Electrophysiology

Clinical classification schemes for predicting hemorrhage: Results from the National Registry of Atrial Fibrillation (NRAF)

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Background Although warfarin and other anticoagulants can prevent ischemic events, they can cause hemorrhage. Quantifying the rate of hemorrhage is crucial for determining the risks and net benefits of prescribing antithrombotic therapy. Our objective was to find a bleeding classification scheme that could quantify the risk of hemorrhage in elderly patients with atrial fibrillation.

Methods We combined bleeding risk factors from existing classification schemes into a new scheme, HEMORR$_2$HAGES, and validated all bleeding classification schemes. We scored HEMORR$_2$HAGES by adding 2 points for a prior bleed and 1 point for each of the other risk factors: **h**epatic or renal disease, **e**thanol abuse, **m**alignancy, **o**lder (age > 75 years), **r**educed platelet count or function, **h**ypertension (uncontrolled), **a**nemia, **g**enetic factors, **e**xcessive fall risk, and **s**troke. We used data from quality improvement organizations representing 7 states to assemble a registry of 3791 Medicare beneficiaries with atrial fibrillation.

Results There were 162 hospital admissions with an *International Classification of Diseases, Ninth Revision, Clinical Modification* code for hemorrhage. With each additional point, the rate of bleeding per 100 patient-years of warfarin increased: 1.9 for 0, 2.5 for 1, 5.3 for 2, 8.4 for 3, 10.4 for 4, and 12.3 for ≥5 points. In patients prescribed warfarin, HEMORR$_2$HAGES had greater predictive accuracy (*c* statistic 0.67) than other bleed prediction schemes ($P < .001$).

Conclusions Adaptations of existing classification schemes, especially a new bleeding risk scheme, HEMORR$_2$HAGES, can quantify the risk of hemorrhage and aid in the management of antithrombotic therapy. (Am Heart J 2006;151:713-9.)

Although warfarin and other anticoagulants can prevent stroke,[1-3] myocardial infarction,[4,5] and venous thromboembolism,[6,7] they often cause bleeding.[8-11] Anticoagulants, primarily warfarin, cause 10% of drug-related adverse events in Medicare outpatients.[12,13] Not only do these hemorrhages decrease the net benefit of anticoagulant therapy, but the fear of iatrogenic hemorrhage causes physicians to avoid anticoagulants in some patients with atrial fibrillation who are likely to benefit from them.[14-17]

Quantifying the risk of hemorrhage could improve the use of antithrombotic therapy in several ways. First, it would aid in patient selection by allowing clinicians to identify patients for whom the benefits of anticoagulants outweigh the risks. For example, clinical prediction rules for stroke[18-21] could be combined with bleeding risk schemes to identify patients with atrial fibrillation who are likely to benefit, rather than be harmed, from anticoagulant therapy.[22] Second, a valid bleeding risk scheme would allow clinicians to monitor antithrombotic therapy more carefully in patients at high risk of bleeding, thereby decreasing their risk of hemorrhage.[23] Finally, a prediction rule could help identify which asymptomatic patients with a supratherapeutic international normalized ratio (INR) should receive vitamin K. To date, no bleeding risk scheme has been developed or tested in elderly atrial fibrillation population, a growing population in whom clinicians are reluctant to prescribe anticoagulants because of fear of hemorrhage.[14-16,24,25]

Here, we adapt 3 previously published bleeding risk schemes[9-11] to Medicare beneficiaries with atrial

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fibrillation and form a new scheme. Then we compare the accuracy of all 4 schemes in predicting hemorrhage.

Methods

Existing classification schemes for predicting hemorrhage

To find the existing clinical prediction rules for hemorrhage, we searched PubMed with keywords {anticoagulant OR coumarin} AND {Bleed# OR hemorrhage} AND {scheme OR risk assessment OR prediction rule OR decision support techniques OR statistical model#}. This search identified 195 references. We obtained the full text of English-language articles that appeared to be relevant based on their title and abstract. We reviewed the bibliographies of relevant articles for pertinent references and searched an electronic database of >1000 articles about antithrombotic therapy that we update weekly.

We excluded 3 schemes that correlated risk of bleeding to maximum achieved INR because maximum INR is not known at the start of anticoagulant therapy.[26-28] We excluded one scheme because it performed no better than chance[29] and another that was tailored for patients receiving heparin.[30]

Ultimately, we were left with 3 schemes that quantified the association between comorbid conditions and bleeding: the Outpatient Bleeding Risk Index of Landefeld and Goldman[8] and Beyth et al,[9] the scheme of Kuijer et al,[10] and the scheme of Kearon et al.[11] None of these schemes had been developed in or evaluated in an elderly atrial fibrillation population.

Landefeld and Goldman[8] derived their original scheme in a cohort of 562 patients prescribed warfarin, primarily for placement of a prosthetic heart valve. It included 4 risk factors for major bleeding, each scored as 1 point: (1) age ≥65 years, (2) history of gastrointestinal bleeding, (3) history of stroke, and (4) any of 4 specific comorbid conditions (recent myocardial infarction, anemia, renal insufficiency, or atrial fibrillation). Nieuwenhuis et al[30] found that the original Landefeld scheme was not a valid predictor of short-term hemorrhage in 194 patients with acute venous thromboemboli. Subsequently, Beyth et al [9] modified the scheme by replacing atrial fibrillation with diabetes mellitus and found that this Landefeld-Beyth scheme performed well in an inception cohort of 264 participants.

Kuijer et al[10] developed 2 versions of a bleeding risk classification scheme in 241 patients with venous thromboembolism. They advocated use of the version that included 3 risk factors for major bleeding: age >60 years (1.6 points), female sex (1.3 points), and presence of malignancy (2.2 points).

In a study of 738 patients with prior venous thromboemboli, Kearon et al[11] evaluated the following risk factors for bleeding: age ≥65 years, previous stroke, previous peptic ulcer disease, previous gastrointestinal bleeding, renal impairment, anemia, thrombocytopenia, liver disease, diabetes mellitus, and the use of antiplatelet therapy. The rate of major bleeds per 100 patient-years of warfarin therapy was greater in patients who had ≥1 of these risk factors than in patients who had none.

To adapt these 3 schemes to this elderly population and to allow for a fair comparison, we used the same definition of increased age (≥75 years) for all schemes rather than the younger ages originally proposed. We chose 75 years as the threshold because of an increased risk of hemorrhage after this age,[31-33] and because 75 is the median age of the atrial fibrillation population.[34]

Development of the new classification scheme HEMORR$_2$HAGES

To form a new scheme, we included bleeding risk factors from the following sources: the 3 prior clinical prediction rules, a recent systematic review,[35] and our PubMed search. When combined, the predictors of major bleeding spelled "HEMORRHAGES": **h**epatic or renal disease, **e**thanol abuse, **m**alignancy, **o**lder (age > 75 years), **r**educed platelet count or function,[11,30] **r**ebleeding risk, **h**ypertension (uncontrolled), **a**nemia,[9,11,36] **g**enetic factors (CYP 2C9 single-nucleotide polymorphisms),[37-41] **e**xcessive fall risk (including neuropsychiatric disease),[42] and **s**troke. The relative risks (RRs) for each bleeding risk factor varied widely among studies, but the median RRs for most factors ranged from approximately 1.4 to 2.4.[35] Based on this observation and the merits of simplicity, we elected to weigh each bleeding risk factor 1 point, except that we awarded 2 points for a prior bleed (R in the mnemonic) because of its greater RR and named the new scheme "HEMORR$_2$HAGES." In a post hoc analysis, we awarded 1 point for prior bleed, but the results were similar to using 2 points and, therefore, are not shown. We identified these factors from structured medical record abstraction supplemented with *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes (Appendix A). Because we did not have access to DNA, we were not able to capture genetic risk factors for bleeding.

Formation of the National Registry of Atrial Fibrillation data set

As previously detailed,[18] the National Registry of Atrial Fibrillation (NRAF) contains de-identified patient records gathered by 5 quality improvement organizations (QIO). The participating QIOs serve 7 states (California, Connecticut, Louisiana, Maine, Missouri, New Hampshire, and Vermont). These QIOs had assembled state-specific cohorts of patients with atrial fibrillation for quality improvement projects under the Health Care Quality Improvement Initiative of the Centers for Medicare and Medicaid Services (CMS)[43]; no additional charts were abstracted to create the NRAF data set. Using Medicare Provider Analysis and Review (MEDPAR) Part A records, QIO reviewers used the appropriate *ICD-9-CM* code (427.31) in either a principal or secondary diagnosis to identify Medicare beneficiaries who had atrial fibrillation. Through structure medical record review, QIO reviewers confirmed the presence of chronic or recurrent atrial fibrillation during the index hospitalization. They also documented comorbid conditions and the antithrombotic therapy prescribed at hospital discharge.

To obtain outcomes, reviewers linked abstractions of index hospitalizations to MEDPAR records and the denominator file of living Medicare beneficiaries. After linking follow-up data and removing identifiers, the QIOs sent the de-identified records to Washington University for inclusion into the NRAF data set. The study was approved by the human subjects' committee at the Washington University Medical Center, the participating QIOs, and CMS.

We used the QIO records to develop the NRAF data set of Medicare beneficiaries who had chronic or recurrent atrial fibrillation. We obtained 7 bleeding risk factors from the

Table I. NRAF participants

Bleeding risk factor	Warfarin (n = 1604)	Aspirin (n = 660)	Neither (n = 1527)
Hepatic or renal disease (%)	7.9	12	12
Ethanol abuse (%)	0.7	0.5	0.9
Malignancy (%)	4.8	3.2	9
Older (age >75 y) (%)	69.2	78.4	76.6
Reduced platelet count or function* (%)	9.6	100	5.2
Rebleeding risk (%)	15.9	21.4	22.1
Hypertension (uncontrolled) (%)	0.4	0.5	0.6
Anemia (%)	8.5	10.5	14.8
Genetic factors (%)	NA	NA	NA
Excessive fall risk or neuropsychiatric disease (%)	18.8	27.7	24.1
Stroke (%)	37.2	30	23.6
Mean $HEMORR_2HAGES$ score	1.9	3.1	2.1

NA, Not available.
*When aspirin use is excluded, the percentages are 2.6, 1.7, and 5.2.

medical record reviews and 4 from the appropriate *ICD-9-CM* codes from the index hospitalization (Appendix A).

Outcomes assessment

The study outcome was time to hospitalization for hemorrhage, as determined by Medicare claims. To identify major bleeds from the MEDPAR data, we used *ICD-9-CM* codes validated by White et al,[44] except that we excluded 3 *ICD-9-CM* codes that were unrelated to antithrombotic therapy and added *ICD-9-CM* codes that had appropriate definitions or high positive predictive value.[45] To improve sensitivity in identifying major bleeds and based on recent findings, we included *ICD-9-CM* codes for hemorrhage in any position, rather than only the primary one. To improve specificity, we used the fifth digit to include only active hemorrhage.

We censored beneficiaries at the time of the first post–baseline hospitalization or at a maximum of 1000 days after the baseline hospitalization. We excluded patients who died outside of hospital and had no post–baseline hospitalizations because the presence of hemorrhage at the time of death could not be determined.

Statistical analyses

We used the κ statistic[46] to quantify the agreement (corrected for chance) between the schemes in classifying patients into low-, medium-, or high-risk for hemorrhage. We quantified the discriminant ability of the classification schemes with the *c* statistic.[47] In this setting, *c* reflects concordance of predicted and observed hemorrhage-free time, with $c = 0.5$ for no discriminative ability and $c = 1.0$ for perfect discriminative ability. We compared *c* values of the schemes in 500 bootstrapped samples[48] and derived 95% CIs for the differences between schemes, using the percentile method. We also compared how well schemes improved the prediction of hemorrhage using a Cox proportional hazard model and Graf-modified Brier scores.[49] Because these 2 statistics agreed with the *c* statistics, we report only the latter. We performed statistical analyses in SAS (SAS Institute Inc, Cary, NC). All comparisons were 2-tailed, and P values $< .05$ were considered statistically significant.

Table II. Risk of major bleeding in NRAF participants prescribed warfarin, stratified by $HEMORR_2HAGES$ score

$HEMORR_2HAGES$ score*	n	No. of bleeds	Bleeds per 100 point-years warfarin (95% CI)
0	209	4	1.9 (0.6-4.4)
1	508	11	2.5 (1.3-4.3)
2	454	20	5.3 (3.4-8.1)
3	240	15	8.4 (4.9-13.6)
4	106	9	10.4 (5.1-18.9)
≥5	87	8	12.3 (5.8-23.1)
Any score	1604	67	4.9 (3.9-6.3)

*$HEMORR_2HAGES$ is scored by adding 1 point for each bleeding risk factor: hepatic or renal disease, ethanol abuse, malignancy older (age > 75 years), reduced platelet count or function, rebleeding risk (2 points), hypertension (uncontrolled), anemia, genetic factors (not available in this study), excessive fall risk, and stroke.

Results

The NRAF data set included 3932 Medicare beneficiaries with chart-confirmed atrial fibrillation. After excluding records with missing information (n = 141), we analyzed the remaining 3791 patients. Mean age was 80.2 years, and 57% of the cohort was women. During 3138 patient-years of follow-up, there were 162 admissions with a bleed (5.2 bleeds per 100 patient-years). Two thirds (67.3%) of these bleeds were gastrointestinal hemorrhages, 15.4% were intracranial, and 17.3% were in other locations. The 30-day mortality of patients admitted with a bleed (in any location) was 21.6%.

One thousand six hundred four (1604) patients were discharged on warfarin (113 of whom also received aspirin), 660 patients were discharged on aspirin (or a thienopyridine) alone, and 1527 were prescribed no antithrombotic therapy on discharge. Compared with patients discharged on warfarin (mean age 79 years), patients discharged on aspirin or no antithrombotic therapy were older (mean age 81 years) and had more risk factors for bleeding (Table I): the mean $HEMORR_2HAGES$ score was 1.9 in patients prescribed warfarin, 3.1 in patients prescribed aspirin (2.1 if aspirin use did not count toward reduced platelet count/function), and 2.1 in patients not prescribed with antithrombotic therapy ($P < .001$). Unadjusted bleeding rates were slightly greater in the aspirin cohort: 4.9 bleeds per 100 point-years warfarin, 5.9 bleeds per 100 patient-years aspirin, and 5.1 bleeds per 100 patient-years without antithrombotic therapy.

Agreement between the bleeding risk schemes

To assess agreement, we classified patients with a score of 0 or 1 on $HEMORR_2HAGES$ or the scheme of Kearon as low-risk, 2 or 3 as intermediate-risk, and ≥4 as high-risk. Then we compared low-, medium-, and high-risk cohorts from all 4 schemes. Weighted κ statistics indicated poor agreement between schemes, ranging from a low of 0.14

Table III. Risk of major bleeding in NRAF participants prescribed warfarin, stratified by prior risk-classification schemes

Scheme	Risk score	n	Bleeds per 100 patient-years warfarin (95% CI)	Originally reported bleeds per 100 point-years warfarin* (95% CI or range)
Landefeld and Goldman,[8]	0	169	1.1 (0.3-4.3)	0-3
Beyth et al,[9] and Wells et al[54]	1-2	1174	4.9 (3.6-6.5)	4.3-12
	3-4	261	8.8 (5.6-14.0)	30-48
Kuijer et al[10]	0	225	2.9 (1.3-6.5)	0-4
	>0 and <3	1312	5.2 (4.0-6.7)	1-8
	≥3	67	7.5 (2.8-19.9)	24-43
Kearon et al[11]	0	181	2.5 (1.1-6.1)	0.2-0.4
	1	603	2.5 (1.4-4.3)	1.8-2.0
	2	537	6.5 (4.5-9.4)	1.0-2.3
	3	229	9.3 (5.7-15.3)	NA
	≥4	54	15.3 (6.4-36.8)	NA

*Bleeding rates from Kuijer et al[10] are cumulative percentages for 3 months rather than 1 year.

Table IV. *c* Indices quantifying ability of schemes to predict major hemorrhage, stratified by therapy

	c Indices (SD), stratified by cohort		
Scheme	Warfarin (n = 1604)	Aspirin (n = 660)	Neither (n = 1527)
Landefeld and Goldman[8] and Beyth et al[9]	0.65 (0.03)	0.69 (0.05)	0.65 (0.03)
Kuijer et al[10]	0.58 (0.03)	0.58 (0.05)	0.47 (0.03)
Kearon et al[11]	0.66 (0.03)	0.64 (0.05)	0.66 (0.04)
HEMORR$_2$HAGES	0.67* (0.04)	0.72* (0.05)	0.66 (0.04)

*P < .001 compared with the other 3 schemes (analysis of variance test).

(for Kuijer vs Kearon) to a high of 0.52 (for HEMORR$_2$HAGES vs Kearon). Thus, the 4 bleeding schemes classified patients very differently.

Bleeding rates were lower in low-risk patients and greater in high-risk patients, validating all schemes (Tables II and III). The highest bleeding rate was 15.3 per 100 patient-years of warfarin in patients with a Kearon score of ≥4.

Validation of the schemes in patients prescribed warfarin (n = 1604)

Among Medicare beneficiaries prescribed warfarin, HEMORR$_2$HAGES had the best discriminant ability (Table IV). In 500 bootstrapped samples, the *c* index for HEMORR$_2$HAGES was 0.67, significantly greater than the *c* index for the other schemes (P < .001).

The 660 patients prescribed aspirin on discharge were admitted with 30 bleeds. HEMORR$_2$HAGES also had a better discriminant ability than the other schemes in this cohort: the *c* statistic for HEMORR$_2$HAGES was 0.72, significantly (P < .001) greater than *c* for the other schemes (Table IV). Comparison of the likelihood ratio χ^2 values from Cox models corroborated our finding that HEMORR$_2$HAGES was the most accurate predictor of bleeding in the warfarin and aspirin cohorts.

The 1527 patients prescribed no antithrombotic therapy at hospital discharge were admitted with 65 bleeds. In this cohort, HEMORR$_2$HAGES and Kearon et al[11] both had the greater *c* index (0.66).

Discussion

HEMORR$_2$HAGES and adaptations of 3 previously existing bleeding risk classification schemes successfully quantified the rate of hemorrhage in 3791 Medicare beneficiaries with atrial fibrillation. Our finding that the schemes, especially HEMORR$_2$HAGES, accurately predicted bleeding is important because although prior studies have quantified the rate of stroke in atrial fibrillation,[18,21,50] only 2 smaller studies have quantified the rate of bleeding in this growing population.[31,51] Quantifying the rate of bleeding is important because fear of hemorrhage is a major reason why antithrombotic therapy has been underused in patients with atrial fibrillation.[14,16]

The average rate of hospitalization for bleeding in patients prescribed warfarin was 4.9 per 100 patient-years, but the rate depended on the number of comorbid conditions. High-risk patients identified by any of the schemes had a hemorrhage rate (7.5-15.3) much greater than the rate in low-risk patients (1.1-2.9), validating the ability of the schemes to risk-stratify elderly patients with atrial fibrillation. For comparison, the rate of major bleeding in atrial fibrillation trials averaged 2.4 major bleeds per 100 patient-years of warfarin therapy.[2,3,52] Trial participants were elderly (mean age 72 years) but, otherwise, had few risk factors for bleeding.

Studies that exclusively enrolled patients new to warfarin reported greater rates of bleeding.[8-10,53,54] In particular, bleeding in the inception cohorts studied by Landefeld and Goldman,[8] Beyth et al,[9] and Kuijer et al[10]

had higher rates of bleeding, at least in high-risk cohorts (Table III). In contrast, participants enrolled by Kearon et al[11] (Table III) had successfully taken warfarin therapy for at least 3 months before enrolling in that trial, which contributed to their low bleeding rates. Half of the participants of Kearon were randomized to low-dose warfarin (target INR 1.5-1.9), which also may have prevented bleeds.

Adaptations of the 3 original schemes to the Medicare beneficiaries had lower discriminant ability than reported from the original studies. In 264 outpatients beginning warfarin, Beyth et al [9] found a *c* statistic of 0.78, whereas we found a value of 0.65 for their scheme in the Medicare beneficiaries with atrial fibrillation who were prescribed warfarin. Likewise, Kuijer et al[10] found an area under the curve of 0.82 in their derivation cohort of 241 patients beginning a coumarin for an acute venous thromboembolism, whereas we calculated a *c* index of 0.58 for their scheme. The lower discriminant accuracy in our study, compared with the original smaller studies, highlights the need to study clinical prediction rules in different populations.

Our study had limitations inherent to use of inpatient administrative data. First, we imputed several bleeding risk factors from *ICD-9-CM* codes and used validated *ICD-9-CM* codes to identify incident hemorrhages. Thus, we could only capture bleeds that resulted in an in-state hospitalization. Second, we knew the antithrombotic therapy prescribed at hospital discharge but could not identify changes in or compliance with that therapy. The net effect of these 2 limitations is that all schemes might perform better in clinical practice than reported here. A minor limitation is that we could not determine whether supratherapeutic INR values or other factors (eg, use of heparin or invasive procedures) contributed to bleeding.

These limitations are offset by important strengths. First, the bleeding risk schemes were validated in a cohort of Medicare beneficiaries from 7 states representing diverse geographic regions of the United States. Second, we had more patients and more major bleeds in our study than prior studies of bleeding schemes combined.[8-11,54] Third, because HEMORR$_2$HAGES was derived from the literature rather than being data-driven, our study validates HEMORR$_2$HAGES in Medicare beneficiaries with atrial fibrillation. Fourth, our study population had many bleeding risk factors, allowing us to quantify the risk of hemorrhage for a wide range of comorbid conditions with precision. Finally, we used structured medical record review, rather than *ICD-9-CM* claims, to document the presence of atrial fibrillation, prescription of antithrombotic therapy, and most of the bleeding risk factors.

Although the present study validates HEMORR$_2$HAGES in Medicare beneficiaries with atrial fibrillation, the scheme was developed without reference to a specific patient population and therefore should be generalizable to other populations. For example, clinicians could use HEMORR$_2$HAGES to help select patients with a recent myocardial infarction who could be treated with aggressive antithrombotic therapy rather than aspirin alone,[4,55-57] patients with venous thromboemboli who can safely be treated long-term with an anticoagulant,[6,11] and patients with mechanical valves who could add aspirin to their anticoagulant.[58,59] For all 3 of these disease states, the more aggressive antithrombotic regimens are more effective at preventing ischemic events but can only be justified when they are unlikely to cause bleeding. Because HEMORR$_2$HAGES was a valid predictor of hemorrhage in patients who were prescribed warfarin or aspirin, it may be a valid predictor of hemorrhage in patients prescribed newer anticoagulants.[3,52]

In summary, the decision to take antithrombotic therapy should be based on individual risks and benefits. For example, by combining HEMORR$_2$HAGES with a clinical prediction rule for stroke,[18,21,50] clinicians can trade off the risks and benefits of prescribing anticoagulant versus antiplatelet therapy in elderly patients with atrial fibrillation.[22] Patients with a high risk of bleeding could avoid anticoagulants unless their risks of stroke were high enough to justify the risks, in which case they could take anticoagulants with vigilant monitoring.

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Appendix A

Data source for bleeding risk factors

Bleeding risk factor	Data source
Hepatic or renal disease	Chart review: some QIOs included only end-stage renal disease; others included patients with a creatinine >2.5 mg/dL and patients with end-stage liver disease or cirrhosis
Ethanol abuse	*ICD-9-CM* codes: 291.0-2, 303.x, 305.0x, 571.0-3, 535.3
Malignancy	*ICD-9-CM* codes: 141-172, 174-208
Older age	Chart review for age >75 years
Reduced platelet count or function	Chart review for aspirin use or thrombocytopenia; QIO review captured blood dyscrasias (eg, hemophilia) in some states
Rebleeding risk	Chart review for prior bleeding
Hypertension (uncontrolled)	*ICD-9-CM* codes: 401.0, 402.0x, 403.0x, 404.0x, 405.0x
Anemia	*ICD-9-CM* codes: 280.x, 281.x, 282.0-4, 282.60, 282.69, 283.x, 284.x, 285.x
Genetic factors	Not available in this study
Excessive fall risk	Chart review for: high risk of falling, dementia, Parkinson disease, or psychiatric disease
Stroke	Chart review or *ICD-9-CM* codes 434-436 in the primary position

ICD-9-CM codes are from the baseline hospitalization.