A Risk Score for Predicting Stroke or Death in Individuals With New-Onset Atrial Fibrillation in the Community

The Framingham Heart Study

Thomas J. Wang, MD
Joseph M. Massaro, PhD
Daniel Levy, MD
Ramachandran S. Vasan, MD
Philip A. Wolf, MD
Ralph B. D'Agostino, PhD
Martin G. Larson, ScD
William B. Kannel, MD
Emelia J. Benjamin, MD, ScM

Context Prior risk stratification schemes for atrial fibrillation (AF) have been based on randomized trial cohorts or Medicare administrative databases, have included patients with established AF, and have focused on stroke as the principal outcome.

Objective To derive risk scores for stroke alone and stroke or death in community-based individuals with new-onset AF.

Design, Setting, and Participants Prospective, community-based, observational cohort in Framingham, Mass. We identified 868 participants with new-onset AF, 705 of whom were not treated with warfarin at baseline. Risk scores for stroke (ischemic or hemorrhagic) and stroke or death were developed with censoring when warfarin initiation occurred during follow-up. Event rates were examined in low-risk individuals, as defined by the risk score and 4 previously published risk schemes.

Main Outcome Measures Stroke and the combination of stroke or death.

Results During a mean follow-up of 4.0 years free of warfarin use, stroke alone occurred in 83 participants and stroke or death occurred in 382 participants. A risk score for stroke was derived that included the following risk predictors: advancing age, female sex, increasing systolic blood pressure, prior stroke or transient ischemic attack, and diabetes. With the risk score, 14.3% of the cohort had a predicted 5-year stroke rate ≤7.5% (average annual rate ≤1.5%), and 30.6% of the cohort had a predicted 5-year stroke rate ≤10% (average annual rate ≤2%). Actual stroke rates in these low-risk groups were 1.1 and 1.5 per 100 person-years, respectively. Previous risk schemes classified 6.4% to 17.3% of subjects as low risk, with actual stroke rates of 0.9 to 2.3 per 100 person-years. A risk score for stroke or death is also presented.

Conclusion These risk scores can be used to estimate the absolute risk of an adverse event in individuals with AF, which may be helpful in counseling patients and making treatment decisions.

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ATRIAL FIBRILLATION (AF) IS the most common cardiac rhythm disturbance, affecting more than 2 million individuals in the United States.[1] As the population ages and the prevalence of cardiovascular disease increases, the prevalence of this arrhythmia is expected to rise.[2] Much of the morbidity associated with AF is attributable to a 5- to 6-fold increased risk of stroke.[3] Because this stroke risk is variable, numerous studies have attempted to define clinical criteria that may be used to classify participants with AF as being at low or high risk.[4-8] Risk stratification may aid in prognostication and in the selection of appropriate candidates for therapies such as warfarin.[4,9]

The 2 best known risk stratification schemes for AF are based on follow-up of randomized trial cohorts.[4-6] Participants in trials are slightly younger, more likely to be men, and generally have fewer comorbidities than those in the community with AF[4,10,11] although the rates of stroke and major bleeding with anticoagulation may be similar.[10] Recently, Gage and colleagues[7] proposed an alternate stroke risk scheme for AF ($CHADS_2$), based on a combination of risk factors identified in earlier prediction algorithms. They tested this scheme using Medicare claims data from patients who were hospitalized for AF but did not receive anticoagulation therapy. A po-

See also p 1093 and Patient Page.

Author Affiliations: Framingham Heart Study, Framingham (Drs Wang, Massaro, Levy, Vasan, Wolf, D'Agostino, Larson, Kannel, and Benjamin); Cardiology Division, Massachusetts General Hospital, Harvard Medical School (Dr Wang); Divisions of Cardiology and Epidemiology, Beth Israel Deaconess Hospital, Harvard Medical School (Dr Levy); Department of Mathematics, Boston University (Drs Massaro and D'Agostino), Boston; National Heart, Lung, and Blood Institute, Bethesda, Md (Dr Levy); and Department of Neurology (Dr Wolf), Division of Cardiology (Drs Levy, Vasan, and Benjamin), and Department of Preventive Medicine (Drs Levy, D'Agostino, Wolf, Kannel, and Benjamin), Boston University School of Medicine, Boston.
Corresponding Author and Reprints: Emelia J. Benjamin, MD, ScM, Framingham Heart Study, 73 Mt Wayte Ave, Suite No. 2, Framingham, MA 01702-5827 (e-mail: emelia@fram.nhlbi.nih.gov).

tential limitation of this approach is selection bias, because clinical features associated with nonuse of warfarin or hospitalization for AF are likely to influence stroke risk. Also, some strokes may be missed by hospital discharge data if they are small, immediately lethal, or improperly coded. Previous risk stratification scores were also based on patients with new-onset or established AF. Arguably clinicians are particularly interested in risk stratifying patients with newly diagnosed AF.

Management strategies should take into account a patient's absolute risk of having an adverse outcome, particularly when therapies have potential toxic effects.[12] Accordingly, it would be useful to have a scheme for predicting the absolute risk of an adverse event in a patient with AF. Although existing risk schemes provide absolute event rates for 3 to 7 levels of risk, it may be beneficial to have more specific estimates of risk. Additionally, available risk scores do not include mortality as an end point although studies have indicated that AF is an independent risk factor for death as well as stroke[13-15] and therapies for AF may affect mortality.[4] Our objective was to derive a clinical risk score for patients with AF in the community, focusing on 2 outcomes: stroke alone and stroke or death.

METHODS

Subjects

The design of the Framingham Heart Study has been described previously.[16,17] The original cohort was recruited in 1948; members have been followed up biennially since then. The offspring cohort was initiated in 1971 with the recruitment of offspring (and their spouses) of the original Framingham cohort. Participants in the offspring cohort have been examined approximately every 4 years.

Participants in the original and offspring cohorts aged 55 to 94 years at the time of AF diagnosis were eligible for this study (n=1216). We excluded individuals for the following reasons: AF prior to the first Framingham examination in the offspring cohort (n=1) or prior to 1960 in the original cohort (n=23); missing covariate data (n=160); stroke, transient ischemic attack (TIA), or death within 30 days of AF diagnosis (n=153); and rheumatic mitral stenosis (n=11). We excluded participants with an event in the first 30 days following AF because we thought that a risk score would have less clinical relevance for individuals with a very short life expectancy. Of the remaining 868 eligible individuals with new-onset AF, 705 were not treated with warfarin at baseline and were used in the derivation of the risk scores.

Clinical Evaluation

At each Framingham Study clinic examination, participants underwent a medical history, physical examination, and electrocardiogram. If a participant saw a physician or was admitted to the hospital between Framingham examinations for symptoms that could be related to AF or another cardiovascular event, the records and electrocardiograms from that visit were obtained. The diagnosis of AF was made if AF or atrial flutter was present on an electrocardiogram obtained from the Framingham clinic visit, hospital charts, or physician office record. The electrocardiographic interpretation was confirmed by 1 of 2 Framingham Heart Study cardiologists.

Baseline risk factor data were derived from the examination cycle prior to and closest to the onset of AF. Systolic and diastolic blood pressure values were the means of 2 physician-obtained measurements. Diabetes was defined by history of a fasting glucose of at least 140 mg/dL (7.8 mmol/L), a random glucose of at least 200 mg/dL (11.1 mmol/L), or use of insulin or hypoglycemic medications. Persons were classified as current cigarette smokers if they reported having smoked cigarettes during the previous year. Because echocardiographic data were unavailable for most subjects, valvular heart disease was defined clinically by the presence of at least a grade 3 out of 6 systolic murmur, or any diastolic murmur. Electrocardiographic left ventricular hypertrophy (ECG LVH) was determined by the presence of voltage criteria accompanied by lateral repolarization abnormalities.[18] Warfarin and aspirin use was determined by self-report at routine Framingham examinations and by a review of outside medical records.

Adjudication of Stroke Outcomes

A panel of 3 Framingham investigators, including a neurologist, adjudicated the diagnosis of stroke or TIA, based on a review of all relevant medical records and Framingham clinical data. In addition, a study neurologist examined most subjects with a suspected cerebrovascular event. For analytic purposes, previous stroke or TIA was considered as a potential risk factor, but subsequent stroke (not TIA, n=21) was considered the outcome event. A prior stroke or TIA was defined as a stroke or TIA occurring prior to the first documented onset of AF. Participants with a stroke or TIA diagnosed on the same day as AF were excluded because we treated these events as occurring within the first 30 days after AF onset.

Statistical Analyses

The primary outcomes were stroke alone and stroke or death. We used Cox proportional hazards models to assess predictors for developing each outcome. The proportional hazards assumption was confirmed by examining log-log survival plots and by comparing the regression coefficients from models censored at 2, 5, and 10 years. The beginning of the follow-up period was the date of the AF diagnosis. Follow-up after 10 years was censored. Continuous variables for age and systolic blood pressure were forced into the multivariable models given the importance of these characteristics in prior studies of stroke after AF.[4,6,19] The following additional variables were entered into the Cox models in stepwise fashion, using a threshold of $P<.10$ as the criterion for inclusion: use of antihypertensive medication, prior myocardial infarction (MI) or congestive heart failure (CHF), prior stroke or TIA, current smoking, ECG LVH, diabetes, and clinical valvular heart dis-

ease (except for mitral stenosis, which was an exclusion criterion).

Analyses were performed before and after the exclusion of subjects taking warfarin. In models excluding warfarin users, individuals taking warfarin were censored when warfarin use was first recorded (at baseline or during follow-up). The warfarin-censored analyses were used as the primary models in the development of the risk scores and calculation of event rates. In secondary analyses, we estimated models excluding those with atrial flutter and those with prior stroke or TIA. We also tested for interactions between age, sex, warfarin use, aspirin use, and cohort status (original vs offspring cohort) and each of the other risk factors. We also constructed models in which warfarin use was considered as a time-dependent covariate.

A risk scoring system for each outcome was developed based on the warfarin-censored Cox models, using previously established methods.[20,21] Briefly, points were assigned to each risk factor according to the product of the corresponding β coefficient and the value of the risk factor. Fractional values were converted to integer values by dividing by a constant. For each possible score, a linear function was computed and corrected for the means of the risk factors in the cohort. The result was inserted into a survival function, using a 5-year baseline hazard at the means of the risk factors to produce an estimate of 5-year risk.

To assess *calibration*, the agreement between predicted outcomes and actual outcomes, we compared predicted and observed 5-year event rates for Framingham participants in different quintiles of predicted risk. Differences between predicted and observed event rates were used to calculate a Hosmer-Lemeshow statistic.[22] To assess *discrimination*, we calculated a *c* statistic for each risk scheme.[22] Analogous to the area under the receiver operating characteristic curve, the *c* statistic corresponds to the probability that a scoring system correctly ranks 2 randomly selected observations with respect to an outcome of interest.[23] Values for the *c* statistic range from 0.5 (noninformative test) to 1.0 (perfect test discrimination). We performed an internal validation of the *c* statistics using a bootstrap analysis in which the cohort was resampled 1000 times with replacement.

We also evaluated whether the risk score had the ability to identify low-risk participants, using the following thresholds of 5-year stroke risk: 10% (average annual rate 2%), 7.5% (average annual rate 1.5%), and 5% (average annual rate 1%). We determined the proportion of participants with predicted stroke rates at or below each threshold and the actual event rates in each group. Event rates were also reported for subjects in the lowest risk strata for existing risk schemes developed by the Atrial Fibrillation Investigators (AFI),[4] the Stroke Prevention in AF (SPAF) investigators,[5,6] Gage et al ($CHADS_2$),[7] and van Walraven et al.[8] For these comparisons, we used the same variable definitions that were used in the original studies,[4-8] except that we substituted a history of CHF for recent CHF ($CHADS_2$, SPAF). Analyses were performed using SAS version 8.1 (SAS Institute Inc, Cary, NC).

Table 1. Baseline Characteristics*

Characteristics	Overall (n = 868)	Not Taking Warfarin (n = 705)†
Age, mean (SD), y	75 (9)	75 (9)
Women	406 (47)	336 (48)
Blood pressure, mean (SD), mm Hg		
Systolic	145 (23)	146 (24)
Diastolic	76 (12)	77 (12)
Hypertension therapy	445 (51)	351 (50)
Diabetes	133 (15)	108 (15)
Smoking	150 (17)	127 (18)
Prior CHF or MI	302 (35)	243 (34)
Prior stroke or TIA	131 (15)	102 (14)
ECG LVH	122 (14)	105 (15)
Significant murmur	118 (14)	94 (13)

Abbreviations: CHF, congestive heart failure; ECG LVH, electrocardiographic left ventricular hypertophy; MI, myocardial infarction; TIA, transient ischemic attack.
*Data are presented as number (percentage) unless otherwise indicated.
†Excludes participants who were receiving warfarin at baseline. Distribution of the decade of onset of atrial fibrillation cases: 1960-1969, 8%; 1970-1979, 19%; 1980-1989, 28%; 1990-1999, 41%; 2000-2001, 4%.

RESULTS

Study Sample and Incident Events

Characteristics of participants who were alive and stroke-free 30 days after the onset of AF are shown in TABLE 1. During a mean follow-up of 4.3 years (range, 30 days-10 years), stroke occurred in 111 subjects (13%), and stroke or death in 485 subjects (56%). After follow-up was censored for warfarin use, there were 83 strokes and 382 stroke or death events during a mean follow-up of 4.0 years. Crude incidence rates were 2.9 per 100 person-years for stroke (95% confidence interval [CI], 2.3-3.5) and 13.4 per 100 person-years for stroke or death (95% CI, 12.5-14.3), after censoring for warfarin use.

Multivariable Models

Results of the Cox proportional hazards analyses for stroke and stroke or death are shown in TABLE 2. After warfarin censoring and adjustment for age and systolic blood pressure, the following predictors entered stepwise models for stroke: female sex, diabetes, and prior stroke or TIA. The following predictors entered the model for the combined outcome of stroke or death: smoking, prior MI or CHF, diabetes, heart murmur, and ECG LVH. For both outcomes, there was no significant interaction between warfarin or aspirin use and any of the predictors. For the overall analyses, model coefficients were essentially unchanged when warfarin was considered as a time-dependent covariate. There was also no significant effect modification by age, sex, or cohort status for any of the predictors.

Risk Scores

The risk scores for stroke and stroke or death are shown in FIGURE 1 and FIGURE 2. For an individual patient, the probability of stroke can be estimated by calculating a point score based on risk-factor information. For instance, a 75-year-old man with a systolic blood pressure of 150 mm Hg and diabetes receives a score of 12 for predicting stroke: 5 points for age, 0 points for sex, 2 points for systolic blood pressure, 5 points for diabetes, and 0 points for prior stroke or TIA. This score corresponds to a predicted 5-year stroke risk of 16%. The probability of stroke or death can be estimated in a similar manner, using the point score shown in Figure 2. The incremental influence of selected characteristics on the risk of stroke or death for 60- and 70-year-old men and women is depicted in FIGURE 3.

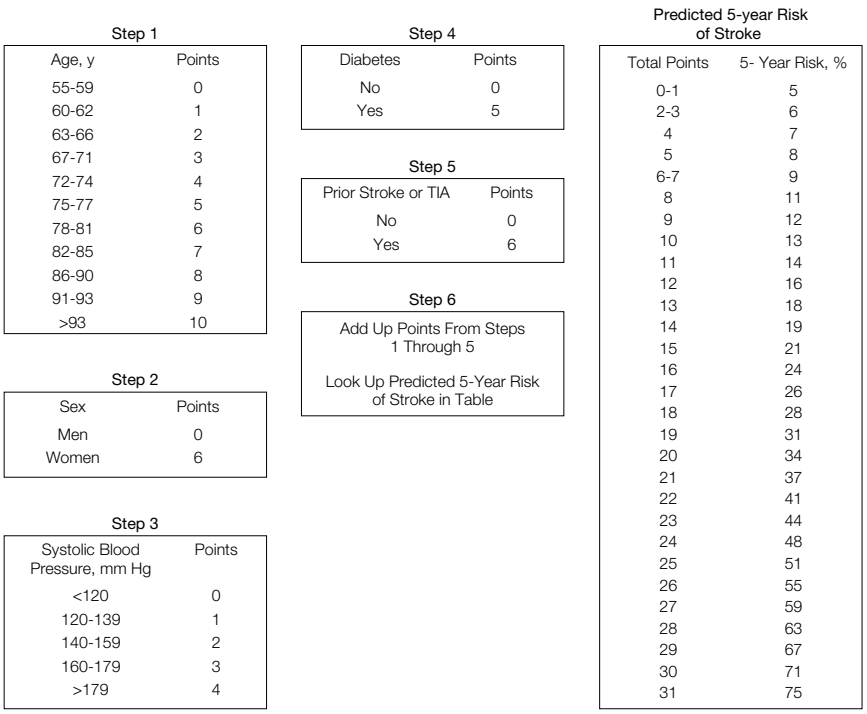
A computerized spreadsheet that allows for individual risk prediction for stroke and stroke or death can be downloaded for use at http://www.nhlbi.nih.gov/about/framingham/stroke.htm.

Table 2. Multivariable-Adjusted Hazards Ratios*

	Hazards Ratio (95% Confidence Interval)			
	Stroke		Stroke or Death	
Variables	Overall	Warfarin Censored	Overall	Warfarin Censored
No. of participants with an event on follow-up	111	83	485	382
Age, per 10 y	1.34 (1.06-1.71)	1.32 (1.02-1.76)	2.13 (1.89-2.40)	2.13 (1.86-2.44)
Women	1.73 (1.16-2.59)	1.92 (1.20-3.07)	. . .	. . .
Systolic blood pressure per 10-mm Hg increments	1.10 (1.01-1.19)	1.06 (0.97-1.17)	1.07 (1.03-1.11)	1.06 (1.02-1.11)
Diabetes mellitus	1.98 (1.25-3.13)	1.80 (1.43-3.13)	1.47 (1.16-1.85)	1.40 (1.07-1.83)
Prior stroke or TIA	1.69 (1.06-2.71)	1.88 (1.09-3.26)	1.29 (1.02-1.63)	. . .
Prior CHF or MI	. . .	. . .	1.64 (1.37-1.97)	1.65 (1.34-2.04)
Smoking	. . .	. . .	1.73 (1.35-2.22)	1.64 (1.23-2.18)
Significant murmur	. . .	. . .	1.57 (1.24-1.98)	1.43 (1.10-1.86)
ECG LVH	. . .	. . .	. . .	1.18 (0.98-1.42)

Abbreviations: CHF, congestive heart failure; ECG LVH, electrocardiographic left ventricular hypertrophy; ellipses, predictors that were not retained in the stepwise models; MI, myocardial infarction; TIA, transient ischemic attack.
*Age and systolic blood pressure were forced into all models. Other variables entering the model at the 0.10 level of significance are included. Analyses exclude participants who had an event within 30 days of atrial fibrillation onset, and follow-up was censored after 10 years. The stroke outcome does not include TIA.

Figure 1. Predicted 5-Year Risk of Stroke



The point-based risk estimate approximates the more precise equation-based risk function provided as an Excel spreadsheet available at http://www.nhlbi.nih.gov/about/framingham/stroke.htm. The point-based risk estimate may differ from the equation-based one, particularly for patients with uncommon combinations of characteristics. TIA indicates transient ischemic attack.

Accuracy and Comparison

Ranking participants into quintiles according to their stroke-risk score yielded predicted 5-year stroke rates of 7% (lowest quintile), 10%, 14%, 20%, and 33% (highest quintile). These predicted rates corresponded closely with actual 5-year stroke rates in each quintile: 8%, 9%, 13%, 20%, and 29%. The stroke-risk score and stroke or death–risk score had Hosmer-Lemeshow statistics of 7.6 and 6.5, respectively; values of 20 or less indicate good calibration. The *c* statistics were 0.66 for stroke and 0.70 for stroke or death. Mean bootstrap validated *c* statistics (SD) were 0.66 (0.03) for stroke and 0.70 (0.01) for stroke or death. The *c* statistics for other stroke risk schemes tested in our sample were 0.62 ($CHADS_2$), 0.62 (SPAF), and 0.61 (AFI).

The accuracy of the stroke score was similar among aspirin users (n=156; *c* statistic 0.67; Hosmer-Lemeshow statistic, 14.1) and nonaspirin users (n=549, with censoring at the initiation of aspirin therapy; *c* statistic, 0.64; Hosmer-Lemeshow statistic, 5.1). Results were also similar in analyses excluding participants with atrial flutter (n=91) or prior stroke or TIA (n=102).

The ability of the different schemes to identify low-risk persons is pre-

sented in TABLE 3. The proportion of Framingham participants classified as low risk using the risk score ranged from 3.3% to 30.6%, depending on the threshold. Fourteen percent of the cohort had a Framingham risk score of 4 or less, corresponding to a predicted stroke rate of 7.5% or less (average annual rate, ≤1.5%); these subjects had an actual stroke rate of 1.1 per 100 person-years. When we used criteria for the lowest-risk stratum from each of the other risk schemes, 6.4% (AFI) to 17.3% (SPAF) were classified as low risk, and these participants had actual stroke rates ranging from 0.9 to 2.3 per 100 person-years.

COMMENT

We examined the predictors of stroke alone and stroke or death among individuals with new-onset AF and derived clinical risk scores for these outcomes. These risk scores can be used to estimate the absolute risk of an adverse event in individuals diagnosed with AF, which may be helpful in counseling patients and in making treatment decisions. Our data indicate that although AF is associated with a high overall risk of stroke or death, risk factors can be used to easily stratify patients at particularly high or low risk.

Risk Factors for Stroke or Death

Several prior studies have examined risk factors for stroke in clinical trial cohorts. The AF Investigators reported that individuals with the following risk factors were at moderate or high risk of stroke: age 65 years or older, hypertension, diabetes, or prior stroke or TIA.[4] These results were based on analysis of 81 stroke events obtained from pooling the control arms of 5 randomized trials. Investigators from SPAF III, which had 36 strokes and 23 TIAs, proposed similar risk factors but did not include diabetes and confined the age criterion for high-risk subjects to women.[5] In addition, the SPAF investigators included CHF or left ventricular dysfunction as a risk factor. The American College of Chest Physicians synthesized these data in formulating its 1998 recommendations for anticoagulation use for patients with AF.[24] These clinical risk factors also have been incorporated into subsequent AF risk stratification schemes.[7,8]

The results of the current study are similar to those of prior studies with respect to risk factors such as advanced age, diabetes, and elevated blood pressure. The relative risk associated with prior stroke or TIA in our study was lower than that observed in other studies. Although chance may have played a role, it is also important to note that we focused on individuals with new-onset AF. Thus, the prior strokes in these people may not have been embolic in origin because the events did not occur in the setting of documented AF. We did not study individuals with prior stroke occurring in the setting of AF because there is broad consensus that these individuals are at

Figure 2. Risk Score for Stroke or Death

Step 1

Age, y	Points
55	0
56	1
57	2
58-59	3
60	4
61	5
62	6
63	7
64-65	8
66	9
67	10
68	11
69	12
70-71	13
72	14
73	15
74	16
75	17
76-77	18
78	19
79	20
80	21
81	22
82-83	23
84	24
85	25
86	26
87	27
88	28
89	29
90-91	30
92	31
93	32
94	33

Step 2

Systolic Blood Pressure, mm Hg	Points
<120	0
120-139	1
140-159	2
160-179	3
>179	5

Step 3

Diabetes	Points
No	0
Yes	4

Step 4

Smoker	Points
No	0
Yes	5

Step 5

Prior MI or CHF	Points
No	0
Yes	6

Step 6

Murmur	Points
No	0
Yes	4

Step 7

ECG LVH	Points
No	0
Yes	2

Step 8

Add Up Points From Steps 1 Through 7

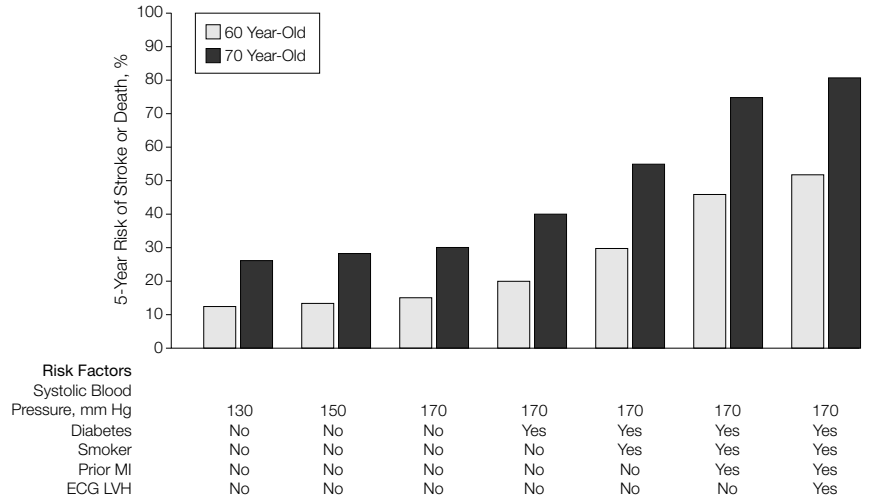
Look Up Predicted 5-Year Risk of Stroke or Death in Table

Predicted 5-year Risk of Stroke or Death

Total Points	5- Year Risk, %
0	8
1	9
2-3	10
4	11
5	12
6	13
7	15
8	16
9	17
10	19
11	20
12	22
13	24
14	26
15	28
16	30
17	32
18	35
19	37
20	40
21	43
22	46
23	49
24	52
25	55
26	58
27	61
28	65
29	68
30	71
31	75
32	78
≥33	>80

The point-based system approximates the more precise equation-based risk function provided as an Excel spreadsheet available at http://www.nhlbi.nih.gov/about/framingham/stroke.htm. The point-based risk estimate may differ from the equation-based one, particularly for patients with uncommon combinations of characteristics. CHF indicates congestive heart failure; ECG LVH, electrocardiographic left ventricular hypertrophy; MI, myocardial infarction.

Figure 3. Impact of Selected Risk Factors on the Predicted 5-Year Risk of Stroke or Death



Predicted event rates apply to men and women without clinical valvular disease. ECG LVH indicates electrocardiographic left ventricular hypertrophy; MI, myocardial infarction.

high risk of events and should receive anticoagulation if possible.

We also found female sex to be an independent risk factor for stroke among those with AF. Higher rates of stroke in women compared with men have been reported in prior observational studies[25,26] and a report from the SPAF investigators.[19] Possible mechanisms for a sex-related difference in stroke with AF have not been fully elucidated. Sex-related differences in thrombotic tendency[27] or atrial remodeling[28] with AF are possibilities that warrant investigation. Female sex was not significantly associated with the combined end point of stroke or death, probably because of the higher risk of mortality from other causes in men.

Comparison of Risk Schemes

There are few data regarding the prediction of long-term outcomes among patients with AF in the community. Existing risk schemes have been derived from trial cohorts followed up over relatively short periods (<2 years). Ideally, a scheme for predicting absolute risk would be based on longer follow up to minimize the influence of acute events that confer short-term risk. Furthermore, prior studies have not necessarily followed up participants from the onset of AF. Thus, survival bias and lead-time bias are potential limitations of these studies and may influence predicted event rates.

Our risk scheme was derived by use of a community-based cohort, a potential strength because patients with AF in typical practice may resemble individuals in a community-based cohort more than participants in a randomized trial. One of our goals was to document the performance of existing risk classification schemes when applied in a community setting.[29] However, a direct comparison between our risk scheme and other schemes requires an independent data set because a risk scheme will always perform best in the cohort from which it was derived.

In evaluating the internal validity of the risk score, we found that actual event rates were closely correlated with predicted event rates for participants at different levels of risk.[30] A formal test of this observation, the Hosmer-Lemeshow statistic, indicated good calibration, both for the overall sample and several subgroups. The *c* statistics for stroke and stroke or death were lower than for risk scores in other settings, such as acute coronary syndromes,[31] which is probably attributable to the longer follow-up period covered by the AF score, the competing risk of mortality, and the multifactorial nature of stroke in older individuals. Additionally, we found *c* statistics for other stroke schemes that were lower than those reported in a previous study by Gage et al,[7] which may be attributable to differences in the study samples (hospitalized Medicare patients with prevalent AF vs community-based individuals with new-onset AF) and follow-up periods (mean follow-up 1.2 years vs 4.0 years).

Using Different Risk Schemes

An important function of risk prediction schemes for AF is to identify patients at low risk of stroke. Individuals with an annual stroke risk of 2% or less (approximately 10% over 5 years) may not realize additional benefit from warfarin compared with aspirin[9,32] and their risk of stroke may not exceed the risk of life-threatening bleeding with warfarin.[33] Schemes with stringent age and clinical criteria successfully identify individuals with a low risk of stroke but may miss some older individuals who are also at low risk (Table 3). On the other hand, criteria that are too liberal have the possibility of labeling too many individuals as being at low risk of stroke.

A potential advantage of the Framingham scheme over existing risk schemes is the greater flexibility provided by a point-scoring system because a given score may be attained by different combinations of patient characteristics. Additionally, in contrast to prior schemes, the Framingham score allows the use of different thresholds of risk, an important feature because the amount of risk that is tolerable may vary according to the clinical situation. However, further studies are necessary to confirm that this score successfully identifies low-risk patients in other cohorts.

Limitations

Several limitations should be acknowledged. Because echocardiograms were not available during the first 2 decades of this study, we did not include the results of echocardiography in the risk scores. Of the prior risk schemes, only

SPAF included echocardiography. In that scheme, evidence of left ventricular dysfunction by echocardiogram could be substituted for clinical CHF.[5,6,34] However, given the association of left ventricular dysfunction with age and cardiovascular disease, the results of echocardiography often do not change the risk stratification based on clinical criteria alone.[35] Nevertheless, our risk score may underestimate the stroke risk for individuals with significant left ventricular systolic dysfunction. The impact of other echocardiographic findings, including left atrial enlargement and mitral annular calcification, has been inconsistent.[34,36] Existing guidelines recommend echocardiography on patients with new-onset AF because it may elucidate the etiology of AF.[37]

Individuals who were receiving warfarin therapy were censored in the models used to derive the risk scores. Because warfarin therapy was not assigned randomly, it is possible that censoring removed some of the highest-risk individuals from our cohort, resulting in an indication bias. However, results of multivariable models for stroke were similar before and after censoring and in models including warfarin as a time-dependent covariate. Additionally, we did not find any significant interaction between warfarin use and covariates in our models.

Some of our participants were receiving aspirin therapy, which reduces the risk of thromboembolism in AF.[38] Thus, our event rates may underestimate the risk of stroke for patients not receiving aspirin therapy. However, it is likely that patients with AF who do not get warfarin would start aspirin therapy or would be receiving aspirin already for other cardiovascular indications. Additionally, the risk score performed similarly in both aspirin and nonaspirin users.

We did not distinguish between paroxysmal and chronic AF or between AF and atrial flutter. There are some data to suggest that the stroke risk associated with paroxysmal AF is similar to that associated with chronic AF.[39] Although some studies suggest that the stroke risk in atrial flutter may be lower than in AF, a large proportion of individuals presenting with atrial flutter have subsequent episodes of documented AF, and results of the risk prediction model were similar when those with atrial flutter were excluded.[40-42] We did not adjust for use of hormone replacement therapy[19] because ascertainment of this therapy was not uniform at all examination cycles. We also did not examine the influence of noncardiovascular comorbidities, such as cancer, on our outcomes.

Although it is possible that the different examination intervals in the Framingham offspring and original cohorts affected our results, the clinical end points (stroke and death) did not rely on attendance at a Framingham examination. Also, there was no significant interaction between cohort status and any predictors in the models. Although participation in an observational cohort study may lead to earlier diagnoses of AF, 76% of AF diagnoses were based on outside hospital or physician records.

Finally, it should be noted that the Framingham cohort is overwhelmingly white. Although the Framingham risk score for coronary heart disease performs reasonably well in ethnically and geographically diverse cohorts,[30] we acknowledge that the same may not be true for this risk score. Our cohort was also elderly, which reflects the age at which AF most commonly presents in the community.

Several strengths of the investigation deserve comment as well. The Framingham Heart Study cohorts have been followed up longitudinally over many decades, which provides the unique opportunity to study the natural history of AF prior to the widespread use of anticoagulant therapy. The continuous surveillance of the cohorts for cardiovascular events, the adjudication of all stroke diagnoses by a physician panel, and the routine ascertainment of antecedent cardiovascular risk factors (facilitating multivariable analyses) are additional strengths of this investigation.

Clinical Implications

Although AF is an important source of morbidity and mortality in the community, the risk associated with this disor-

Table 3. Stroke Rates in Low-Risk Individuals, Using Alternative Risk Schemes

Study	Criteria for Low Risk	Proportion of Participants, %*	Actual Stroke Rate in Framingham Cohort per 100 Person-Years†
Framingham	Risk score ≤7 (predicted 5-year stroke rate ≤10%)	30.6	1.5
Framingham	Risk score ≤4 (predicted 5-year stroke rate ≤7.5%)	14.3	1.1
Framingham	Risk score ≤1 (predicted 5-year stroke rate ≤5%)	3.3	0
SPAF[5]	Not a woman aged >75 years; no CHF, prior stroke or TIA, or hypertension‡	17.3	2.3
van Walraven et al[8]	No hypertension, angina, prior myocardial infarction, diabetes, prior stroke or TIA§	15.7	1.9
$CHADS_2$[7]	Age <75 years; no CHF, hypertension, diabetes, or prior stroke or TIA‖	10.2	1.7
AFI[4]	Age <65 years; no hypertension, diabetes, or prior stroke or TIA‖	6.4	0.9

Abbreviations: AFI, Atrial Fibrillation Investigators; CHF, congestive heart failure; SPAF, Stroke Prevention in Atrial Fibrillation Investigators; TIA, transient ischemic attack.
All follow-up on warfarin is censored.
*Proportion of participants classified as low risk by applying criteria from each risk scheme to the Framingham cohort.
†Actual stroke rate based on participants in the Framingham cohort. Some, but not all, participants were receiving aspirin therapy, which reduces rates of stroke.
‡Hypertension is defined as systolic blood pressure ≥160 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive therapy.
§Hypertension is defined as systolic blood pressure ≥140 mm Hg or use of antihypertensive therapy.
‖Hypertension is defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive therapy.

der is highly variable. Accordingly, it has become increasingly important for clinicians to be able to risk-stratify patients with AF. We propose risk scores that enable the prediction of the risk of stroke or death over a 5-year period in an individual patient at the time of diagnosis. An understanding of absolute risk is fundamental to many clinical decisions involving patients with AF, such as the decisions to initiate anticoagulant therapy or temporarily stop anticoagulation for surgical procedures.[7,43] Anticoagulation therapy may not be justified in individuals with low predicted rates of stroke. Because several risk schemes for AF now exist, it will be critical to validate this risk prediction instrument in an independent cohort and to assess its performance relative to other risk schemes.

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Acquisition of data: Wang, Levy, D'Agostino, Larson, Benjamin.
Analysis and interpretation of data: Wang, Massaro, Levy, Vasan, D'Agostino, Kannel, Benjamin.
Drafting of the manuscript: Wang, Levy, Vasan, Benjamin.
Critical revision of the manuscript for important intellectual content: Massaro, Levy, Vasan, Wolf, D'Agostino, Larson, Kannel, Benjamin.
Statistical expertise: Massaro, Levy, D'Agostino, Larson.
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