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Original Research

THROMBOEMBOLISM

Refining Clinical Risk Stratification for Predicting Stroke and Thromboembolism in Atrial Fibrillation Using a Novel Risk Factor-Based Approach

The Euro Heart Survey on Atrial Fibrillation

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Background: **Contemporary clinical risk stratification schemata for predicting stroke and thromboembolism (TE) in patients with atrial fibrillation (AF) are largely derived from risk factors identified from trial cohorts. Thus, many potential risk factors have not been included.**

Methods: **We refined the 2006 Birmingham/National Institute for Health and Clinical Excellence (NICE) stroke risk stratification schema into a risk factor-based approach by reclassifying and/or incorporating additional new risk factors where relevant. This schema was then compared with existing stroke risk stratification schema in a real-world cohort of patients with AF (n = 1,084) from the Euro Heart Survey for AF.**

Results: **Risk categorization differed widely between the different schemes compared. Patients classified as high risk ranged from 10.2% with the Framingham schema to 75.7% with the Birmingham 2009 schema. The classic $CHADS_2$ (Congestive heart failure, Hypertension, Age > 75, Diabetes, prior Stroke/transient ischemic attack) schema categorized the largest proportion (61.9%) into the intermediate-risk strata, whereas the Birmingham 2009 schema classified 15.1% into this category. The Birmingham 2009 schema classified only 9.2% as low risk, whereas the Framingham scheme categorized 48.3% as low risk. Calculated C-statistics suggested modest predictive value of all schema for TE. The Birmingham 2009 schema fared marginally better (C-statistic, 0.606) than $CHADS_2$. However, those classified as low risk by the Birmingham 2009 and NICE schema were truly low risk with no TE events recorded, whereas TE events occurred in 1.4% of low-risk $CHADS_2$ subjects. When expressed as a scoring system, the Birmingham 2009 schema (CHA_2DS_2-VASc acronym) showed an increase in TE rate with increasing scores (*P* value for trend = .003).**

Conclusion: **Our novel, simple stroke risk stratification schema, based on a risk factor approach, provides some improvement in predictive value for TE over the $CHADS_2$ schema, with low event rates in low-risk subjects and the classification of only a small proportion of subjects into the intermediate-risk category. This schema could improve our approach to stroke risk stratification in patients with AF.**

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Abbreviations: ACC/AHA/ESC = American College of Cardiology/American Heart Association/ European Society of Cardiology; ACCP = American College of Chest Physicians; AF = atrial fibrillation; BAFTA = Birmingham Atrial Fibrillation Treatment of the Aged; CHADS = Congestive heart failure, Hypertension, Age > 75, Diabetes, prior Stroke/TIA; NICE = National Institute for Health and Clinical Excellence; OR = odds ratio; ROC = receiver-operating characteristic; SPAF = Stroke Prevention in Atrial Fibrillation; TE = thromboembolism; TIA = transient ischemic attack; VKA = vitamin K antagonist

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder, which is associated with a substantial risk of mortality and morbidity from stroke and thromboembolism (TE). A substantial evidence base is in favor of anticoagulation with the vitamin K antagonists (VKAs, eg, warfarin), which reduce this risk by two-thirds, whereas antiplatelet therapy decreases stroke risk only by 22%.[1] VKAs are

clearly superior to aspirin for stroke prevention, even in patients with AF aged ≥ 75 years. For example, in the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) Study, the use of VKA (INR 2-3) reduced the primary end point of TE by 52% compared with aspirin 75 mg daily, with no difference in major bleeding events between VKA or aspirin.[2] Even in low-risk subjects with AF, aspirin may be no better than control for reducing TE events, with a tendency to more adverse effects (especially bleeding) with aspirin.[3]

The risk of stroke and TE in AF is not homogeneous, and various clinical and echocardiographic features have been identified to help stratify risk into high-, intermediate-, or low-risk categories.[1] However, contemporary clinical risk stratification schema for predicting stroke, transient ischemic attack (TIA), or TE for patients with AF are largely derived from risk factors identified from non-VKA arms of trial cohorts, and one cohort study (Framingham). Thus, many potential risk factors have not been adequately assessed, as not all potential risk factors have been systematically documented in the clinical trial populations. The Stroke in AF Working Group[4] performed a systematic review of these stroke risk factors and concluded that only four clinical features (prior stroke/TIA, advancing age, hypertension, and diabetes) were consistent independent risk factors. Also, existing stroke risk stratification schema have widely varying proportions categorized into high-, intermediate-, and low-risk strata, and are generally of modest predictive value in predicting stroke and TE (C-statistics of approximately 0.6).[5] Again, some of the validation studies comparing the performance of different schema are limited by having been performed in anticoagulated trial cohorts,[6] retrospective analyses of anticoagulated AF registries,[7] and in some, non-VKA arms of trial cohorts whereby antiplatelet therapy and/or subtherapeutic VKA (eg, INR < 1.5) were used.[8] Other data on "real life" AF populations were provided in the ATRIA study,[9] but this study did not compare some contemporary risk stratification schema as used in current guidelines.[10-12]

Nonetheless, there are increasing data that other risk factors should be considered in refining stroke and TE risk stratification for AF. For example, female gender increased TE risk in the Euro Heart Survey and other cohorts.[13-15] Also, vascular diseases, including myocardial infarction, peripheral artery disease, and complex aortic plaque, all increase TE risk in AF.[16-20] Furthermore, stroke risk in AF increases at age > 65 years onwards, and age as a risk factor is not a yes/no phenomenon. Indeed, the BAFTA trial showed that VKA was clearly superior thromboprophylaxis to aspirin in elderly (aged ≥ 75 years) subjects with AF in a primary care setting, which shows that the frequently reported fear of bleeding as an excuse for not prescribing warfarin to elderly patients is not justified.[1,2]

In 2006, the Birmingham stroke risk stratification schema was compared against the $CHADS_2$ (Congestive heart failure, Hypertension, Age > 75, Diabetes, prior Stroke/transient ischemic attack) schema in a cohort of 994 patients with AF, and it was found that the accuracy of both clinical risk stratification schemes was similar for predicting ischemic strokes and vascular events.[8] The Birmingham schema was subsequently refined for the evidence-based UK National Institute for Health and Clinical Excellence (NICE) guidelines on AF management, which formulated an algorithm-based approach to stroke risk stratification.[12] Since 2006, it is apparent that stroke risk stratification needs to be simple, yet consider new data on other risk factors (female gender, age, vascular disease, and so forth) that have emerged, and recognize that an artificial categorization into high-, intermediate-, and low-risk categories *per se* may be less helpful. Current treatment guidelines recommend VKA for high-risk subjects and (usually) aspirin for low-risk subjects, but for intermediate risk, many guidelines state "either warfarin or aspirin" can be used.[10-12] The latter can sometimes cause uncertainty for clinicians managing such patients, especially if a large proportion of a particular cohort of patients with AF are classified into this intermediate-risk category. This "either warfarin or aspirin" recommendation is also sometimes used as an excuse not to prescribe warfarin in intermediate-risk patients. Also, clinicians need reassurance that those classified as low risk are truly low risk, with no TE events in such patients.

The objective of this analysis is to refine the 2006 Birmingham/NICE stroke risk stratification schema into a risk factor-based approach, by reclassifying and/or incorporating additional new risk factors as relevant. This novel schema (Birmingham 2009) was

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then compared with existing schema in a real world AF patient cohort in the Euro Heart Survey for AF, where longitudinal data on outcomes have previously been published.[21]

Methods

Validation Cohort

To test the predictive ability of the refined Birmingham schema, and to compare this with the performance of other schema, we used the Euro Heart Survey on AF population. Survey methods, center participation, patient characteristics, management and definitions of the baseline and follow-up survey of the Euro Heart Survey on AF have previously been described.[21,22] In summary, 5,333 ambulant and hospitalized patients with AF were enrolled from the cardiology practices of 182 hospitals among 35 countries in 2003 to 2004. Patients were enrolled if they were ≥ 18 years old and if they had an ECG or Holter recording showing AF during the qualifying admission/consultation or in the preceding 12 months. A follow-up was performed to assess mortality and incidence of major adverse events during 1 year.

For the current analysis we selected 1,577 patients without mitral stenosis or previous heart valve surgery and who did not use either VKA or heparin at discharge of the qualifying visit. We had survival status during 1 year for 1,150 (73%) of these patients and the TE status for 1,084 (69%). Compared with patients with known survival status at follow-up, patients with unknown survival status were at baseline of similar age (66 ± 15 vs 66 ± 14 years; $P = .624$), were as often female (45% vs 40%; $P = .103$), and equally as often had diabetes (15% vs 17%; $P = .244$) or a prior stroke/TIA (9% vs 8%; $P = .359$), whereas they more often had heart failure (41% vs 24%; $P < .001$) and less often vascular disease (35% vs 42%; $P = .015$) and hypertension (62% vs 67%; $P = .032$). Patients with known survival status at follow-up but unknown TE status were more often deceased compared with patients who had both survival and TE status known (24% vs 4%; $P < .001$).

Description of Stroke Risk Stratification Schema

The various stroke risk schema compared and/or validated in this real world European cohort are summarized in Table 1. In case of multiple available schema, we chose to use the most recent one: for example, the Stroke Prevention in Atrial Fibrillation (SPAF) 1999 schema (rather than the SPAF 1995 schema),[23] the second American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) guidelines (2006),[11] and the eighth American College of Chest Physicians (ACCP) guidelines (2008).[10] We did use the AF Investigators 1994 schema,[24] since the 1998 analysis explored the additional value of echocardiography parameters, but did not explicitly recommend a new schema. The Framingham and $CHADS_2$ schema are point-based scores, with the Framingham based on a mathematical equation[25] and the $CHADS_2$ based on one point for CHAD and two points for stroke/TIA.[26]

In order to compare their predictive ability with other schema for distinguishing low, intermediate, and high risk, we categorized the scores into three groups. We defined the $CHADS_2$ score in two ways: (1) *classic*, whereby scores of 0 = low, 1 to 2 = intermediate, > 2 = high risk; or (2) *revised*, whereby scores of 0 = low, 1 = intermediate, ≥ 2 = high risk. We categorized the Framingham score in a similar manner to that proposed by Fang et al,[9] as follows: score 0 to 7 = low, 8 to 15 = intermediate, 16 to 31 = high risk. In addition to these categorized definitions (commonly used in clinical practice), the Framingham and $CHADS_2$ scores were also tested as continuous variables.

We refined the 2006 Birmingham (or NICE) TE risk schema into a risk factor-based approach, by defining definitive risk factors (previous stroke/TIA/TE and age ≥ 75 years) and combination risk factors (heart failure/moderate-severe cardiac dysfunction, hypertension, diabetes, vascular disease, female gender, and age 65-74 years). If we wished to artificially categorize these subjects, high risk was defined as one definitive or two or more combination risk factors, intermediate risk was essentially defined as one combination risk factor, and low risk was defined as no risk factors being present. This refined (2009) Birmingham schema was also tested with a point-based scoring system, the CHA_2DS_2-VASc score (see Table 2 for definition), whereby scores of 0 = low, 1 = intermediate, and ≥ 2 = high risk.

Definitions of End Points and Risk Factors

Ischemic stroke was defined as a focal neurologic deficit of sudden onset as diagnosed by a neurologist, lasting > 24 h and caused by ischemia. TIA was defined as a focal neurologic deficit of sudden onset as diagnosed by a neurologist, lasting < 24 h. Peripheral embolism was defined as TE outside the brain, heart, eyes, and lungs. Pulmonary embolism was defined by the responsible physician. TE as outcome variable of the validation analysis was defined as either an ischemic stroke, peripheral embolism, or pulmonary embolism. Definitions of risk factors, such as diabetes, hypertension, heart failure, peripheral artery disease, and so forth, are provided in the online supplement.

Statistical Analysis

We used descriptive analyses with proportions and means (± SD) to describe the validation cohort, categorization of the three risk groups per schema, and the event rates per risk group. We calculated the 95% CI of event rates using the binomial approximation. We performed logistic regression with each schema, containing three risk groups, as independent variable and TE during 1 year as dependent variable. The probability that this model predicted the correct classification of each patient (TE or not) was saved. Following this we plotted this probability in a receiver-operating characteristic (ROC) curve against TE as dependent variable. The area under the curve for this ROC curve represents the ability of a schema to correctly classify risk for TE, which is also referred to as the C-statistic (Harrell's C). As a subsidiary analysis, we also ran the same analyses on 843 patients within this group who were not on anticoagulation at both baseline and 1-year follow-up.

To assess the effect of individual risk factors on the occurrence of TE in this cohort, we performed multivariable logistic regression with the following independent variables: age, gender, diabetes, coronary artery disease, heart failure, hypertension, prior stroke/TIA, prior other thromboembolism, and peripheral vascular disease. To assess whether the effect of systolic blood pressure at baseline was different than that of hypertension, we performed the same analysis while replacing systolic blood pressure for hypertension and we report these results in the text only. Further, since recent echocardiography was not available for 400 (37%) patients, we repeated the initial analysis with the addition of left ventricular ejection fraction to assess its effect and whether other effects were changed by this addition. Variables were removed stepwise from the model when the P value exceeded .10. Variables with P value < 0.05 in the final model were considered to be significant contributors to TE prediction and we report the net odds ratio (OR), 95% CI, and P value for these variables. Variables in the final model were tested for interaction(s), if any.

Table 1—*Risk Stratification Schemes Used To Predict Thromboembolism in Atrial Fibrillation*

Risk Scheme	Low Risk	Intermediate Risk	High Risk
AFI Investigators (1994)[24]	Age < 65 y and no risk factors	Age > 65 y and no other risk factors	Prior stroke/TIA, hypertension, diabetes
SPAF investigators[23]	No risk factors	Hypertension, diabetes	Prior stroke/TIA, women > 75 y, men > 75 y with hypertension
$CHADS_2$ (2001)—classic[26]	Score 0	Score 1-2	Score 3-6
$CHADS_2$—revised	Score 0	Score 1	Score 2-6
Framingham (2003)[25]	Score 0-7	Score 8-15	Score 16-31
NICE guidelines (2006)[12]	Age < 65 y with no moderate/high-risk factors	Age ≥ 65 y with no high-risk factors Age < 75 y with hypertension, diabetes, or vascular disease[a]	Previous stroke/TIA or thromboembolic event Age ≥ 75 y with hypertension, diabetes, or vascular disease Clinical evidence of valve disease or heart failure, or impaired left ventricular function
ACC/AHA/ESC guidelines (2006)[11]	No risk factors	Age ≥ 75 y, or hypertension, or heart failure, or LVEF ≤ 35%, or diabetes	Previous stroke, TIA or embolism, or ≥ 2 moderate risk factors: age ≥ 75 y, hypertension, heart failure, LVEF ≤ 35%, diabetes
Eighth ACCP guidelines (2008)[10]	No risk factors	Age > 75 y, or hypertension, or moderately or severely impaired LVEF and/or heart failure, or diabetes	Previous stroke, TIA or embolism, or ≥ 2 moderate risk factors: age ≥ 75 y, hypertension, moderately or severely impaired LVEF and/or heart failure, diabetes
Birmingham (2009)	No risk factors	One combination risk factor: heart failure/LVEF ≤ 40, hypertension, diabetes, vascular disease,[a] female gender, age 65-74	Previous stroke, TIA or embolism, or age ≥ 75 y, or ≥ 2 combination risk factors: heart failure/LVEF ≤ 40, hypertension, diabetes, vascular disease,[a] female gender, age 65-74

ACC = American College of Cardiology; ACCP = American College of Chest Physicians; AFI = Atrial Fibrillation Investigators; AHA = American Heart Association; $CHADS_2$ = Congestive heart failure, Hypertension, Age > 75, Diabetes, prior Stroke/TIA; ESC = European Society of Cardiology; LVEF = left ventricular ejection fraction; NICE = National Institute for Health and Clinical Excellence; SPAF = Stroke Prevention in Atrial Fibrillation; TIA = transient ischemic attack.
[a]Myocardial infarction, peripheral artery disease, or aortic plaque.

Results

The 1,084 patients with nonvalvular AF, who were not on anticoagulation at baseline and for whom we knew TE status at 1 year, were on average 66 years old and 40.8% were women (Table 3). Hypertension was the most prevalent stroke risk factor (67.3%), followed by coronary artery disease (38.4%). Antiplatelet drugs were taken by 74.0%. In univariate analyses, female gender, history of vascular disease, prior stroke/TIA, and diabetes were associated with an increased incidence of TE (all $P < .05$; Table 4). When assessing the independent effect of all potential risk factors on TE occurrence in multivariate analysis, female gender (OR = 2.53 [1.08-5.92]; $P = .029$) was the only significant associated factor, whereas the effect of vascular disease was near significant (OR = 2.27 [0.94-5.46]; $P = .064$) (Table 4). Taking into account systolic blood pressure at baseline, rather than the diagnosis of hypertension, showed that also systolic blood pressure was not significantly associated with TE occurrence (OR = 0.99 [0.97-1.01] per mm Hg increase; $P = .319$).

Table 2—*The 2009 Birmingham Schema Expressed as a Point-Based Scoring System, With the Acronym CHA_2DS_2-VASc*

Risk Factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75 y	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
Age 65-74 y	1
Sex **c**ategory (ie female gender)	1

LV = left ventricular; TE = thromboembolism. See Table 1 for expansion of other abbreviations.

The proportions of patients categorized as high, intermediate or low risk are shown in Table 5. Risk categorization differed widely between the different schemes. Patients classified as high risk ranged from 10.2% with the Framingham schema to 75.7% with the Birmingham 2009 schema. The classic $CHADS_2$ categorized the largest proportion (61.9%) of subjects into the intermediate-risk strata, whereas the AF Investigators and Birmingham 2009 schema classified 12.2% and 15.1%, respectively, into this category.

Table 3—*Clinical Characteristics of 1,084 Nonvalvular Atrial Fibrillation Patients Not Receiving Oral Anticoagulation and Heparin at Discharge of the Baseline Euro Heart Survey and With Known Thromboembolic Follow-up Status During 1 Year*

Clinical Characteristic	No. (%) or Mean ± SD
Age, y	66 ± 14
Age ≥ 75 y	309 (28.5)
Women	442 (40.8)
Past medical history	
Stroke	45 (4.2)
TIA	46 (4.3)
Other systemic embolism	6 (0.6)
CAD	412 (38.4)
Peripheral vascular disease	62 (5.8)
Hypertension	729 (67.3)
Diabetes	187 (17.3)
Heart failure	253 (23.5)
Systolic blood pressure, mm Hg	139 ± 23
LVEF, %	53 ± 14
Drugs	
ACEI	480 (44.3)
ARB	139 (12.8)
ACEI/ARB	607 (56.0)
Statins	252 (23.2)
Antiplatelet drugs	802 (74.0)

ACEI = ACE inhibitor; ARB = angiotensin II receptor blocker; CAD = coronary artery disease. See Table 1 for expansion of other abbreviations.

The Birmingham 2009 schema classified only 9.2% as low risk, whereas the Framingham scheme categorized 48.3% as low risk.

The C-statistics all suggested modest predictive value of all schema for TE, with C-statistics ranging from 0.549 (SPAF) to 0.638 (Framingham), whereby the Framingham schema was the only one to predict TE better than chance in this cohort. If Framingham and $CHADS_2$ scores were tested as continuous variables a slightly improved C-statistic was obtained compared with their respective categorized scores. The Birmingham 2009 schema fared marginally better (C-statistic, 0.606) than $CHADS_2$, whether classic (0.561) or revised (0.586), or as a continuous variable (0.602) (Table 5).

Those classified as low risk by Birmingham 2009 and the NICE schema were truly low risk, with no TE events recorded, whereas TE events occurred in 1.4% of low-risk $CHADS_2$ subjects and 1.8% of SPAF low-risk subjects. Also, where most intermediate-risk groups had an event rate around 3%, the intermediate-risk group using the Birmingham 2009 schema had only 1 event (0.6%). When expressed as a scoring system (Table 6), the Birmingham 2009 schema (with the CHA_2DS_2-VASc acronym) showed an increase in TE rate with increasing scores (*P* value for trend = .003); those with a score of 0 (ie, low risk) had no TE events, whereas a score of 1 (ie, intermediate risk) had TE events in 0.6%

A secondary analysis of a cohort of subjects who were not treated with anticoagulation at baseline and at follow-up are presented in the online supplement, and accepting the caveat of lower study numbers, this does not substantially change our observations.

Discussion

In this article, we have provided a validation for a novel risk factor-based approach to stroke risk stratification (Birmingham 2009), in comparison with other published schema, in a real world European cohort. This Birmingham 2009 schema considers patients with a prior stroke/TIA or patients ≥ 75 years as high risk and as candidates for warfarin. Furthermore, a combination of at least two risk factors from hypertension, heart failure, diabetes, age 65 to 75, female gender, and vascular disease are also considered to be high risk; we provide strong evidence from the Euro Heart Survey for the addition of the latter two risk factors. To aid risk scoring, we also provide a risk score for the Birmingham 2009 schema, using the CHA_2DS_2-VASc acronym, with a clear increase in stroke risk with an increasing score, whereas those with a score of 0 to 1 (that is, low to moderate risk) had low event rates. We also confirm the results of recent comparisons[5-9,14] showing a modest predictive

Table 4—*Univariate and Multivariate Predictive Power of Risk Factors for Thromboembolic Events*

	Event Rate With Risk Factor	Event Rate Without Risk Factor	Univariate *P* Value	OR[a]	Multivariate *P* Value[a]
Age > 75	11 (3.6)	14 (1.8)	.083	1.46 (0.63-3.35)	.383
Female	16 (3.6)	9 (1.4)	.017	2.53 (1.08-5.92)	.029
Stroke/TIA/TE	5 (5.9)	20 (2.0)	.023	2.22 (0.78-6.35)	.163
Hypertension	19 (2.6)	6 (1.7)	.349	1.01 (0.38-2.66)	.992
Diabetes	8 (4.3)	17 (1.9)	.048	1.79 (0.73-4.40)	.220
Heart failure	6 (2.4)	19 (2.3)	.967	0.72 (0.27-1.88)	.493
LVEF < 40	1 (0.8)	12 (2.1)	.335	0.34 (0.04-2.73)	.243
Vascular disease[b]	16 (3.6)	9 (1.5)	.022	2.27 (0.94-5.46)	.063

OR = odds ratio. See Tables 1 and 2 for expansion of other abbreviations.

[a]All results other than LVEF from model without LVEF.

[b]Coronary artery disease, peripheral vascular disease, or a previous thromboembolism other than stroke/TIA.

Table 5—*Risk Categorization, Incidence of TE,[a] and Predictive Ability for Contemporary Risk Stratification Schema Among Euro Heart Survey Patients Who Did not Receive Anticoagulation at Baseline*

	Categorization of TE Risk			Predictive Ability	
	Low	Intermediate	High	C Statistic (95% CI)	*P* Value
AFI 1994					.209
% in risk category	16.7	12.2	71.1	0.573	
TE events, No. (%)	1 (0.6)	4 (3.0)	20 (2.6)	(0.470-0.676)	
SPAF 1999					.405
% in risk category	26.2	44.8	29.0	0.549	
TE events, No. (%)	5 (1.8)	11 (2.3)	9 (2.9)	(0.435-0.662)	
$CHADS_2$—classic					.296
% in risk category	20.4	61.9	17.7	0.561[b]	
TE events, No. (%)	3 (1.4)	16 (2.4)	6 (3.2)	(0.450-0.672)	
$CHADS_2$—revised					.140
% in risk category	20.4	34.9	44.7	0.586[b]	
TE events, No. (%)	3 (1.4)	7 (1.9)	15 (3.1)	(0.477-0.695)	
Framingham					.018
% in risk category	48.3	41.5	10.2	0.638[b]	
TE events, No. (%)	6 (1.2)	14 (3.2)	5 (4.6)	(0.532-0.744)	
NICE 2006					.094
% in risk category	13.1	39.2	47.7	0.598	
TE events, No. (%)	0 (0.0)	13 (3.1)	12 (2.3)	(0.498-0.698)	
ACC/AHA/ESC 2006					.228
% in risk category	19.6	32.6	47.8	0.571	
TE events, No. (%)	3 (1.4)	7 (2.0)	15 (2.9)	(0.461-0.680)	
ACCP 2008					.204
% in risk category	19.6	33.4	47.0	0.574	
TE events, No. (%)	3 (1.4)	7 (1.9)	15 (3.0)	(0.465-0.683)	
Birmingham 2009					.070
% in risk category	9.2	15.1	75.7	0.606	
TE events, No. (%)	0 (0.0)	1 (0.6)	24 (3.0)	(0.513-0.699)	

See Tables 1 and 2 for expansion of abbreviations.

[a]Ischemic stroke, pulmonary embolism, or peripheral embolism.

[b]The C statistics for the Framingham and $CHADS_2$ scores, if tested as continuous variables, are as follows: Framingham: 0.693 (0.603-0.784); $P = .001$; and $CHADS_2$: 0.602 (0.486-0.718); $P = .081$.

value of older published stroke risk stratification schema for stroke and TE in patients with AF, but extend this work by showing the modest performance of the most recent ACC/AHA/ESC, ACCP, and NICE schemata.

There is some justification for the addition of female gender, vascular disease, and age 65 to 74 years into the combination risk factor category. The impact of female gender on stroke and TE risk has recently been reviewed by us.[15] Compared with men, women

Table 6—*Stroke or Other TE at 1 Year Based on the 2009 Birmingham (CHA_2DS_2-VASc) Scoring System*

CHA_2DS_2-VASc Score	No.	Number of TE Events	TE Rate During 1 y (95% CI)	TE Rate During 1 y, Adjusted for Aspirin Prescription,[a] %
0	103	0	0% (0-0)	0
1	162	1	0.6% (0.0-3.4)	0.7
2	184	3	1.6% (0.3-4.7)	1.9
3	203	8	3.9% (1.7-7.6)	4.7
4	208	4	1.9% (0.5-4.9)	2.3
5	95	3	3.2% (0.7-9.0)	3.9
6	57	2	3.6% (0.4-12.3)	4.5
7	25	2	8.0% (1.0-26.0)	10.1
8	9	1	11.1% (0.3-48.3)	14.2
9	1	1	100% (2.5-100)	100
Total	1,084	25	*P* Value for trend 0.003	

See Tables 1 and 2 for expansion of abbreviations.

[a]Theoretical TE rates without therapy: corrected for the % of patients receiving aspirin within each group, assuming that aspirin provides a 22% reduction in TE risk, based on Hart et al.[28]

are more likely to suffer a TE event or ischemic stroke when not taking warfarin, but when they are prescribed warfarin they have comparable INR control, are not more likely to suffer a major bleed, and demonstrate a greater TE risk reduction.[15] The impact of vascular disease, particularly myocardial infarction, on increasing TE risk in AF has also been systematically reviewed.[16-19] Furthermore, the presence of AF in association with peripheral artery disease is associated with a substantial mortality and morbidity, and the impact of atherothrombotic disease is also clearly illustrated by the presence of complex aortic plaque on the descending aorta being an independent predictor for stroke and TE in AF.[17,20] Last, stroke incidence increases with advancing age, and in AF this is no exception. Given that age is not a yes/no effect on stroke, and that anticoagulation has marked benefit in elderly subjects[2] our proposal is that age $\geq$ 75 years is a definitive (high) risk factor, and age 65 to 74 plus one additional combination risk factor also merits anticoagulation, thus improving thromboprophylaxis for large absolute numbers of AF patients who would otherwise be at risk. Our proposal is supported by data that the relative ischemic stroke risk reduction of antiplatelet drugs decreases with aging, whereas oral anticoagulation maintains its preventive power.[27]

The Framingham schema[25] had the highest C-statistic (0.638) but is based on a complicated mathematical formula and has not been incorporated into current treatment guidelines. In addition, it classified most patients of our cohort into low and moderate risk categories. Thus, many patients could have been denied VKA treatment on this basis, exposing them to the risk of stroke and TE. The AF Investigators schema[24] is based on the original (and now, historical) placebo-controlled trials of warfarin vs control, and again, represents historical interest given that many schema (eg, Birmingham/NICE and $CHADS_2$) have since evolved from this schema. Similarly, the SPAF risk stratification schema is of historical interest and the $CHADS_2$ schema was an amalgamation of the AF Investigators and SPAF schema, but the SPAF schema was the only one to have previously included female gender as a risk factor.[23] Since publication of the Stroke in AF Working Group analysis,[5] the eighth ACCP guidelines have been published,[10] and the current analysis provides a comparison of this against other schema. Because the eighth ACCP schema is broadly similar to the revised $CHADS_2$ schema (score 1 as intermediate risk group), it is unsurprising that the performance of this schema is comparable to $CHADS_2$.

The $CHADS_2$ schema is widely used due to its simplicity and ease. The $CHADS_2$ schema has been validated in its classic form, and we are unaware of a formal validation or comparison against other published schema with its revised (0, 1, $>$1) form.[9,26] As our analysis (and that of others[5-9]) has shown, the classic $CHADS_2$ version generated a large intermediate risk group ($>$60%) for whom it is unclear which treatment (warfarin or aspirin) to apply. The revised $CHADS_2$ provided some improvement, with a low proportion classified as intermediate risk, but with the addition of vascular disease, female gender, or age 65 to 74 years to a risk factor-based schema (Birmingham 2009) there was further refinement of TE risk stratification for AF with an improved C-statistic.

Current guidelines divide subjects into high-, intermediate-, and low-risk strata, but one advantage of a risk factor-based approach as proposed in the current analysis is the possibility to state "consider anticoagulation if AF present with one or more TE risk factors." Indeed, the presence of one definitive factor merits oral anticoagulation with (for example) an oral VKA (to a target INR 2-3). Patients with two or more combination risk factors should all be considered for oral anticoagulation. Thus, those with one definitive factor or two or more combination risk factors represent the old-style high-risk category. The small group of patients with one combination risk factor (15% of this cohort) would represent the old-style intermediate-risk category and should be managed with antithrombotic therapy, either as oral anticoagulation therapy (eg, VKA, target INR 2-3) or as aspirin 75 to 325 mg daily, although the recent ACCP guidelines suggest considering a VKA rather than aspirin if possible.[10] In Figure 1, we propose a clinical flowchart, based on the Birmingham 2009 schema. Our refined schema can thus be presented in three ways: (1) in a narrative manner (high risk is one definitive risk factor, or two or more combination risk factors), (2) scoring system (CHA_2DS_2-VASc score $\geq$ 2 is high risk), or (3) as a algorithm-based flow diagram.

Where possible, patients at intermediate risk should be considered for oral anticoagulation rather than aspirin, since undertreatment is more harmful than overtreatment.[28,29] Full discussion with the patient with one combination risk factor would enable agreement to use oral anticoagulation instead of aspirin to allow greater protection against ischemic stroke, especially if these patients value stroke prevention much more than the (theoretical) lower risk of hemorrhage with aspirin and the inconvenience of anticoagulation monitoring.[10] As mentioned, the BAFTA trial found no difference in major bleeding between warfarin (INR 2-3) and aspirin 75 mg in an elderly AF population in primary care,[2] and aspirin cannot be regarded as a much safer alternative to VKA.

Patients with no risk factors are at low risk (essentially patients aged $<$ 65 years with lone AF, with

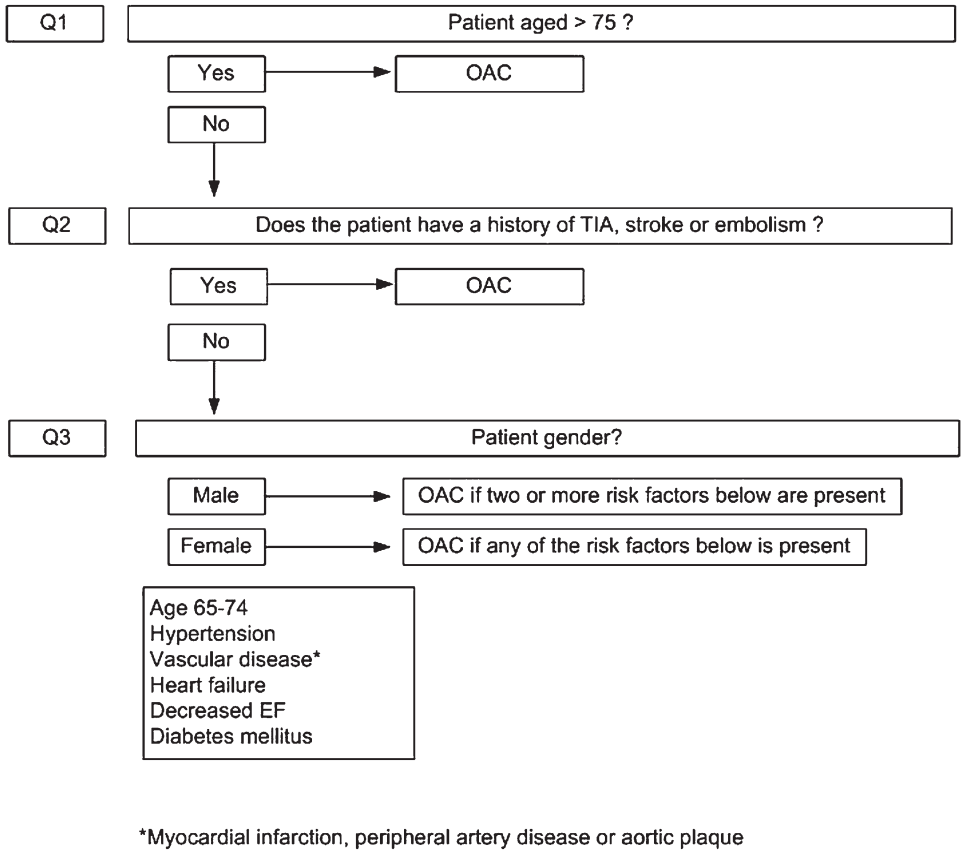

FIGURE 1. Proposed clinical flowchart for the use of oral anticoagulation for stroke prevention in atrial fibrillation.

none of the risk factors, whether high, moderate, or less validated), as confirmed by the absence of TE events in this group in our analysis, and can be managed with aspirin 75 to 325 mg daily or no antithrombotic therapy, given the limited data on the benefits of aspirin in this patient group (that is, lone AF) and the potential for adverse effects.[3] Indeed, the 22% reduction in stroke risk with antiplatelet therapy in the latest metaanalysis is largely driven by the SPAF-I clinical trial, in which internal inconsistencies in TE events with the aspirin vs control arms are apparent.[30] Also, it is likely that the magnitude of aspirin effect is related to the stroke prevention seen by giving antiplatelet therapy in patients with vascular disease.[1,27,31] It is notable that if trials with aspirin alone (and not other antiplatelet drugs) are considered in the recent metaanalysis by Hart et al,[28] the 95% confidence intervals of the aspirin effect also include zero. Interestingly, more recent trials in vascular disease have not shown any significant benefit for aspirin in the primary prevention of vascular disease.[32,33]

Hesitance to prescribe VKA to patients at high or intermediate risk is substantially related to the need for monitoring VKA and the many interactions of food and drugs with VKAs. These limitations can cause a patient to spend a low proportion of time within the therapeutic target INR range, which is associated with an increase TE risk.[34] Implementation of methods shown to improve quality of VKA management, such as an anticoagulation clinic, and the development of new oral anticoagulants that can be given as a fixed dose with few food/drug interactions and no requirement for monitoring, provide an opportunity for guidelines to adopt this risk factor-based approach to simply state "consider oral anticoagulation if AF is present with one or more TE risk factors" (ie, CHA_2 DS_2 -VASc score of 1 or more). The Birmingham 2009 schema also allows identification of a truly low-risk population, in whom no TE events were recorded in the low-risk subjects classified as no risk factors (ie, CHA_2 DS_2 -VASc score = 0) and such patients may not need any antithrombotic therapy.

This analysis is limited by its dependence upon a survey database, and although we have made efforts to ensure accurate coding and validation, all possible sources of bias and recording errors cannot be excluded. An important limitation is the absence of information on TE occurrence during 1 year for 31% of patients from the baseline survey. Also, we have based our primary analysis on 1,084 subjects who

were not anticoagulated at baseline, but during the 1 year of follow-up, a small proportion (18%) were started on VKA, which could have influenced TE end points. However, confining our analysis to a secondary cohort of subjects who were not treated with anticoagulation at baseline or during follow-up does not change our conclusions. Also, these analyses may have included some patients who were not started on VKA because of comorbidities, poor compliance (or inability to have adequate monitoring), and/or intolerance of anticoagulation, and furthermore, the numbers of end points in this subset are much lower. We recognize our modest follow-up period (1 year) in a contemporary real life clinical practice survey, but follow-up durations in other analyses are only marginally better. For example, the (older) $CHADS_2$ validation exercise only had an average of 1.25 years of follow-up.[26]

In conclusion, our novel, simple stroke risk stratification schema, based on a risk factor approach, provides some improvement in predictive value for TE over the $CHADS_2$ schema, with low event rates in low risk subjects and the classification of only a small proportion of subjects into the intermediate risk category. This schema could improve our approach to stroke risk stratification in patients with AF. Ongoing validations of the Birmingham 2009 risk schema in other AF populations from different race/ethnic groups will confirm its true value.

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Dr Pisters: contributed to drafting and revision of the manuscript.
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