Validation of Clinical Classification Schemes for Predicting Stroke

Results From the National Registry of Atrial Fibrillation

Brian F. Gage, MD, MSc
Amy D. Waterman, PhD
William Shannon, PhD
Michael Boechler, PhD
Michael W. Rich, MD
Martha J. Radford, MD

Context Patients who have atrial fibrillation (AF) have an increased risk of stroke, but their absolute rate of stroke depends on age and comorbid conditions.

Objective To assess the predictive value of classification schemes that estimate stroke risk in patients with AF.

Design, Setting, and Patients Two existing classification schemes were combined into a new stroke-risk scheme, the $CHADS_2$ index, and all 3 classification schemes were validated. The $CHADS_2$ was formed by assigning 1 point each for the presence of congestive heart failure, hypertension, age 75 years or older, and diabetes mellitus and by assigning 2 points for history of stroke or transient ischemic attack. Data from peer review organizations representing 7 states were used to assemble a National Registry of AF (NRAF) consisting of 1733 Medicare beneficiaries aged 65 to 95 years who had nonrheumatic AF and were not prescribed warfarin at hospital discharge.

Main Outcome Measure Hospitalization for ischemic stroke, determined by Medicare claims data.

Results During 2121 patient-years of follow-up, 94 patients were readmitted to the hospital for ischemic stroke (stroke rate, 4.4 per 100 patient-years). As indicated by a *c* statistic greater than 0.5, the 2 existing classification schemes predicted stroke better than chance: *c* of 0.68 (95% confidence interval [CI], 0.65-0.71) for the scheme developed by the Atrial Fibrillation Investigators (AFI) and *c* of 0.74 (95% CI, 0.71-0.76) for the Stroke Prevention in Atrial Fibrillation (SPAF) III scheme. However, with a *c* statistic of 0.82 (95% CI, 0.80-0.84), the $CHADS_2$ index was the most accurate predictor of stroke. The stroke rate per 100 patient-years without antithrombotic therapy increased by a factor of 1.5 (95% CI, 1.3-1.7) for each 1-point increase in the $CHADS_2$ score: 1.9 (95% CI, 1.2-3.0) for a score of 0; 2.8 (95% CI, 2.0-3.8) for 1; 4.0 (95% CI, 3.1-5.1) for 2; 5.9 (95% CI, 4.6-7.3) for 3; 8.5 (95% CI, 6.3-11.1) for 4; 12.5 (95% CI, 8.2-17.5) for 5; and 18.2 (95% CI, 10.5-27.4) for 6.

Conclusion The 2 existing classification schemes and especially a new stroke risk index, $CHADS_2$, can quantify risk of stroke for patients who have AF and may aid in selection of antithrombotic therapy.

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THE ATRIAL FIBRILLATION (AF) population is heterogeneous in terms of ischemic stroke risk. Subpopulations have annual stroke rates that range from less than 2% to more than 10%.[1-5] Because the relative risk reductions from warfarin sodium (62%) and aspirin (22%) therapy are consistent across these subpopulations,[2,6-8] the absolute benefit of antithrombotic therapy depends on the underlying risk of stroke. Although there has been agreement that warfarin therapy is favored when the risk of stroke is high and that aspirin is favored when the risk of stroke is low,[9,10] there has been little agreement about how to predict the risk of stroke.[11-13] Thus, an accurate, objective scheme to estimate the risk of stroke in the AF population would allow physicians and patients to choose antithrombotic therapy more judiciously.

The Atrial Fibrillation Investigators (AFI) pooled data from several trials to form a unified stroke classification scheme. Among trial participants who did not receive antithrombotic therapy, these researchers found that the risk of stroke increased by a factor of 1.4 per decade of age and by 3 clinical risk factors: hypertension, prior cerebral ischemia (either stroke or transient ischemic attack [TIA]), and diabetes mellitus (DM).[2,8] There were 5.9 to 10.4 strokes per 100 patient-years among participants randomized to no antithrombotic therapy who had at least 1 of the 3 clinical risk factors.[2,8] In contrast to

Author Affiliations: Divisions of General Medical Sciences (Drs Gage, Waterman, and Shannon) and Cardiology (Dr Rich), Washington University School of Medicine, St Louis, Mo; Innovative Emergency Management Inc, Baton Rouge, La (Dr Boechler); and Center for Outcomes Research and Evaluation, Yale–New Haven Hospital, New Haven, Conn (Dr Radford).
Corresponding Author and Reprints: Brian F. Gage, MD, MSc, Division of General Medical Sciences, Washington University School of Medicine Campus, Box 8005, 660 S Euclid Ave, St Louis, MO 63110 (e-mail: bgage@im.wustl.edu).

these high-risk participants, Medicare-aged participants without any of these risk factors were at moderate risk of stroke, averaging 2.7 to 4.3 strokes per 100 patient-years. Participants younger than age 65 years who had none of the 3 risk factors were at low risk for stroke, averaging 1.0 to 1.8 strokes per 100 patient-years, and if they also lacked 2 equivocal stroke risk factors—coronary artery disease and congestive heart failure (CHF)—they had 0.0 to 1.6 strokes per 100 patient-years.[2,8,14]

The Stroke Prevention and Atrial Fibrillation (SPAF) investigators reported their classification scheme from SPAF participants who were treated with aspirin therapy. Based on data from their first 2 trials, the SPAF investigators identified 4 independent risk factors for stroke: blood pressure higher than 160 mm Hg, prior cerebral ischemia, recent heart failure (ie, active within the past 100 days) or documented by echocardiography, or the combination of 75 years or older and being female.[15] In SPAF III, participants with hypertension lacking these risk factors had an annual stroke rate of 3.2 to 3.6 per 100 patient-years of aspirin therapy,[3,13] and the rate was only 1.1 in those who also lacked hypertension.

The promulgation of 2 stroke-risk classification schemes (AFI and SPAF), each with cautions about how equivocal risk factors influenced the risk of stroke in low-risk participants, complicates the estimation of stroke risk. First, the 2 schemes conflict: many patients classified as low risk by one scheme are classified as moderate or high risk by the other.[11-13,16] Second, the classification schemes are sometimes ambiguous. For example, into which SPAF risk group should one classify a patient who initially presented with a systolic blood pressure higher than 160 mm Hg but whose blood pressure is controlled on follow-up evaluation? Third, the development of both classification schemes was data driven, and therefore the schemes could have captured apparent risk factors that represented idiosyncrasies in the data set rather than true associations.[17] Fourth, because the original schemes were based on trial participants whose average age was 69 years, their performance in older and frailer populations is not well characterized.[12] Given these limitations, we decided to validate the 2 existing classification schemes and their variations[10,18,19] in an independent sample.

Our goal was to find a convenient and accurate classification scheme to estimate stroke risk in a national registry of Medicare-aged patients who have nonrheumatic AF and were not prescribed warfarin at the time of hospital discharge.

METHODS

Formation of $CHADS_2$

We amalgamated the 2 classification schemes to form a new stroke-risk index, $CHADS_2$. We then assessed the predictive accuracy of the AFI, SPAF, and $CHADS_2$ schemes using data from a registry of Medicare beneficiaries who had AF. To create the $CHADS_2$ index, we included independent risk factors that were identified in either the AFI or SPAF schemes: prior cerebral ischemia, history of hypertension, DM, CHF, and age 75 years or older. We included a history of hypertension, rather than having blood pressure higher than 160 mm Hg, because even well-controlled hypertension is an independent risk factor for stroke.[20] We included age 75 years or older rather than the combination of age 75 years or older plus female sex, because there is an age-related increase in stroke in both women and men.[2,5,21,22] We included recent CHF exacerbation, rather than any CHF, because the former is similar to the CHF definition used in the SPAF scheme.

To create $CHADS_2$, we assigned 2 points to a history of prior cerebral ischemia and 1 point for the presence of other risk factors because a history of prior cerebral ischemia increases the relative risk (RR) of subsequent stroke commensurate to 2 other risk factors combined.[2,4,5,23,24] We calculated $CHADS_2$ by adding 1 point each for any of the following—recent CHF, hypertension, age 75 years or older, and DM—and 2 points for a history of stroke or TIA. Thus, $CHADS_2$ is an acronym for the risk factors and their scoring. For example, an 82-year-old (+1) patient who had hypertension (+1) and a prior stroke (+2) would have a $CHADS_2$ score of 4.

State-Specific Cohorts

The NRAF data set contained anonymous patient records gathered by 5 quality improvement/peer review organizations (QIO/PROs) that serve 7 states (California, Connecticut, Louisiana, Maine, Missouri, New Hampshire, and Vermont). These QIO/PROs had assembled state-specific cohorts of patients with AF for quality improvement projects under the Health Care Quality Improvement Initiative of the Health Care Financing Administration.[25] Using Medicare Part A claims records (MEDPAR), the QIO/PRO analysts used the appropriate *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) code 427.31 in either a principal or secondary diagnosis to identify Medicare beneficiaries who may have had AF.

Through record review, including electrocardiographic and physician documentation, QIO/PRO reviewers confirmed the presence of chronic or recurrent AF during the index hospitalization: Medicare beneficiaries who had acute AF and beneficiaries who died during hospitalization were excluded. During their chart abstractions, QIO/PRO reviewers documented stroke risk factors, other comorbid conditions, and the antithrombotic therapy prescribed at hospital discharge. No additional charts were abstracted to create the NRAF dataset. Abstractors used standardized abstraction forms and statewide sampling techniques that had been adapted by each QIO/PRO participant, but QIO/PRO protocols were sufficiently similiar to allow the statewide data sets to be combined. The 2 QIO/PRO reviewers who calculated the inter-rater reliability for the chart abstraction found agreement between abstractors of more than 90%.

To obtain outcomes, each QIO/PRO linked chart abstractions from the index hospitalizations to MEDPAR. The QIO/PRO analyst obtained the dates of death from a separate source, the denominator file of living Medicare beneficiaries. After linking a maximum of 3 years of follow-up data and removing all patient and provider identifiers, the QIO/PRO analysts sent the unidentified records to Washington University for inclusion into the NRAF data set. The study was approved by the human subjects committee at Washington University Medical Center and by the participating PRO/QIOs.

Formation of the NRAF Data Set

We used the QIO/PRO records to develop an NRAF data set of Medicare beneficiaries who had documented chronic or recurrent nonrheumatic AF. With few exceptions, we obtained the potential stroke-risk factors from the chart reviews. One exception is that we defined recent CHF as an index hospitalization that carried the principal diagnosis of CHF based on *ICD-9-CM* codes 398.91, 402.01, 402.11, 402.91, 428.x, or 518.4. The other exceptions were that 1 PRO/QIO did not document DM in Medicare beneficiaries and 2 did not exclude the presence of rheumatic heart disease. For these missing fields, we imputed the relevant history from the appropriate *ICD-9-CM* codes (250.x for DM and 393.x-398.x for rheumatic heart disease) and then excluded patients who had rheumatic heart disease.

From the original NRAF data set of 3932 Medicare beneficiaries who had documented AF, we excluded 2199 beneficiaries from the original data set for the following reasons: 229 for mitral stenosis or rheumatic heart disease; 555 for recent surgery or trauma; 81 for transfer to another acute care facility; 65 whose ages were younger than 65 or older than 95 years; and 1269 for being discharged with a prescription for warfarin. Thus, the study cohort included 1733 patients, aged 65 to 95 years, who had nonrheumatic AF and who were not prescribed warfarin therapy at the time of hospital discharge.

Outcomes Assessment

The study outcome was hospitalization for ischemic stroke as determined by Medicare claims. To identify stroke from the MEDPAR data, we used the following *ICD-9-CM* codes in the primary position: 434 (occlusion of cerebral arteries), 435 (transient cerebral ischemia), and 436 (acute, but ill-defined, cerebrovascular disease). We did not use the *ICD-9-CM* code of 433 (occlusion and stenosis of precerebral arteries) because that code is used for asymptomatic carotid artery disease.[26] We had a minimum of 365 days of follow-up claims for all Medicare beneficiaries, and we censored beneficiaries at the time of nonstroke death or at a maximum of 1000 days after the index hospitalization. For beneficiaries who experienced multiple strokes, we excluded events and patient-days of follow-up that occurred after the initial stroke.

Statistical Analyses

To calculate the stroke rate as a function of $CHADS_2$, we used an exponential survival model.[27] We used the survival model to measure how the hazard rate for stroke was affected by each 1-point increase in $CHADS_2$ and by prescription of aspirin. We also used the model to predict the annual rate of stroke as a function of $CHADS_2$ and of aspirin use. We confirmed the appropriateness of using an exponential survival model graphically (by plotting the negative of the logarithm of the survival curve vs time).[28] We performed our survival analyses in SAS (Version 6.12; SAS Institute Inc; Cary, NC) using the LIFEREG and LIFETEST procedures.[28] We calculated the RR reduction from aspirin therapy as 1 minus the relative hazard of prescribing aspirin (as obtained from the exponential model).

To determine the predictive validity of each of the 3 classification schemes, we performed additional time-to-event analyses. We censored deaths that were not accompanied by a hospitalization for stroke and then calculated the stroke rate based on patient-years of follow-up data[29] for each risk group identified by each classification scheme. We calculated the 95% confidence interval (CI) of these rates using the binomial approximation. We quantified the predictive validity of the classification schemes by using the *c* statistic[17] to test the hypothesis that these classification schemes performed significantly better than chance (indicated by a *c* statistic of 0.5).

To determine the predictive accuracy of the classification schemes, we used the bootstrap analysis to generate 95% CIs using the percentile method.[30] We calculated the *c* statistic on a random sample of all patients 1000 times and then noted the 2.5% and 97.5% percentiles. We declared the classification schemes statistically significantly different if these CIs did not overlap.

RESULTS

Baseline Characteristics of the NRAF Cohort

Compared with participants in the AF trials, the 1733 patients in the NRAF cohort were more likely to be women and elderly and more often had stroke risk factors: history of CHF (56%), CHF as the reason for the index hospitalization (14%); history of hypertension (56%); DM (23%); and history of cerebral ischemia (25%) (TABLE 1). The mean $CHADS_2$ score was 2.1 for the 1204 members of the NRAF cohort who were not prescribed any antithrombotic therapy and 2.3 for the 529 members who were prescribed aspirin.

Stroke Rate in the NRAF Cohort

The 1733 patients were followed up for a mean (median) of 1.2 (1.0) years. During the 2121 patient-years of follow-up, 94 NRAF patients were readmitted for an ischemic event (rate, 4.4 per 100 patient-years), 71 patients were admitted for a stroke as indicated by *ICD-9-CM* codes 434 or 436, and 23 patients were admitted for transient cerebral ischemia as indicated by *ICD-9-CM* code 435. We refer to all of these events as stroke for simplicity and because 8 of the 23 patients had a subsequent hospitalization with *ICD-9-CM*

code 434 or 436. Of the 94 patients admitted for a stroke, 25 (27%) died within 30 days of the hospital admission.

The stroke rate was lowest among the 120 patients in the NRAF cohort who had a $CHADS_2$ score of 0, a crude stroke rate of 1.2, and an adjusted rate of 1.9 per 100 patient-years without antithrombotic therapy (TABLE 2). The stroke rate increased by a factor of 1.5 (95% CI, 1.3-1.7) for each 1-point increase in the $CHADS_2$ score ($P<.001$). Aspirin was associated with a hazard rate of 0.80 (95% CI, 0.5-1.3), corresponding to a nonsignificant 20% RR reduction in the rate of stroke ($P=.27$).

The AFI and the SPAF classification schemes also identified patients at low risk for stroke. The 303 patients (17%) in the NRAF cohort identified as low risk according to the SPAF scheme had 1.5 strokes per 100 patient-years of follow-up (TABLE 3), which is similar to the published rate of thromboembolism for this population, 1.1 per 100 patient-years of aspirin therapy.[3] The 490 cohort members (27%) classified as moderate risk, according to the AFI scheme, averaged 2.2 strokes per 100 patient-years of follow-up (Table 3), which is similar to the published stroke rate of 2.7 to 4.3 for this population.[2,8] When we excluded all cohort members aged 75 years or older from the AFI moderate-risk cohort, the stroke rate was 1.1 per 100 patient-years of follow-up, but only 130 patients (8%) of the NRAF population were in this cohort.

Accuracy of the Stroke Classification Schemes

The AFI scheme had a *c* statistic of 0.68 (95% CI, 0.65-0.71); the SPAF scheme, 0.74 (95% CI, 0.71-0.76); and $CHADS_2$ 0.82 (95% CI, 0.80-0.84). Variations of the classification schemes did not improve their predictive accuracy. When we included all patients aged 75 years or older as high risk in the AFI scheme, its corresponding *c* statistic was 0.49. A variation of the SPAF scheme that included patients with DM in the moderate risk group and did not include CHF as risk factor[18] had a *c* statistic of

Table 1. Comparison of National Registry of Atrial Fibrillation (NRAF) Participants and Clinical Trial Participants*

Characteristics	NRAF† (n = 1733)	AFI Trials‡ (n = 3432)	SPAF Trials§ (n = 2012)
Age, mean, y	81	69	69
Congestive heart failure	56	22	21
Hypertension	56	46	52
Women	58	34	28
Diabetes	23	15	15
Prior stroke or TIA	25	17	8
Prescribed aspirin	31	38	100

*Data are presented as percentages, unless otherwise indicated. AFI indicates Atrial Fibrillation Investigators; SPAF, Stroke Prevention in Atrial Fibrillation; TIA, transient ischemic attack.
†Data are from patients who were not prescribed warfarin.
‡Data are from patients who were not prescribed warfarin.[2,8] Use of aspirin in the AFI trials was approximately 3% greater than shown because of participants in a control arm who took aspirin.
§Data are from patients who were not prescribed warfarin.[3,13,15,18]

Table 2. Risk of Stroke in National Registry of Atrial Fibrillation (NRAF) Participants, Stratified by $CHADS_2$ Score*

$CHADS_2$ Score	No. of Patients (n = 1733)	No. of Strokes (n = 94)	NRAF Crude Stroke Rate per 100 Patient-Years	NRAF Adjusted Stroke Rate, (95% CI)†
0	120	2	1.2	1.9 (1.2-3.0)
1	463	17	2.8	2.8 (2.0-3.8)
2	523	23	3.6	4.0 (3.1-5.1)
3	337	25	6.4	5.9 (4.6-7.3)
4	220	19	8.0	8.5 (6.3-11.1)
5	65	6	7.7	12.5 (8.2-17.5)
6	5	2	44.0	18.2 (10.5-27.4)

*$CHADS_2$ score is calculated by adding 1 point for each of the following conditions: recent congestive heart failure, hypertension, age at least 75 years, or diabetes mellitus and adding 2 points for having had a prior stroke or transient ischemic attack. CI indicates confidence interval.
†The adjusted stroke rate is the expected stroke rate per 100 patient-years from the exponential survival model, assuming that aspirin was not taken.

Table 3. Two Existing Risk-Classification Schemes and Their Stroke Rates*

Classification Scheme	Scheme Definition	NRAF Stroke Rate per 100 Patient-Years, (95% CI)	Published Stroke Rate per 100 Patient-Years	Reference
Stroke Prevention in Atrial Fibrillation trial†				
Low risk	None of the following risk factors	1.5 (0.5-2.8)	1.1	3
Moderate risk	Hypertension	3.3 (1.7-5.2)	3.2-3.6	3, 13
High risk	Prior ischemia, women >75 years, recent CHF or LV ≤25%, SBP >160 mm Hg	5.7 (4.4-7.0)	5.9-7.9	15, 31
Atrial Fibrillation Investigators‡				
Low risk	None of the following risk factors	. . .	1.0-1.8	2, 8
Moderate risk	Age >65 years	2.2 (1.1-3.5)	2.7-4.3	2, 8
High risk	Prior ischemia, hypertension, DM	5.4 (4.2-6.5)	5.9-10.4	2, 8

*NRAF indicates National Registry of Atrial Fibrillation; CI, confidence interval; HTN, hypertension; CHF, congestive heart failure; LV, left ventricular fractional shortening as measured by echocardiography; SBP, systolic blood pressure; ellipses, not available; and DM, diabetes mellitus.
†The NRAF stroke rates are from cohorts identified by clinical factors alone; LV fractional shortening and SBP were not available in the NRAF data set. Published rates are from Stroke Prevention in Atrial Fibrillation participants who took aspirin,[3,13] sometimes in combination with ineffective doses of warfarin.[15,31]
‡Published rates are from Atrial Fibrillation Investigators participants randomized to no antithrombotic therapy.[2,8]

0.72, not significantly different from the original SPAF scheme. A variation of $CHADS_2$ that counted 1 point for the presence of any CHF had a *c* statistic of 0.82, identical to $CHADS_2$ that included CHF only if it were the principal diagnosis coded on admission.

In post hoc analyses, we found that $CHADS_2$ was a more accurate predictor of stroke both in cohort members who did (n=529) and who did not (n=1204) receive aspirin. For example, in NRAF cohort members who were not prescribed aspirin the *c* statistics were 0.71 for the AFI scheme, 0.76 for the SPAF scheme, and 0.84 for $CHADS_2$ scheme.

We also performed post hoc analyses to determine whether the greater predictive accuracy of $CHADS_2$ was due to its greater number of risk strata. We collapsed the 7 $CHADS_2$ strata (Table 2) into 3 strata: low risk ($CHADS_2$ 0 or 1), moderate risk ($CHADS_2$ 2 or 3), or high risk ($CHADS_2$ 4, 5, or 6) ; $CHADS_2$ with 3 strata had a *c* statistic of 0.78, which was 0.04 less than the value obtained from the complete $CHADS_2$. We also collapsed $CHADS_2$ into 2 strata by combining scores 0 with 1 and then scores 2 through 6; $CHADS_2$ with 2 strata had a *c* statistic of 0.71.

COMMENT

This study validated 2 existing stroke-risk classification schemes and a combination of these schemes, $CHADS_2$, in Medicare beneficiaries with nonrheumatic AF who had been followed up from 365 to 1000 days after an index hospitalization. The AFI and SPAF schemes successfully identified cohorts with stroke rates of 1.5 to 2.2 per 100 patient-years, whereas $CHADS_2$ identified a low-risk cohort with an adjusted stroke rate of 1.5 per 100 patient-years without antithrombotic therapy. Overall, $CHADS_2$ had greater predictive accuracy than did either AFI or SPAF schemes.

Other studies support our finding that Medicare-aged patients with AF at low risk for stroke can be identified prospectively. Feinberg et al[19] observed a stroke rate of 1.7 per 100 patient-years without warfarin therapy in 66 patients classified as low risk according to the SPAF definition and observed a stroke rate of 2.4 per 100 patient-years without warfarin therapy in 47 patients classified as moderate risk according to the AFI scheme. Hellemons et al[32] found an annual rate of stroke of approximately 2.1 per 100 patient-years of aspirin therapy in an AF trial that excluded patients who had a prior stroke or TIA or age greater than 77 years. During long-term follow-up of 55 elderly patients with lone AF, Kopecky et al[1] found a stroke rate of 0.9 per 100 patient-years, despite a low use of warfarin. These studies support the premise that by applying a classification scheme, clinicians can identify AF patients who are at low risk for stroke even without warfarin therapy.

Because the net benefit of antithrombotic therapy correlates with the underlying risk of stroke, $CHADS_2$ may be helpful in several clinical settings. For example, in identifying low-risk patients, a $CHADS_2$ score of 0 defines an AF population who should be offered the option of aspirin therapy. In addition, $CHADS_2$ could aid in decision making for patients with AF and who are undergoing surgical or dental procedure because perioperative management depends on their risk of hemorrhage from the procedure compared with the underlying thrombotic risk.[33] Also, in patients for whom taking warfarin would be burdensome,[34,35] $CHADS_2$ could facilitate risk stratification and selection of antithrombotic therapy based on a patient-specific risk of stroke.[36,37]

Our study has several strengths. First, we used chart review, rather than *ICD-9-CM* claims, to document the presence of AF and to identify the stroke risk factors. These chart reviews also identified patients who were discharged from the hospital and received aspirin, enabling adjustment for the prescription of aspirin in our calculations of the $CHADS_2$-specific stroke rates. Because of the number of strokes (94), we were able to calculate stroke rates with precision (Table 2). The NRAF cohort included Medicare beneficiaries from 7 states that represented all geographic regions of the United States. Because we formulated $CHADS_2$ based on previous studies, rather than on the NRAF data set, our study validates $CHADS_2$. In addition, because we validated $CHADS_2$ in Medicare beneficiaries who were recently hospitalized, rather than in healthier trial participants, $CHADS_2$ should be generalizable to frail or elderly patients who have nonrheumatic AF.

The $CHADS_2$ scheme with either definition of CHF that we tested in $CHADS_2$—any CHF as identified on chart review and CHF identified as the principal diagnosis by *ICD-9-CM* code—had a *c* statistic of 0.82. We used the later definition in $CHADS_2$ because it was closer to the definition of CHF that was an independent predictor of stroke in other studies: CHF that caused symptoms within the past 100 days was an independent predictor of stroke in SPAF,[4,15] and moderate or severe left-ventricular systolic dysfunction on echocardiography was an independent predictor of stroke in both SPAF and AFI.[14,15,23] We did not have access to echocardiographic results, which would have allowed us to assess how they could have improved the predictive accuracy of $CHADS_2$ and SPAF.

Our study had several important limitations. First, NRAF cohort members were older and sicker than participants in clinical trials (Table 1), and the AFI and SPAF schemes may have performed better in a healthier population that included patients younger than 65 years. Because $CHADS_2$ was based on the AFI and SPAF schemes, it too might have performed better in a younger or healthier population. Second, we used a single chart review to assess most of the stroke risk factors and had no way of capturing new risk factors if they developed. Third, we studied patients who had been hospitalized and who were not prescribed warfarin from our analyses. Future analyses are needed to evaluate $CHADS_2$ and the other classification schemes in other populations. Fourth, we used Medicare claims to ascertain ischemic events and have no way to verify these events. Because Medicare claims

cannot be expected to capture all strokes, our estimates of the $CHADS_2$-specific stroke rates may be biased downward. Comparison of stroke rates that we observed with published rates (Table 3) suggests that this ascertainment bias is modest. In contrast, the $CHADS_2$-specific stroke rates may significantly underestimate the stroke rate in patients who have high-risk conditions that we did not consider, such as mitral stenosis, cardiac thrombus, mechanical heart valve, recent anterior myocardial infarction, or high-grade carotid artery stenosis. Likewise, $CHADS_2$ may underestimate stroke risk in patients with hypertension that exceeds 160 mm Hg[5,15] or in patients with a prior stroke or TIA that occurred in the previous 3 months.[7,38]

Although the 20% risk reduction for aspirin effectiveness in preventing stroke was not statistically significant in this study, it does have clinical significance when combined with other research. Our finding is consistent with a recent meta-analysis that estimated a 22% risk reduction for aspirin therapy[6] but differs from a subgroup analysis that found no effectiveness of aspirin in AF populations aged 75 years or older.[8] Thus, although our nonrandomized study could not determine the effectiveness of aspirin, our results suggest that aspirin therapy should be prescribed for elderly patients with AF who are not suitable candidates for warfarin.

In summary $CHADS_2$ is an easy-to-use classification scheme that estimates the risk of stroke in elderly patients with AF. Physicians and patients could use $CHADS_2$ to make decisions about antithrombotic therapy based on patient-specific risk of stroke.

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Acquisition of data: Gage, Waterman, Boechler, Radford.
Analysis and interpretation of data: Gage, Waterman, Shannon, Rich, Radford.
Drafting of the manuscript: Gage, Waterman.
Critical revision of the manuscript for important intellectual content: Gage, Waterman, Shannon, Boechler, Rich, Radford.
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An active field of science is like an immense anthill; the individual almost vanishes into the mass of minds tumbling over each other, carrying information from place to place, passing it around at the speed of light.
—Lewis Thomas (1913-1994)