

# Implications of Stroke Risk Criteria on the Anticoagulation Decision in Nonvalvular Atrial Fibrillation

## The Anticoagulation and Risk Factors In Atrial Fibrillation (ATRIA) Study

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**Background**—Warfarin dramatically reduces the risk of stroke in patients with nonvalvular atrial fibrillation (NVAf) but increases the likelihood of bleeding. Accurately identifying patients who need anticoagulation is critical. We assessed the potential impact of prominent stroke risk classification schemes on this decision in a large sample of patients with NVAf.

**Methods and Results**—We used clinical and electrocardiographic databases to identify 13 559 ambulatory patients with NVAf from July 1996 through December 1997. We compared the proportion of patients classified as having a low enough stroke risk to receive aspirin using published criteria from the Atrial Fibrillation Investigators (AFI), American College of Chest Physicians (ACCP), and the Stroke Prevention in Atrial Fibrillation Investigators (SPAF). In this cohort, AFI criteria classified 11% as having a low stroke risk, compared with 23% for ACCP and 29% for SPAF ( $\kappa$  range, 0.44 to 0.85). This 2- to 3-fold increase in low stroke risk patients by ACCP and SPAF criteria primarily resulted from the inclusion of many older subjects (65 to 75 years  $\pm$  men  $>$ 75 years) with no additional clinical stroke risk factors.

**Conclusions**—The age threshold for assigning an increased stroke risk has a dramatic impact on whether to recommend warfarin in populations of patients with NVAf. Large, prospective studies with many stroke events are needed to precisely determine the relationship of age to stroke risk in AF and to identify which AF subgroups are at a sufficiently low stroke risk to forego anticoagulation. (*Circulation*. 2000;102:11-13.)

**Key Words:** fibrillation ■ anticoagulants ■ risk factors ■ stroke

Warfarin substantially decreases the risk of stroke in patients with nonvalvular atrial fibrillation (NVAf), but it increases the risk of major bleeding.<sup>1,2</sup> To optimize the use of warfarin in patients with NVAf, it is critical to accurately identify which patients are at an increased risk for stroke and would benefit most from anticoagulation therapy and which patients are at a low enough risk for stroke to safely avoid the risks of anticoagulation.

Stroke risk classification schemes have been proposed by the Atrial Fibrillation Investigators (AFI), who performed a pooled analysis of 5 primary prevention trials<sup>1</sup>; the American College of Chest Physicians' Consensus Conference on Antithrombotic Therapy (ACCP), which used expert committees who reviewed available published literature<sup>3</sup>; and the Stroke Prevention in Atrial Fibrillation Investigators (SPAF),

who analyzed patients from a series of clinical trials.<sup>4</sup> These risk classification schemes were based primarily on post hoc analyses of randomized trial populations. Resulting treatment recommendations overlap but have several differences (Table). The implications of these differences for the use of warfarin therapy in "real world" populations of NVAf patients are unknown.

To address this issue, we evaluated the impact of these 3 stroke risk classification schemes on the anticoagulation decision in a large cohort of ambulatory patients with NVAf.

## Methods

### Study Population

The cohort assembly has been described previously.<sup>5</sup> Briefly, we constructed a cohort of patients with NVAf between July 1, 1996

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**Criteria for Classification as at Low Stroke Risk by Stroke Risk Stratification Scheme**

Classification Scheme	Criteria for Low Stroke Risk Status*
AFI	None of the following: age $\geq 65$ years; prior stroke; or history of hypertension, diabetes, or left ventricular dysfunction†
ACCP	None of the following: age $>75$ years, prior stroke, hypertension, or heart failure
SPAF	None of the following: women $>75$ years, prior stroke, systolic blood pressure $>160$ mm Hg,‡ or recent heart failure or fractional shortening $<25\%$ on echocardiography†

\*Defined as a low enough stroke risk that aspirin was an acceptable preventive therapy. Note: ACCP specifies aspirin or warfarin as acceptable for patients aged 65 to 75 years with no other risk factors.

†Approximated using a diagnosis of previous heart failure.

‡Approximated using a diagnosis of hypertension.

and December 31, 1997 who were treated within a large health maintenance organization. We identified all patients who had (1) an AF diagnosis (code 427.31 from the *International Classification of Diseases*, 9<sup>th</sup> Revision) recorded in an automated outpatient database plus an ECG showing AF found in an ECG database or (2)  $>1$  outpatient diagnosis of AF during the study period. A total of 23% of patients had  $>1$  outpatient AF diagnosis only. Chart review of a random sample of 50 such patients revealed that 78% had  $\geq 1$  ECG demonstrating AF, with essentially all such ECGs performed before the start of the ECG database in 1994.

To identify adult NVAF patients with adequate data, we excluded patients without prior health plan membership, an age  $<18$  years, transient AF due to recent cardiac surgery, known valvular heart disease, concomitant hyperthyroidism, or lack of internal medicine or cardiology care after the AF diagnosis.

We defined transient perioperative AF as a single outpatient AF diagnosis occurring up to 30 days after coronary bypass, pericardial, or cardiac repair surgery. Valvular disease was defined as an inpatient or outpatient diagnosis of mitral stenosis or prosthetic valve or previous mitral and/or aortic valve repair or replacement. Hyperthyroidism was defined as an inpatient or outpatient diagnosis of hyperthyroidism or thyrotoxicosis, an antithyroid medication prescription, or a low serum thyroid-stimulating hormone level ( $<0.03$   $\mu\text{g/mL}$ ) during the 12 months before the first noted AF diagnosis. Corresponding diagnoses used for exclusion purposes were ascertained from comprehensive hospital discharge, billing claims, and outpatient databases for health plan admissions, out-of-network emergent care, and visits to emergency departments and outpatient clinics, respectively. The codes used have been previously described.<sup>5</sup>

### Patient Characteristics

Proposed risk factors from 3 prominent stroke risk classification schemes were identified<sup>1,3,4</sup> (Table). We approximated 2 of the SPAF criteria by using a hypertension diagnosis for a "systolic blood pressure  $>160$  mm Hg" and a heart failure diagnosis for "recent heart failure or fractional shortening  $<25\%$  on echocardiography."<sup>4</sup> We examined the outpatient database between June 1, 1994 and December 31, 1997 for diagnoses of previous stroke, hypertension, heart failure, and diabetes. The utility of this database for these diagnoses ranged from good to outstanding.<sup>5</sup> For previous stroke and heart failure, we supplemented outpatient data with hospital discharge diagnoses within 5 years before the AF diagnosis.

### Comparison of Stroke Risk Criteria

Using the  $\kappa$  statistic,<sup>6</sup> we compared, across the stroke risk criteria, the proportion of patients classified as having a low enough risk for stroke that aspirin was an acceptable therapy; this was defined as having none of the risk factors proposed by the AFI,<sup>1</sup> ACCP,<sup>3</sup> or SPAF<sup>4</sup> criteria.

## Results

### Patient Characteristics

A total of 13 559 patients met the criteria for NVAF during the study period. Their mean age was 71.6 years, and 43%

were women. More than 75% of the cohort was  $\geq 65$  years, and 45% was  $\geq 75$  years.

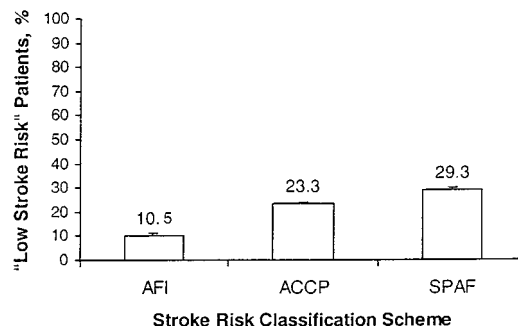
Overall, 9% of patients had a previous ischemic stroke, 31% had previously diagnosed heart failure, 51% had hypertension, 17% had diabetes, and 29% had known coronary disease. Compared with patients in the first 5 primary prevention trials for AF,<sup>1</sup> our cohort was older, had a higher proportion of women, and had a higher prevalence of stroke-related comorbidities.

### Comparison of Stroke Risk Criteria

We compared the proportion of NVAF patients who would be categorized as having a "low stroke risk," in which aspirin would be a reasonable alternative to warfarin, across the 3 stroke risk criteria (Figure). The AFI criteria classified 10.5% ( $n=1426$ ) as having a low stroke risk, compared with 23.3% ( $n=3155$ ) for the ACCP criteria and 29.3% ( $n=3973$ ) for the SPAF criteria (Figure). Inclusion of patients with hyperthyroidism did not change the results significantly. There was fair agreement between AFI and ACCP ( $\kappa=0.56$ ) and AFI and SPAF ( $\kappa=0.44$ ) and excellent agreement between ACCP and SPAF ( $\kappa=0.85$ ). More than 90% of the difference in the proportion of patients considered to have a low stroke risk by the ACCP and SPAF criteria compared with AFI was explained by the inclusion of older patients (65 to 75 years and men  $>75$  years) with no other stroke risk factors.

## Discussion

Despite demonstrated efficacy in reducing stroke, controversy persists over which NVAF patients would benefit most



Proportion of 13 559 NVAF patients in the Anticoagulation and Risk Factors In Atrial Fibrillation study cohort considered at a low stroke risk by various stroke risk criteria. Error bars represent the upper 95% confidence limit.

from warfarin.<sup>7</sup> Using the largest sample reported to date, we assessed the clinical implications of 3 prominent stroke risk classification schemes designed to guide the use of anticoagulants in NVAF. Comparing these criteria, we found up to 3-fold differences in the proportion of patients considered to have a low enough stroke risk to recommend aspirin over warfarin. Differences were primarily explained by whether certain age or age/sex categories (65 to 75 years and men over 75 years) were thought to increase the risk of stroke independently.

Previous studies have reported varying estimates of the proportion of patients who should be considered for warfarin therapy,<sup>8–10</sup> but they were hampered by relatively small sample sizes<sup>8,9</sup> or by using randomized trial populations, which are not representative of NVAF patients in actual clinical care.<sup>10</sup> The predictive ability of existing stroke risk criteria are based primarily on data from randomized trials that included relatively few stroke events.<sup>1,4,11</sup> These classification schemes were variably effective in predicting stroke risk in one relatively small population-based AF cohort.<sup>9</sup> We showed that the choice of stroke risk criteria can have substantial impact on treatment recommendations within a large, ambulatory population of NVAF patients in usual clinical care.

Our study had limitations. We approximated 2 of the SPAF criteria (systolic blood pressure >160 mm Hg and left ventricular dysfunction) using diagnoses of hypertension and heart failure, respectively. However, this likely served to categorize fewer patients at low risk than if explicit SPAF criteria were used, which suggests even greater differences exist between the various schemes. We lacked echocardiographic data, which can provide additional relevant clinical information,<sup>12</sup> but its marginal benefit above clinical risk factors for determining stroke risk remains unclear.<sup>8</sup> It is possible that the exclusion of patients without health plan membership or outpatient follow-up care may affect the generalizability of our results. Finally, we could not distinguish between paroxysmal and persistent/permanent AF, but previous studies suggest that the risk of stroke is similar in these subgroups.<sup>13</sup>

In conclusion, prominent risk stratification schemes for NVAF patients differ substantially in the proportion of patients considered to have a low enough risk of stroke to recommend aspirin instead of warfarin. These differences depend primarily on whether the age 65 to 75 years, by itself, is viewed as a sizable risk factor for stroke in NVAF. These differences have important implications for the ≈2 200 000

Americans with NVAF. Depending on the risk criteria, the number of US NVAF patients considered at low risk would range from ≈225 000 to nearly 650 000. Further compounding this problem is the more marked variation in locally produced treatment guidelines for AF.<sup>7</sup> Therefore, large, prospective studies with many stroke events are needed to precisely specify the risk of stroke associated with increasing age and its interaction with other stroke risk factors in the setting of NVAF.

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