disease was found. The rate of major bleeding was 9.4% in the derivation cohort and 9.6% in the validation cohort (P=NS for cross-cohort comparisons). Among the patients with major bleeding, the (nonexclusive) occurrence of the individual components of the CRUSADE major bleeding definition were as follows: Intracranial hemorrhage, 0.7%; documented retroperitoneal bleed, 1.9%; hematocrit drop ≥12% (baseline to nadir), 44.4%; any red blood cell transfusion when baseline hematocrit was ≥28%, 68.6%; or any red blood cell transfusion when baseline hematocrit was <28% with witnessed bleed, 2.9%. Patients who experienced a CRUSADE major bleed (n=6701) had higher rates of in-hospital heart failure (15.9% versus 6.5%), cardiogenic shock (7.7% versus 1.5%), and mortality (8.5% versus 2.1%; all $P<0.0001$) than those who did not.

Table 2. Univariable Relationship Between Continuous Baseline Characteristics and In-Hospital Major Bleeding in the Derivation Cohort

Continuous Variables	Median (25th, 75th Percentiles)	P*
Age, y		<0.0001
Major bleeding	74 (63, 82)	
No major bleeding	67 (55, 78)	
Weight, kg		<0.0001
Major bleeding	74.8 (63.5, 88.5)	
No major bleeding	81.6 (69.0, 96.0)	
Hematocrit, baseline %		<0.0001
Major bleeding	37.1 (32.0, 43.2)	
No major bleeding	40.9 (37.0, 44.2)	
Heart rate, bpm		<0.0001
Major bleeding	90 (75, 107)	
No major bleeding	82 (70, 98)	
Systolic blood pressure, mm Hg		<0.0001
Major bleeding	142 (118, 167)	
No major bleeding	144 (124, 165)	
Creatinine clearance, mL/min†		<0.0001
Major bleeding	48.2 (30.1, 73.4)	
No major bleeding	72.9 (46.0, 104.1)	

*P value test (Cochran-Mantel-Haenszel statistics stratified by center).

†Creatinine clearance estimated by the Cockcroft-Gault formula.

Univariate Associations With Major Bleeding

CRUSADE major bleeding was associated with older age (median 74 versus 67 years), lower weight (median 74.8 versus 81.6 kg), higher heart rate (median 90 versus 82 bpm), and lower systolic blood pressure (median 142 versus 144 mm Hg; all $P<0.0001$). Major bleeding was also significantly associated with lower baseline hematocrit and lower creatinine clearance (Table 2). Tables 2 and 3 describe the continuous (Table 2) and dichotomous (Table 3) risk factors used in the development of the bleeding model.

CRUSADE Bleeding Model and Risk Score

From multivariable analysis, the factors independently associated with major bleeding included baseline hematocrit,

Table 3. Univariable Relationship Between Dichotomous Baseline Characteristics and In-Hospital Major Bleeding in the Derivation Cohort

Dichotomous Variables	Major Bleeding, %	P*
Sex		<0.0001
Male	7.2	
Female	12.7	
Hypertension		<0.0001
No	7.1	
Yes	10.4	
Diabetes mellitus		<0.0001
No	8.1	
Yes	12.1	
Current/recent smoker		<0.0001
No	10.2	
Yes	7.4	
Hyperlipidemia		NS
No	9.5	
Yes	9.3	
Prior vascular disease†		<0.0001
No	8.4	
Yes	14.0	
Prior myocardial infarction		0.016
No	9.2	
Yes	10.0	
Prior PCI		NS
No	9.5	
Yes	8.9	
Prior CABG		0.017
No	9.3	
Yes	9.9	
Prior CHF		<0.0001
No	8.4	
Yes	14.4	
Signs of CHF		<0.0001
No	7.7	
Yes	15.1	

NS indicates not significant; PCI, percutaneous coronary intervention; and CHF, congestive heart failure.

*P value test (Cochran-Mantel-Haenszel statistics stratified by center).

†Prior vascular disease is defined as history of peripheral arterial disease or prior stroke.

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 (Table 4). Although age was a univariate predictor, it did not remain an independent predictor of major bleeding after adjustment for other covariates. The final regression model (the CRUSADE major bleeding model) discriminated patients who did and did not have a major bleeding event in both the derivation (*c* statistic=0.72) and validation (*c* statistic=0.71) cohorts.

The CRUSADE bleeding score (Table 5) was derived by assigning weighted integers to each independent predictor on

Table 4. Multivariate Predictors of In-Hospital Major Bleeding

Variable	χ^2	Derivation Cohort OR (95% CI)	Validation Cohort OR (95% CI)
Baseline hematocrit <36% (vs ≥36%)	434.6	2.28 (2.11–2.46)	2.17 (1.92–2.44)
CrCl (per 10-mL/min decrease)*	433.2	1.12 (1.10–1.13)	1.11 (1.09–1.13)
Heart rate (per 10-bpm increase)	159.2	1.08 (1.07–1.10)	1.09 (1.07–1.12)
Female sex	77.8	1.31 (1.23–1.39)	1.33 (1.19–1.50)
Signs of CHF at presentation	37.7	1.23 (1.15–1.31)	1.13 (1.01–1.28)
SBP ≤110 mm Hg (vs 110–180 mm Hg)	33.6	1.26 (1.16–1.36)	1.27 (1.10–1.47)
SBP ≥180 mm Hg (vs 110–180 mm Hg)		1.24 (1.14–1.35)	1.18 (1.02–1.37)
Prior vascular disease†	30.4	1.19 (1.12–1.27)	1.10 (0.98–1.24)
Diabetes mellitus	26.6	1.16 (1.10–1.23)	1.25 (1.12–1.40)
c Statistic		0.72	0.71

CI indicates confidence interval; OR, odds ratio; CrCl, creatinine clearance; CHF, congestive heart failure; and SBP, systolic blood pressure.

*Creatinine clearance estimated by the Cockcroft-Gault formula.

†Prior vascular disease defined as history of peripheral artery disease or prior stroke.

the basis of its coefficient in the regression model. The sum of the weighted integers (range 1 to 100 points) estimates the risk of in-hospital major bleeding. Figure 1 demonstrates the curvilinear relationship between CRUSADE bleeding score and predicted probabilities of major bleeding observed in the derivation cohort, in which the rate of bleeding increased 10-fold (<3% to >30%) from the lowest to the highest scores. Similar to the multivariable model, the CRUSADE bleeding score had good ability to discriminate between patients who did and did not have a major bleeding event in the derivation (*c* statistic=0.71) and validation (*c* statistic=0.70) cohorts. The CRUSADE bleeding model was similarly able to predict rates of moderate to severe bleeding according to the GUSTO [Global Utilization of Streptokinase and t-PA for Occluded coronary arteries) definition (*c* statistic=0.71; data not shown).

Figure 2 compares the rates of in-hospital major bleeding across quintiles of risk according to CRUSADE bleeding score in the derivation and validation cohorts. In the derivation cohort, the rates of major in-hospital bleeding across the quintiles of risk groups were 3.1% (very low risk), 5.5% (low risk), 8.6% (moderate risk), 11.9% (high risk), and 19.5% (very high risk). The rate of major bleeding also increased across quintiles of risk groups in the validation cohort (P_{trend} <0.001; Figure 2).

CRUSADE Bleeding Score in Treatment Subgroups

CRUSADE includes patients who underwent an initial invasive strategy with cardiac catheterization (n=52 048) and subsequent revascularization (n=38 209), as well as those managed medically (without catheterization, n=6407). Treatments (ie, invasive care or antithrombotics) that increase the risk of bleeding were intentionally omitted

Table 5. Algorithm Used to Determine the Risk Score of CRUSADE In-Hospital Major Bleeding

Predictor	Score
Baseline hematocrit, %	
<31	9
31–33.9	7
34–36.9	3
37–39.9	2
≥40	0
Creatinine clearance,* mL/min	
≤15	39
>15–30	35
>30–60	28
>60–90	17
>90–120	7
>120	0
Heart rate (bpm)	
≤70	0
71–80	1
81–90	3
91–100	6
101–110	8
111–120	10
≥121	11
Sex	
Male	0
Female	8
Signs of CHF at presentation	
No	0
Yes	7
Prior vascular disease†	
No	0
Yes	6
Diabetes mellitus	
No	0
Yes	6
Systolic blood pressure, mm Hg	
≤90	10
91–100	8
101–120	5
121–180	1
181–200	3
≥201	5

CHF indicates congestive heart failure.

*Creatinine clearance was estimated with the Cockcroft-Gault formula.

†Prior vascular disease was defined as history of peripheral artery disease or prior stroke.

from the CRUSADE bleeding score; however, the performance of the CRUSADE bleeding score across treatment subgroups was confirmed by formal testing.

The model had preserved discrimination in groups of patients who received ≥2 antithrombotic medications and those who received <2 antithrombotic medications (*c* statistics 0.72 and 0.73, respectively). With the derivation cohort, the incidence of major bleeding was 8.2% among those who received ≥2 antithrombotic medications (n=50 969) versus 6.9% among those who received <2 antithrombotic medications (n=5931). The rate of major in-hospital bleeding was higher when ≥2 antithrombotic medications were given than when <2 antithrombotic medications were given in every risk quintile: 3.1% versus 1.9% (very low risk), 5.5% versus 2.6% (low risk), 8.4% versus 5.3% (moderate risk), 12.0% versus 6.7% (high risk), and 19.9% versus 13.5% (very high risk; P_{trend} <0.001 within each of the 2 strata; Figure 3). However, the absolute difference in bleeding was greater in the high-risk and very-high-risk groups.

Among patients receiving ≥2 antithrombotic medications, the *c* statistic of the model in those treated with a conservative approach (no catheterization) was 0.68, whereas the *c* statistic of the model in those treated with an invasive approach (catheterization) was 0.73. The rate of major in-hospital bleeding was higher if patients underwent an invasive approach than if they were treated with a conservative approach in every risk quintile: 3.1% versus 2.5% (very low risk), 5.6% versus 3.2% (low risk), 8.6% versus 6.4% (moderate risk), 13.4% versus 6.4% (high risk), and 22.6% versus 13.9% (very high risk; Figure 4). Similarly, the absolute difference in major bleeding was magnified in the high-risk and very-high-risk groups. In-hospital mortality rates increased along with the CRUSADE bleeding risk quintiles. The rate of in-hospital mortality is also shown for patients who did and did not have a bleeding event within each CRUSADE bleeding risk group; in each bleeding risk quintile, patients who experienced a major bleed had higher mortality than those who did not (Figure 5).

Discussion

The CRUSADE bleeding score, which predicts baseline risk of in-hospital major bleeding, was developed and validated in >89 000 community-treated NSTEMI patients. It is unique in that it only considers admission variables, including baseline characteristics, clinical presentation, and key laboratory data. The 8 variables in the final model were female sex, history of diabetes, prior vascular disease, heart rate, systolic blood pressure, signs of congestive heart failure, baseline hematocrit <36%, and creatinine clearance. Although postadmission treatments were not included in the model, the CRUSADE bleeding score demonstrated preserved discrimination across treatment subgroups. Therefore, it complements ischemic risk prediction, enabling clinicians to consider net clinical outcomes in patients with NSTEMI.

Bleeding is a common problem that complicates treatment of NSTEMI, with important immediate and late clinical consequences. Clinical trials involving almost 48 000 patients with NSTEMI have demonstrated that major bleeding is associated with a 5-fold increase in 30-day mortality.[8,9] Observations from a randomized trial comparing antithrombotic agents suggest that a reduction in bleeding events translates into improved survival.[14] Prevention of major bleeding may represent an achievable step in improving outcomes by balancing safety and efficacy in the treatment of NSTEMI.

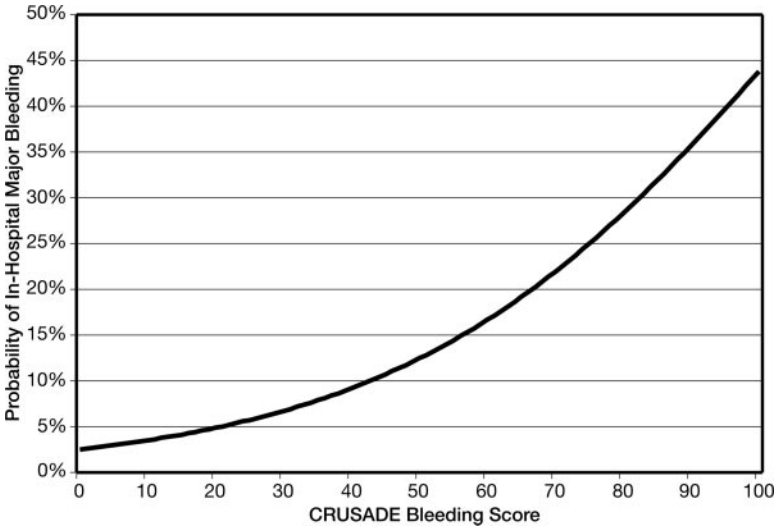

Figure 1. Predicted probability of in-hospital major bleeding across the spectrum of CRUSADE bleeding score in the derivation cohort.

Several studies have examined predictors of major bleeding or developed predictive instruments for the estimation of bleeding risk in this population.[9,10,13,19] Moscucci et al[10] determined independent predictors of bleeding among 24 045 STEMI and NSTEMI patients in the GRACE registry. Similar to the present results, they observed that female sex, renal insufficiency, and blood pressure were independent predictors of major bleeding. More recently, Spencer et al[13] also found that female sex, peripheral artery disease, heart rate, and renal insufficiency were among the predictors of major bleeding in the first 30 days after admission in GRACE. Only 1 other study has developed a risk stratification tool or bleeding score. Nikolsky et al[19] used 6002 patients enrolled in the REPLACE (Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events)-2 trial to derive and 1056 patients enrolled in REPLACE-1 to validate a risk score to predict major bleeding for patients undergoing elective or urgent percutaneous coronary intervention via the femoral approach. Similar to the CRUSADE bleeding score, Nikolsky et al[19] found that female sex, baseline anemia, and lower creatinine clearance were independent predictors of bleeding. However, REPLACE-2 enrolled a highly selected population, all of whom underwent percutaneous coronary intervention by the femoral approach, which limits its generalizability. Furthermore, the predictive model from GRACE[10,13] and the risk score from REPLACE-2[19] included treatment variables (eg, invasive procedures and antithrombotics), which limits their utility for assessing bleeding risk at presentation. These studies, therefore, do not address baseline risk in a community population.

The CRUSADE bleeding score builds on these studies in several ways. It was developed in a diversely treated community population that included those undergoing initial invasive strategy and revascularization and those conservatively managed without catheterization. It includes only baseline factors, including creatinine clearance, a more precise estimate of renal function than creatinine or a history of renal insufficiency. Age was a significant univariate predictor of bleeding; however, it did not remain significant in multivariable testing owing to other variables such as creatinine clearance that may account for age-associated risk.[24–26] How-

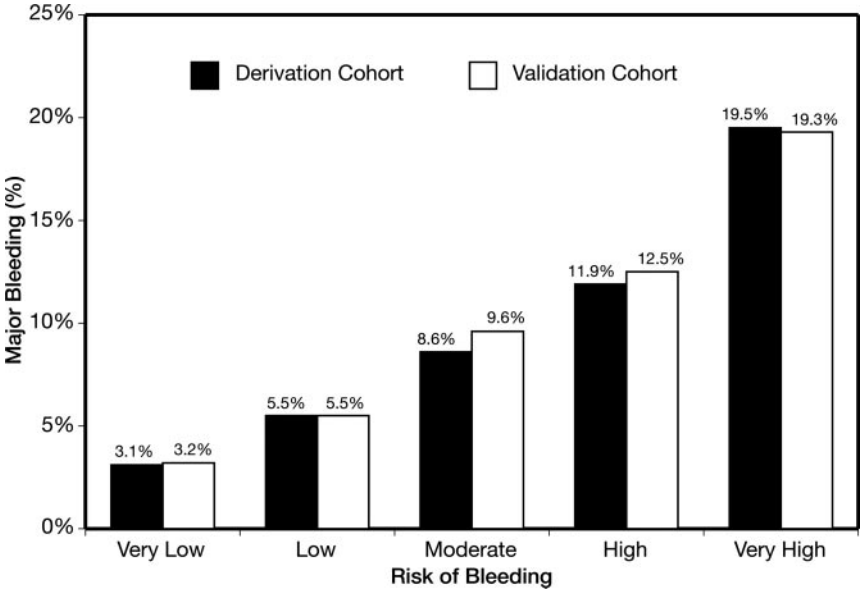

Figure 2. Rate of major bleeding across CRUSADE bleeding score risk groups in the derivation and validation cohorts. Very low (bleeding score ≤20): derivation n=19 486 and validation n=4920; low (bleeding score 21 to 30): derivation n=12 545 and validation n=3141; moderate (bleeding score 31 to 40): derivation n=11 530 and validation n=2873; high (bleeding score 41 to 50): derivation n=10 961 and validation n=2787; and very high (bleeding score >50): derivation n=15 210 and validation n=3761. P_{trend} <0.001.

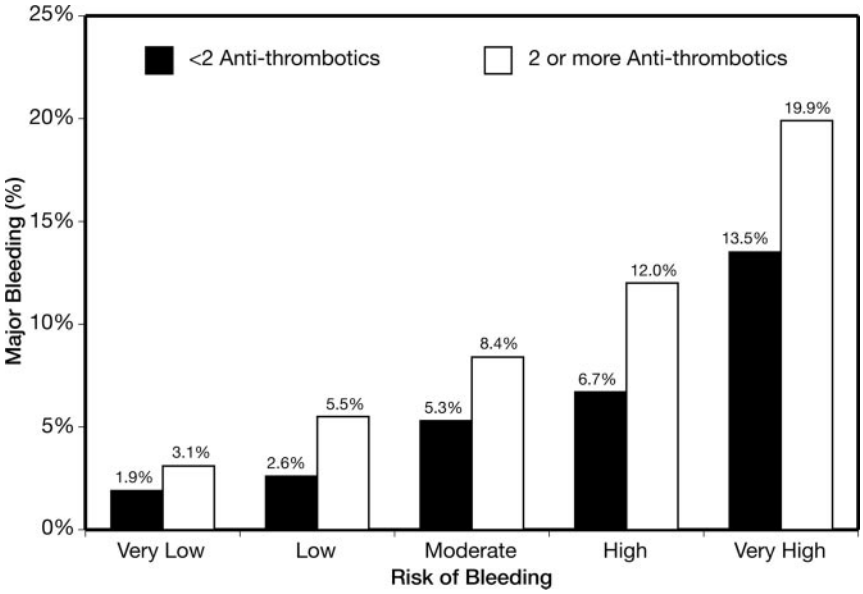

Figure 3. Rate of major bleeding among patients treated with <2 vs ≥2 antithrombotic drugs across CRUSADE bleeding score in the derivation cohort. Quintiles were defined as follows: Very low (≤20), n=18 406; low (21–30), n=11 368; moderate (31–40), n=9871; high (41–50), n=8290; and very high (>50), n=8965. P_{trend} <0.001 within each of the 2 strata.

ever, female sex, diabetes, and signs of congestive heart failure continue to contribute unique information on bleeding risk. Importantly, the CRUSADE bleeding score has preserved discrimination regardless of treatment (eg, antithrombotic medications or invasive care), which increases its utility in clinical decision making.

The effect of treatment strategy on the incidence of bleeding in the study population is evident (Figures 3 and 4), because multiple antithrombotic agents or an invasive approach increased the risk of bleeding in every CRUSADE bleeding score quintile. Furthermore, the gradient of bleeding risk related to treatment appears magnified in the high and very high quintiles of the CRUSADE bleeding score. These findings imply that those at high risk may have reduced bleeding rates with careful treatment selection, although the effect of such adjustments in treatment strategy on outcomes will require confirmation by prospective testing.

The CRUSADE bleeding score identifies baseline factors associated with an increased propensity for bleeding. Moreover, those who experience a bleeding event have higher in-hospital mortality across all quintiles of baseline risk. The mortality among those who experience a bleeding event is also higher within each quintile (Figure 5). Identification of patients with a higher propensity for bleeding can lead to improvements in NSTEMI care by prompting clinicians to make judicious treatment selections, carefully dose antithrombotic medications, and select invasive strategies to optimize patient-centered care.[27,28] With a growing number of antithrombotic agents available,[5,14,15,29,30] appreciation of baseline bleeding provides an objective starting point either for treatment selection or for strategy comparison. The CRUSADE bleeding score provides a complement to existing risk stratification.

Study Limitations

Several limitations of the present analysis should be considered. Given the dependence on registry data for this analysis, we chose to limit our population to those with NSTEMI, to

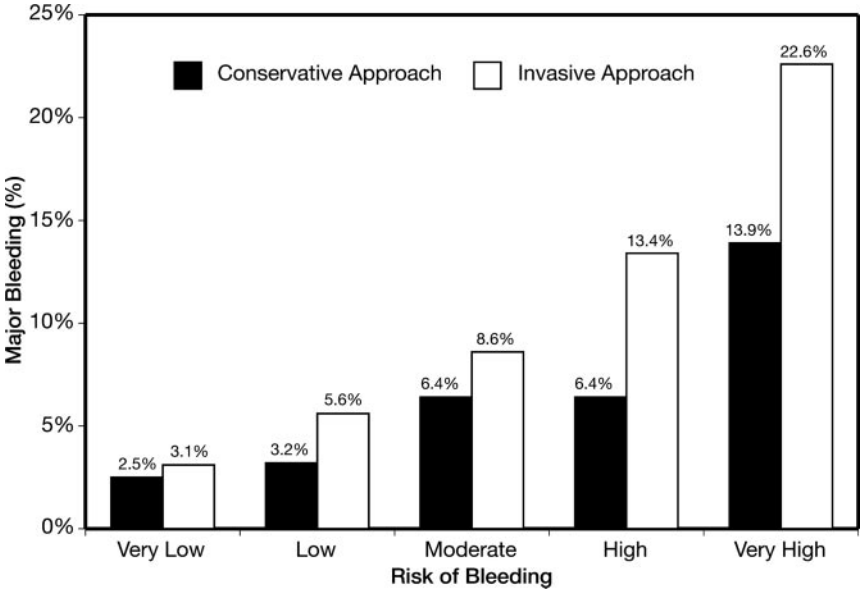

Figure 4. Rate of major bleeding among patients treated with ≥2 antithrombotic drugs undergoing an invasive approach (catheterization) vs a conservative approach (no catheterization) across CRUSADE bleeding score in the derivation cohort. Quintiles were defined as follows: Very low (≤20), n=16 974; low (21–30), n=10 067; moderate (31–40), n=8142; high (41–50), n=6105; and very high (>50), n=5404. P_{trend} <0.001 within each of the 2 strata.

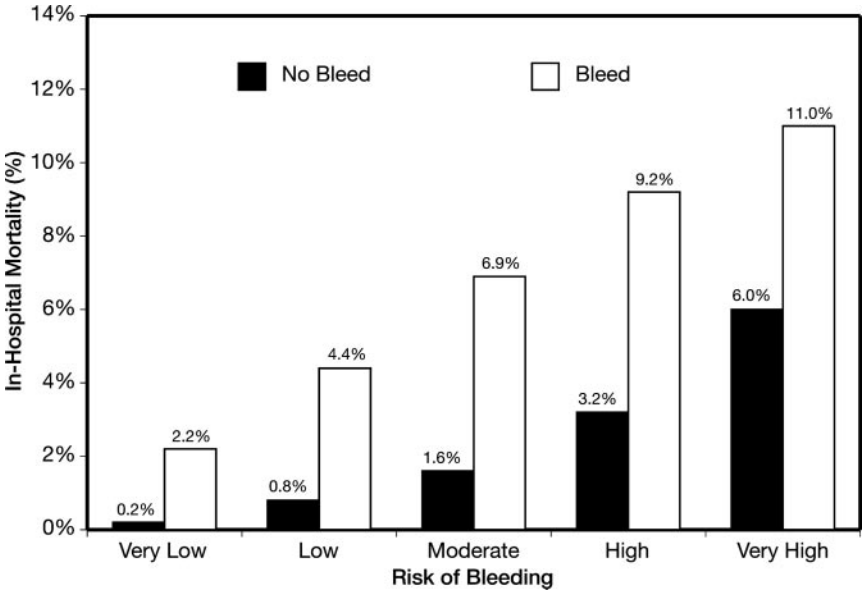

Figure 5. In-hospital mortality among patients having a major bleed vs those without a major bleed across CRUSADE bleeding score quintiles in the derivation cohort. Within each risk quintile, the *P* value for difference between patients who had a bleed vs those who did not was <0.0001 (χ^2 adjusted for hospital clustering).

limit the number of false-positives. When unstable angina patients were included (n=5462), the model *c* statistic did not change (*c* statistic=0.72). We conclude our model will predict bleeding events in the high-risk acute coronary syndrome population. Another possible limitation could be that some initial bleeding events were not included, because patients who died within 48 hours of hospitalization were excluded from the analysis; however, a validation analysis that included early deaths (n=1311) did not alter the *c* statistic of the model (*c* statistic=0.71). The rate of major bleeding is higher in CRUSADE than in other studies because of the complex patient population or the definition of major bleeding. The definition of in-hospital major bleeding used in the present study has been published previously[31] and is an adaptation of existing major bleeding definitions as applicable to the CRUSADE data collection methods.[5,32,33] CRUSADE collected only hematocrit levels (not hemoglobin). In addition, a history of prior bleeding or bleeding diathesis, both of which are recognized predictors of in-hospital bleeding,[13] was not collected in CRUSADE. Patients taking warfarin at admission were excluded, so additive risk was not considered. Finally, the *c* statistic of the CRUSADE in-hospital major bleeding model at 0.72 in the derivation cohort and 0.71 in the validation cohort is modest but nevertheless better than that of other bleeding models.[10,19]

Conclusions

The CRUSADE bleeding score combines 8 baseline factors that predict the propensity for major bleeding into a simple validated tool to assist with risk assessment and optimize care of patients with NSTEMI.

An automated Web tool for calculation of the CRUSADE Bleeding Score is available at http://www.crusadebleedingscore.org.

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Disclosures

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CLINICAL PERSPECTIVE

With renewed emphasis in the American College of Cardiology/American Heart Association non–ST-segment elevation acute coronary syndrome practice guidelines on patient risk stratification and an expanding array of antithrombotic therapies with varying bleeding hazards, consideration of both safety and efficacy may improve selection of optimal treatment strategies for patients with non–ST-segment elevation myocardial infarction. The Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) bleeding score complements existing ischemic risk stratification tools by providing an assessment of baseline bleeding risk. The CRUSADE bleeding score combines 8 readily available variables (baseline hematocrit, creatinine clearance, female sex, diabetes, peripheral vascular disease, signs of heart failure, systolic blood pressure, and heart rate on admission) into a validated bleeding risk score (range 1 to 100 points). This score stratifies baseline bleeding risk across quintiles: Very low risk (score $\leq$20), low risk (21 to 30), moderate risk (31 to 40), high risk (41 to 50), and very high risk ($>$50). In CRUSADE, observed rates of major in-hospital bleeding across quintiles of risk were 3.1% (very low risk), 5.5% (low risk), 8.6% (moderate risk), 11.9% (high risk), and 19.5% (very high risk). By providing an estimation of baseline risk of bleeding, application of the CRUSADE bleeding score will better equip providers to consider the safety and efficacy implications of various treatment strategies for a patient with non–ST-segment elevation myocardial infarction.

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