

Editorial

The Improved but Unfinished Business of Stroke Risk Stratification in Atrial Fibrillation

Avances incompletos en la estratificación del riesgo de ictus en la fibrilación auricular

Amitava Banerjee,^a Francisco Marín,^{a,b} and Gregory Y.H. Lip^{a,*}^aUniversity of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom^bServicio de Cardiología, Hospital Universitario Virgen de la Arrixaca, Universidad de Murcia, El Palmar, Murcia, Spain

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With an estimated lifetime risk of 1 in 4 men and women >40 years of age,¹ atrial fibrillation (AF) is the most common arrhythmia worldwide and poses a significant burden of morbidity and mortality from stroke and thromboembolism (TE). As with other areas of cardiovascular medicine (eg, acute coronary syndromes²), risk stratification schemes for AF aim to individualize risk prediction of disease to guide therapies for both primary and secondary prevention. Improved risk stratification schemes for AF will also enable clinicians to treat the patients at greatest risk of stroke and TE and avoid treatment in patients at negligible risk. Given that oral anticoagulation (OAC) is the most effective drug to prevent TE in AF, there is now a paradigm shift towards getting better at identifying “truly low risk” patients with AF who do not need any antithrombotic therapy whilst others with ≥ 1 stroke risk factors should be considered for OAC.^{3,4} The process of refinement and improvement of risk stratification requires validation and comparison of existing and new scores in different populations and different clinical scenarios.

Although AF can be classified as paroxysmal, persistent, or permanent, guidelines suggest that patients with paroxysmal AF should be regarded as having a stroke risk similar to those with persistent or permanent AF, in the presence of risk factors.⁵ Patients aged < 60 years, with “lone AF” – defined by no clinical history or echocardiographic evidence of cardiovascular disease (CVD) – carry a very low cumulative stroke risk, estimated to be 1.3% over 15 years.⁵ The probability of stroke in young patients with lone AF increases with age and the development of risk factors. Therefore, the regular re-assessment of risk factors is essential for stroke prevention in patients with AF over time.

The CHADS₂ (Cardiac failure, Hypertension, Age, Diabetes, Stroke [Doubled]) score is the most commonly used and widely validated risk-scoring system for patients with AF,⁶ and utilizes information from the patient’s medical history, namely congestive cardiac failure, hypertension, age >75 years, diabetes mellitus, and stroke (2 points). OAC therapy is currently indicated in patients with a CHADS₂ score ≥ 2 .⁵ However, the risk of stroke increases

continuously from CHADS₂ = 0 to CHADS₂ = 6 and there is proven benefit of OAC therapy even in patients with CHADS₂ = 1.^{3,7} The many limitations of the CHADS₂ score have been discussed by Karthikeyan et al.⁸

The CHA₂DS₂-VASc (C_{ardiac failure or dysfunction}, H_{ypertension}, A_{ge} ≥ 75 [Doubled], D_{iabetes}, S_{troke}[Doubled] – V_{ascular disease}, A_{ge} 65-74 and S_{ex} c_{ategory} [Female]) scoring system arose from recognition that stroke risk prediction with the CHADS₂ may be improved by the inclusion of common TE risk factor data from “real-world” patient populations instead of trial cohort data.⁹ The CHA₂DS₂-VASc score incorporates history of vascular disease (1 point), assigns 1 point for female sex), and divides age into <65 (0 points), 65-74 (1 point) and >75 years (2 points). The new scoring system¹⁰ has better predictive value (as measured by the c-statistic) for stroke and TE and classifies relatively fewer patients at low risk of stroke than the CHADS₂ score. Indeed, recent guidelines⁵ suggest that OAC should be considered in patients with CHA₂DS₂-VASc ≥ 1 and is indicated in patients with CHA₂DS₂-VASc ≥ 2 .

In their article published in *Revista Española de Cardiología*, Rodríguez-Mañero et al.¹¹ report on the impact of the CHA₂DS₂-VASc risk stratification scheme for stroke and TE in a European population of patients with AF. Across multiple centers, they conducted a cross-sectional prevalence study of AF and its associated risk factors. The adult study population was recruited from outpatient cardiology (10.9%) and primary care clinics (89.1%). In line with previous studies of AF, their AF study population was older and had a greater burden of risk factors and CVD than the population without AF. Interestingly, 77.3% of patients with AF had a moderate- to high-risk TE profile (CHADS₂ score ≥ 2) and would, by the current European Society of Cardiology guidelines, warrant chronic OAC therapy.⁵ Amongst their patients aged <75 years, 42.3% had a CHA₂DS₂-VASc = 2; 23.7% CHA₂DS₂-VASc = 3, and 1.1% CHA₂DS₂-VASc = 4; this means that many patients with a CHADS₂ score <2 and no contraindications will have indication for OAC, as per the current guidelines.⁵

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* Corresponding author: University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham B18 7QH, United Kingdom.

E-mail address: g.y.h.lip@bham.ac.uk (Gregory Y.H. Lip).

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PATIENT SELECTION

Patients with AF present to the whole spectrum of healthcare settings. The clinical setting and the population in which a risk

score is used are important factors influencing the prevalence of AF, cardiovascular risk factors, and CVD and the pre-test probabilities of stroke and TE. For example, the risk of stroke will be higher amongst patients in the secondary care and clinic settings. In the cross-sectional study by Rodríguez-Mañero et al.,¹¹ the population was mostly from primary care, but 10.9% were from cardiology clinics. These two healthcare settings would be very different in terms of both patient characteristics and clinician practices, and the patient characteristics and outcomes should perhaps be reported separately by subgroup to enable an assessment of comparability, allow for proper analyses, and avoid possible confounding of observed associations.

THE NEED FOR PROSPECTIVE VALIDATION

Cross-sectional analyses such as the study by Rodríguez-Mañero et al.¹¹ are important to illustrate current treatment practices with regard to OAC. Although they highlight the proportion of patients eligible for OAC that actually receive OAC, they cannot assess the accuracy of current risk scoring systems in prediction of stroke and TE in AF patients.

Risk stratification schemes require validation in prospective population-based cohorts to gain the most valuable information regarding the validity and accuracy of risk prediction using this particular score. Research in prospective cohorts with longer-term follow-up will inform the use of the stroke (and bleeding) scores in risk prediction over longer time periods. Given the high lifetime risk of AF, the long-term risk of incident and recurrent stroke and TE need to be better characterized in order to more accurately assess the risk to individual AF patients over their lifetime.

A recent study used Danish population registry data to prospectively evaluate the CHA₂DS₂-VASc score in 73 538 patients with AF not treated with OAC in Denmark in the period 1997-2006.¹⁰ In patients at “low risk” (score = 0), the rate of TE per 100 person years was 1.67 (95% CI 1.47 to 1.89) with CHADS₂ and 0.78 (0.58 to 1.04) with CHA₂DS₂-VASc at 1-year follow-up. In patients at “intermediate risk” (score = 1), this rate was 4.75 (4.45 to 5.07) with CHADS₂ and 2.01 (1.70 to 2.36) with CHA₂DS₂-VASc. When patients were categorized into low, intermediate, and high risk groups, c statistics at 10 years’ follow-up were 0.81 (0.80 to 0.83) with CHADS₂ and 0.89 (0.88 to 0.90) with CHA₂DS₂-VASc. Thus, those classified by CHADS₂ as low risk (score = 0) were not truly low risk, in comparison with the CHA₂DS₂-VASc score, and the latter was better than the CHADS₂ score in predicting those at high risk for TE.

A separate validation study included 79 844 AF patients from the United Kingdom General Practice Research Database followed for an average of 4 years (and an average of 2.4 years up to the start of OAC therapy).¹² The c-statistic for CHA₂DS₂-VASc was 0.67 for predicting stroke recorded by the general practitioner or in hospital, and 0.74 for death resulting from stroke as reported on death certificates. The difference in c-statistics for CHA₂DS₂-VASc between these two studies illustrates the earlier point that risk stratification differs based on the clinical setting and the study population.

UNMET NEED FOR ANTICOAGULATION

A recent systematic review of 54 studies concerning current treatment practices for stroke prevention in AF highlighted the underuse of OAC therapy in real-world AF patients with an elevated risk of stroke.¹³ According to Rodríguez-Mañero et al.,¹¹

41.7% of the low-to-moderate risk population (CHADS₂ score 0 or 1) were not receiving OAC, and most of these patients were aged >75 years (63.4%, versus 36.6% overall in their age group, compared to 56.8% versus 43.2% in the group <75 years). In addition, the authors comment that there is “a paradox in the fact that, although the great majority of medical registries have shown that anticoagulants have been consistently underused, each new edition of the clinical guidelines for patients with AF widens the indications for this type of treatment”. Whilst this may be the case, it is also possible that clinicians in everyday practice are anticoagulating patients with a CHADS₂ score = 0 by informally considering some of the additional common risk factors for TE, such as female sex, age 65–74 years, and vascular disease, in their decision-making process. Indeed, a 74-year-old man with peripheral artery disease is at very high risk of TE, and most clinicians would offer this hypothetical patient OAC despite a CHADS₂ score of zero.

The gap between need for OAC and the prescription of OAC can be divided into: a) patient values and preferences; b) clinician values, preferences and practices, and c) patient characteristics. Patient preferences and values may be based on past experience with OAC or accounts of the experience of other patients and may greatly affect initiation of, and adherence to, OAC. Clinician practices and preferences may lead to increased or decreased OAC prescription, depending on the method used by clinicians to stratify the particular stroke risk of AF patients. Finally, patient characteristics, in terms of both risk factors and history of TE, influence whether a patient is prescribed OAC. The CHADS₂ and CHA₂DS₂-VASc scores use slightly different criteria to decide which patients ultimately receive OAC. Probably the most important patient characteristic pertaining to the decision to initiate OAC is the risk of bleeding.¹⁴ The current study by Rodríguez-Mañero et al.¹¹ does not provide data on bleeding risk of patients. Therefore, it is unclear what proportion of the AF patients who were not on OAC (despite meeting criteria for initiation of OAC) had high bleeding risk.

THE APPLICATION AND SIMPLIFICATION OF RISK SCORING

An ideal risk scoring system would correctly identify low-risk patients and avoid unnecessary OAC, and also identify high-risk patients, ensuring treatment in high-risk individuals. The CHA₂DS₂-VASc score has consistently performed better than other risk scores in identifying “truly low risk” subjects who do not need any antithrombotic therapy.^{9,10,12} Patients with CHA₂DS₂-VASc score = 0 have a genuinely low risk of stroke and do not require antithrombotic therapy. Oral anticoagulation (or acetylsalicylic acid) can be considered in patients with CHA₂DS₂-VASc = 1 and patients with CHA₂DS₂-VASc ≥ 2 should receive OAC, in the absence of contraindications.⁵

In the study by Rodríguez-Mañero et al.,¹¹ 14.4% of patients in this group were >75 years (thus CHA₂DS₂-VASc score = 2), and 40% were 65–74 years of age. In the 65–74 age group, 67.1% had 2 or more risk factors (42.3% CHA₂DS₂-VASc score of 2, 23.7% CHA₂DS₂-VASc score of 3, and 1.1% CHA₂DS₂-VASc score of 4).¹¹ Also, 30.7% had a risk factor (CHA₂DS₂-VASc score of 1), and should be considered for OAC (or acetylsalicylic acid). Only 2.2% had no risk factors (CHA₂DS₂-VASc of 0) and truly low enough risk of stroke for OAC not to be indicated. Although the percentage of patients in this study with an indication for OAC (in the absence of contraindications) would increase to 81.5% (67.1% of those younger than 75 years and 14.4% of those with age >75 as their only risk factor), the CHA₂DS₂-VASc scoring system would mean that the patients who are at negligible risk of stroke are more accurately identified.

CHOICE OF ANTITHROMBOTIC THERAPY

Rodríguez-Mañero et al.¹¹ also show that among high-risk patients not receiving OAC, the preferred alternative treatment was antiplatelet medication with acetylsalicylic acid or clopidogrel (67.4%). Also, 8.9% were receiving dual antiplatelet therapy (DAT) and, of concern, 23.7% received no drug treatment at all. These data illustrate the challenge of translating evidence-based guidelines into clinical practice when it comes to OAC in patients with AF.

Trial data have comprehensively shown the superiority of OAC versus DAT with clopidogrel plus acetylsalicylic acid, as well as no difference in bleeding events between treatment arms.⁵ Although stroke and TE are reduced with DAT versus single antiplatelet therapy, the risk of bleeding is increased to the level seen with OAC. DAT is often used in patients who are thought to be unsuitable for OAC, but evidence shows that DAT should not be used as an alternative therapy in patients with high bleeding risk.⁵ Such considerations highlight the need for improved therapies for stroke prevention in AF.

The advent of dabigatran and other novel OAC therapies which will not require international normalized ratio monitoring have the potential to change both patient and clinician preferences towards use of OAC, perhaps leading to a greater bridging of the current gap between indication for OAC and actual usage of OAC in AF patients.¹⁵ Challenges still remain in extending OAC to an increasing proportion of “real-world” AF patients with a genuine indication for OAC.

CONFLICTS OF INTEREST

Professor Lip has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, and Boehringer and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer, and Sanofi. Dr. Marín has received a research grant from Abbott Laboratories and Boston Scientific. Dr Banerjee – none declared.

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