

# Assessment of Three Schemes for Stratifying Stroke Risk in Patients with Nonvalvular Atrial Fibrillation

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**PURPOSE:** The risk of ischemic stroke varies widely among patients with nonvalvular atrial fibrillation, influencing the choice of prophylactic antithrombotic therapy. We assessed three schemes for stroke risk stratification in these patients who were treated with aspirin and who did not have prior cerebral ischemia.

**SUBJECTS AND METHODS:** Criteria from three schemes of risk stratification were applied to a longitudinally observed cohort of patients with atrial fibrillation who did not have prior cerebral ischemia and who were treated with aspirin alone or aspirin combined with low, ineffective doses of warfarin in a multicenter clinical trial. The ability of the schemes to identify patients at high ( $\geq 6\%$ ), low ( $\leq 2\%$ ), and intermediate annual risks of ischemic stroke was assessed.

**RESULTS:** During a mean follow-up of 1.8 years, 48 ischemic strokes occurred among 1,073 patients with atrial fibrillation who were taking aspirin (rate = 2.5 per 100 person-years). Each

of the three schemes predicted stroke and disabling stroke, and successfully identified patients at low risk (observed stroke rates of 0.3 to 1.1 per 100 person-years), although the fractions of the cohort that were categorized as low risk varied from 14% to 45%. The observed rates of ischemic stroke among patients categorized as high risk ranged from 3.5 to 7.2 per 100 person-years among the stratification schemes. Two schemes considered all patients  $>75$  years old as high risk (observed stroke rate 4.2 per 100 person-years), while the remaining scheme classified one third of patients in this age group as low risk (observed stroke rate 0.6 per 100 person-years).

**CONCLUSIONS:** When tested in a large cohort of patients with atrial fibrillation who were treated with aspirin, available risk-stratification schemes successfully identified patients with low rates of ischemic stroke, but less consistently identified high-risk patients. *Am J Med.* 2000;109:45–51. ©2000 by Excerpta Medica, Inc.

Nonvalvular atrial fibrillation is a strong, independent risk factor for stroke. Adjusted-dose warfarin is highly effective for stroke prevention in these patients, whereas aspirin offers only modest protection (1). The risk of stroke varies widely among patients with atrial fibrillation. Patients with prior stroke or transient ischemic attack have an annual risk of subsequent stroke of 10% to 12% despite aspirin use, and benefit substantially from treatment with adjusted-dose warfarin (2,3). Other patients with atrial fibrillation have relatively low rates of stroke during aspirin therapy and may not gain sufficient benefit from anticoagulation to outweigh

its risks and the need for close medical monitoring (4–6). Estimating the risk of stroke for an individual patient is a crucial factor in deciding whether anticoagulation is indicated (7).

The threshold risk of stroke that warrants anticoagulation is controversial. Patients whose annual stroke risk is  $\leq 2\%$  when taking aspirin do not benefit substantially from treatment with warfarin: more than 100 patients must be treated with warfarin for 1 year to prevent one stroke (1). For high-risk patients with an annual stroke risk on aspirin  $\geq 6\%$ , the comparable number is 25 or fewer, strongly favoring the use of adjusted-dose warfarin. Opinions remain divided about the routine use of warfarin for patients at intermediate levels of stroke risk.

Three clinical schemes have recently been proposed to stratify the risk of ischemic stroke in patients with atrial fibrillation, based directly or indirectly on analyses of cohorts of participants in clinical trials of antithrombotic therapy (4,8,9). The primary objective of this study was to determine whether these schemes are useful in stratifying the risk of stroke in patients with atrial fibrillation who are taking aspirin. Because patients with atrial fibrillation who have had a recent or remote stroke or transient ischemic attack are at high risk for subsequent stroke

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**Table 1.** Risk-Stratification Schemes for Primary Prevention of Stroke in Patients with Nonvalvular Atrial Fibrillation\*

Criteria; (year), (ref. no.)	High Risk	Intermediate Risk	Low Risk
Atrial Fibrillation Investigators (1994)(8)		Age $\geq 65$ years History of hypertension Diabetes mellitus	Age $< 65$ years No high-risk features
American College of Chest Physicians Consensus (1998)(9)	Age $> 75$ years History of hypertension Left ventricular dysfunction <sup>†</sup> $> 1$ moderate risk factor	Age 65 to 75 years Diabetes mellitus Coronary disease (Thyrotoxicosis)*	Age $< 65$ years No risk factors
Stroke Prevention in Atrial Fibrillation (1995)(4)	Women $> 75$ years Systolic blood pressure $> 160$ mm Hg Left ventricular dysfunction <sup>‡</sup>	History of hypertension No high-risk features	No high-risk features No history of hypertension

\* Prior stroke or transient ischemic attack conferred high-risk status in each of these schemes, but is not included here. Patients with thyrotoxicosis were excluded from participation in the test cohort.

<sup>†</sup> Moderate-to-severe left ventricular systolic dysfunction on echocardiography.

<sup>‡</sup> Impaired left ventricular function included recent congestive heart failure or fractional shortening  $\leq 25\%$  by M-mode echocardiography.

(2,3,8,10), our analyses included only patients without prior cerebral ischemia.

## MATERIAL AND METHODS

### Risk-Stratification Schemes

We considered three sets of criteria for stratifying patients by their risk of ischemic stroke (Table 1). The criteria of the Atrial Fibrillation Investigators (AFI) were based on a multivariate pooled analysis of 1,593 participants who were assigned to placebo or to avoid anticoagulation in five randomized trials (8). During a mean follow-up of 1.4 years, 106 ischemic strokes occurred (Table 2). The

AFI scheme divided patients into two strata: low risk and all others (combining intermediate and high risk). Echocardiographic features were not considered initially, but subsequent analysis of three of the trials identified abnormal left ventricular systolic function as an independent predictor of stroke (11). Because participants assigned to placebo in the Stroke Prevention in Atrial Fibrillation (SPAF)-I study were included in the derivation data set for the AFI criteria, the risk-stratification scheme based on the SPAF-I study analysis of placebo-treated patients was not considered separately (12,13).

The SPAF study criteria were based on multivariate analysis of 854 participants assigned to aspirin treatment

**Table 2.** Characteristics of the Cohorts

Characteristic	Derivation Cohorts		Test Cohort
	AFI(8) (n = 1,593)	SPAF-I and -II(14) (n = 854)	SPAF-III Aspirin* (n = 1,073)
	Mean $\pm$ SD or Percent		
Follow-up (years)	1.4 <sup>†</sup>	2.3 <sup>†</sup>	1.8 $\pm$ 1.1
Assigned treatment	Placebo	Aspirin	Aspirin
Ischemic stroke			
N	106	68	48
Rate (per 100 person-years)	4.6	3.4	2.5
Age (years)	69 <sup>†</sup>	69 $\pm$ 11	68 $\pm$ 10
Women	28	31	26
Blood pressure (torr)	140/82 <sup>†</sup>	138 $\pm$ 21/80 $\pm$ 11	133 $\pm$ 18/78 $\pm$ 10
Hypertension	47	53	50
Diabetes mellitus	15	16	13
Heart failure	20	21	16
Prior myocardial infarction	13	9	8
Prior stroke/transient ischemic attack	6	7	0

\* Participants (n = 109) with prior stroke or transient ischemic attack are excluded.

<sup>†</sup> SD not available from publications.

AFI = Atrial Fibrillation Investigators; SPAF = Stroke Prevention in Atrial Fibrillation.

in the SPAF-I and SPAF-II clinical trials. Participants were observed for a mean of 2.3 years, during which 68 ischemic strokes occurred (Table 2) (14).

The recommendations of the Fifth Consensus Conference on Antithrombotic Therapy of the American College of Chest Physicians (ACCP) (9) emerged from the consensus of experts based on consideration of the AFI analyses (8,11) and of results of the SPAF-III study (Table 1) (2,4).

The AFI criteria separate patients into those at low risk and those at intermediate to high risk, while the SPAF study and ACCP consensus criteria each classify patients into low-, intermediate-, and high-risk groups.

### *Description of the Test Cohort*

The test cohort consisted of 1,073 subjects who participated in either the SPAF-III randomized trial (2) or in the affiliated cohort study (4). We included only those participants who had no prior stroke or transient ischemic attack and who were assigned to aspirin or aspirin plus an ineffective dose of warfarin; all were adults with nonvalvular atrial fibrillation. Recruitment took place at 20 clinical sites in North America from 1993 to 1996. Participants were excluded if they had thyrotoxicosis or were under age 60 years and had no associated cardiovascular disease (ie, lone atrial fibrillation). None were involved in the SPAF-I or -II trials. Ischemic strokes required focal neurologic deficits persisting >24 hours and were validated by an events committee; neuroimaging or autopsy to exclude hemorrhagic stroke was available for >90% of patients with strokes.

### *Definitions and Statistical Methods*

In the SPAF studies, a diagnosis of hypertension required a systolic blood pressure >160 mm Hg or a diastolic blood pressure >90 mm Hg on more than one occasion during 3 months before entry, or a history of antihypertensive therapy; systolic blood pressure >160 mm Hg was based on two measurements on separate days with one exceeding 160 mm Hg and the other exceeding 150 mm Hg or documented systolic blood pressure >160 mm Hg within the prior 3 months. Criteria for hypertension were not specified for the AFI and ACCP consensus schemes. Coronary artery disease was diagnosed in the presence of definite angina pectoris, a history of myocardial infarction, or a coronary intervention. Diabetes mellitus was defined as chronic elevation of the fasting blood glucose level or use of hypoglycemic medications. Strokes were judged disabling when the modified Rankin score was at least II (a score of II indicates a restricted lifestyle, but independent living is still possible) after 1 to 3 months. For these analyses, annual risks of ischemic stroke of  $\leq 2\%$  were considered low risk, 3% to 5% was intermediate risk, and  $\geq 6\%$  was high risk (15).

Stroke rates were estimated by dividing the number of

observed strokes by the person-years of observation, and 95% confidence intervals (CI) for rates were computed using the Poisson distribution. The ability of a classification scheme to identify low-, intermediate-, and high-risk patients was assessed by comparing rates among strata using a Poisson regression model (likelihood ratio test; EGRET statistical software, Cytel, Cambridge, Massachusetts). When no strokes were observed in a stratum, a value of 0.5 was used as the numerator to calculate the upper bound of the confidence interval. Reproducibility of the classification between schemes was assessed by computing the Kappa statistic; a Kappa value close to 0 indicates agreement at the level of chance, whereas a Kappa of 1 is perfect agreement. All tests were two-sided, and statistical significance was accepted at the 0.05 level unless otherwise noted.

## RESULTS

Clinical features of the two cohorts from which the AFI and SPAF schemes were derived were similar, and characteristics of the SPAF-III test cohort were similar to the derivation cohorts (Table 2). Exclusion of 109 (9%) patients with prior stroke or transient ischemic attack contributed to a lower stroke rate (2.5 per 100 person-years) in the SPAF-III test cohort compared with the derivation cohorts (Table 2). During a mean follow-up of 1.8 years, 48 ischemic strokes occurred, of which 22 (46%) were disabling.

When applied to the test cohort, all three stratification schemes were able to classify patients by stroke risk ( $P$  for trend  $\leq 0.001$  for each) and to identify those with low stroke rates (less than about 2 strokes per 100 person-years, Table 3). The SPAF study criteria and ACCP consensus scheme classified patients differently (Kappa = 0.05): the SPAF study criteria classified many more patients as low risk than did the ACCP consensus criteria (45% versus 14%). Conversely, fewer were classified as high risk by the SPAF study criteria than by the ACCP consensus guidelines (17% versus 66%), and their observed stroke rate was twice as great (7.2 per 100 person-years versus 3.5 per 100 person-years, Table 3).

All three sets of criteria were able to identify patients at varying degrees of stroke risk (Figure). For example, patients classified as intermediate risk using the SPAF study scheme had an observed stroke rate that was significantly higher ( $P = 0.002$ ) than those classified as low risk, and significantly lower ( $P = 0.03$ ) than those classified as high risk. The observed stroke rate was 1.0 per 100 person-years (95% CI 0.4 to 2.8 per 100 person-years) among the 197 patients classified as intermediate risk based on being between ages 65 and 75 years using the ACCP consensus criteria.

All patients aged 76 years and older ( $n = 228$ ) were

**Table 3.** Observed Rates of Ischemic Stroke by Categories from Risk-Stratification Schemes\*

	High-Risk Criteria	Intermediate-Risk Criteria	Low-Risk Criteria <sup>†</sup>	P Value <sup>‡</sup>
	Rate per 100 Person-Years (95% Confidence Interval)			
AFI Criteria (1994) <sup>§</sup>				
Percent of participants		85	15	
All ischemic strokes		2.9 (2.2–3.9)	0.3 (0.04–2.3)	0.001
Disabling ischemic strokes		1.4 (0.9–2.1)	0.0 (0.0–2.5)	0.03
SPAF Study Criteria (1995)				
Percent of participants	17	38	45	
All ischemic strokes	7.2 (4.1–13)	3.2 (2.2–4.8)	1.1 (0.6–2.0)	<0.001
Disabling ischemic strokes	4.8 (2.4–9.6)	1.3 (0.7–2.4)	0.4 (0.1–1.1)	<0.001
ACCP Consensus Criteria (1998)				
Percent of participants	66	20	14	
All ischemic strokes	3.5 (2.6–4.7)	1.2 (0.5–2.8)	0.3 (0.05–2.5)	<0.001
Disabling ischemic strokes	1.6 (1.1–2.6)	0.5 (0.1–1.9)	0.0 (0.0–2.8)	0.02

\* Patients with prior stroke or transient ischemic attack excluded. Disabling strokes were modified Rankin score of 11 (restricting lifestyle without prevent independent living) or greater 1 to 3 months after onset.

<sup>†</sup> The upper bound of a one-sided 95% confidence interval for the observed rate of all ischemic stroke among those predicted to be low-risk was 1.7 per 100 person-years using the AFI criteria, and 1.8 per 100 person-years using the SPAF study criteria or the ACCP criteria.

<sup>‡</sup> Test for trend.

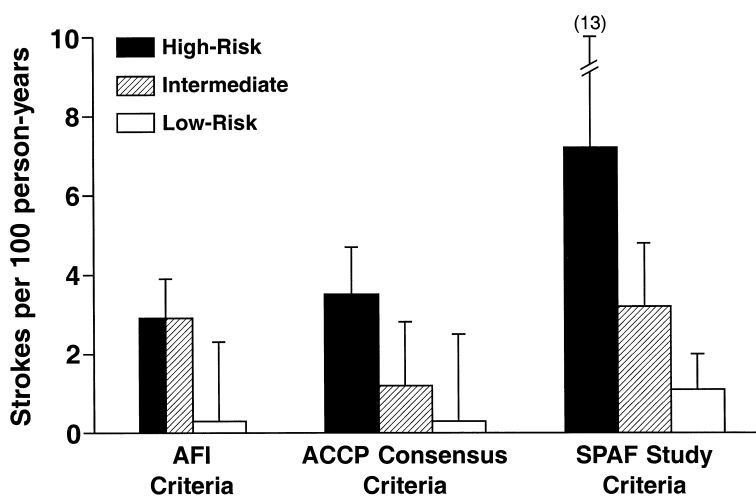
<sup>§</sup> The AFI criteria divided patients into only two strata (low versus high-intermediate risk).

ACCP = American College of Chest Physicians; AFI = Atrial Fibrillation Investigators; SPAF = Stroke Prevention in Atrial Fibrillation.

categorized as high risk by the ACCP consensus scheme and as high-intermediate risk by AFI criteria (which did not provide an intermediate-risk category). Their observed stroke rate was 4.2 per 100 person-years (95% CI 2.5 to 6.9 per 100 person-years). In contrast, the SPAF study scheme categorized 35% of those >75 years old as low risk (n = 80), with an observed stroke rate of 0.6 per 100 person-years (95% CI 0.08 to 4.1 per 100 person-years). Among those of this age predicted to be high risk

by the SPAF study scheme (n = 81 [36%]), the observed stroke rate was 14 per 100 person-years (95% CI 7.5 to 26 per 100 person-years) while the stroke rate in those deemed intermediate risk (n = 67 [29%]) was 3.4 per 100 person-years (95% CI 1.3 to 9.1 per 100 person-years).

When just disabling ischemic strokes were analyzed, each scheme was able to distinguish patients in different categories of risk (Table 3). The observed rates of disabling stroke were low among those classified as low risk



**Figure** Stroke rates among patients with atrial fibrillation and without prior stroke who were treated with aspirin, as classified by three risk-stratification schemes. The vertical line represents the upper bound of the two-sided 95% confidence interval for the stroke rate. The AFI scheme divided patients into only two strata: low versus high-intermediate risk. ACCP = American College of Chest Physicians; AFI = Atrial Fibrillation Investigators; SPAF = Stroke Prevention in Atrial Fibrillation.

**Table 4.** Evaluation of Stratification Schemes According to Criteria for Levels of Annual Stroke Risk\*

Stratification Scheme	High Risk	Intermediate Risk	Low Risk
Low risk defined as $\leq 2\%$	$\geq 6\%$	$> 2\%$ to $< 6\%$	$\leq 2\%$
AFI criteria	----- ++ -----		++
SPAF study criteria	+	++	++
ACCP consensus	-	-	++
Low risk defined as $\leq 1\%$	$\geq 5\%$	$> 1\%$ to $< 5\%$	$\leq 1\%$
AFI criteria	----- ++ -----		+
SPAF study criteria	+	++	-
ACCP consensus	-	+	+

\* (+) indicates that the observed point estimate of annual stroke risk in the test cohort falls within the predicted range; (++) indicates that the relevant 95% confidence interval (one-sided for low-risk) is within the predicted range; (-) indicates that the point estimate is not within the predicted range. The AFI criteria stratified into only two strata: low-risk and all others, and hence high and intermediate risks are considered together. ACCP = American College of Chest Physicians; AFI = Atrial Fibrillation Investigators; SPAF = Stroke Prevention in Atrial Fibrillation.

(0.2 to 0.4 per 100 person-years). Those categorized as high risk by the SPAF study scheme had a higher rate of disabling ischemic stroke (4.8 per 100 person-years) than those deemed high risk by the ACCP consensus criteria (1.6 per 100 person-years).

## DISCUSSION

The relative efficacy and safety of warfarin and aspirin for prevention of stroke in patients with atrial fibrillation are well established (1). Accurate prediction of stroke risk, so that patients receive the most appropriate antithrombotic management, has become the salient clinical issue. We evaluated three risk-stratification schemes for the prediction of initial ischemic stroke in patients with non-valvular atrial fibrillation. Although each scheme was able to classify low-, intermediate-, and high-risk patients, the differences between them were potentially important for patient management (Table 4). The AFI criteria and the ACCP consensus guidelines both identified a small fraction of the test cohort (about 15%) with a very low rate of stroke, while nearly half were accurately classified as low risk by the SPAF study scheme. The SPAF study scheme classified one third of patients  $> 75$  years old as low risk, whereas the other two schemes classified all patients  $> 75$  years old as high risk.

Stratification of stroke risk identifies patients with atrial fibrillation who benefit most, or least, from lifelong anticoagulation. The threshold for use of anticoagulation, however, is controversial. Opinion is particularly divided about anticoagulation for those at intermediate risk for stroke (annual risk of 3% to 5%). For example, with an annual stroke risk of 4% on aspirin, the number of patients needed-to-treat for 1 year is about 50 to prevent one stroke, and about twice as many for disabling stroke (1). Some advocate routinely anticoagulating those with stroke risks in this range (16). Alternatively, selective anticoagulation of those at intermediate risk

may be sensible, weighing bleeding risks and patient preferences after explanation of the advantages and disadvantages of anticoagulation. The threshold at which patients choose anticoagulation varies; some at intermediate risk elect anticoagulation whereas others do not (17). Given these divergent viewpoints, the clinical importance of distinguishing patients with an intermediate stroke risk from those at high risk is disputed. Additional evidence-based analyses of patient preferences are warranted to address this issue.

Our study has several limitations. The AFI criteria (from which the ACCP consensus criteria were developed) were based on analyses of placebo-treated patients with atrial fibrillation who had an average stroke rate of 4.6 per 100 person-years (8). The test cohort in these analyses received aspirin, which reduces the rate of ischemic stroke by about 20% in these patients (1). Restricting the test cohort in this analysis to primary prevention, as well as including the use of aspirin, contributed to the lower overall stroke rate. Nevertheless, to be clinically relevant, a risk-stratification scheme must, in our view, reliably predict the risk of initial stroke among patients given aspirin.

In the SPAF study cohorts, the criteria for diagnosis of hypertension and the measurement of systolic blood pressure were the same in the derivation and test cohorts. Thus our results may be better than what can be expected in clinical practice. Finally, the number of observed strokes in some categories of predicted risk was relatively small, and consequently the confidence intervals were wide.

Several consistent risk factors for ischemic stroke in patients with nonvalvular atrial fibrillation have been identified, including hypertension, increasing age, and diabetes mellitus (8,10,12,14,18). Others, such as female sex, systolic blood pressure  $> 160$  mm Hg and left ventricular dysfunction, have been variably linked to stroke risk (10,11,19,20). Left atrial diameter is less useful as a

predictor of stroke (10,11). Other factors that may affect coagulation, such as postmenopausal hormone replacement therapy (increasing stroke risk) and moderate ethanol use (decreasing stroke risk), have been suggested (10), but these require independent confirmation before incorporation into risk-stratification schemes. An additional risk-stratification scheme has recently been proposed (10); but it was derived from multivariate analysis of the test cohort, and its value was not assessed in a separate group of patients.

The fraction of the test cohort that was predicted to be at low risk of stroke varied from 14% to 45% depending on the scheme, but the observed stroke rates were  $\leq 2$  per 100 person-years for these patients with each scheme. Extrapolated to the estimated 2 million Americans with atrial fibrillation who have not had a prior stroke (21), the number who are predicted to be at low risk differs by more than half a million people depending on the criteria used. Further research to establish the reliability of these schemes, and patient preferences regarding levels of risk and the necessary benefits of anticoagulation, is important.

The predictive value of these risk-stratification schemes among patients in clinical practice may not be the same as for investigational cohorts. In the general population (6,21) and in general medical practices (22–26), patients with atrial fibrillation are typically older than those in clinical trials and are more often women. The SPAF study scheme has been previously tested in a population-based cohort of patients and successfully identified those with low and intermediate risks of stroke (6). Patients  $>75$  years old with atrial fibrillation have a greater stroke risk than younger patients, and anticoagulation is underused in elderly patients (27). Nevertheless, some subgroups of patients  $>75$  years old with atrial fibrillation appear to have relatively low rates of stroke and may not benefit substantially from anticoagulation.

Clinicians regularly confront the issue of estimating stroke risk in patients with atrial fibrillation. This analysis illustrates the relative strengths and limitations of three available risk-stratification schemes. Distinguishing patients with annual risks of stroke of  $\leq 2\%$  versus 3% to 5% is inherently difficult. Nevertheless, reliable identification of patients with atrial fibrillation who are at high risk of stroke is critical, as adjusted-dose warfarin reduces their stroke risk substantially. On the other hand, many patients have relatively low rates of stroke and receive little benefit from anticoagulation. For those at intermediate risk, consideration of the risk of bleeding and patient preferences should influence decisions about anticoagulation. The choice between the available schemes for risk stratification largely depends upon whether the objective is to identify a small fraction of patients with atrial fibrillation who have a very low risk of stroke (using the AFI or

ACCP consensus criteria) or to distinguish a larger fraction at low risk from those at intermediate risk (using the SPAF study scheme).

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