Contemporary risk model for inpatient major bleeding for patients with acute myocardial infarction: The acute coronary treatment and intervention outcomes network (ACTION) registry®—Get With The Guidelines (GWTG)®

Nihar R. Desai, MD, MPH, a Kevin F. Kennedy, MS, b David J. Cohen, MD, MSc, b Traci Connolly, BSN, MS, c Deborah B. Diercks, MD, MSc, d Mauro Moscucci, MD, MBA, e,f Stephen Ramee, MD, g John Spertus, MD, b Tracy Y. Wang, MD, MHS, MSc, h and Robert L. McNamara, MD, MHS a New Haven, CT; Kansas City, MO; Washington DC; Dallas, TX; Baltimore, MD; Ann Arbor, MI; New Orleans, LA; and Durham, NC

Background 
Major bleeding is a frequent complication for patients with acute myocardial infarction (AMI) and is associated with significant morbidity and mortality.

Objective 
To develop a contemporary model for inpatient major bleeding that can both support clinical decision-making and serve as a foundation for assessing hospital quality.

Methods 
An inpatient major bleeding model was developed using the Acute Coronary Treatment and Intervention Outcomes Network Registry—Get With the Guidelines (ACTION Registry—GWTG) database. Patients hospitalized with AMI between January 1, 2012 and December 31, 2013 across 657 hospitals were used to create a derivation cohort (n=144,800) and a validation cohort (n=96,684). Multivariable hierarchal logistic regression was used to identify significant predictors of major bleeding. A simplified risk score was created to enable prospective risk stratification for clinical care.

Results 
The rate of major bleeding in the overall population was 7.53%. There were 8 significant, independent factors associated with major bleeding: presentation after cardiac arrest (OR 2.99 [2.77-3.22]); presentation in cardiogenic shock (OR 2.22 [2.05-2.40]); STEMI (OR 1.72 [1.65-1.80]); presentation in heart failure (OR 1.55 [1.47-1.63]); baseline hemoglobin less than 12 g/dL (OR 1.55 [1.48-1.63]); heart rate (per 10 beat per minute increase) (OR 1.13 [1.12-1.14]); weight (per 10 kilogram decrease) (OR 1.12 [1.11-1.14]); creatinine clearance (per 5-mL decrease) (OR 1.07 [1.07-1.08]). The model discriminated well in the derivation (C-statistic = 0.74) and validation (C-statistic = 0.74) cohorts. In the validation cohort, a risk score for major bleeding corresponded well with observed bleeding: very low risk (2.2%), low risk (5.1%), moderate risk (10.1%), high risk (16.3%), and very high risk (25.2%).

From the aSection of Cardiovascular Medicine, Yale University School of Medicine, Center for Outcomes Research and Evaluation, Yale New Haven Health System, New Haven, CT, bSaintLuke’s Mid America Heart Institute and University of Missouri-Kansas City School of Medicine, Kansas City, MO, cAmerican College of Cardiology, Washington, DC, dUniversity of Texas Southwestern Medical Center, Dallas, TX, eSinai Hospital of Baltimore, Baltimore, MD, fUniversity of Michigan Health System, Ann Arbor, MI, gOchsner Medical Center, New Orleans, LA, and hDuke University Medical Center and Duke Clinical Research Institute, Durham, NC.

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Reprint requests: Robert L. McNamara, MD, MHS, Section of Cardiovascular Medicine, Yale School of Medicine, PO Box 208017, New Haven, CT 06520.
Email: robert.mcnamara@yale.edu:
0002-8703
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Conclusion The new ACTION Registry–GWTG inhospital major bleeding risk model and risk score offer a robust, parsimonious, and contemporary risk-adjustment method to support clinical decision-making and enable hospital quality assessment. Strategies to mitigate risk should be developed and tested as a means to lower costs and improve outcomes in an era of alternative payment models. [Am Heart J 2017;194:16-24.]

Background
Bleeding complications commonly occur among patients with acute coronary syndromes and are associated with worse clinical outcomes. A risk model to predict the development of bleeding complications would enable providers to more optimally balance competing risks of ischemic and bleeding complications, leading to more individualized care and improved outcomes. In addition, a robust bleeding model would enable risk adjustment to more accurately assess hospital performance, identify opportunities to improve patient care, and focus quality improvement interventions.

Although several risk models of inhospital major bleeding have been developed for patients with AMI, few have included a representative sample from real-world clinical practice. A prior model from the Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry®–Get With The Guidelines™ (ACTION Registry–GWTG) included patients from over 250 hospitals presenting with AMI from January 2007 through September 2008. However, since that time, the number of hospitals participating in the ACTION Registry–GWTG has increased considerably, and new, prognostically important data elements, such as presentation with cardiac arrest have been added. In addition, use of background antiplatelet and antithrombotic therapy has evolved and may have important implications for bleeding complications.

In order to provide more comprehensive, generalizable, and contemporary risk assessment, we aimed to develop and validate a risk model to predict inhospital bleeding for patients after AMI using data collected at presentation in ACTION Registry–GWTG from January 2012 through December 2013. This risk model could be used to provide specific feedback to hospitals for quality improvement efforts. In addition, we aimed to create a parsimonious risk score based on this model to facilitate and inform clinical decision-making at the bedside. Taken together, this work could lay the foundation for more efficient and safer care, which is increasingly essential as payers introduce new payment models for AMI care.

Methods
The ACTION Registry–GWTG is an ongoing National Cardiovascular Data Registry (NCDR) program for patients with acute myocardial infarction (AMI). Inclusion and exclusion criteria, data collection, and variables have been described previously. Briefly, participating hospitals collect data using standardized data collection tools that do not require direct patient contact. Data collected include patient demographics; presenting features; pre-hospital, inhospital, and hospital discharge therapy; timing of care delivery; laboratory tests; procedure use; and inhospital patient outcomes. The NCDR has a data quality program, including data abstraction training, data quality thresholds for inclusion, site data quality feedback reports, independent auditing, and data validation. Regular audits have demonstrated 93% agreement between registry data and clinical chart data.

Study population
All patients admitted with AMI and reported to the ACTION Registry–GWTG from January 1, 2012, to December 31, 2013, were included in the initial study population (n = 254,066, Figure 1). We excluded patients who were transferred out of the reporting hospitals to ensure complete capture of bleeding events (n = 10,626) and patients with missing data related to major bleeding (n = 1959). The remaining study population (n = 241,484) was divided by random sampling into a derivation cohort (60%, n = 144,800) for model development and a validation cohort (40%, n = 96,684).

Definitions
ACTION Registry–GWTG defines inhospital major bleeding as any of the following: intracranial hemorrhage, documented or suspected retroperitoneal bleed, any red cell blood transfusion with baseline hemoglobin ≥9 g/dl, any red cell transfusion with hemoglobin <9 g/dl in a patient with a suspected bleeding event (defined by a hemoglobin drop of ≥3 g/dl or procedural intervention/surgery at the bleeding site to reverse/stop or correct the bleeding (e.g. surgical repair/exploration of the arteriotomy site, balloon angioplasty to seal an arterial tear, endoscopy with cautery of a GI bleed) or an absolute hemoglobin decrease of ≥4 g/dl (baseline to nadir). Patients undergoing CABG were classified as having a major bleeding event if they fulfilled the above criteria with the exception of site-adjudicated CABG-related transfusions.

Standard definitions for the data elements captured in the ACTION Registry–GWTG database are available online. Cardiac arrest was an added variable to this
updated analysis, and is defined as “evaluated by EMS or ED personnel and either (1) received attempts at external defibrillation (by lay responders or emergency personnel) or chest compressions by organized EMS or ED personnel or (2) were pulseless at the time of presentation.” Heart failure on admission was defined by unusual dyspnea with light exertion, recurrent dyspnea occurring in the supine position, fluid retention, 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 reconstruction, 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 cardiac dysfunction, lasting >30 minutes, with a systolic blood pressure of <90 mm Hg or a cardiac index <2.2 L/min/m² or the need for inotropic or vasopressive agents or mechanical support to maintain blood pressure and cardiac index. Creatinine clearance was calculated using the Cockcroft-Gault formula.

The percentage of missing data was low (<1%) for all covariates in the model. For systolic blood pressure and heart rate on admission, missing values were imputed to the STEMI- or NSTEMI-specific median of non-missing values. For weight, baseline hemoglobin and baseline serum creatinine, missing values were similarly set to the gender and STEMI/NSTEMI-specific median of non-missing values. For categorical variables, missing values were imputed to the most frequent group.

**Statistical analysis**

The overall cohort was divided into derivation and validation cohorts by random number generation from a uniform (0,1) distribution. Initial candidate variables were selected on the basis of their previous associations with bleeding events or clinical importance as well as their availability at the time of hospital presentation. Continuous variables are presented as mean (standard deviation) and categorical variables are presented as frequencies. Continuous variables (age, weight, baseline hemoglobin, baseline serum creatinine, baseline estimated creatinine clearance, heart rate, and systolic blood pressure on presentation) were tested for nonlinear associations with major bleeding. When applicable, plots for each continuous variable versus rates for inhospital major bleeding were examined to create dichotomous cut points.

Bivariate associations between each candidate variable and bleeding were examined using Student’s t-test for continuous variables and chi-square tests for categorical variables. To account for clustering of patients within hospitals, hierarchical logistic regression was used with site as a random effect to generate the risk model from the selected variables, along with associated odds ratios (OR) and 95% confidence intervals (CI). To establish a parsimonious model, we used a backward selection process until 90% of the full model R-square was retained. We assessed discrimination using the c-statistic and compared the reduced model with the full model with IDI statistics. We then tested calibration in the validation cohort and computed the c-statistic and calibration slope and intercept, with a slope of 1 and intercept of 0 indicating perfect calibration. Calibration and the range of predicted risks were visualized by plotting the predicted versus observed rate of inhospital major bleeding, according to population deciles of predicted risk. Model performance was examined in pre-specified subgroups of age, sex, race, diabetes, type of MI, cardiac arrest, cardiogenic shock, and renal function.

The ACTION Registry-GWTG inhospital bleeding risk score was created by assigning weighted integers to each variable on the basis of each variable's coefficient in the final inhospital major bleeding model. The final risk score was calculated by adding the individual weighted values. To assess risk score performance, rates of observed inhospital major bleeding were determined in the derivation and validation cohorts across five risk groups: very low risk (≤15 points), low risk (16 to 20), moderate risk (21 to 25), high risk (26 to 30), and very high risk (>30).

All comparisons were 2-tailed, and \( P < .05 \) was considered statistically significant. Institutional review
Results

Between January 2012 and December 2013, a total of 254,066 patients with AMI were admitted to 659 participating hospitals. After exclusions, the final population consisted of 241,484 patients enrolled across 657 United States centers, who were randomly assigned to a derivation (n = 144,800; 60%) and validation (n = 96,684; 40%) cohorts (Figure 1). Baseline characteristics of the derivation cohort and bivariate relationships between patients’ characteristics and inhospital major bleeding are shown in Table 1. The observed rate of inhospital major bleeding in the derivation and validation cohorts was 7.5% and 7.6% respectively.
A complete model including all predictor variables had a C-statistic of 0.77. In creating a more parsimonious model, 8 significant, independent factors were identified: presentation after cardiac arrest (OR 2.99 [2.77-3.22]); presentation in cardiogenic shock (OR 2.22 [2.05-2.40]); STEMI (OR 1.72 [1.65-1.80]); presentation in heart failure (OR 1.55 [1.47-1.63]); baseline hemoglobin less than 12 g/dL (1.55 [1.48-1.63]); heart rate per 10 beat per minute increase (OR 1.13 [1.12-1.15]); creatinine clearance per 5 mL/minute decrease (OR 1.07 [1.07-1.08]); weight per 10 kilogram decrease (OR 1.10 [1.08, 1.12]) (Table II).

The ACTION Registry-GWTG bleeding model showed good calibration between observed and predicted rates of bleeding, with a slope of 0.98 and an intercept of 0.003. (Figure 2). The model also showed good discrimination between patients who did and did not have major bleeding events in both the derivation (C-statistic = 0.74) and validation (C-statistic = 0.74) cohorts. In addition, the model had good discrimination across subgroups of age, sex, race, diabetes, AMI type, transfer status, and renal function (Table III). Given their strong association with bleeding, model performance among patients with cardiac arrest and cardiogenic shock was more modest (0.60 and 0.59 respectively, Table III).

The ACTION Registry-GWTG inhospital bleeding risk score was derived by assigning weighted values to the covariates in the multivariable model (Figure 3). The distribution of bleeding score in the validation cohort was: ≤15 points, n = 30,847 (32%), 16 to 20 points, n = 30,939 (32%); 21 to 25 points, n = 10,054 (10%); and >25 points, n = 6127 (6%). The observed rates of inhospital major bleeding increased steadily across increasing risk score categories in the derivation and validation cohorts (Figure 3).

**Discussion**

Using a large, national registry of patients with AMI, we developed and validated a contemporary risk model to predict inhospital major bleeding. Specifically, weight, heart rate, presentation after cardiac arrest, presence of cardiogenic shock, heart failure, and STEMI on admission, creatinine clearance, and baseline hemoglobin were identified as significant, independent factors associated with major bleeding complications. The model performed well in an independent validation cohort, as well as across various clinically important subgroups and served as the basis for the development of a simplified integer score that correlated well with observed rates of bleeding. Taken together, these tools will facilitate risk adjustment required for meaningful assessment of hospital quality as well as support prospective risk stratification and clinical decision-making.

The currently developed ACTION Registry-GWTG major bleeding model builds upon and further extends prior risk models. Many of the initial major bleeding
models were derived from clinical trial datasets. While robust in their predictive capacity, not only are there well-established selection biases in clinical trial cohorts as compared with the general population, but the models often included adjunctive antithrombotic therapy and other treatment-related factors as covariates. Given that models used for comparing outcomes across hospitals should not include treatments provided after presentation, such models are not appropriate for quality assessment purposes. Previous registry based models also had limitations, particularly with regard to patient population as they included patients with unstable angina (a heterogeneous group of patients) while other efforts did not include patients with STEMI. A model from ACTION Registry–GWTG was developed prior to the introduction of cardiac arrest as a new variable in the registry. In our analysis, presentation after cardiac arrest was the strongest independent predictor of major bleeding and as such, strengthens the ability of the model to adequately adjust for patient-risk and provide more accurate estimates of hospital performance.

The updated ACTION Registry–GWTG bleeding risk model discriminated well in both the derivation and validation cohorts (c-statistics of 0.74) as well as across key subgroups. However, its performance was more modest among the less than 4% of patients with cardiogenic shock and cardiac arrest, in part because all of these patients are at high risk for adverse events including bleeding and the other variables did not discriminate as much in this cohort of patients. Nevertheless, the inclusion of these patients in the recent ACTION Registry–GWTG mortality model and the

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**Figure 2**

**Observed/Expected plot in Validation Cohort**

Predicting Bleeding

Calibration curve for the validation cohort. The expected inhospital major bleeding rate plotted against expected inhospital major bleeding rate for each decile of patient risk.
desire to fully capture the quality of AMI care with our complementary bleeding model as well as the desire to focus attention on the care of these challenging patients, supports including them in the model. As such, this new model represents the most contemporary, representative, and parsimonious inhospital major bleeding model for patients with AMI. Not only is this model suitable for risk-adjustment and hospital performance assessment, but it can also be leveraged to support quality improvement activities, such as care pathways for patients with AMI and adoption of bleeding avoidance strategies.

In parallel, variables that are available at the time of hospital presentation can be used to calculate the ACTION Registry–GWTG bleeding risk score and guide clinical care. For instance, it could be used to provide patients individualized estimates of bleeding, facilitating more informed choices and allowing providers to help tailor treatment approaches based on a patient’s predicted risk. Selection of the optimal adjunctive antithrombotic therapy, arterial access location for angiography, use of an arterial closure device, and even the type of stent may all be informed by a patient’s risk of bleeding complications.

These data should be interpreted in the context of the following limitations. First, while ACTION Registry–GWTG is the largest national registry of AMI, participation in the registry is voluntary and therefore patients, care patterns, and outcomes including major bleeding in these centers may not be generalizable to all hospitals. Second, patients transferred from one hospital to another pose a challenge for outcome attribution. For this model, patients transferred into an ACTION Registry–GWTG hospital were included and major bleeding was attributed to the receiving hospital. In this regard, it is reassuring that the model performed similarly in these patients compared with patients not transferred in. On the other hand, patients transferring out of the ACTION Registry–GWTG hospital were excluded, as major bleeding could not be captured, but they represented a small proportion of patients (4.2%). Third, the candidate risk adjustment variables were limited to those available in the ACTION Registry–GWTG. It is conceivable that more information regarding patients’ baseline health status, such as frailty, and other acute non-cardiac, co-existing conditions, may be strongly associated with bleeding. In addition, a prior history of bleeding is likely an infrequent but important predictor of future bleeding events but is not a data element in the ACTION Registry–GWTG. It is conceivable that more information regarding patients’ baseline health status, such as frailty, and other acute non-cardiac, co-existing conditions, may be strongly associated with bleeding. In addition, a prior history of bleeding is likely an infrequent but important predictor of future bleeding events but is not a data element in the ACTION Registry–GWTG. It is conceivable that more information regarding patients’ baseline health status, such as frailty, and other acute non-cardiac, co-existing conditions, may be strongly associated with bleeding. In addition, a prior history of bleeding is likely an infrequent but important predictor of future bleeding events but is not a data element in the ACTION Registry–GWTG. It is conceivable that more information regarding patients’ baseline health status, such as frailty, and other acute non-cardiac, co-existing conditions, may be strongly associated with bleeding. In addition, a prior history of bleeding is likely an infrequent but important predictor of future bleeding events but is not a data element in the ACTION Registry–GWTG. It is conceivable that more information regarding patients’ baseline health status, such as frailty, and other acute non-cardiac, co-existing conditions, may be strongly associated with bleeding. In addition, a prior history of bleeding is likely an infrequent but important predictor of future bleeding events but is not a data element in the ACTION Registry–GWTG.

In conclusion, the new ACTION Registry–GWTG inhospital major bleeding risk model and risk score represent robust, parsimonious, and contemporary risk-adjustment methodology to enable meaningful assessment of hospital quality as well as support individualized clinical decision-making.

### Table III. Inhospital major bleeding model performance overall and in key subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Sample size</th>
<th>C-statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full validation cohort</td>
<td>96,684</td>
<td>0.742</td>
</tr>
<tr>
<td>Caucasian</td>
<td>81,838</td>
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<tr>
<td>African American</td>
<td>11,327</td>
<td>0.753</td>
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<tr>
<td>Other race</td>
<td>3587</td>
<td>0.759</td>
</tr>
<tr>
<td>Male</td>
<td>63,069</td>
<td>0.756</td>
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<tr>
<td>Female</td>
<td>33,615</td>
<td>0.700</td>
</tr>
<tr>
<td>Age &lt;75 years</td>
<td>71,917</td>
<td>0.761</td>
</tr>
<tr>
<td>Age ≥75</td>
<td>24,767</td>
<td>0.690</td>
</tr>
<tr>
<td>Transfer in</td>
<td>28,094</td>
<td>0.753</td>
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<tr>
<td>Not transfer in</td>
<td>69,590</td>
<td>0.737</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>32,475</td>
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</tr>
<tr>
<td>No diabetes mellitus</td>
<td>64,171</td>
<td>0.745</td>
</tr>
<tr>
<td>Creatinine clearance &lt;50 mL/min per 1.73 m²</td>
<td>20,329</td>
<td>0.650</td>
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<tr>
<td>Creatinine clearance ≥50 mL/min per 1.73 m²</td>
<td>76,355</td>
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<tr>
<td>STEMI</td>
<td>37,556</td>
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<td>NSTEMI</td>
<td>59,128</td>
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<tr>
<td>Cardiac arrest</td>
<td>3877</td>
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<td>No arrest</td>
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<tr>
<td>Shock</td>
<td>3900</td>
<td>0.590</td>
</tr>
<tr>
<td>No shock</td>
<td>92,732</td>
<td>0.721</td>
</tr>
</tbody>
</table>

STEMI, ST-segment elevation myocardial infarction; NSTEMI, Non-ST-segment elevation myocardial infarction.
References


