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How Well do Stroke Risk Scores Predict Hemorrhage in Patients with Atrial Fibrillation?

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Abstract

The decision to use anticoagulants for atrial fibrillation depends on comparing a patient's estimated risk of stroke to their bleeding risk. Several of the risk factors in the stroke risk schemes such as overlap with hemorrhage risk. We compared how well two stroke risk scores (CHADS₂ and CHA₂DS₂-VASc) and two hemorrhage risk scores (the ATRIA bleeding score and the HAS-BLED score) predicted major hemorrhage on and off warfarin in a cohort of 13,559 community-dwelling adults with AF. Over a cumulative 64,741 person-years of follow up, we identified a total of 777 incident major hemorrhage events. The ATRIA bleeding score had the highest predictive ability out of all of the scores in patients on-warfarin (c-index of 0.74 [0.72-0.76] compared to 0.65 [0.62-0.67] for CHADS₂, 0.65 [0.62-0.67] for CHA₂DS₂-VASc, and 0.64 [0.61-0.66] for HAS-BLED) as well as in patients off-warfarin (0.77 [0.74-0.79] compared to 0.67 [0.64-0.71] for CHADS₂, 0.67 [0.64-0.70] for CHA₂DS₂-VASc, and 0.68 [0.65-0.71] for HAS-BLED). In conclusion, although CHADS₂ and CHA₂DS₂-VASc stroke scores were better at predicting hemorrhage than chance alone, they were inferior to the ATRIA bleeding score. Our study supports the use of dedicated hemorrhage risk stratification tools to predict major hemorrhage in atrial fibrillation.

Keywords

Anticoagulation; atrial fibrillation; warfarin; bleeding risk

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Introduction

Anticoagulant therapy significantly reduces the risk of ischemic stroke from atrial fibrillation, and guidelines recommend using stroke risk stratification schemes to estimate the risk of stroke and determine the need for anticoagulation^{1–6}. However, the bleeding complications associated with anticoagulation deter many clinicians from prescribing such therapy. Stroke risk schemes, while developed to predict ischemic stroke, contain variables that are also risk factors for anticoagulant-associated hemorrhage, leading to suggestions that stroke risk schemes can be used as proxies for hemorrhage risk⁷. The objective of our study was to test whether two widely used stroke risk stratification schemes, the CHADS₂ and CHA₂DS₂-VASc scores, could effectively predict major hemorrhage in anticoagulated patients, and compared their predictive ability to two validated hemorrhage risk scores (ATRIA and HAS-BLED)

Methods

The ATRIA Study is a cohort of 13,559 adults enrolled in Kaiser Permanente Northern California diagnosed with nonvalvular atrial fibrillation^{6,8}. Subjects were enrolled in the cohort between July 1, 1996, and December 31, 1997 and followed until September 30, 2003. Patients were included if they had serial outpatient diagnoses of atrial fibrillation, with the large majority having electrocardiographic evidence of atrial fibrillation. Demographic data and dates of hospitalization were available from health plan administrative databases.

We compared the CHADS₂⁹ and CHA₂DS₂-VASc¹⁰ stroke risk scores with the ATRIA bleeding score¹¹ and the HAS-BLED¹² scores. The individual components of the risk scores are presented in Table 1. The presence of specific medical conditions included in the risk scores was identified by searching for relevant *International Classification of Diseases, Ninth Edition* (ICD-9) codes as previously described⁸. Diabetes mellitus diagnoses were obtained from a validated diabetes registry. Laboratory data on hemoglobin, estimated glomerular filtration rate, and international normalized ratio (INR) were obtained from outpatient laboratory databases⁸. Exposure to warfarin was determined using a combination of information from prescriptions and INR measurements in pharmacy and laboratory databases using a previously developed and validated algorithm¹³. Longitudinal warfarin exposure was based on number of days of supply per prescription and intervening INRs. Data on prescription antiplatelet medications were obtained from outpatient pharmacy databases, but use of over-the-counter medications (e.g., aspirin and non-steroidal anti-inflammatory drugs [NSAIDs]) was not available.

The primary outcome of the study was major hemorrhage, defined as fatal, requiring transfusion of ≥ 2 units of packed red blood cells, or hemorrhage into a critical anatomic site (such as intracranial or retroperitoneal)^{6,8}. Potential events in the cohort were identified from clinical databases by searching for hospitalizations with a primary discharge diagnosis of extracranial hemorrhage those with a primary or secondary diagnosis of intracranial hemorrhage. Medical charts from potential hemorrhagic events were reviewed by a

physician-led clinical outcomes committee using a formal study protocol in order to determine whether the events were valid and met major hemorrhage criteria^{6,8,11}.

The cohort was divided into on and off-warfarin periods based on the warfarin algorithm. Exposure to individual clinical risk factors was assessed using a time-varying approach where the presence of risk factors was allowed to change over time based on changes in clinical factors (such as increasing age or new medical diagnoses). Major hemorrhage rates were calculated for on and off-warfarin periods as events per 100 person-years. The predictive ability of each risk score was measured by calculating a c-index from a logistic regression model, using risk scores in their continuous form. We also divided risk scores into low, intermediate, and high risk categories in order to calculate the net reclassification improvement between risk scores, a measure of the proportion of patients correctly moved from 1 risk category to another based on outcomes¹⁴.

Results

A total of 13,559 patients contributed 32,611 person-years on-warfarin and 32,130 off-warfarin. There were 777 major hemorrhages in the cohort. The CHADS₂ and CHA₂DS₂-VASc stroke risk scores performed better than chance alone in predicting major hemorrhage in patients on-warfarin as well as off-warfarin, although the difference in hemorrhage rates between low and high risk categories was small (Table 2). However, stroke risk scores did not perform as well as the ATRIA bleeding score, which predicted hemorrhage better than CHADS₂, CHA₂DS₂-VASc, and HAS-BLED (Table 2).

Discussion

Although the CHADS₂ and CHA₂DS₂-VASc stroke risk scores have some predictive ability for major hemorrhage, they should not be used in lieu of a validated hemorrhage risk stratification schemes in patients both on and off warfarin. In this study, the ATRIA bleeding score was the highest performing risk score. Although clinical risk factors overlap somewhat between stroke and bleeding risk scores, our study supports calculating bleeding risk separately from stroke risk using separate, distinct tools.

Our study has several limitations. Observational studies of bleeding risk are prone to selection bias because clinicians may avoid anticoagulation in the highest risk patients, leading to underestimates of a patient's true risk for hemorrhage. However, we found that the bleeding risk scores predicted hemorrhage in non-anticoagulated patients as well. There is no widely-accepted cut-off of hemorrhage risk where anticoagulation is considered contraindicated, and low/intermediate/high risk categories may be somewhat arbitrary. Our cohort did not collect data on over-the-counter medication use in patients without hemorrhage events, and we are therefore unable to ascertain longitudinal aspirin or NSAID use which may contribute to bleeding risk. We also relied on ICD-9 codes to define clinical risk factors, which are subject to potential misclassification.

Our study supports the use of dedicated hemorrhage risk stratification tools to predict major hemorrhage and highlights the need for better tools that can simultaneously integrate both stroke and bleeding risk when considering anticoagulation for atrial fibrillation.

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Table 1
Stroke and Bleeding Risk Scores in Atrial Fibrillation

CHADS₂	
Variables	Points
Congestive heart failure	1
Hypertension	1
Age ≥ 75 years	1
Diabetes mellitus	1
Stroke/TIA	2
Scoring: Continuous or Low (0 points), Intermediate (1 point), and High (2-6 points)	
CHA₂DS₂-VASc	
Variables	Points
Congestive heart failure	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke/TIA	2
Vascular disease	1
Age 65-74 years	1
Female sex	1
Scoring: Continuous or Low (0 points), Intermediate (1 point), and High (2-10 points)	
ATRIA Bleeding Score	
Variables	Points
Anemia	3
Severe renal disease	3
Age ≥ 75 years	2
Prior bleeding	1
Hypertension	1
Scoring: Continuous or Low (0-3 points), Intermediate (4 points), and High (5-10 points)	
HAS-BLED	
Variables	Points
Hypertension	1
Abnormal renal/liver function	1-2
Stroke history	1
Bleeding history or predisposition	1
Labile INR	1
Age > 65 yrs	1
Drugs/alcohol concomitantly	1-2
Scoring: Continuous	

International normalized ratio (INR); Transient ischemic attack (TIA)

Table 2

Comparison of CHADS₂, CHA₂DS₂-VASC, ATRIA Bleeding Score, and HAS-BLED in predicting major hemorrhage. Hemorrhage rate is the number of major hemorrhages per 100 person-years of follow-up

a: During periods when patients were on warfarin									
Risk Scheme	Low Risk		Intermediate Risk		High Risk		c-index (95% CI) for 3-category score	c-index (95% CI) continuous score	Net Reclassification Improvement
	% pyrs	Hemorrhage rate	% pyrs	Hemorrhage rate	% pyrs	Hemorrhage rate			
CHADS ₂	10.3%	0.32	27.1%	0.97	62.6%	1.76	0.63 (0.61-0.65)	0.65 (0.62-0.67)	Referent
CHA ₂ DS ₂ -VASC	2.6%	0.23	8.0%	0.49	89.4%	1.51	0.56 (0.55-0.57)	0.65 (0.62-0.67)	-12.9%
ATRIA bleeding score	83.3%	0.76	6.7%	2.9	10.1%	5.66	0.68 (0.66-0.71)	0.74 (0.72-0.76)	28.0%
HAS-BLED score	8.3%	0.41	74.2%	1.15	17.5%	2.91	0.61 (0.59-0.63)	0.64 (0.61-0.66)	0.4%

b: During periods when patients were off warfarin									
Risk Scheme	Low Risk		Intermediate Risk		High Risk		c-index (95% CI) for 3-category score	c-index (95% CI) continuous score	Net Reclassification Improvement
	% pyrs	Hemorrhage rate	% pyrs	Hemorrhage rate	% pyrs	Hemorrhage rate			
CHADS ₂	19.0%	0.21	31.0%	0.56	49.9%	1.55	0.63 (0.60-0.66)	0.67 (0.64-0.71)	Referent
CHA ₂ DS ₂ -VASC	7.8%	0.16	11.9%	0.21	80.3%	1.18	0.57 (0.55-0.59)	0.67 (0.64-0.70)	-17.9%
ATRIA bleeding score	83.1%	0.56	6.27%	1.64	10.61%	3.97	0.68 (0.65-0.72)	0.77 (0.74-0.79)	22.1%
HAS-BLED score	14.8%	0.13	69.5%	0.88	15.7%	2.3	0.64 (0.62-0.67)	0.68 (0.65-0.71)	-9.7%