In-Hospital Major Bleeding During ST-Elevation and Non–ST-Elevation Myocardial Infarction Care: Derivation and Validation of a Model from the ACTION Registry®-GWTG™

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Bleeding, a common complication of acute myocardial infarction (AMI) treatment, is associated with worse outcomes. A contemporary model for major bleeding associated with AMI treatment can stratify patients at elevated risk for bleeding and is needed to risk-adjust AMI practice and outcomes. Using the Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With the Guidelines (ACTION Registry–GWTG) database, an in-hospital major bleeding risk model was developed in a population of patients with ST-segment elevation myocardial infarction and non–ST-segment elevation myocardial infarction. The model used only baseline variables and was developed (n = 72,313) and validated (n = 17,960) in patients with AMI (at 251 United States centers from January 2007 to December 2008). The 12 most statistically and clinically significant variables were incorporated into the final regression model. The calibration plots are shown, and the model discrimination is demonstrated in derivation and validation cohorts, as well as across key subgroups. The rate of major bleeding in the overall population was 10.8%. The 12 factors associated with major bleeding in the model were heart rate, baseline hemoglobin, female gender, baseline serum creatinine, age, electrocardiographic changes, heart failure or shock, diabetes, peripheral artery disease, body weight, systolic blood pressure, and home warfarin use. The risk model discriminated well in the derivation (C-statistic = 0.73) and validation (C-statistic = 0.71) cohorts. A risk score for major bleeding corresponded well with observed bleeding: very low risk (3.9%), low risk (7.3%), moderate risk (16.1%), high risk (29.0%), and very high risk (39.8%). In conclusion, the ACTION Registry–GWTG in-hospital major bleeding model stratifies risk for major bleeding using variables at presentation and enables risk-adjusted bleeding outcomes for quality improvement initiatives and clinical decision making. **(Am J Cardiol 2011;107:1136–1143)**

Using the Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With the Guidelines (ACTION Registry–GWTG) database, we developed and validated an in-hospital major bleeding risk model that assesses bleeding risk in the acute myocardial infarction (AMI) population. In developing this model, our objectives were to (1) provide a clinically useful tool for risk stratification, (2) describe the ACTION Registry–GWTG risk adjustment model for quality improvement feedback, and (3) use data from this registry for future research in bleeding outcomes.

Methods

The ACTION Registry–GWTG is an ongoing National Cardiovascular Data Registry program for patients with ST-segment elevation myocardial infarction (STEMI) and those with non-STEMI (NSTEMI) admitted to participating

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The Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With the Guidelines (ACTION Registry–GWTG) is an initiative of the American College of Cardiology Foundation, Washington, District of Columbia, and the American Heart Association, Dallas, Texas, with partnering support from Society of Chest Pain Centers, Dublin, Ohio, the Society of Hospital Medicine, Philadelphia, Pennsylvania, and the American College of Emergency Physicians, Irving, Texas. The registry is sponsored by Bristol-Myers Squibb (New York, New York)/Sanofi Pharmaceuticals (St. Louis, Missouri). This project received infrastructure support from the Agency for Healthcare Research and Quality, Rockville, Maryland, under grant U18HS016964. The content is solely the responsibility of the investigators and does not necessarily represent the official views of the Agency for Healthcare Research and Quality. The funding source had no role in the design or implementation of the study or in the decision to seek publication.

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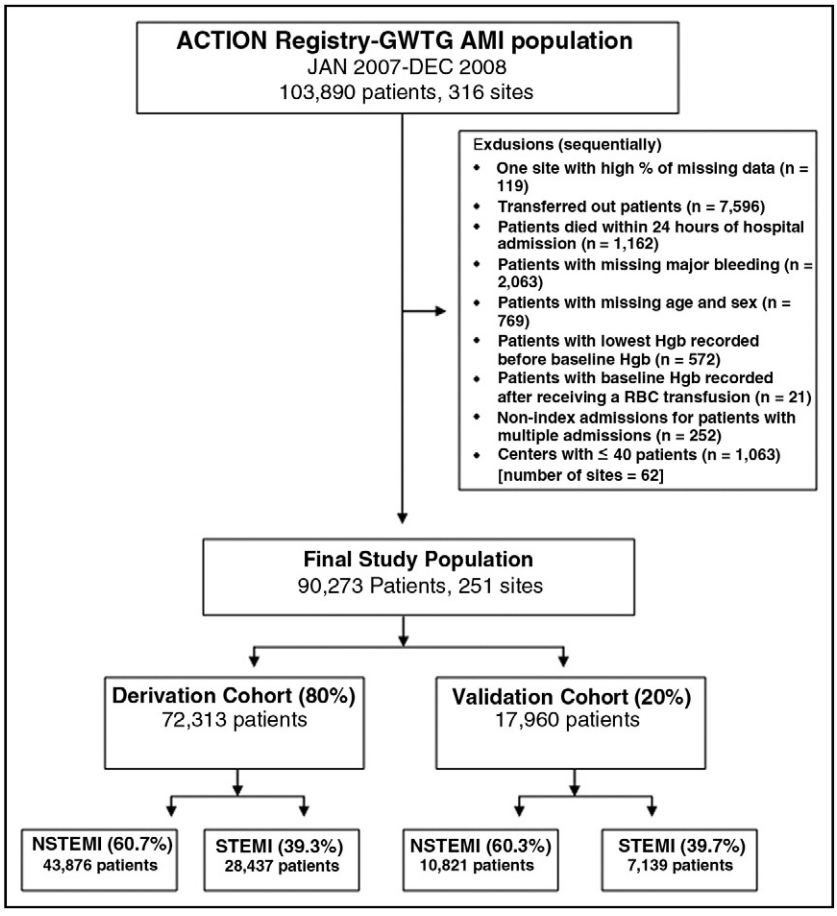

Figure 1. Population flow diagram. The initial study population was broken down (after exclusions) into a final study population and then further broken down into derivation and validation cohorts of patients with STEMI and those with NSTEMI.

hospitals across the United States.[1] The registry is an initiative of the American College of Cardiology Foundation and the American Heart Association, with partnering support from the Society of Chest Pain Centers, the Society of Hospital Medicine, and the American College of Emergency Physicians. The Action Registry–GWTG is sponsored by Bristol-Myers Squibb (New York, New York)/ Sanofi Pharmaceuticals (St. Louis, Missouri).

Inclusion and exclusion criteria, data collection, and variables have been described previously.[1] The individual institutional review board of each reporting hospital approved participation in the ACTION Registry–GWTG.

All patients admitted with AMI and reported to the ACTION Registry–GWTG from January 1, 2007, to December 31, 2008, were included in the initial study population (Figure 1). Sequentially, we excluded centers with high percentages of missing data; patients who were transferred out of the reporting hospitals because in-hospital outcomes could not be collected; patients who died within the first 24 hours of hospital admission (because these patients did not have the opportunity to develop major bleeding); and patients with missing data related to major bleeding, age, and gender. Also excluded were patients with the lowest hemoglobin (Hgb) values recorded before the baseline value, patients with baseline Hgb values recorded only after transfusions, nonindex admissions for patients with multiple admissions, and patients from centers with no more than 40 patients with AMI during the study period (because of the possibility that a low caseload might not provide representative data for evaluation). The remaining study population was divided by simple random sampling into a derivation cohort (80% of the total) for model development and a validation cohort (20% of the total) for model validation.

Major bleeding was defined as an absolute Hgb decrease of $\geq$4 g/dl (baseline to nadir), intracranial hemorrhage, documented or suspected retroperitoneal bleed, any red cell blood transfusion with baseline Hgb $\geq$9 g/dl, or any red cell transfusion with Hgb $<$9 g/dl and a suspected bleeding event. Given that most patients who undergo coronary artery bypass grafting receive blood transfusions related to the surgery, bleeding events were considered only if they occurred before coronary artery bypass grafting. Creatinine clearance was calculated using the Cockcroft-Gault formula. Signs of heart failure on admission were indicated by unusual dyspnea with light exertion, recurrent dyspnea occurring in the supine position, fluid retention, rales, jugular venous distension, pulmonary edema on physical examination, or pulmonary edema on chest x-ray presumed to be due to cardiac dysfunction. Previous peripheral artery disease was defined as claudication (either with exertion or at rest), amputation for arterial vascular insufficiency, vascular re-

Table 1
Baseline characteristics of derivation and validation cohorts

Variable	Derivation Cohort (n = 72,313)	Validation Cohort (n = 17,960)
Age (years)	64.0 (54.0, 76.0)	64.0 (54.0, 76.0)
Weight (kg)	83.2 (70.9, 97.5)	83.0 (71.0, 97.0)
Female gender	35.3%	35.3%
White race	84.5%	84.3%
Black race	8.5%	8.3%
Hypertension	68.9%	68.5%
Diabetes mellitus	29.6%	28.8%
Previous stroke	7.8%	7.6%
Peripheral arterial disease	9.5%	9.3%
Dyslipidemia	55.0%	55.3%
Previous percutaneous coronary intervention	22.1%	22.7%
Previous coronary bypass	14.2%	14.3%
Currently on dialysis	2.0%	1.9%
Signs and symptoms at presentation		
Cardiogenic shock	2.6%	2.7%
Signs of heart failure	15.2%	15.4%
Heart rate (beats/min)	80 (68.0, 96.0)	80 (68.0, 96.0)
Systolic blood pressure (mm Hg)	142 (121, 162)	142 (121, 161)
Baseline serum creatinine (mg/dl) (patients not on dialysis)	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)
Baseline Hgb (g/dl)	13.9 (12.5, 15.0)	13.8 (12.5, 15.0)
Electrocardiographic features at presentation		
STEMI	39.3%	39.7%
ST-segment depression or transient ST-segment elevation	17.8%	17.4%
Home medications		
Aspirin	42.7%	43.4%
Clopidogrel	13.7%	13.6%
β blockers	37.3%	36.9%
Warfarin	5.3%	5.2%
Angiotensin-converting enzyme inhibitors	27.0%	27.0%
In-hospital clinical events		
Mortality	3.7%	3.7%
Major bleeding	10.8%	10.7%

Data are expressed as percentages or as median (25th and 75th percentile).

Table 2
Multivariate model: factors associated with in-hospital major bleeding for derivation cohort

Variable	Chi-Square	Odds Ratio (95% Confidence Interval)
Heart rate on admission (per 10 beats/min increase)	379.4	1.11 (1.10–1.12)
Baseline Hgb <12 mg/dl (vs ≥12 g/dl)	298.8	2.29 (2.08–2.52)
Female gender	120.1	1.37 (1.29–1.45)
Baseline serum creatinine (per 1 mg/dl increase)	118.3	1.17 (1.14–1.20)
Age (per 5-year increase)	85.5	1.04 (1.03–1.05)
Electrocardiographic changes	80.9	
ST-segment changes (vs no ST-segment changes)		1.25 (1.17–1.34)
ST-segment elevation (vs no ST-segment changes)		1.76 (1.65–1.88)
Heart failure or/and shock on admission	60.7	
Signs of heart failure without shock (vs none)		1.19 (1.11–1.29)
Signs of heart failure with shock (vs none)		3.87 (3.36–4.45)
Diabetes mellitus	53.8	1.21 (1.15–1.28)
Previous peripheral artery disease	35.2	1.27 (1.17–1.37)
Weight (per 5-kg decrease)	26.8	1.02 (1.01–1.03)
Systolic blood pressure on admission	20.3	
≤130 mm Hg (vs 130–160 mm Hg)		1.15 (1.09–1.21)
≥160 mm Hg (vs 130–160 mm Hg)		1.09 (1.03–1.16)
Home warfarin use	11.0	1.18 (1.07–1.30)
C-statistic		0.73

construction, bypass surgery or percutaneous intervention to the extremities, documented aortic aneurysm with or without repair, and positive noninvasive test results (ultrasound, magnetic resonance, computed tomography, or angiographic imaging) demonstrating >50% diameter stenosis in any peripheral artery. Cardiogenic shock on presentation was defined as an episode of hypotension due to heart failure, lasting >30 minutes, with a systolic blood pressure of <90 mm Hg and/or a cardiac index <2.2 L/min/m^2 and/or the need for inotropic or vasopressive agents or mechanical support to maintain blood pressure and cardiac index above those levels. ST-segment changes included ST depressions or transient ST elevations. Patients with only T-wave inversions on the presenting electrocardiogram were combined with patients who had no electrocardiographic changes; therefore, these 2 groups were combined and included as a derived variable termed "no ST-segment changes" for the multivariate analysis.

The percentage of missing data was <0.7% for all covariates in the model. We handled missing variables in the following ways. For systolic blood pressure and heart rate on admission, missing values were imputed to the STEMI- or NSTEMI-specific median of the nonmissing values. For weight, baseline Hgb and baseline serum creatinine, missing values were similarly set to the gender- and STEMI- or NSTEMI-specific median of the nonmissing values. For categorical variables, missing values were imputed to the most frequent group. The impact of these imputations is an anticonservative estimation of the standard errors of the covariates being estimated.

Potential covariates were selected on the basis of their previous associations with bleeding events and/or clinical importance (Appendix). The risk factors considered were

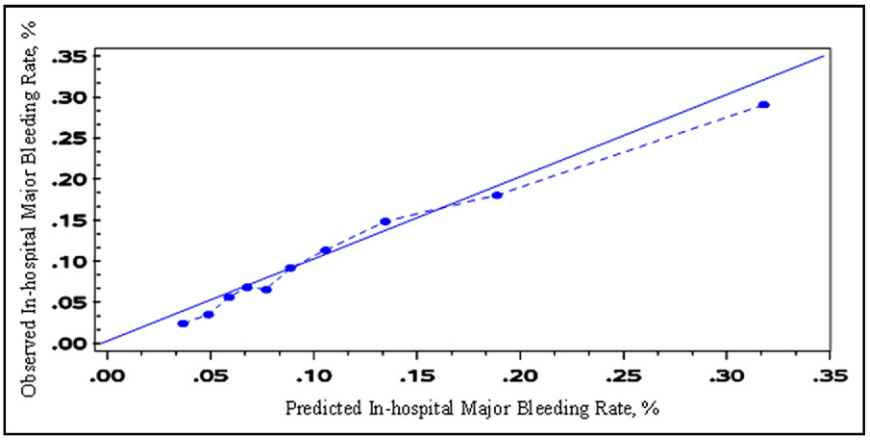

Figure 2. Comparison of predicted versus observed in-hospital major bleeding rate for the validation cohort. The ACTION Registry–GWTG bleeding model showed good calibration between observed and predicted rates of bleeding.

limited to those patient factors known at the time of initial hospital presentation. Continuous variables are presented as median (25th and 75th percentiles), and categorical variables are presented as frequencies. Furthermore, continuous variables (age, weight, baseline Hgb, baseline serum creatinine, baseline estimated creatinine clearance, heart rate, and systolic blood pressure on presentation) were tested for nonlinearity by evaluating their associations with major bleeding.

When applicable, plots for each continuous variable versus rates for in-hospital major bleeding were examined to create dichotomous cut points. Cut-off points were considered where the relation between the variable and in-hospital major bleeding became flat or nonlinear; these were finalized once they were determined to be clinically appropriate. Weight ≥105 kg was set to 105 kg, and weight ≤45 kg was set to 45 kg, because curves were relatively flat beyond this range. Similarly, baseline serum creatinine cut-off points of ≤0.8 and ≥6.0 mg/dl (for patients not on dialysis) were used, because the slope became flat after these points. The baseline serum creatinine was set to 6.0 mg/dl for patients currently on dialysis. For heart rate, values ≥150 beats/min were set to 150 beats/min, and values ≤60 beats/min were set to 60 beats/min. There was a U-shaped relation with unadjusted major bleeding and systolic blood pressure; therefore, we analyzed it as a categorical variable, with systolic blood pressure ≤130, 130 to 160, and ≥160 mm Hg.

We explored the univariate relations between all potential covariates and in-hospital major bleeding. We then performed a model including all the potential covariates. Last, we selected 12 covariates for the final regression model (i.e., the ACTION Registry–GWTG in-hospital major bleeding model) on the basis of the strength of statistical significance (i.e., the largest adjusted chi-square values) and clinical importance. Baseline creatinine and creatinine clearance were examined separately. Because of the ease of using a directly measured variable over a calculated one, we chose to use baseline creatinine instead of creatinine clearance.

The logistic generalized estimating equations method with exchangeable working correlation matrix was used to account for within-hospital clustering because patients at the same hospital were more likely to have similar responses, relative to patients at other hospitals (i.e., within-center correlation for responses). This method produced estimates similar to those from logistic regression, but variances were adjusted for the correlation of outcomes within a hospital.[2] The discriminative performance of all the models was evaluated with C-statistics. The accuracy of calibration was assessed by plotting the predicted versus observed in-hospital major bleeding, according to population deciles of predicted risk.

Table 3
Model C-statistics for individual patient subgroups

Patient Subgroup	Derivation Cohort	Validation Cohort
Male	0.73	0.73
Female	0.68	0.67
Age ≥75 years	0.68	0.66
Age <75 years	0.74	0.72
Diabetes	0.73	0.72
No diabetes	0.71	0.70
STEMI	0.72	0.70
NSTEMI	0.73	0.72

The ACTION Registry–GWTG in-hospital bleeding risk score was created by assigning weighted integers to each variable (on the basis of each variable's coefficient) in the final in-hospital major bleeding model. The final risk score was calculated by adding up the individual weighted values. Using this as a continuous variable, the predicted probability of in-hospital major bleeding was plotted against the bleeding risk score. To compare rates of observed in-hospital major bleeding, the bleeding risk score was divided into quintiles: very low risk (≤20), low risk (21 to 30), moderate risk (31 to 40), high risk (41 to 50), and very high risk (>50). The in-hospital major bleeding model and the bleeding risk score were then tested in the validation cohort and in the following clinically relevant patient subgroups in the derivation and validation cohorts: male, female, those aged ≥75 years of age, those aged <75 years of age, patients with diabetes, those without diabetics, STEMI, and NSTEMI. Last, we explored the impact of missing data

Table 4
The Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With the Guidelines prediction score and nomogram for in-hospital major bleeding

Age (years)	Points	Baseline Serum Creatinine (mg/dl)	Points	Systolic Blood Pressure on Admission (mm Hg)	Points	Baseline Hgb (g/dl)	Points	Heart Rate on Admission (beats/min)	Points
≤40	0	<0.8	0	≤90	4	<5	17	≤40	0
41–50	1	0.8–1.59	1	91–100	3	5–7.9	15	41–60	2
51–60	2	1.6–1.99	2	101–120	2	8–9.9	13	61–70	3
61–70	3	2.0–2.99	4	121–140	1	10–10.9	12	71–80	5
71–80	4	3.0–3.99	6	141–170	0	11–13.9	9	81–100	6
81–90	5	4.0–4.99	8	171–200	1	14–15.9	6	101–110	8
≥91	6	5.0–5.99	10	≥201	2	≥16	2	111–120	9
		≥6	11					121–130	11
								131–150	12
		On dialysis	11					≥151	14

Weight (kg)	Points	Gender	Points	Home Warfarin Use	Points	Diabetes Mellitus	Points
≤50	5	Female	4	No	0	No	0
51–70	4	Male	0	Yes	2	Yes	3
71–100	3						
101–120	2						
121–140	1						
≥141	0		y				

Heart Failure ± Shock on Admission	Points	Electrocardiographic Changes	Points	Previous Peripheral Artery Disease	Points
None	0	No ST-segment changes	0	No	0
Heart failure only	3	ST-segment depression or transient elevation	3	Yes	3
Heart failure with shock	15	ST-segment elevation	7		

Add up the points for all 12 variables and look up the corresponding risk for in-hospital major bleeding on the risk curve (Figure 3).

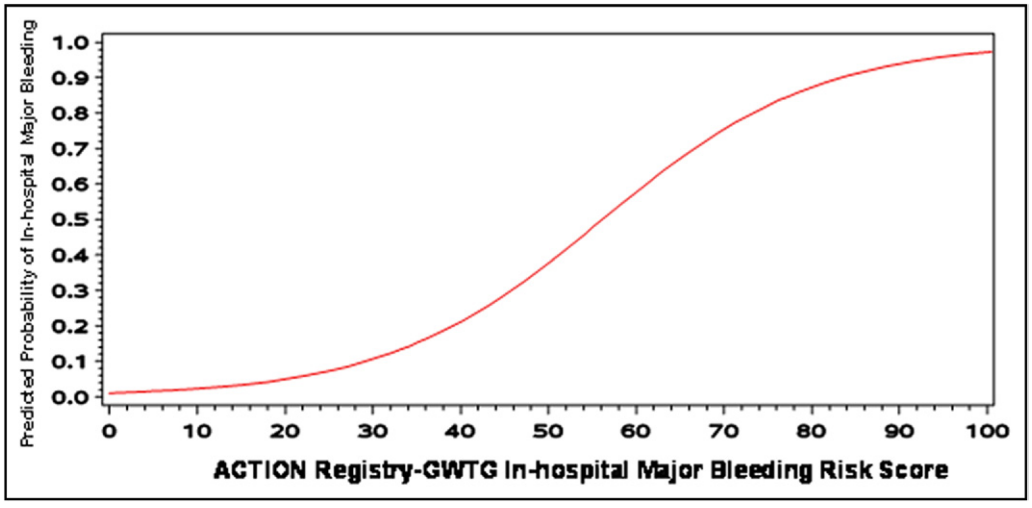

Figure 3. Major bleeding risk score versus predicted probability. The line graph illustrates the association between the ACTION Registry–GWTG in-hospital major bleeding risk score and the predicted probability of an in-hospital major bleeding for the derivation cohort.

imputation by carrying out a complete case analysis. The results of the complete case analysis were similar to the main analysis, and therefore, only the main results were reported.

All comparisons were 2 tailed, and p values <0.05 were considered statistically significant. The analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

Results

A total of 103,890 patients with AMI were admitted to 316 participating hospitals. After exclusions, the final population consisted of 90,273 patients enrolled across 251 United States centers (Figure 1). Derivation (80% [n = 72,313]) and validation (20% [n = 17,960]) cohorts were then randomly created. In-hospital major bleeding occurred

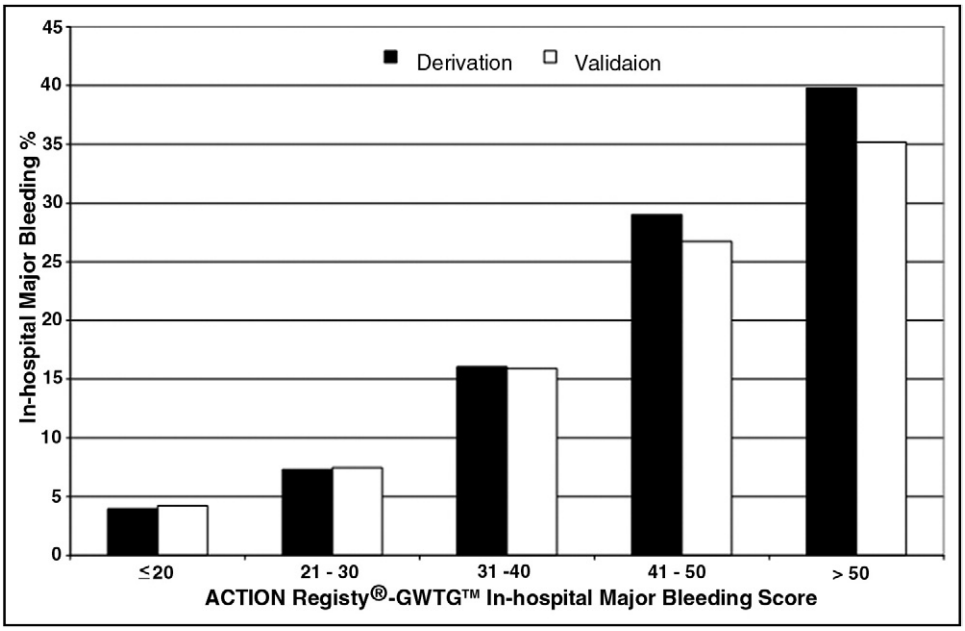

Figure 4. Major bleeding risk score versus observed bleeding. The bar graph illustrates the association between the rate of observed in-hospital major bleeding across ACTION Registry–GWTG in-hospital major bleeding risk score categories in the derivation and validation populations.

in 10.8% in the derivation and validation cohorts. Major bleeding occurred in 10.2% of patients with NSTEMI and 11.8% of those with STEMI in the derivation cohort. Baseline characteristics and in-hospital major bleeding were similar between the derivation and validation cohorts (Table 1).

Patients who developed major bleeding were older, weighed less, had higher baseline heart rates, lower systolic blood pressures, increased baseline serum creatinine, and lower Hgb than those who did not have major bleeding.

With multivariate analysis, we determined the factors associated with major bleeding. The factor with the strongest association was heart rate on admission, followed by baseline Hgb <12 g/dl, female gender, baseline serum creatinine, age, electrocardiographic changes, heart failure and/or shock on admission, diabetes mellitus, previous peripheral artery disease, weight, systolic blood pressure on admission, and home warfarin use (Table 2).

The ACTION Registry–GWTG bleeding model showed good calibration between observed and predicted rates of bleeding (Figure 2). The model also showed good discrimination between patients who did and did not have major bleeding events in the derivation (C-statistic = 0.73) as well as the validation (C-statistic = 0.71) cohorts. In addition, the model had good discrimination across subgroups of gender, age, diabetes, and AMI type (STEMI and NSTEMI; Table 3).

A risk score was derived from the model for use in categorizing patients. The score was developed by assigning weighted values to the variables in the regression model (Table 4). Figure 3 demonstrates the relation between bleeding risk score and the predicted probabilities of in-hospital major bleeding in the derivation cohort. The steepest portion of the sigmoid relation between bleeding risk score and the probability of in-hospital major bleeding occurred at a range of 30 to 70. Most patients in the derivation cohort had bleeding risk scores of 21 to 40, with the distribution as follows: ≤20, n = 12,168 (16.8%), 21 to 30, n = 35,057 (48.5%); 31 to 40, n = 19,769 (27.3%); 41 to 50, n = 4,575 (6.3%); and >50, n = 744 (1.0%). The observed rates of in-hospital major bleeding increased steadily across increasing risk score categories in the derivation and validation cohorts (Figure 4). The ACTION Registry–GWTG risk score showed adequate discrimination among patients with various degrees of in-hospital major bleeding risk in the derivation (C-statistic = 0.69) and validation (C-statistic = 0.68) data sets.

Most patients with STEMI and NSTEMI had bleeding risk scores of 21 to 40 (i.e., low to moderate bleeding risk). Although patients with STEMI and NSTEMI had similar rates of major bleeding across most risk scores in the derivation cohort, those with STEMI experienced higher rates of major bleeding at the lowest (7.5% vs 3.4%) and highest (43.4% vs 32.8%) risk quintiles.

Discussion

Treatment for AMI should be selected with an understanding of an individual's baseline risk for ischemic outcomes, as well as for bleeding complications.[3–9] The test performance measures on excess antithrombotic dosing target safety of care, but comparisons of hospitals related to their AMI care should be risk adjusted. The ACTION Registry–GWTG major bleeding model allows such risk adjustment of bleeding on site feedback reports. In addition, the model enables baseline risk assessment of patients with AMI. We believe the inclusion of baseline factors, as well as patients with STEMI and those with NSTEMI, is necessary for quality improvement efforts. Furthermore, these inclusions distinguish our model from others. For example, 1 previous bleeding risk score in patients who undergo percutaneous coronary intervention (the Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical

Events [REPLACE]) included glycoprotein IIb/IIIa inhibitors and the use of intra-aortic balloon pumps to predict major bleeding.[10] In a model derived from the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) and Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trials, anticoagulants were also predictive of 30-day bleeding rates.[11] These and other risk models consider treatment in determining bleeding risk, which limits their use at baseline for risk stratification. In addition, models based on specific patient populations may limit generalizability. For instance, the Global Registry of Acute Coronary Events (GRACE) investigators used a community population of patients with acute coronary syndromes, which included those with unstable angina.[5] A more recent example is the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines (CRUSADE)[12] bleeding risk model. Because the CRUSADE score was developed by studying an older cohort of predominantly patients with NSTEMI, treatment decisions will be different from those in a more inclusive group of patients presenting with STEMI or NSTEMI. This observation was supported in an analysis of bleeding risk among patients with STEMI and NSTEMI in the ACTION Registry–GWTG using the CRUSADE risk score.[13] The 2 groups differed in baseline risk stratification, as well as observed rates of bleeding, which likely reflects treatment decisions in patients with STEMI.[13] Therefore, for increased generalizability, it is necessary to develop a model in a population composed of patients with STEMI as well as those with NSTEMI. Our intention in developing the ACTION Registry–GWTG risk score was not to have our model replace existing models; rather, we wanted to create a contemporary bleeding model that could be applied to all patients with AMI, thereby expanding on scores derived from previous models.

The variables selected for this model overlap with those selected for major bleeding adjustment of other acute coronary syndrome populations.[5,10,11] Nearly all bleeding models include baseline anemia or Hgb, renal function, age, female gender, and diabetes. However, there are some important distinctions, for example, the inclusion of home warfarin use. Systemic anticoagulation is a concern in the management of patients with AMI, particularly in those with STEMI.[14] Historically, patients taking warfarin were excluded from the populations from which models were developed. Nevertheless, there is an increasing prevalence of previous warfarin use in patients with AMI. The inclusion of home warfarin as a model variable allows the determination of baseline anticoagulation additive risk in patients admitted for ischemic heart disease. In addition, the current model uses baseline serum creatinine instead of creatinine clearance, so weight, age, and gender are more directly accounted for.

Several limitations should be considered. First, participation of centers in the ACTION Registry–GWTG is voluntary. Second, although consistent with previous models, the ACTION Registry–GWTG bleeding definition is distinct from previous definitions and is based on available variables and data collection procedures. Third, it is possible that some bleeding events may have been missed when deaths within 24 hours of admission were excluded. In addition, previous bleeding history is not a collected variable, although it is a predictor in other models.[5] Finally, as with all observational studies, there is the potential for unmeasured confounding.

Appendix

Full List of Potential Variables Considered in the Modeling Process

Demographics
Age (years)
Female gender
Race (white vs nonwhite)
Weight (kg)
Body mass index (kg/m^2)
Signs and symptoms at presentation
Heart failure
Cardiogenic shock
Heart rate (beats/min)
Systolic blood pressure (mm Hg)
Electrocardiographic findings
Laboratory results
Baseline Hgb (g/dl)
Baseline creatinine clearance (ml/min) estimated by the Cockcroft-Gault formula
Baseline serum creatinine (mg/dl)
Medical history
Hypertension
Diabetes mellitus
Peripheral arterial disease
Current/recent smoker
Dyslipidemia
Previous myocardial infarction
Previous percutaneous coronary intervention
Previous coronary artery bypass graft surgery
Previous congestive heart failure
Previous stroke
Currently on dialysis
Home medications
Aspirin
Clopidogrel
Warfarin
β-blockers
Angiotensin-converting enzyme inhibitors
Angiotensin receptor blockers
Aldosterone blocking agents
Statins
Nonstatin lipid-lowering agents

1. Peterson ED, Roe MT, Rumsfeld JS, Shaw RE, Brindis RG, Fonarow GC, Cannon CP. A call to ACTION (Acute Coronary Treatment and Intervention Outcomes Network): a national effort to promote timely clinical feedback and support continuous quality improvement for acute myocardial infarction. *Circ Cardiovasc Qual Outcomes* 2009; 2:491–499.
2. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986;42:121–130.
3. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC Jr, Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL,

Hiratzka LF, Hunt SA, Jacobs AK. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction; a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). *J Am Coll Cardiol* 2004;44:E1–E211.

4. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, Chavey WE II, Fesmire FM, Hochman JS, Levin TN, Lincoff AM, Peterson ED, Theroux P, Wenger NK, Wright RS, Smith SC Jr, Jacobs AK, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *Circulation* 2007;116:e148–e304.
5. Moscucci M, Fox KAA, Cannon CP, Klein W, Lopez-Sendon J, Montalescot G, White K, Goldberg RJ, for the GRACE Investigators. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J* 2003;24:1815–1823.
6. Manoukian SV, Feit F, Mehran R, Voeltz MD, Ebrahimi R, Hamon M, Dangas GD, Lincoff AM, White HD, Moses JW, King SB III, Ohman EM, Stone GW. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUITY trial. *J Am Coll Cardiol* 2007;49:1362–1368.
7. Bassand J-P, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernandez-Aviles F, Fox KAA, Hasdai D, Ohman EM, Wallentin L, Wijns W, ESC Committee for Practice Guidelines, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Kristensen SD, Widimsky P, McGregor K, Sechtem U, Tendera M, Hellemans I, Gomez JLZ, Silber S, Funck-Brentano C, Andreotti F, Benzer W, Bertrand M, Betriu A, DeSutter J, Falk V, Ortiz AF, Gitt A, Hasin Y, Huber K, Kornowski R, Lopez-Sendon J, Morais J, Nordrehaug JE, Steg PG, Thygesen K, Tubaro M, Turpie AGG, Verheugt F, Windecker S. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: the Task Force for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology. *Eur Heart J* 2007;28:1598–1660.
8. Boersma E, Harrington RA, Moliterno DJ, White H, Théroux P, Van de Werf F, de Torbal A, Armstrong PW, Wallentin LC, Wilcox RG, Simes J, Califf RM, Topol EJ, Simoons ML. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. *Lancet* 2002;359:189–198.
9. Rao SV, O'Grady K, Pieper KS, Granger CB, Newby LK, Van de Werf F, Mahaffey KW, Califf RM, Harrington RA. Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes. *Am J Cardiol* 2005;96:1200–1206.
10. Nikolsky E, Mehran R, Dangas G, Fahy M, Na Y, Pocock SJ, Lincoff AM, Stone GW. Development and validation of a prognostic risk score for major bleeding in patients undergoing percutaneous coronary intervention via the femoral approach. *Eur Heart J* 2007;28:1936–1945.
11. Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dangas GD, Kirtane AJ, Parise H, Fahy M, Manoukian SV, Feit F, Ohman ME, Witzenbichler B, Guagliumi G, Lansky AJ, Stone GW. A risk score to predict bleeding in patients with acute coronary syndromes. *J Am Coll Cardiol* 2010;55:2556–2566.
12. Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, Wang TY, Gibler WB, Ohman EM, Roe MT, Pollack CV Jr, Peterson ED, Alexander KP. 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. *Circulation* 2009;119:1873–1882.
13. Kadakia MB, Desai NR, Alexander KP, Chen AY, Foody JM, Cannon CP, Wiviott SD, Scirica BM. Utilization of antithrombotic agents among patients admitted with myocardial infarction in the ACTION Registry-GWTG. *J Am Coll Cardiol* 2009;53:A324.
14. Wang TY, Chen AY, Peterson ED, Becker RC, Gibler WB, Ohman EM, Roe MT. Impact of home warfarin use on treatment patterns and bleeding complications for patients with non-ST-segment elevation acute coronary syndromes: observations from the CRUSADE quality improvement initiative. *Eur Heart J* 2008;29:1103–1109.