Development of a Contemporary Bleeding Risk Model for Elderly Warfarin Recipients

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Development of a Contemporary Bleeding Risk Model for Elderly Warfarin Recipients*

Theresa I. Shireman, PhD, RPh; Jonathan D. Mahnken, PhD; Patricia A. Howard, PharmD; Timothy F. Kresowik, MD; Qingjiang Hou, MS; and Edward F. Ellerbeck, MD, MPH

Background and purpose: Develop and validate a contemporary bleeding risk model to guide the clinical use of warfarin in the elderly atrial fibrillation (AF) population.

Methods: Chart-abstracted data from the National Registry of Atrial Fibrillation was combined with Medicare part A claims to identify major bleeding events requiring hospitalization. Using a split-sample technique, candidate variables that provided statistically stable relationships with major bleeding events were selected for model development. Three risk categories were created and validated. The new model was compared to existing bleeding risk models using c-statistics and Kaplan-Meier curves.

Results: Model development and validation was conducted on 26,345 AF patients who were ≥ 65 years of age and had been discharged from the hospital while receiving warfarin therapy. The following eight variables were included in the final risk score model: age ≥ 70 years; gender; remote bleeding; recent (ie, during index hospitalization) bleeding; alcohol/drug abuse; diabetes; anemia; and antiplatelet use. Bleeding rates were 0.9%, 2.0%, and 5.4%, respectively, for the groups with low, moderate, and high risk, compared to the bleeding rates for groups with moderate risk (1.5% and 1.0%) and high risk (1.8% and 2.5%) from other models.

Conclusions: Using a nationally derived data set, we developed a model based on contemporary practice standards for determining major bleeding risk among AF patients receiving warfarin therapy. The larger sample size afforded the opportunity to incorporate additional risk factors. In addition, since the majority of our population was ≥ 65 years of age, we had greater ability to stratify risk among the elderly.

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Key words: adverse effects; anticoagulants; atrial fibrillation; complications; drug therapy; epidemiology; hemorrhage; risk; therapeutic use; warfarin

Abbreviations: AF = atrial fibrillation; HR = hazard ratio; INR = international normalized ratio; MI = myocardial infarction; NSAID = nonsteroidal antiinflammatory drug; OBRI = Outpatient Bleeding Risk Index; ROC = receiver operating characteristic

Warfarin has been proven to be the most effective antithrombotic agent for the primary or secondary prevention of stroke in patients with atrial fibrillation (AF), yet it is associated with a risk of major bleeding events. Numerous studies have documented the underutilization of warfarin therapy in eligible patients with AF, and physician surveys

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have shown that, while most believe warfarin is efficacious, fears of bleeding may prevent its utilization.6

Previously, two bleeding risk models have been developed and validated to assist clinicians in balancing the risks and benefits of antithrombotic therapy. The Outpatient Bleeding Risk Index (OBRI) considers age > 65 years, prior stroke, prior GI bleeding, and any of four comorbidities (eg, recent myocardial infarction [MI], anemia, diabetes, or renal insufficiency) in order to stratify patients into three risk groups.7–10 Kuijer et al11 developed another model that uses age > 60 years, gender, and malignancy to stratify patients into three risk groups.

While these models have proven validity, there remains a need for a model that more fully addresses the contemporary use of warfarin therapy in elderly AF patients. Both the OBRI model and the Kuijer et al11 model stratified risk by age at 60 to 65 years, while the mean age of AF patients is 75 years.1 Since advanced age has consistently been associated with the underutilization of warfarin therapy,1,3–12 a model that can address issues among the elderly is clearly needed. Second, these models did not include many other known factors that may be predictive of bleeding.7,8,11,13–19 Given the extremely low incidence of the bleeding events, much larger sample sizes are needed to adequately model additional risk factors. Third, while there are an increasing number of medications that may alter bleeding risks when used concurrently with warfarin,20,21 previous bleeding risk models22–24 have not accounted for common drug interactions in AF patients. Finally, prior models13–16 were primarily developed prior to the use of lower intensity warfarin anticoagulation therapy. The goals of our study were to develop a contemporary bleeding risk model for users of warfarin to help predict a given elderly patient’s risk for major bleeding events, to examine the capability of this new model to predict bleeding events in a validation cohort, and to compare our new model with predictions based on previous bleeding risk models.

Materials and Methods

The study design was a retrospective cohort analysis using the National Registry of Atrial Fibrillation. Briefly, the Centers for Medicare & Medicaid Services authorized the collection of data on a national, random sample of patients discharged from the hospital between April 1998 and March 1999, and between July 2000 and June 2001 with a diagnosis of AF (Classification of Diseases, ninth revision, clinical modification, codes 427.31) as part of the National Stroke Project.4,5 We used the hospitalization selected in this random sample as the index hospitalization. Patients who were at least 65 years of age were included in the present study if they had been discharged from the hospital while receiving warfarin therapy. The exclusion criteria included situations in which inadequate follow-up data or hospital discharge information would have been available, as follows: transfer to another acute care hospital; death during the hospitalization; discharged from the hospital against medical advice; and enrollment in a Medicare managed care organization during the 90-day follow-up period.

Data Sources

The following four sources of data were linked to carry out this study: (1) the initial Medicare part A claim identifying the index AF hospitalization; (2) the Medicare enrollment database to identify dates of death and managed care enrollment; (3) data abstracted from the medical record for the index AF hospitalization; and (4) 90-day follow-up Medicare part A claims. Data were obtained through collaboration with the Iowa Foundation for Medical Care and the Centers for Medicare & Medicaid Services. Data reliability for the chart-abstracted data ranged from 80 to 95%; the median interrater reliability was 90%.4

Study Variables

The primary outcome variable was hospitalization for a major acute bleeding event within 90 days of the hospital discharge date from the index AF hospital admission for either a GI hemorrhage (Diagnosis-Related Group code 174 or 175) or intracranial hemorrhage (International Classification of Diseases, ninth revision, clinical modification, codes 430 [subarachnoid], 431 [intracerebral], and 432 [other intracranial hemorrhage]).24–26 We classified bleeding events by the presence/absence of a bleeding event and the time to the bleeding event (ie, the number of days between hospital discharge and readmission for a major bleeding event). Only the first bleeding event for a study subject was included in the analysis. Predictor variables were determined from the chart-abstracted data. A host of risk factors for bleeding events have been identified in the literature.7,8,11,13–21 In general, these risk factors can be grouped into demographics (age, gender, and nursing facility residence), current or remote bleeding event, alcohol/drug abuse, concomitant diseases (anemia, cancer, stroke, transient ischemic attacks, MI, hypertension, heart failure/cardiomyopathy, ischemic heart disease, diabetes, hepatic failure, or peptic ulcer disease), concomitant risks for injury (risk for falls, cognitive impairment, or surgery during index hospitalization), and concurrent medications that can influence hemostasis. Anemia was defined as a hematocrit of < 30% during the index hospitalization. Concurrent medications prescribed at hospital discharge included aspirin, ticlopidine, and clopidogrel, and drugs from the following classes that have documented interactions: nonsteroidal antiinflammatory drugs (NSAIDs); dipyridamole; antibiotics; antiarrhythmic agents; histamine-2 antagonists; proton pump inhibitors; antifungal agents; pulmonary drugs; leukotriene antagonist agents; and lipid-lowering agents. We also tracked whether warfarin therapy was initiated during the index hospitalization or the subject had been admitted to the hospital while receiving warfarin therapy.

Statistical Analysis

We randomly split the sample for model development (75%) and validation (25%) using a random number generator. Bivariate relationships between the predictors and bleeding risk were examined using Kaplan-Meier curves, the log rank test, and Cox regression hazard ratios (HRs). Predictors with sufficient num-
bers and potential association indicated by at least one of the bivariate methods were considered for inclusion in the multivariable model.

Stepwise selection was used to determine the final Cox regression model (p < 0.15 to enter the study; p < 0.1 to remain in the study). Selected predictor variables were checked for collinearity. Risk scores were then created for each subject based on their adjusted HR of a bleeding event from the final model. All possible sets of cut points to determine a low, moderate, or high bleeding risk based on these scores were tested as predictors of a bleeding event using the development cohort. The cut points with the largest log-likelihood were selected as the optimal set of cut points for the contemporary bleeding risk model.

Risk scores were then generated for subjects in the validation sample and categorized based on the cut points as low, moderate, or high risk. The Pearson χ² statistic was used to compare the proportion of bleeding events across risk categories. Unconditional logistic regression predicting bleeding events by risk category was used to perform pairwise comparisons of bleeding event proportions and to estimate the area under the receiver operating characteristic (ROC) curve. Area under the ROC curve was estimated using the c-statistic. Kaplan-Meier survival curves were generated for each risk category, and the HRs of a bleeding event were compared using the log-rank test for trend.

Using the validation sample, subjects were categorized into risk groups based on the model of Kuijer et al. Modifications were made to best fit this risk model to the data available in our data set. The OBRI model combined all prior bleeding events, while we differentiated between bleeding events occurring during index hospitalization and remote bleeding events. Likewise, the OBRI included only recent MIs, whereas our data only contained a variable indicating any prior MI. Last, our data did not allow for us to examine the effect of renal insufficiency, thereby excluding one of the comorbidities from the OBRI model. Because all subjects were > 65 years old, there was no low-risk group in either the model of Kuijer et al or the OBRI model. The comparisons of our model to the Kuijer et al and OBRI models followed the same steps as our validation process. The University of Kansas Advisory Committee on Human Experimentation approved the research protocol.

**Results**

The cohort consisted of 76,177 unique observations. Reasons and counts for exclusion were made in the following order: failure to match with the Medicare denominator file; death before hospital discharge; discharged from the hospital while receiving another medication with potential bleeding effects; and newly prescribed warfarin.

### Table 1—Demographic, Clinical, and Outcome Descriptions of the AF Bleeding Risk Model Development and Validation Cohorts

<table>
<thead>
<tr>
<th>Predictor or Outcome Variable</th>
<th>Development Cohort</th>
<th>Validation Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases, No. (%)</td>
<td>19,875 (100)</td>
<td>6,470 (100)</td>
</tr>
<tr>
<td>Age ≥ 70 yr</td>
<td>88.0</td>
<td>88.6</td>
</tr>
<tr>
<td>Female gender</td>
<td>52.5</td>
<td>53.1</td>
</tr>
<tr>
<td>Nursing home residence</td>
<td>17.0</td>
<td>16.5</td>
</tr>
<tr>
<td>Previous bleeding event</td>
<td>11.9</td>
<td>12.1</td>
</tr>
<tr>
<td>Recent bleeding event</td>
<td>13.0</td>
<td>13.0</td>
</tr>
<tr>
<td>Alcohol/drug abuse</td>
<td>1.9</td>
<td>1.5</td>
</tr>
<tr>
<td>Known malignancy</td>
<td>2.5</td>
<td>2.6</td>
</tr>
<tr>
<td>Stroke</td>
<td>32.1</td>
<td>32.2</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>72.1</td>
<td>72.0</td>
</tr>
<tr>
<td>Heart failure/ cardiomyopathy</td>
<td>59.8</td>
<td>59.9</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>68.5</td>
<td>68.8</td>
</tr>
<tr>
<td>Endocrine and metabolic disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes*</td>
<td>29.6</td>
<td>28.3</td>
</tr>
<tr>
<td>Anemia</td>
<td>7.5</td>
<td>7.6</td>
</tr>
<tr>
<td>History of hepatic or renal failure</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Ulcer disease</td>
<td>12.3</td>
<td>12.2</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>9.7</td>
<td>9.1</td>
</tr>
<tr>
<td>Risk for falls</td>
<td>4.6</td>
<td>4.6</td>
</tr>
<tr>
<td>Concurrent medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>22.3</td>
<td>22.7</td>
</tr>
<tr>
<td>NSAID</td>
<td>5.9</td>
<td>6.4</td>
</tr>
<tr>
<td>Antibiotic</td>
<td>27.6</td>
<td>26.7</td>
</tr>
<tr>
<td>Other medication</td>
<td>35.8</td>
<td>36.2</td>
</tr>
<tr>
<td>Newly prescribed warfarin</td>
<td>28.7</td>
<td>29.2</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1.6</td>
<td>1.5</td>
</tr>
</tbody>
</table>

*Values are given as %, unless otherwise indicated. p = 0.05.

### Table 2—Final Variables Included in the Bleeding Risk Model Development*

<table>
<thead>
<tr>
<th>Variable</th>
<th>LN (HR)</th>
<th>HR</th>
<th>95% CI HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 70 years</td>
<td>0.49129</td>
<td>1.63</td>
<td>1.08–2.48</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.31771</td>
<td>1.37</td>
<td>1.09–1.73</td>
</tr>
<tr>
<td>Remote bleeding event</td>
<td>0.58454</td>
<td>1.79</td>
<td>1.36–2.37</td>
</tr>
<tr>
<td>Recent bleeding event</td>
<td>0.61738</td>
<td>1.85</td>
<td>1.41–2.44</td>
</tr>
<tr>
<td>Alcohol or drug abuse</td>
<td>0.70653</td>
<td>2.03</td>
<td>1.07–3.83</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.27049</td>
<td>1.39</td>
<td>1.07–1.80</td>
</tr>
<tr>
<td>Anemia</td>
<td>0.92878</td>
<td>2.36</td>
<td>1.76–3.17</td>
</tr>
<tr>
<td>Antiplatelet drug</td>
<td>0.32928</td>
<td>1.38</td>
<td>1.07–1.78</td>
</tr>
</tbody>
</table>

*LN = log normal; CI = confidence interval.
equation combining the eight risk factors to compute an individual’s risk score, as follows:

\[
\text{Risk score} = 0.49 \times X_{\text{Age}70+} + 0.32 \times X_{\text{Female}} + 0.58 \times X_{\text{Remote Bleed}} + 0.62 \times X_{\text{Recent Bleed}} + 0.71 \times X_{\text{Alcohol/Drug Abuse}} + 0.27 \times X_{\text{Diabetes}} + 0.86 \times X_{\text{Anemia}} + 0.32 \times X_{\text{Antiplatlet}}
\]

where \(X_j\) equals 1 when the specific characteristic is present and 0 otherwise. Based on the results of the log-likelihood scores, bleeding risk scores of \(\leq 1.07\), > 1.07 but < 2.19, and \(\geq 2.19\), respectively, were classified as low, moderate, and high risk.

In the validation sample, 35 of the low-risk individuals (0.9%), 48 of the moderate-risk individuals (2.0%), and 12 of the high-risk individuals (5.4%) had major bleeding events \((p < 0.0001)\). Looking further at the pairwise comparisons, we found a statistically significant difference between low-risk and high-risk subjects \((p < 0.0001)\), between the low-risk moderate-risk subjects \((p < 0.001)\), and between moderate-risk and high-risk subjects \((p < 0.01)\). The area under the ROC curve was 0.632, a level between “no discrimination” and “acceptable discrimination.”27 Kaplan-Meier curves for the three risk categories are shown in Figure 1, top left, A.

In the application of the Kuier et al11 model to the validation sample, 1.5% of the intermediate-risk individuals experienced bleeding events, and 1.8% of those individuals who were at high risk experienced bleeding events \((p = 0.74)\); the area under the ROC curve was 0.503, representing “no discrimination.”27 The Kaplan-Meier curves (Fig 1, top right, B) for these two risk categories showed no significant difference between the high-risk and intermediate-risk groups \((p = 0.75)\).

The OBRI model7–10 performed better than the Kuier et al11 model, with 1.0% of the intermediate-risk individuals and 2.5% of the high-risk individuals having experienced bleeding events \((p < 0.0001)\). The area under the ROC curve was 0.613, representing a level between “no discrimination” and “acceptable discrimination.”27 Kaplan-Meier curves (Fig 1, bottom, C) also showed the expected trends in the risk of bleeding events \((p < 0.0001)\).

**Discussion**

We were able to identify eight variables that were significant predictors of major bleeding events. The resulting model combining these risk factors performed well in differentiating among low-risk, moderate-risk, and high-risk groups, and likewise performed well when compared with two previous bleeding risk models. Our contemporary model improved the discrimination between subjects at risk for a bleeding event based on areas under the ROC curve and had three categories that demonstrated a trend toward increasing bleeding risk with increasing risk category. The bleeding event rate was greatest in the high-risk group from our contemporary model. In addition, the bleeding rate of the high-risk group was more than twice that of the moderate-risk group in our model, and more than twice that of the high-risk categories from the other models.

Our entire study population was > 65 years of age, and 43% of subjects were ≥ 80 years of age, which is a substantially higher rate than that reported in either of the previous models. For instance, in the second OBRI model,8 only 6% of persons in the derivation and validation cohorts were > 80 years of age. Advanced age has consistently been associated with the underutilization of warfarin therapy, despite the fact that benefits are potentially greater since the risk of stroke and death increase with age.1,3,12 Women have inconsistently been found to have higher bleeding rates.11,13,15,19

A clinically important advantage of our model over the two existing models is the identification of additional risk factors and our ability to separately quantify the effects of each risk factor. The added bleeding risk associated with concomitant antiplatelet therapy is particularly important given its prevalent use in treating comorbidities such as coronary heart disease. Approximately 20% of AF patients received concomitant warfarin-antiplatelet therapy,22,24 and antiplatelet therapy increases major bleeding rates in warfarin users, as noted in a previous analysis of these data and other work.24,31

In examining the weights for the eight risk factors, alcohol/drug abuse and anemia were particularly important risk factors. While the OBRI model7–10 includes anemia as one of several important comorbidities, it did not include alcohol/drug abuse. Chronic alcohol/drug abuse is likely to cause liver impairment, and although it is considered to be a contraindication to warfarin therapy, its presence was noted in nearly 2% of the study cohort.

The finding that bleeding risk was increased in diabetic patients is significant given the epidemiologic association between AF and diabetes,32,33 and the increasing prevalence of this comorbidity. Our findings confirm recent findings34 showing increased bleeding risk in AF patients with diabetes. As with the Kuier et al model11 and other studies,12,13,18,19 we found increased bleeding rates among women, although gender was not included in the OBRI model.7–10

Limitations to our approach included the lack of
ability to track compliance with, continuation of, or initiation of drug therapy after hospitalization and the inability to observe clinical laboratory values. We were left with the assumption that patients continued to receive the therapies they had been prescribed at hospital discharge throughout the study period, which is an intention-to-treat approach. We limited the follow-up time to 90 days, although this

Figure 1. Kaplan-Meier curves for each bleeding risk model. Top left, A: current study. Top right, B: model of Kuijer et al.11 Bottom, C: OBRI model.7–10
time frame should be adequate since studies 15, 19, 35–37 have shown that major bleeding events most often occur early in the course of warfarin therapy. However, we found no significant difference in the number of bleeding events between those who had been admitted to the hospital while receiving warfarin therapy and new users.

International normalized ratio (INR) values at hospital discharge or during follow-up were not documented in our data set. While INRs are used to monitor warfarin levels and to adjust therapy in order to avoid bleeding events, additional patient characteristics must also be considered. The availability of INR values may have improved the strength of the predictive model; however, the ability to stratify risk indicates that there was significant variation in bleeding events based on other patient-specific factors. These variables can assist clinicians who want to estimate the bleeding risk prior to drug initiation and INR monitoring.

Finally, we only examined risk among persons receiving warfarin therapy, and it is quite likely that additional AF patients who were not discharged from the hospital while warfarin therapy would have benefited from antithrombotic therapy. The Stroke Patient Outcomes Research Team concluded that improved antithrombotic therapy in AF patients could prevent an additional 40,000 strokes annually and save an estimated $600 million.38 Nonetheless, clinicians must weigh the potential benefits against each individual patient’s risk for major bleeding. For example, although diabetes and age were independent risk factors for bleeding, they were also independent risk factors for stroke. The 5.4% risk of major bleeding events that was seen in our group with the highest risk of stroke must be weighed against the >7% annual stroke risk faced by the highest risk patients with AF.39 At the patient level, this tradeoff can be difficult for clinicians to estimate.40

**SUMMARY**

Using a nationally derived data set, we have developed a model based on contemporary practice standards for determining the risk of major bleeding events among AF patients receiving warfarin therapy. Risk scores can be computed for individuals considering the following eight separately weighted factors: age; gender; recent bleeding event; remote bleeding event; alcohol/drug abuse; diabetes; anemia; and concomitant antiplatelet therapy. Validation of this model in other study populations is warranted.

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**REFERENCES**


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