

A Clinical Prediction Rule to Identify Patients With Atrial Fibrillation and a Low Risk for Stroke While Taking Aspirin

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Background: We sought to derive and internally validate a simple and easily applied clinical prediction rule to identify patients with nonvalvular atrial fibrillation (AF) whose stroke risk while taking aspirin is, irrespective of age, low enough that oral anticoagulation therapy is unnecessary.

Methods: We included 2501 patients with AF treated with aspirin during participation in 6 clinical trials. Patients were randomly divided into derivation and validation sets. Recursive partitioning was used to identify patients in the derivation set whose risk for stroke (ischemic or hemorrhagic) or transient ischemic attack was comparable to that observed in an age- and sex-matched cohort from the Framingham Heart Study. The derived prediction rules were tested on the validation set.

Results: Overall, 166 patients (6.6%) had an event during 4688.6 person-years (PYs) of observation for an incident rate of 3.5 events per 100 PYs. Patients in the deri-

vation set classified as low risk (no previous stroke or transient ischemic attack, no treated hypertension or systolic blood pressure equal to or exceeding 140 mm Hg, no symptomatic coronary artery disease, and no diabetes) experienced 1.0 events per 100 PYs, compared with an age- and sex-matched rate of 1.2 events per 100 PYs. In the validation set, low-risk patients experienced 1.1 events per 100 PYs (expected rate of 1.2 events per 100 PYs). Low-risk patients made up 24% of the cohort and 16% of patients older than 75 years. Low-risk patients who were randomized to therapeutic oral anticoagulation therapy experienced 1.5 events per 100 PYs.

Conclusion: Irrespective of age, patients with AF and none of these 4 clinical features and who take aspirin have stroke rates comparable to those of age-matched community cohorts and would not benefit substantially from anticoagulation.

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ATRIAL FIBRILLATION (AF) more than quadruples the risk for stroke.¹ Oral anticoagulation and aspirin therapy decrease this risk,² and the balance of evidence indicates that oral anticoagulation is considerably more efficacious than aspirin for preventing stroke in patients with AF (hereafter referred to as AF patients).² Oral anticoagulation, however, is more troublesome³ and has a greater likelihood of complications.⁴ Since stroke risk varies extensively in AF patients,⁵ several risk stratification schemes have identified AF patients whose stroke risk is low enough to safely avoid oral anticoagulation.^{3,5,6-9}

These risk-stratification schemes have a common limitation. Each considers age to determine whether stroke risk exceeds an arbitrary threshold. Since stroke risk in all people increases sharply with advancing age, this does not isolate the incremental risk due to AF. The Framingham Heart Study showed that an-

nual stroke risk increased from approximately 0.45% for people younger than 60 years to 2.3% for octogenarians.¹⁰ Therefore, applying a common threshold, below which patients are deemed low risk and above which they are deemed high risk, to all AF patients is too conservative for older patients and too liberal for younger ones. In addition, using age as a risk stratifier while not considering that stroke rates increase in the elderly in the community could result in the use of anticoagulation therapy in older AF patients who have stroke rates similar to those without AF. Since complication rates with warfarin are greater in the elderly,^{4,11-13} this should be avoided.

Furthermore, all previously published decision rules predict stroke rates for AF patients. Physicians and patients find it difficult to determine the appropriate numeric risk threshold that warrants anticoagulation.¹⁴ We think that a decision rule that uses a comparative method based on a user-friendly reference point could facilitate this decision.

For these reasons, we derived and internally validated an age-independent clinical prediction rule to identify patients with nonvalvular AF whose all-cause stroke risk while receiving aspirin is acceptably low. We defined *acceptably low* as an observed stroke rate lower than or equal to that expected in an age- and sex-matched group of people in the community.

METHODS

This study is an exploratory analysis of original data combined from 6 clinical trials that studied stroke prophylaxis with aspirin in patients with nonvalvular AF. These trials included the first¹⁵ and second¹⁶ Atrial Fibrillation, Aspirin, Anticoagulation studies (AFASAK), the Primary Prevention of Arterial Thromboembolism in Patients With Non-rheumatic Atrial Fibrillation in Primary Care (PATAF),¹⁷ and the Stroke Prevention in Atrial Fibrillation studies (SPAF) I,¹⁸ II,¹⁹ and III.⁷ In all trials except the SPAF III, patients were randomly assigned to aspirin. Data from the European Atrial Fibrillation Trial²⁰ were not included because transient ischemic attacks (TIAs) were not recorded as outcomes and because all eligible patients had a previous stroke or TIA.

All patients in the included studies were adults with nonvalvular AF. Patients were free from stroke or TIA for at least 6 to 24 months before entering each study. All patients received aspirin therapy at dosages ranging from 75 to 325 mg/d. Adherence to aspirin regimens was very good and exceeded 85% in the studies in which it was reported.^{7,17,18}

The exclusion criteria varied slightly between the studies. Five of the studies randomized patients to oral anticoagulation or aspirin. Therefore, patients were excluded if they had clinical indications for or contraindications to oral anticoagulation or aspirin therapy. These contraindications included pregnancy, alcoholism, renal or hepatic failure, thrombocytopenia, or bleeding disorders. With the exception of the AFASAK studies,^{15,16} patients were also excluded if they had a recent acute coronary syndrome or cardiac revascularization. Patients in the SPAF II who had been randomized to aspirin therapy in the SPAF I were excluded from this analysis to ensure that all observations were truly independent.

BASELINE FACTORS

Patient features were collected before the initiation of therapy by research coordinators and physicians. These features included a previous stroke or TIA, hypertension, any cardiac disease, and diabetes and were based on patient history at baseline. All studies classified patients as hypertensive if they were taking medications to lower blood pressure.

OUTCOMES

The primary outcome for this study was stroke or TIA. Transient ischemic attacks were combined with ischemic and hemorrhagic strokes in accordance with the Framingham Heart Study.¹⁰ A TIA was defined as an acute and focal neurological deficit that resolved within 24 hours. Events were classified as a stroke if deficits persisted for longer than 24 hours and included ischemic and hemorrhagic types. Hemorrhagic strokes included parenchymatous and subarachnoid hemorrhages.

Patients were routinely seen every 3 to 6 months by the study staff or when an outcome event was suspected. With the exception of patients in the first AFASAK, a central events com-

mittee reviewed and confirmed all events. Of all stroke events, 97% underwent computed tomographic imaging.

ANALYSIS

Our goal was to derive and validate a simple and easily applied clinical prediction rule to identify patients with nonvalvular AF whose risk for stroke or TIA while taking aspirin was acceptably low. Since point-based prediction rules can be difficult to remember and apply,²¹ we wanted to develop a categorical and algorithmic decision rule similar to others that have been successfully implemented in clinical medicine.²²⁻²⁴

To define *acceptably low stroke risk*, we sought to avoid an arbitrary numeric risk threshold (eg, 1% per year) because physicians and patients can find it difficult to determine the risk threshold that warrants anticoagulation.²⁵⁻³¹ We defined an acceptably low stroke risk as that which did not exceed the observed stroke rate in an age- and sex-matched population from the Framingham Heart Study.¹⁰ Those with AF who meet this criterion have a stroke risk that is comparable to that of people in the community with the same age and sex. Use of a comparator outcome for the decision rule (ie, similar risk for stroke of people without AF) rather than a numeric risk threshold makes the rule easier for patients and physicians to understand and may enhance its general utility.

The population in the Framingham Study was chosen as the comparator population because that is one of the largest prospective studies to determine absolute stroke risk in a community cohort. The Framingham Heart Study enrolled men and women living in Massachusetts between 1948 and 1952. To calculate incident event rates, 5734 men and women aged 55 to 84 years (mean age, 66 years) who were free of TIA and stroke in 1964 were seen every 2 years until 1974 or until they experienced a stroke, TIA, or intracerebral or subarachnoid hemorrhage. Age- and sex-specific stroke rates have been published.¹⁰

Because of our large sample size, we used a split-sample design rather than resampling techniques to derive and internally validate our prediction rule. To derive the prediction rule for identifying these patients, we randomly chose two thirds of patients and applied recursive partitioning methods³² in which the outcome was the rate of TIA or stroke. This was expressed as an incidence density with events per 100 person-years (PYs) of observation as the unit of measure. Patient observation was censored after the first event to avoid double counting. Observation also ended when the study finished or the patient died.

Because of the computational intensity of our analysis, and because proprietary recursive partitioning packages did not meet our specific needs, a user-written program (or macro) in the SAS statistical package³³ was created (available from the authors upon request). To build a decision rule, this macro went through the following steps:

1. The macro first took one of the split variables³² listed in **Table 1** and calculated event rates for patients with and without that variable. Age and sex were not used as risk stratifiers, since indirect age-sex standardization was used to determine the expected number of strokes.

2. If these rates differed significantly at the 2-sided 5% level,³⁴ the macro determined which patient group (ie, those with or without the split variable) had the lower event rate. The statistical comparison of rates was based on a Poisson model,³⁴ and its method of calculation is cited in **Figure 1**.

3. The macro then compared the observed event rate for patients with the lower event rate with that expected for an age- and sex-matched group. The expected event rate was calculated using indirect standardization,³⁶ with the Framingham Heart Study as the standard population.¹⁰

Table 1. Patient Characteristics Used for Derivation of the Prediction Rule*

History of diabetes?
 Treated hypertension?
 History of congestive heart failure?
 History of MI?
 History of angina?
 History of transient ischemic attack or stroke?
 Type of AF (paroxysmal or constant)?
 Was AF present for greater than 1 year?
 Did SBP equal or exceed 130 mm Hg?
 Did SBP equal or exceed 140 mm Hg?
 Did SBP equal or exceed 160 mm Hg?
 Treated hypertension or did SBP equal/exceed 130 mm Hg?
 Treated hypertension or did SBP equal/exceed 140 mm Hg?
 Treated hypertension or did SBP equal/exceed 160 mm Hg?
 Established coronary artery disease (ie, previous MI or angina)
 Established heart disease (ie, previous MI, angina, or congestive heart failure)
 Atherosclerosis, established or risk factors for (ie, previous MI, angina, diabetes, hypertension)
 Was the patient white?

Abbreviations: AF, atrial fibrillation; MI, myocardial infarction; SBP, systolic blood pressure.

*Provides a detailed description of how the prediction rule was derived.

Crude Data

	With Factor	Without Factor	Total
Events	A1	A0	M1
Person-Time	T1	T0	T

If true event rates for those with and without the factor were the same, the expected (E) number of cases in the group with the factor is

$$E = (M1 \times T1) / T.$$

The variance (V) of the expected number of cases in the group with the factor over multiple study repetitions is

$$V = (E \times T0) / T.$$

For testing the null hypothesis that the event rate for those with and without the factor is the same,

$$\chi \text{ Score} = (A1 - E) / V^{1/2}.$$

The χ score is compared with a standard normal table to determine its associated P value.

To calculate the 95% confidence interval, the normal approximation of the Poisson distribution was used. For the group with the factor, the lower 95% confidence interval is

$$[(A1)^{1/2} - (1.96 \times 0.5)]^2 / T1.$$

The lower 95% confidence interval is

$$[(A1)^{1/2} + (1.96 \times 0.5)]^2 / T1.$$

Figure 1. Formulas used to compare event rates between a group of patients with and without a particular factor. Adapted from Greenland and Rothman³⁴ and Hirsch and Riegelman.³⁵

4. If the event rate observed for these patients exceeded that expected for an age- and sex-matched group, the macro repeated steps 1 through 3 using only the patients whose value for the significant split variable was that with the lower event rate.

5. Partitioning stopped when a patient group was identified with an observed event rate that equaled or was less than the expected event rate, or when no remaining variables had statistically significant splits.

The macro repeated these steps for all variables listed in Table 1. Duplicate rules (ie, those that used the same variables but in a

different order as another rule) were deleted. In the derivation group of patients, 3 distinct prediction rules identified AF patients whose event rate equaled or was less than that for an age- and sex-matched group from the Framingham Heart Study. Only one of these rules identified patients in the validation group who met this criterion, and it was selected as our prediction rule. We validated our analysis using the product-limit method.

SENSITIVITY ANALYSIS

For sensitivity analyses of our prediction rule, we applied it separately to patients within each study by sex, specific age groups, and aspirin dosage. The decision rule was also applied to patients from participating trials who were randomized to therapeutic warfarin.¹⁵⁻¹⁹ To test the rule for stroke alone as the outcome event, and to ensure that our rule worked when studies other than the Framingham were used as the standard population, we compared observed stroke rates with expected rates using the Copenhagen City Heart Study³⁷ and the Rotterdam Study³⁸ as the standard populations. The Copenhagen City Heart Study followed up 19698 randomly selected people prospectively for 12 years. The Rotterdam Study followed up 7724 people for an average of 5.2 years. These studies were selected because they provided age- and sex-stratified stroke rates and originated from countries included in our study.

RESULTS

In the 6 studies, 2813 patients were assigned to aspirin. Two hundred forty-three (8.6%) of these patients were excluded because they were SPAF II patients who had been randomized to aspirin in the SPAF I, and 69 (2.5%) were excluded because of missing data. This left a total of 2501 patients who were observed for 4689 PYs.

These patients are described in **Table 2**. During the studies, 166 patients (6.6%) had a TIA or a stroke, resulting in an overall incidence rate of 3.5 events per 100 PYs. Event rates varied slightly across the trials, ranging from a low of 2.3/100 PYs in the PATAF to a high of 4.8/100 PYs in the SPAF II. Patients in the derivation and validation groups were similar (**Table 3**).

During 3120.3 PYs of observation, patients in the derivation group had 103 strokes or TIAs (3.3 events/100 PYs). As expected, this was significantly higher than the expected event rate for an age- and sex-matched group of 1.3/100 PYs. In the derivation group, 4 factors identified patients whose event rate was less than that expected in an age- and sex-matched population (**Figure 2**). The event risk was significantly lower ($P < .001$) if patients had no previous stroke or TIA (event rate 3.1/100 PYs). For patients without a previous stroke or TIA, event risk was significantly lower ($P = .01$) if there was no treated hypertension or systolic blood pressure equal to or exceeding 140 mm Hg (event rate, 1.9/100 PYs). For patients with no previous cerebral events or hypertension, the event risk was significantly lower ($P = .002$) for those without a history of myocardial infarction or angina (event rate, 1.4/100 PYs).

The final split considered patients with no previous cerebral event, no hypertension, and no symptomatic coronary artery disease. In such patients, those with no diabetes had a significantly lower ($P = .005$) event rate of 1.1 per 100 PYs (95% confidence interval [CI], 0.5-2.0).

Table 2. Description of Patients With Nonvalvular AF Assigned to Aspirin Prophylaxis in 6 Clinical Trials*

	Entire Cohort	Study					
		First AFASAK ¹⁵	Second AFASAK ¹⁶	SPAF I ¹⁸	SPAF II ¹⁹	SPAF III ⁷	PATAF ¹⁷
No. of patients in original studies	2813	336	169	552	545	892	319
Missing data	69	3	15	34	9	8	0
Continued from SPAF I	243	NA	NA	NA	243	NA	NA
No. of patients in present study	2501 (88.9)	333 (99.1)	154 (91.1)	518 (93.8)	293 (53.8)	884 (99.1)	319 (100.0)
Age (mean SD), y	70.4 (10.1)	73.3 (8.5)	73.7 (7.1)	67.5 (11.4)	73.0 (10)	67.6 (9.5)	76.2 (7.4)
No. aged ≥65 y	1860 (74.4)	279 (83.8)	137 (89.0)	336 (64.9)	230 (78.5)	589 (66.6)	289 (90.6)
No. aged ≥80 y	390 (15.6)	68 (20.4)	30 (19.5)	56 (10.8)	66 (22.5)	66 (7.5)	104 (32.6)
Male	1668 (66.7)	182 (54.7)	98 (63.6)	367 (70.8)	198 (67.6)	691 (78.2)	132 (41.4)
White	2324 (92.9)	333 (100.0)	154 (100.0)	425 (82.0)	262 (89.4)	831 (94.0)	319 (100.0)
AF >1 year duration	1778 (71.1)	197 (59.2)	92 (59.7)	368 (71.0)	233 (79.5)	683 (77.3)	205 (64.3)
Nonparoxysmal AF	1985 (79.4)	333 (100)	154 (100.0)	381 (73.6)	211 (72.0)	638 (72.2)	268 (84.0)
SBP, mean (SD)	139.8 (20.4)	154.1 (19.6)	147.0 (20.0)	138.0 (20.8)	139.0 (20.0)	130.5 (14.8)	151.1 (19.4)
No. with ≥140 mm Hg	1317 (52.7)	272 (81.7)	109 (70.8)	251 (48.5)	155 (52.9)	304 (34.4)	226 (70.8)
Baseline conditions							
Hypertension	1142 (45.7)	110 (33.0)	66 (42.9)	279 (53.9)	150 (51.2)	406 (45.9)	131 (41.1)
Previous stroke or TIA	81 (3.29)	17 (5.1)	11 (7.1)	32 (6.2)	17 (5.8)	1 (0.1)	3 (0.9)
Angina or MI	492 (19.7)	76 (22.8)	22 (14.3)	153 (29.5)	54 (18.4)	110 (12.3)	68 (21.3)
Congestive heart failure	568 (22.7)	182 (54.7)	110 (71.4)	135 (26.1)	61 (20.8)	80 (9.0)	0
Diabetes	346 (13.8)	25 (7.5)	13 (8.4)	83 (16.0)	53 (18.1)	111 (12.6)	61 (19.1)
Observation and outcomes							
Observation, mean (SD), y	1.9 (1.2)	1.2 (0.7)	1.7 (0.9)	1.3 (0.8)	2.0 (0.8)	1.9 (1.1)	3.2 (1.4)
Total observation, y	4682.6	404.3	260.7	674.7	600.0	1720.2	1023.0
Cerebral events during study†	166 (6.6)	16 (4.8)	10 (6.5)	28 (5.4)	29 (9.9)	59 (6.7)	24 (7.5)
Ischemic stroke	114 (68.7)	15 (93.8)	7 (70.0)	18 (64.3)	21 (72.4)	36 (61.0)	17 (70.8)
TIA	43 (25.9)	1 (0.3)	2 (20.0)	9 (32.1)	7 (24.1)	22 (37.3)	2 (8.3)
Intracranial hemorrhage	8 (4.8)	0	1 (10.0)	1 (3.6)	0	1 (1.7)	5 (20.8)
Subarachnoid hemorrhage	1 (0.6)	0	0	0	1 (3.4)	0	0
No. of cerebral events per 100 person-years	3.5	4.0	3.8	4.1	4.8	3.4	2.3

Abbreviations: AF, atrial fibrillation; AFASAK, Atrial Fibrillation, Aspirin, Anticoagulation studies; MI, myocardial infarction; NA, not applicable; PATAF, Primary Prevention of Arterial Thromboembolism in Patients With Non-rheumatic Atrial Fibrillation in Primary Care; SBP, systolic blood pressure; SPAF, Stroke Prevention in Atrial Fibrillation studies; TIA, transient ischemic attack.

*Unless otherwise indicated, data are expressed as number (percentage) of patients.

†Percentages have been rounded and may not sum to 100.

The event rate in this group was lower than the expected event rate of 1.2 per 100 PYs for an age- and sex-matched group in the Framingham Heart Study. In contrast, all other patients had an event rate of 4.2 per 100 PYs (95% CI, 3.3-4.9) (Figure 2) with an expected rate of 1.3 events per 100 PYs.

When analyzed using the product-limit method, each component of the rule significantly discriminated patients by stroke risk (Figure 3). Patients in the validation group with no previous TIA or stroke, no treated hypertension or systolic blood pressure equal to or exceeding 140 mm Hg, no coronary artery disease, and no diabetes also had a low stroke rate (Figure 4). These patients experienced 3 events during 344.6 PYs of observation (event rate, 0.9 events/100 PYs; expected rate, 1.2 events/100 PYs). These factors were combined into our prediction rule (Figure 5).

When applied to the entire study cohort, patients who satisfied the prediction rule had an event rate of 1.0/100 PYs (95% CI, 0.5-1.7) with an expected rate in an age- and sex-matched population of 1.2 events per 100 PYs (Figure 4). The prediction rule was applied to patients who were randomly assigned to therapeutic oral

anticoagulation in any of the 6 studies. Patients receiving oral anticoagulation who satisfied the prediction rule had an event rate of 1.5/100 PYs (95% CI, 0.6-2.8) (Figure 4). However, moderate- to high-risk patients randomized to oral anticoagulants experienced a lower event rate than moderate- to high-risk patients taking aspirin (3.4/100 vs 4.4/100 PYs).

Of the 2501 patients, the prediction rule classified 588 (23.5%) as low risk. Of these, 139 (23.6%) were female, and the mean age was 66.9 years (SD, 11.8 years). Of patients classified as low risk, 144 (24.5%) were older than 75 years. Of the 900 patients older than 75 years, 16.0% were classified as low risk.

The prediction rule was tested on a priori defined subgroups (Figure 4). In each study, patients satisfying the prediction rule had event rates that were lower than or had 95% CIs that included the expected event rates. With the exception of the PATAF population, patients classified as moderate to high risk had event rates that significantly exceeded those expected in the community. Low-risk patients in all age groups who satisfied the prediction rule had event rates that were less than the expected rates. With the exception of people younger than

Table 3. Description of Patients in the Derivation and the Validation Groups*

	Group	
	Derivation† (n = 1661)	Validation‡ (n = 840)
By study		
First AFASAK	224 (13.5)	109 (13.0)
Second AFASAK	94 (5.7)	60 (7.1)
SPAF I	345 (20.8)	173 (20.6)
SPAF II	191 (11.5)	102 (12.1)
SPAF III	591 (35.6)	293 (34.9)
PATAF	216 (13.0)	103 (12.3)
Observation, mean (SD), y	1.9 (1.2)	1.9 (1.2)
Male	1111 (66.9)	556 (66.2)
Age, mean (SD), y	70.5 (10.2)	70.3 (9.9)
No. aged ≥65 y	1242 (73.7)	618 (73.6)
SBP, mean (SD), mm Hg	139.9 (20.7)	139.7 (19.6)
Baseline medical conditions		
Diabetes	219 (13.2)	127 (15.1)
Hypertension	765 (46.1)	377 (44.9)
Congestive heart failure	369 (22.2)	199 (23.7)
MI	142 (8.5)	78 (9.3)
Angina	229 (13.8)	145 (17.3)
Previous stroke or TIA	55 (3.3)	26 (3.1)
Outcomes		
Stroke or TIA during observation	103 (6.2)	63 (7.5)
Strokes or TIAs per 100 person-years	3.3	4.0

Abbreviations: AFASAK, Atrial Fibrillation, Aspirin, Anticoagulation studies; MI, myocardial infarction; PATAF, Primary Prevention of Arterial Thromboembolism in Patients With Non-rheumatic Atrial Fibrillation in Primary Care; SBP, systolic blood pressure; SPAF, Stroke Prevention in Atrial Fibrillation studies; TIA, transient ischemic attack.

*Patients were randomly assigned in a 2:1 fashion to the derivation or the validation group. Unless otherwise indicated, data are expressed as number (percentage) of patients.

†Used to derive or create the prediction rule.

‡Used to validate or test the derived prediction rule.

65 years, moderate- to high-risk patients had event rates that were significantly higher than those expected in the community. The prediction rule also successfully predicted patient risk regardless of sex or aspirin dosage.

Finally, we tested the prediction rule using a different outcome and different standard populations (Figure 4). For low-risk patients, the observed ischemic and hemorrhagic stroke rates (0.5 strokes/100 PYs; 95% CI, 0.2-1.0) were significantly lower than the rates for age- and sex-matched groups in the Copenhagen City Heart Study³⁷ (1.0 strokes/100 PYs) or the Rotterdam Study (0.6 strokes/100 PYs).³⁸ In contrast, patients classified as moderate to high risk had stroke rates that significantly exceeded the age- and sex-matched rates from either standard population.

COMMENT

Using patient characteristics that are readily available at the bedside, our prediction rule identified AF patients whose annual risk for TIA or stroke while receiving aspirin was comparable to that expected in the community. Irrespective of age, patients without a previous TIA or stroke, without treated hypertension or a systolic blood pressure equal to or exceeding 140 mmHg, without symptomatic coronary artery disease, and without diabetes can take aspirin for stroke prophylaxis in nonvalvular AF and

would not likely benefit from oral anticoagulation prophylaxis. Use of this prediction rule could permit almost one quarter of AF patients, regardless of age, to avoid oral anticoagulation. Since patients treated with oral anticoagulants have higher bleeding rates than those treated with aspirin,³⁹ and since excessive anticoagulation with oral anticoagulation is more common in the elderly,¹¹ we believe that this rule will improve all outcomes in AF stroke prophylaxis.

This study meets most methodological standards that have been proposed for clinical prediction rules.^{40,41} The outcome predicted by our rule is clearly important and was completely captured. The mathematical techniques used for the derivation of the rule were delineated and valid. The rule is clinically sensible, since other studies have found an increased risk for stroke in AF patients with each factor in the prediction rule, including previous stroke or TIA,⁵ hypertension,¹⁰ coronary artery disease,⁴² and diabetes.¹⁰ The rule is easy to use and suggests a course of action. Most important, the rule was internally validated in a group of patients who were not used to derive the prediction rule. This standard was met by less than half of all prediction rules published in high-impact general medical journals from 1991 to 1994.⁴¹

In addition to being methodologically strong, our rule was also robust. Patients who were randomly assigned to therapeutic oral anticoagulation and satisfied the rule had an event rate that was similar to that for low-risk patients receiving aspirin (Figure 4). The rule worked in prespecified subgroups (Figure 4). Most importantly, it also worked when strokes alone were considered as outcomes and when different standard populations were used. As a result, we would recommend aspirin instead of oral anticoagulation for patients with nonvalvular AF who satisfy this prediction rule.

Our data did not address whether patients classified as low risk by our rule would have as favorable of outcomes with no therapy as with aspirin. Among large groups of AF patients with varying stroke risk, aspirin therapy decreases the risk for stroke and vascular events.^{2,43} Whether these benefits of aspirin offset the increased bleeding due to aspirin in low-risk AF patients is unclear. The absolute risk increase for major gastrointestinal tract bleeding in the Hypertension Optimal Treatment trial was small at 0.4% during an average of 3.8 years of observation.⁴⁴ Since strokes are more common events in this patient population and have a greater effect on patient outcomes than gastrointestinal tract bleeds, it seems prudent to recommend that low-risk AF patients be treated with aspirin.

Readers should note that the event rates for low-risk patients, as with all sample-based estimates, have an uncertainty that is quantified by the 95% CI. Despite this, we believe that our rule is safe for practice. The upper bound of the 95% CI for the annual event rate for the low-risk group, which includes TIAs, goes up to 1.7 events per 100 PYs (Figure 4). Even if the true event rate were this high, we believe that most physicians would not recommend that these patients take oral anticoagulants. The fact that event rates for such patients taking oral anticoagulants was 1.5 events per 100 PYs (95% CI, 0.6-2.8) supports this statement. When strokes alone were considered, the upper border of the 95% CI was 1.0 strokes

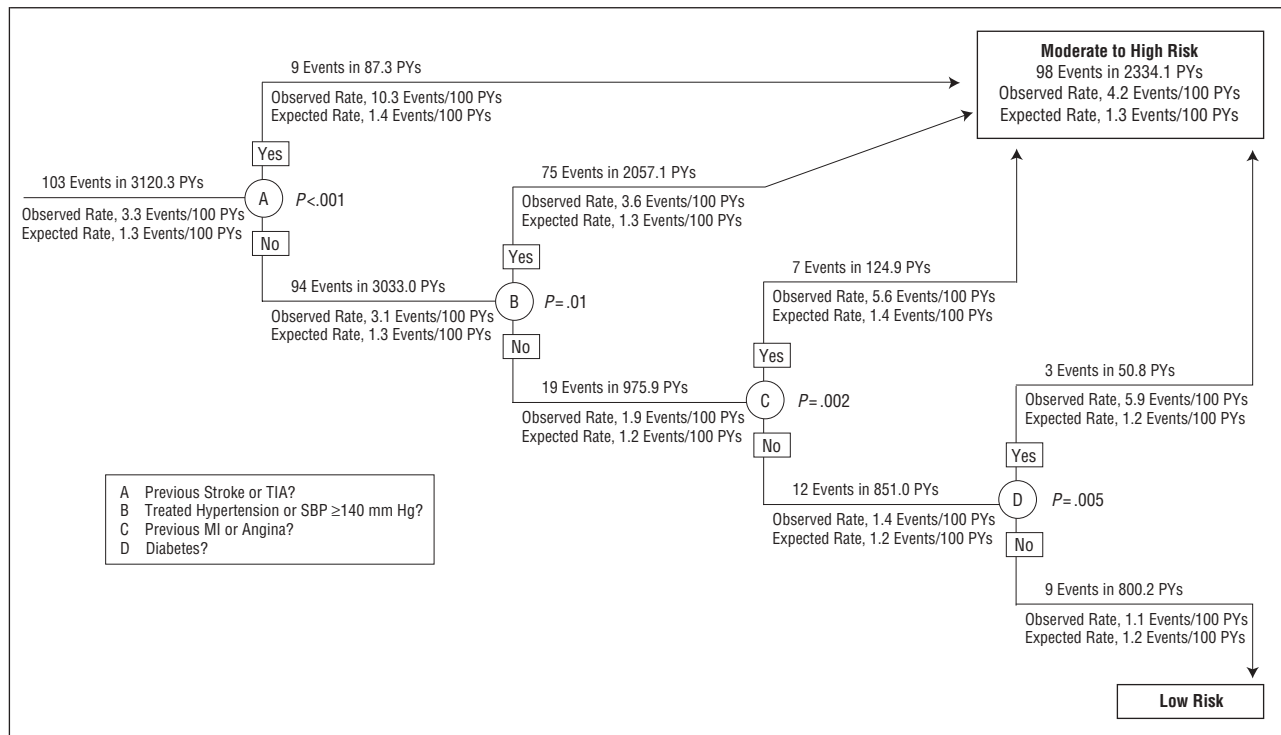


Figure 2. Derivation of the prediction rule and flow of patients in the derivation group through the prediction rule. Events include transient ischemic attacks (TIAs), ischemic strokes, and hemorrhagic strokes. Hemorrhagic strokes include parenchymatous and subarachnoid hemorrhages. Rates are expressed as number of events per 100 person-years (PYs) of observation. These can be interpreted as annual percentages. Therefore, 3.4 events per 100 PYs indicate that 3.4% of patients would be expected to have an event per year. Observed rates are those seen in the derivation group; expected rates, those that one would see in an age- and sex-matched group of patients from the Framingham Heart Study.¹⁰ MI indicates myocardial infarction; SBP, systolic blood pressure.

per 100 PYs of observation. Again, this is very low, and few physicians would recommend oral anticoagulants instead of aspirin to these people. Therefore, despite the uncertainty inherent to sample-based statistics, we believe that this prediction rule is safe for practice. However, further testing of this prediction rule in other patient populations would help to ensure its validity, especially in patient subgroups who had limited representation in the low-risk group of the prediction rule, such as women (Figure 4). Further testing in patients not enrolled in a randomized trial will also measure the generalizability of the rule.⁴⁵

Our risk stratification scheme has additional strengths that distinguish it from others.⁵ First, our scheme considered all, as opposed to just ischemic, strokes. Second, most risk stratification schemes^{3,5,9} classify no AF patients older than 75 years as low risk. Since stroke risk for patients without AF varies extensively by age,¹⁰ we used accepted indirect standardization methodology³⁶ to calculate expected event rates for each age group. By using the expected stroke rates for each age group as comparators to define *low risk*, we ensured that a single risk threshold was not forced onto a patient group with a huge range of baseline stroke risk. As a result, 16% of AF patients older than 75 years in our cohort were classified as low risk by our clinical prediction rule, thereby obviating the need for anticoagulation.

Third, unlike most previous stratifications, this prediction rule was validated. This is key, since many statistical models are shown to be invalid when applied to a separate population. It should be highlighted that this

was an internal validation. Further validation in an external population of patients would be welcome to test the rule further. Finally, our stratification was framed as a series of categorical decisions, which should be more easily used than a scoring system.²¹ We hope that this will improve stroke prophylaxis in patients with AF.

Although it is distinct, our rule should not be used in isolation of other risk stratification schemes. We recommend that physicians use our rule to identify patients who can undergo safe prophylaxis with aspirin. For patients who do not satisfy this rule, or for those with contraindications to aspirin, other stratification schemes^{3,5,9} can be used to quantify the patient's stroke risk and determine whether the benefit of oral anticoagulation exceeds its risk. Whether all such people would benefit importantly from anticoagulation is controversial and is not addressed by these analyses. Other risk stratification schemes have attempted to categorize AF patients into high- vs moderate-risk groups and advocated anticoagulation for the former and anticoagulation or aspirin for the latter depending on individual bleeding risk and patient values or preferences.^{3,7,9}

Any study that uses standardization methods is only as good as the standard population used. In our primary analysis, we used the Framingham Heart Study¹⁰ to calculate expected event rates. As noted, this study determined TIA and stroke rates in previously stroke-free people aged 55 to 84 years who lived in Framingham, Mass, between 1964 and 1974. This prompts 3 comments. First, we consider it valid to apply expected stroke rates calculated with data collected between 1964 and

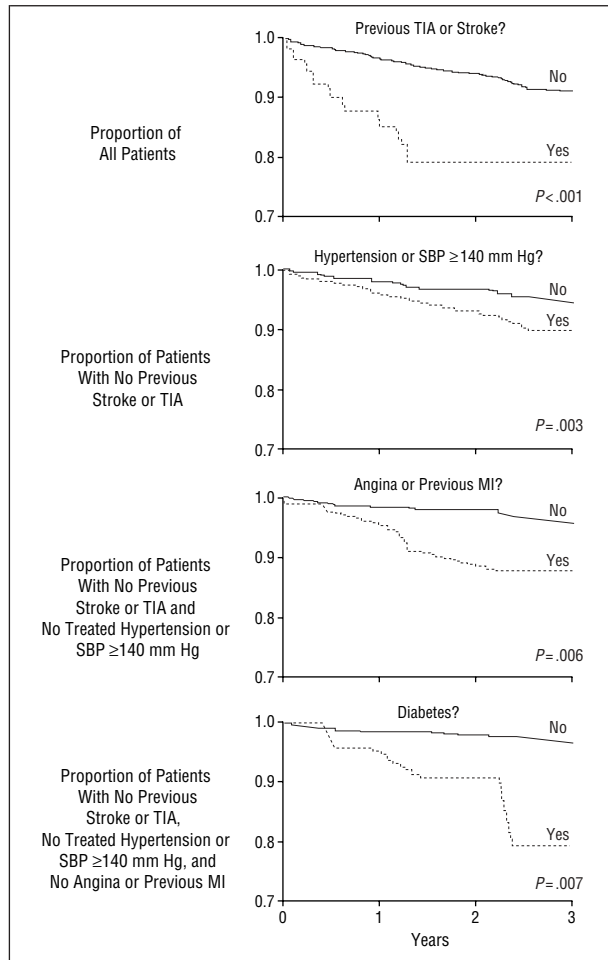


Figure 3. Clinical prediction rule in the derivation population. The product-limit method was used to compare time to transient ischemic attack (TIA) or stroke for patient groups defined by the prediction rule in Figure 2. These groups are listed along the left side. For each group, the Kaplan-Meier plot to the right illustrates time to an event for patients with and without the splitting variable. The solid line in the bottom plot represents patients deemed at low risk by the prediction rule. MI indicates myocardial infarction; SBP, systolic blood pressure.

1974 to patients observed in the 1980s and 1990s. This is because studies have not found clear trends in stroke rates over time.⁴⁶⁻⁴⁸ Second, patients in our study were recruited from the United States, Canada, Denmark, and the Netherlands. Although it is probably valid to apply Framingham data to American and Canadian patients, it might not be for the other study centers. We found, however, that our rule remained valid when we used standard populations from Denmark and the Netherlands.

Finally, is it valid to use TIA and stroke rates from the Framingham Heart Study as our definition of low risk? Although some patients in this cohort had AF, which would increase the event rate in our comparator population, they constituted only 2.8% of men and 2.2% of women. Also, we believe that this comparator (ie, an event rate in a large group of people in a defined community) is much more understandable for patients and physicians than is an absolute event rate (eg, 1% per year) that is deemed to be low risk. We hope that this will improve the use of our prediction rule in comparison with the relatively poor uptake of previous risk stratification schemes.^{49,50}

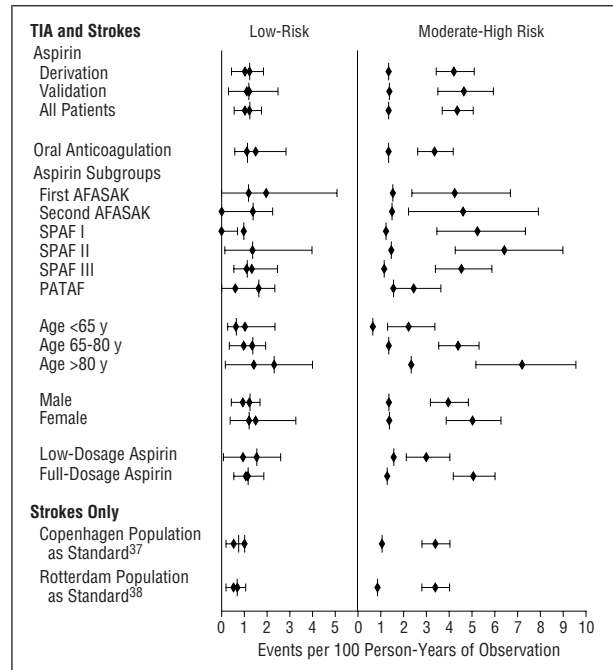


Figure 4. Prediction rule performance in various patient groups. The prediction rule classified patients as low risk or moderate to high risk for a transient ischemic attack (TIA) or stroke. Data are expressed as expected event rates for an age- and sex-matched patient population. AFASAK indicates Atrial Fibrillation, Aspirin, Anticoagulation studies; SPAF, Stroke Prevention in Atrial Fibrillation studies; and PATAF, Primary Prevention of Arterial Thromboembolism in Patients With Non-rheumatic Atrial Fibrillation in Primary Care.

Patients with nonvalvular AF can take aspirin instead of oral anticoagulants to prevent cerebral events if they do not have:

- Previous Stroke or TIA
- Treated Hypertension or SBP ≥ 140 mm Hg
- Angina or Previous MI
- Diabetes

Figure 5. Clinical prediction rule to identify patients with nonvalvular atrial fibrillation at a low risk for transient ischemic attacks (TIAs) or stroke while taking aspirin. The cerebral event rates of these patients while taking aspirin are similar to those of patients in the community. MI indicates myocardial infarction; SBP, systolic blood pressure.

CONCLUSIONS

We have derived a simple and accurate prediction rule that identifies AF patients receiving aspirin who, irrespective of age, have annual risks for TIA or stroke that are comparable to those expected in the community. The rule is explicit and easy to apply, uses readily available clinical information, and has been internally validated. Its use could safely decrease the number of AF patients to whom oral anticoagulation would be recommended.

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