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Comparison of the reliability and validity of four contemporary risk stratification schemes to predict thromboembolism in non-anticoagulated patients with atrial fibrillation

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ABSTRACT

Background: The risk of thromboembolic (TE) complications in atrial fibrillation (AF) patients is not homogeneous. Risk schemes can help target anticoagulant therapy for patients at highest risk of TE complications.
Objectives: To test the predictive ability of 4 risk schemes: The Framingham, the 8th ACCP, the ACC/AHA/ESC 2006, and the CHA_2DS_2-VASc.
Methods: 186 patients with non-valvular AF and off anticoagulant therapy were included. All subjects who experienced a stroke, transient ischemic attack, or peripheral embolism were identified. Each schema was divided into low, intermediate, and high-risk categories. Discrimination was assessed via the c-statistic.
Results: We identified 10 TE events that occurred during 668 person-years off anticoagulation therapy. All risk schemes had fair discriminating ability (c-statistic ranged from 0.59 [for CHA_2DS_2-VASc] to 0.73 [for Framingham]). The proportion of patients assigned to individual risk categories varied widely across schemes. CHA_2DS_2-VASc categorized the fewest patients into low and intermediate-risk categories, whereas the Framingham schema assigned the highest patients into low-risk strata. There were no TE events in the low and intermediate-risk categories using CHA_2DS_2-VASc, whereas the most schemes assigned patients into intermediate-risk category had a event rate ranging from 2.5 (ACC/AHA/ESC and 8th ACCP schemes) to 6% (Framingham). The negative predictive value of TE events was of 100% for the no high-risk patients using CHA_2DS_2-VASc.
Conclusions: Compared to ACC/AHA/ESC, 8th ACCP, and Framingham, CHA_2DS_2-VASc risk stratification schema may be better in discriminating between patients at a low and intermediate risk of TE complications.

Non-valvular atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder with significant burden of stroke and other thromboembolic (TE) complications that are associated with substantial risk of mortality and morbidity. The prevention of TE complications is the cornerstone of AF management. Anticoagulant (ACO) therapy with vitamin K antagonists such as warfarin can substantially reduce the risk of AF-related TE complications [1,2]. However, the risk of stroke and thromboembolism in AF is not homogeneous, and better ways to predict AF-related TE complications are clearly needed to optimize the use of ACO therapy, both to prevent the overuse of this therapy in patients with low absolute risks of TE complications and to target its use those patients who would most greatly benefit [3–5]. Based on stroke risk factors, many risk stratification schemes have been developed in order to categorize a patient's risk of stroke and aid decisions regarding the most appropriate thromboprophylaxis [6–10]. However, the problem with the current TE complications risk stratification schemes is that, when applied to the same cohort of patients, the absolute stroke rates by risk group and the percentage of patients categorized as low, intermediate or high risk would vary considerable depending upon which risk stratification scheme is employed [11]. Thus, the choice of a particular scheme may influence the recommendation of the ACO therapy for individual patients. Given that the consequences of ischemic stroke can be devastating, it is reasonable to choose a risk schema that set treatment thresholds for ACO at fairly

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low absolute risks. The new European guidelines for the management of AF [1] recommend the use of the recently developed CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, and Sex [female]) scoring system, which although has demonstrated, in the validation cohort from the Euro Heart Survey, modest improvement in identifying high-risk patients, the score was able to categorize patients as low risk those who were "truly low risk" being free of TE events at 1 year [12].

However, given the differences that geographic location entails in patient characteristics and medical assistance (i.e., different health systems), when any risk algorithm is to be used outside the environment in which it was created it needs first to be validated for its new context; only then can users be sure that the scores provided are not misleading.

The aim of the present work was to assess the predictive ability of four contemporary stroke risk schemes ((Framingham (2003) [8], the American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) 2006 guidelines risk score [9], the 8th American College of Chest Physicians (8th ACCP) [10], and the recently developed CHA_2DS_2-VASc scoring system [12]) in stratification risk of AF-related TE complications in a real world non-anticoagulated cohort of patients with non-valvular AF.

1. Methods

1.1. Patients

The AFBAR (Atrial Fibrillation in the BARrbanza area) was a prospective study that has been described in detail previously [13]. Briefly, AFBAR was carried out by a team of Primary Care physicians in a single health-service area of Galicia, north-western Spain. AFBAR had aimed to describe the natural history of AF in an unselected population attending by primary care services, and treated at the discretion of their attending physicians. Each physician had enrolled all his/her patients with AF, aged >18 years, during a 3-month period (from Jan-2008 to Apr-2008). All patients had signed a consent form, and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a *priori* approval by the institution's human research committee. The cohort was followed-up through January 2011, a median follow-up was of 33.5 months (interquartile range 28.4 to 34.3 months). Patients' demographic and clinical data, such as previous cardiovascular events and other comorbidities, treatment, and AF complications during follow-up, were ascertained from the patients' clinical interview and hospital records. AFBAR was made of 798 patients. For the purpose of the present study, patients with mitral valve stenosis or valvular surgery, or on ACO therapy at study entry, were excluded. Therefore, the final cohort of this study was made of 186 patients who were on antiplatelet treatment or on not antithrombotic therapy at all.

1.2. Variables and definitions

Diagnosis of stroke or TIA required an acute neurological deficit lasting approximately 24 h, respectively, which could not be explained by other causes (haemorrhage, trauma, infection, etc.) and with at least 1 image test (computed tomography or magnetic resonance) compatible with the diagnosis, as well as confirmation from a neurologist. A diagnosis of peripheral embolism was defined as TE outside the brain, heart, eyes, and lung, as clinically compatible, and an embolus identified by vascular ultrasound, examination during surgery, or anatomopathological findings, always with the confirmation of a vascular surgeon. In patients who suffered more than 1 embolic event, only the first event was considered for the purpose of the analysis.

1.3. Risk stratification schemes

Each of the 4 risk stratification system (Table 1) was constructed to assign patients to low, intermediate, and high tromboembolism risk categories, consistent with previous studies [10–21,12].

1.4. Statistical analysis

Quantitative variables were expressed as mean and standard deviation (SD); qualitative variables were expressed as frequencies and percentages. The Student *t* test was used to compare quantitative variables; the x^2 or Fisher exact test was used as required to compare qualitative variables. Given the length time of follow-up, statistical analysis had to take time at risk into account. Because the aim of the present study was to determine the comparative utility of TE risk schemes for the purpose of informing anticoagulant therapy decision making, we only included TE events that occurred off ACO therapy. For all investigated risk stratification schemes, TE rate per patient-years of follow-up were estimated after stratification of patients into categories of low, intermediate, and high risk. Each classification scheme was entered into separate Cox regression models to test their association with TE complication. The c-statistic, a measure of the area under the receiver-operating characteristic curve, quantified the predictive validity of the classification schemes and tested the hypothesis that these schemes performed significantly better than chance (indicated by a c-statistic >50%).

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

2. Results

2.1. Patient characteristics

A total of 661 person-years of follow-up among patients with AF not taking ACO therapy were available for analysis. The mean age of patients at study entry was 74 [11] years, 50.8% were female, and 98.1% had at least 1 clinical risk factor for TE complications (Table 2).

At study entry, 81.6% of AFBAR patients were on antiplatelet therapy. During the follow-up period, we identified 10 TE events (9 ischemic strokes or TIA and 1 peripheral emboli), for an overall rate of 2.2 per 100 person-years.

2.2. Comparison of the classification schemes

The proportion of AF patients categorized as at low risk varied considerable across the risk schemes. The CHA_2DS_2-VASc schema

Table 1
Risk stratification schemes used to predicted thromboembolism in atrial fibrillation.

Risk schema	Low risk	Intermediate risk	High risk
Framingham (2003)[8]	Score 0–7	Score 8–15	Score 16–31
ACC/AHA/ESC guidelines (2006)[9]	No risk factors		
(score = 0 points)	Age ≥75 years, or hypertension, or heart failure, or LVEF ≤35%, or diabetes		
(score = 1 point)	Previous stroke/TIA/embolism, or ≥2 moderate risk factors		
(Score = >1points)			
8th ACCP guidelines (2008)[10]	No risk factors	Age >75 years, or hypertension, or moderate/severe impaired LVEF and/or heart failure, or diabetes	Previous stroke, TIA or embolism, or ≥2 moderate risk factors.
CHA_2DS_2-VASc (2010)[12]	No risk factors		
(Score = 0 points)	One "clinically relevant non-major risk factors: heart failure/LVEF ≤40%, hypertension, diabetes, vascular disease, female gender, age 65–74 years		
(Score = 1 point)	One "major" risk factors: previous stroke/TIA/embolism, or age ≥75 years		
≥2 "clinically relevant non-major" risk factors (Score = >1 points)			