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Original Research

CARDIOVASCULAR DISEASE

Bleeding and Stroke Risk in a Real-world Prospective Primary Prevention Cohort of Patients With Atrial Fibrillation

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Background: **All stroke risk stratification schemes categorize a history of stroke as a "truly high" risk factor. Therefore, stratifying stroke risk in atrial fibrillation (AF) should perhaps concentrate on primary prevention. However, the risk factors for stroke also lead to an increase in the risk of bleeding. Our objective was to evaluate the agreement among the currently used stroke risk stratification schemes in "real-world" patients with AF in the primary prevention setting, their correlation with adverse events recorded during warfarin treatment, and the relationship between stroke and bleeding risk.**

Methods: **We prospectively followed up 3,302 patients with AF taking warfarin for primary prevention. Stroke risk was assessed using the $CHADS_2$ (congestive heart failure, hypertension, age ≥ 75 years, diabetes, previous stroke or transient ischemic attack), Atrial Fibrillation Investigators, American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy, American College of Cardiology/American Heart Association/European Society of Cardiology, and National Institute for Health and Clinical Excellence schemas, and for bleeding risk, the outpatient bleeding risk index was calculated. Bleeding and thrombotic events occurring during follow-up were recorded.**

Results: **Patients classified into various stroke risk categories differed widely for different schemes, especially for the moderate- and high-risk categories. The rates of bleeding and thrombotic events during follow-up were 1.24 and 0.76 per 100 patient-years, respectively. All stroke stratification schemes correlated closely to bleeding risk. Stroke rate increased progressively from low- to moderate- to high-risk patients.**

Conclusions: **Stroke risk stratification models differed widely when categorizing subjects into the moderate- and high-stroke-risk categories. Bleeding and stroke risk were closely correlated and both were low among low-risk patients and were similarly high among moderate/high-risk groups.**

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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; AFI = Atrial Fibrillation Investigators; $CHADS_2$ = congestive heart failure, hypertension, age ≥ 75 years, diabetes, previous stroke or transient ischemic attack; INR = international normalized ratio; IQR = interquartile range; NICE = National Institute for Health and Clinical Excellence; OAT = oral anticoagulation therapy; OBRI = outpatient bleeding risk index; pt-y = patient-years; TIA = transient ischemic attack; TTR = time in therapeutic range; VKA = vitamin K antagonist

Atrial fibrillation (AF) is an independent risk factor for stroke and thromboembolism, and the use of oral anticoagulation therapy (OAT), usually vitamin K antagonists (VKAs), is an effective strategy for preventing thromboembolic complications.[1] Nonetheless, patients with AF are widely heterogeneous in terms of ischemic stroke risk, which ranges from 1% to 2%, to 12% to 18%, per year.[2,3]

Several clinical characteristics have been associated with an increase of stroke risk: age, hypertension, diabetes, heart failure, cardiac disease, and history of stroke or transient ischemic attack (TIA).[2,3] Currently available stroke risk stratification schemes attribute a variable weight to these risk factors, but all consistently categorize a history of stroke/TIA as a risk factor strong enough to identify truly high-risk patients who would benefit from OAT. Therefore, stroke risk stratification in AF should perhaps concentrate on patients who have never experienced stroke or thromboembolism, essentially those in the primary prevention setting.

In addition, it is known that some of the risk factors for stroke, such as age and history of stroke, also identify patients at increased bleeding risk. Thus, the absolute benefit of antithrombotic therapy in patients with AF depends on both stroke and bleeding risk.[4] Given that the balance between benefit and risk is less clear in a primary prevention setting, evaluation of the relationship between stroke and bleeding risk in this setting merits further study. The aim of the present study was to evaluate the agreement among the currently used stroke risk stratification schemes in "real-world" patients with AF in the primary prevention setting, their correlation with adverse events recorded during warfarin treatment, and the relationship between stroke and bleeding risk.

Materials and Methods

We prospectively studied 3,302 patients with AF referred for the control of OAT to the Thrombosis Centres of Azienda Ospedaliero-Universitaria Careggi and of Cremona Hospital. All patients were treated with warfarin, and the international normalized ratio (INR) was maintained at the intended therapeutic range of 2.0 to 3.0. The quality of anticoagulation was calculated as time in therapeutic range (TTR) using the linear interpolation method of Rosendaal et al.[5] This calculation started at the beginning of treatment. Patients' demographic and clinical data were collected. The presence of traditional cardiovascular risk factors and other characteristics associated with thromboembolic complications in AF were assessed on the basis of patients' interviews and hospital records. All patients gave their informed consent.

Patients were classified as hypertensive if they were taking medications to lower BP. Diabetes mellitus was defined according to American Diabetes Association criteria.[6] Coronary artery disease was defined on the basis of a history of myocardial infarction or stable and unstable angina. Heart failure was defined as the presence of signs and symptoms of either right or left ventricular failure or both, confirmed by noninvasive or invasive measurements demonstrating objective evidence of cardiac dysfunction.

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Stroke Risk Stratification

We classified our patients for stroke risk using previously published stroke risk stratification schemes in AF, as follows: Atrial Fibrillation Investigators (AFI)[7]; ACCP (2008)[8]; congestive heart failure, hypertension, age ≥ 75 years, diabetes, previous stroke or transient ischemic attack ($CHADS_2$) score[9]; National Institute for Health and Clinical Excellence (NICE) (2006)[10]; and the 2006 American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) guidelines.[11] To compare the $CHADS_2$ classification scheme, which is based on point scores of 0 to 6, with schemes that categorize patients as being at low, medium, or high risk, we categorized $CHADS_2$ into three strata, in two different ways: (1) $CHADS_2$ classic, which classifies low-risk patients as $CHADS_2$ score = 0, moderate risk as 1 to 2, and high risk as > 2; and (2) $CHADS_2$ revised, in which low risk = 0, moderate risk = 1, and high risk ≥ 2. We also tested one refinement of the $CHADS_2$ score by Rietbrock et al,[12] which was based on a reweighting of the traditional $CHADS_2$ score that offered a slight improvement in the predictive ability for stroke.

Bleeding Risk Stratification

We classified our patients for bleeding risk using the outpatient bleeding risk index (OBRI) developed by Beyth et al.[13] It was derived from an original hospital cohort of 556 patients and validated in a prospective cohort of 264 patients.

Follow-up and End Points

Follow-up visits were scheduled every 2 to 4 weeks for INR monitoring. Hospital admissions, intercurrent illnesses, and bleeding and thrombotic events during follow-up were recorded. Patients who missed check-ups for > 2 months were contacted (personally or through their family or general practitioner), and the reason for interrupting treatment monitoring was recorded. In the case of death, further information about its cause was requested. When this information was lacking, data from a national register of causes of death and autopsy results (if available) were consulted.

Data were censored after the occurrence of stroke or TIA or major bleeding, after the cessation of OAT, or when the patient stopped being monitored by our Anticoagulation Clinic. Stroke was defined as a syndrome characterized by rapidly developing clinical symptoms and/or signs of focal and, at times, global loss of brain function lasting > 24 h, not explained by other causes and in the absence of primary hemorrhage. Ischemic stroke was defined as a stroke with either a normal brain CT scan or evidence of a recent infarction in the clinically relevant area of the brain on a CT scan or MRI scan within 3 weeks of the event, and previous TIA was diagnosed when neurologic defects lasted < 24 h. Bleeding was classified as "major" when it was fatal, intracranial (documented by imaging), ocular causing blindness, articular, or retroperitoneal; when surgery or transfusion of more than two blood units was required; or when hemoglobin was reduced by ≥ 2 g/dL. All cases of clinically relevant bleeding events that were not classified as major were considered to be "minor."[14]

Statistical Analysis

The SPSS statistical software for Windows, version 11.5 (SPSS Inc; Chicago, Illinois,) was used for data processing. We used descriptive analysis expressed as median and interquartile range (IQR). Incidence rates for ischemic and bleeding events were calculated as the number of events per 100 patient-years (pt-y) of observation. For this calculation, observation started at the beginning of follow-up and ended when patients experienced an adverse event or were censored.

Table 1—*Clinical Characteristics of Atrial Fibrillation Patients and Risk Factors for Ischemic Complications*

No.	3,302
Men, No. (%)	1,826 (55.3)
Age, y, median (IQR)	74 (68-80)
Follow-up period, y	10,019
Follow-up period, y, median (IQR)	2.3 (0.8-4.4)
Medical history, No. (%)	
Heart failure	702 (21.3)
Hypertension	2,592 (78.5)
Diabetes	537 (16.3)
Coronary artery disease/peripheral artery disease	377 (11.4)
Dyslipidemia	652 (19.7)
Time in therapeutic range, %, median (IQR)	68 (56-77)
Time above therapeutic range, %, median (IQR)	7 (14-31)
Time below therapeutic range, %, median (IQR)	21 (3-13)

Following a test of statistical normality, analyses were performed using the Fisher exact test (categoric data), unpaired *t* test (parametric data), and Mann-Whitney test (nonparametric data). The Spearman rank correlation coefficient was calculated for correlations between $CHADS_2$ score for stroke risk and OBRI for bleeding risk. The independent effect of risk factors on the risk of adverse events on OAT was investigated by calculating the incidence rate ratio.[15] A univariate analysis and a Cox regression analysis, adjusted for age, were used to ascertain which factors were significantly associated with the risk of stroke/thromboembolism and of bleeding with OAT. All ORs are given with their 95% CI, and a two-sided value of $P < .05$ was chosen for statistical significance.

Results

We prospectively followed up 3,302 patients with AF (1,826 men, 55.3%) treated with VKA for primary prevention (Table 1). The total observation period was 10,019 pt-y, and median follow-up time was 2.3 (IQR, 0.8-4.4) years. The median age of patients at the beginning of follow-up was 74 years.

The number of patients categorized according to the various stroke risk schemes varied widely (Table 2), with the proportion of patients classed at moderate risk varying from 13.7% with the AFI schema, to 78.7% for $CHADS_2$ refined by Rietbrock et al,[12] whereas high-risk categorization varied from 17.0% for $CHADS_2$ (classic) to 82.5% with the AFI schema. The AFI, NICE, and modified $CHADS_2$ (Rietbrock et al[12]) schemes categorized the lowest proportions into the low-risk category.

Analyzing patients' bleeding risk, the OBRI classed a score = 0 in 353 patients (10.7%), score = 1 in 2,229 (67.6%), score = 2 in 650 (19.7%), and score = 3 in 65 (2.0%). All stroke risk stratification models examined were positively correlated with OBRI. We illustrate this by showing the distribution of patients according to $CHADS_2$ score and OBRI (Table 3), which were positively correlated (Spearman $r = 0.50$, $P < .001$). The positive correlation coefficients for AFI (0.30), ACCP (0.43), NICE (0.35), ACC/AHA/ESC guidelines (0.50), and modified $CHADS_2$ (0.43) were broadly comparable (data not shown).

Stroke and Thromboembolic and Bleeding Events

During follow-up, patients spent a median of 21% (IQR, 14%-31%), 68% (IQR, 56%-77%), and 7% (IQR, 3%-13%) of time below, within, and above the intended INR therapeutic range, respectively. Of the whole cohort, 139 patients died (total mortality rate, 4.2×100 pt-y); eight patients (5.8%) died of hemorrhagic complications (rate, 0.08×100 pt-y) and 108 patients (77.7%) of cardiovascular disease, whereas sudden death occurred in four (2.9%), stroke in one, pulmonary embolism in one, infectious disease in three, and cancer in 14 (10.1%).

While on VKA treatment, 76 thrombotic events (rate, 0.76×100 pt-y) were observed; of these, 35 were TIAs (0.35×100 pt-y) and 41 were strokes (0.41×100 pt-y). Median (IQR) TTR for OAT for event-free patients was 68% (56.0%-77.0%), not different from those who sustained stroke/thrombotic events ($P = .6$).

Rates of stroke/TIA events in relation to risk categorization by various schemes are shown in Table 4. In a univariate model, hypertension ($P = .04$), age ($P = .02$), and heart failure ($P = .05$) were associated

Table 2—*Distribution of Patients According to the Different Stroke Risk Stratification Schemes*

Stroke Risk Stratification Scheme	Low Risk	Moderate Risk	High Risk
AFI	127 (3.8)	454 (13.7)	2,721 (82.5)
$CHADS_2$ (classic)	301 (9.1)	2,440 (73.9)	561 (17.0)
$CHADS_2$ (revised)	301 (9.1)	1,158 (35.1)	1,843 (55.8)
Rietbrock et al[12] (modified $CHADS_2$)	0 (0.0)	2,598 (78.7)	704 (21.3)
NICE	120 (3.6)	1,720 (52.1)	1,462 (44.3)
ACC/AHA/ESC 2006	301 (9.1)	1,158 (35.1)	1,843 (55.8)
ACCP 2008	301 (9.1)	1,158 (35.1)	1,843 (55.8)

Data are presented as No. (%). ACC/AHA/ESC = American College of Cardiology/American Heart Association/European Society of Cardiology; ACCP = ACCP Conference on Antithrombotic and Thrombolytic Therapy; AFI = Atrial Fibrillation Investigators; $CHADS_2$ = congestive heart failure, hypertension, age ≥ 75 y, diabetes, previous stroke or transient ischemic attack; NICE = National Institute for Health and Clinical Excellence.

Table 3—*Distribution of Patients According to CHADS$_2$ Score and OBRI Score*

	CHADS$_2$ Score				
OBRI Score	0	1	2	3	4
0	109 (30.9)	221 (62.6)	23 (6.5)	0 (0.0)	0 (0.0)
1	179 (8.0)	843 (37.8)	987 (44.3)	221 (9.9)	0 (0.0)
2	13 (2.0)	89 (13.7)	249 (38.3)	234 (36.0)	65 (10.0)
3	0 (0.0)	1 (1.5)	23 (35.4)	33 (50.8)	8 (12.3)
Total	301 (9.1)	1,154 (35.0)	1,282 (38.9)	488 (14.8)	73 (2.2)

Data are presented as No. (%). OBRI = outpatient bleeding risk index. See Table 2 legend for expansion of other abbreviation.

with an increased risk of cerebral ischemic events during VKA treatment. Only the presence of hypertension ($P = .04$) was confirmed to be independently associated with cerebral ischemic events also in a Cox regression model. The distribution of stroke and thromboembolic events in relation to the OBRI is reported in Table 5, which shows that highest rate of stroke/TIA was evident among patients with the highest OBRI.

Major hemorrhagic events were recorded in 124 patients (rate, 1.24 × 100 pt-y), of which 27 (0.27 × 100 pt-y) were cerebral bleeds. The rate of bleeding events was higher in men (n = 80; rate, 1.44 × 100 pt-y), than in women (n = 44; rate, 1.0 × 100 pt-y) (relative risk, 1.5; 95% CI, 1.0-2.2; $P = .04$). Median (IQR) TTR for OAT for bleeding-event-free patients was 68% (56.0%-77.0%), whereas for those who sustained bleeding events, the median TTR was 71% (60.0%-78.0%) (Mann-Whitney test, $P = .1$).

Bleeding rates in relation to stroke risk according to the different stroke risk stratification schemes are shown in Table 6. In a univariate model, hypertension ($P = .01$) and male gender ($P = .04$) were significantly associated with an increased risk of bleeding, and both were also independent predictors in a multivariate model (both $P < .05$).

Discussion

This study was conducted on a real-world primary prevention population of patients with AF without a history of cardioembolism and on OAT for the prevention of thromboembolic complications. We show, in this primary prevention cohort, that those classified into various stroke risk categories still differed widely for different schemes, especially for the moderate- and high-risk categories. All stroke stratification schemes were closely correlated to bleeding risk.

The study confirms the poor agreement among the different stratification schemes commonly used,[16-20] with large variations in the number of patients classed in the different risk categories. The CHADS$_2$ score is the simplest to apply and is the most widely used in everyday clinical practice. However, this score has several limitations. First of all, the cutoff of 75 years is inappropriate because stroke risk increases progressively with age. Thus, other stroke risk factors in AF (eg, female gender, age, vascular disease, and so forth) should perhaps be considered. Of note, the 2006 ACC/AHA/ESC and the 2008 ACCP Conference on Antithrombotic and Thrombolytic Therapy schemes are based on CHADS$_2$, so there is no surprise that they were broadly similar in categorization, whereas the NICE scheme evolved from the AFI scheme. Variations in this stroke risk categorization are essentially due to the attribution of a higher risk to age 65 to 75 years by some of the considered models.[7,10] Aging progressively increases stroke risk,[2,3] and, in our analysis, the elderly patients showed a higher risk of cardioembolism. The presence of hypertension was an independent risk factor for stroke occurring on treatment, and hypertensive patients should

Table 4—*Distribution of Thrombotic Events (Rate × 100 pt-y) According to the Different Stroke Risk Stratification Schemes*

Stroke Risk Stratification Scheme	Low	Moderate	RR (95% CI) Low vs Moderate	*P* Value	High	RR (95% CI) Moderate vs High	*P* Value
AFI	0 (0.0)	6 (0.5)	…	…	70 (0.8)	1.8 (0.8.-5.1)	.1
CHADS$_2$ (classic)	1 (0.1)	56 (0.7)	7.1 (1.2-286)	.001	19 (1.2)	1.6 (0.9-2.7)	.09
CHADS$_2$ (revised)	1 (0.1)	21 (0.6)	5.5 (0.8-220)	.05	54 (1.0)	1.8 (1.1-3.1)	.01
CHADS$_2$ (Rietbrock et al[12])	0 (0.0)	54 (0.6)	…	…	22 (1.3)	2.0 (1.2-3.4)	.007
NICE	0 (0.0)	36 (0.6)	…		40 (1.0)	1.7 (1.1-2.8)	.02
ACC/AHA/ESC 2006	1 (0.1)	21 (0.6)	5.3 (0.85-220)	.05	54 (1.0)	1.8 (1.1-3.2)	.01
ACCP 2008	1 (0.1)	21 (0.6)	5.5 (0.9-229)	.04	54 (1.0)	1.8 (1.1-3.1)	.01

Data are presented as No. (rate). pt-y = patient-years; RR = relative risk. See Table 2 legend for expansion of other abbreviations.

Table 5—*Bleeding Events and Stroke/TIA in Relation to OBRI*

OBRI	No. (%)	Stroke/TIA (%)	Rate × 100 pt-y	Major Bleeding (%)	Rate × 100 pt-y
0	353 (10.7)	6 (1.7)	0.52	11 (3.1)	0.95
1	2,229 (67.6)	48 (2.2)	0.72	84 (3.8)	1.26
2	650 (19.7)	17 (2.6)	0.86	24 (3.7)	1.22
3	65 (2.0)	5 (7.7)	2.2	4 (6.2)	1.74

TIA = transient ischemic attack. See Table 3 and 4 legends for expansion of other abbreviations

probably always be considered for OAT. These data are in contrast to a those of large cohort of $CHADS_2 = 1$ patients,[21] where, of the various "single" risk factors, age ≥ 75 years appeared to be a much stronger risk factor than hypertension.

During follow-up, we recorded a rate of cerebral ischemic events of 0.76 × 100 pt-y, lower than previously reported rates,[17,19] due to our selection of a cohort of primary prevention patients, as well as our use of an anticoagulated cohort. Also, stroke rates are declining[22] and are related to good anticoagulation monitoring: Actually, in our cohort the median TTR was 68%. When we examined the distribution of cerebral ischemic events occurring on treatment in relation to stroke risk classifications, we found a progressive increase in the rate from low- to moderate- and high-risk groups. However, the increase is wider when we compare patients at low risk with patients at moderate risk, and it becomes smaller when patients at moderate and high risk are compared. Bleeding and stroke risk are closely related, consistent with previous studies.[23,24] Patients with multiple comorbidities, such as renal failure or liver dysfunction, are frailer and more likely to experience complications and drug-drug interactions that could be particularly severe in anticoagulated patients, and this may be a possible explanation for this association. Accordingly, patients classed at low risk for stroke had a low rate of major bleeding events during VKA treatment. Of note, the bleeding rates were not different between patients classed at moderate or high risk for stroke. Physicians need to decide whether or not their patients should be treated with warfarin, and the classification of stroke risk into three categories is perhaps inadequate. In addition, these patients have a similar bleeding risk and, therefore, the risk/benefit ratio of treatment is a little different within the individual stroke or bleeding risk categories. Again, there was a low mortality rate for bleeding, probably because our patients were a primary prevention cohort. Prior stroke is a strong risk factor for cerebral bleeding that carries the highest mortality rate.[25]

Limitations

We followed only patients on VKA treatment and we did not have a control group of patients without treatment or on aspirin. However, this is an observational study conducted in a real-world clinical practice and for ethical reasons it is necessary to treat patients with the best available therapy. All our patients were on VKA, so they were assumed to be at least at moderate/high risk by the responsible clinician, and thus, we cannot draw too many conclusions about the low-risk category.

Conclusions

In conclusion, stroke risk stratification models differed widely when categorizing subjects into the moderate and high stroke risk categories. Bleeding and stroke risk were closely correlated, and both were low among low-risk patients. In addition, both risks were higher among patients classed at moderate and high risk, suggesting that these patients could be classed

Table 6—*Distribution of Bleeding Events (Rate × 100 pt-y) According to the Different Stroke Risk Stratification Schemes*

Stroke Risk Stratification Scheme	Low	Moderate	RR (95% CI) Low vs Moderate	*P* Value	High	RR (95% CI) Moderate vs High	*P* Value
AFI	1 (0.3)	13 (1.0)	3.7 (0.6-160.2)	.2	110 (1.3)	1.3 (0.7-2.6)	.3
$CHADS_2$ (classic)	4 (0.4)	100 (1.3)	3.2 (1.2-12.1)	.007	20 (1.2)	0.9 (0.5-1.4)	.7
$CHADS_2$ (revised)	4 (0.4)	49 (1.3)	3.1 (1.1-11.8)	.01	71 (1.3)	1.0 (0.7-1.5)	.8
$CHADS_2$ (Rietbrock et al[12])	0 (0.0)	102 (1.2)	….	…	22 (1.3)	1.1 (0.6-1.7)	.7
NICE	1 (0.3)	73 (1.2)	4.1 (0.7-164.3)	.1	50 (1.3)	1.0 (0.7-1.5)	.9
ACC/AHA/ESC 2006	4 (0.4)	49 (1.3)	3.1 (1.1-11.8)	.01	71 (1.3)	1.0 (0.7-1.5)	.8
ACCP 2008	4 (0.4)	49 (1.3)	3.1 (1.1-11.8)	.01	71 (1.3)	1.0 (0.7-1.5)	.8

See Tables 2 and 4 for expansion of abbreviations.

in a single category that would benefit from more aggressive antithrombotic treatment. A new approach to determining the optimal net clinical benefit of primary prevention thromboprophylaxis for patients with AF is needed.

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Dr Grifoni: contributed to the acquisition, analysis, and interpretation of the data and the drafting of the manuscript.
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