Putting risk prediction in atrial fibrillation into perspective

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This editorial refers to ‘Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study’, by L. Friberg et al1, on page 1500

Oral anticoagulation dramatically reduces the risk of ischaemic stroke and improves all-cause survival in patients with atrial fibrillation (AF). However, anticoagulation increases the risk of major bleeding, including uncommon but frequently fatal intracranial haemorrhages. As a consequence, guidelines recommend a risk-based approach to anticoagulation for AF, assuming those patients at higher untreated risk of stroke will gain sufficient absolute risk reduction to outweigh potential harms.1

The most widely used risk assessment tool in AF is the CHADS2 score, which is based on risk factors identified in the early trials of warfarin in non-valvular AF.1 The CHADS2 acronym is easy to remember and has become a fixture of guidelines, clinical practice, and trial design. Unfortunately, its predictive ability is mediocre. The standard assessment of the discriminating ability of a prediction rule is the C-statistic, which is roughly interpretable as the probability the score will be higher in patients who sustain a stroke vs. those who do not (the interpretation varies depending on analytic perspective). A C-statistic of 0.5 indicates that the score conveys no predictive information. In contrast, the gold standard of chronic disease cardiovascular risk prediction, the Framingham score, has demonstrated C-statistics approaching 0.8.2

Typical C-statistics for the CHADS2 score have been in the range of 0.60. Several alternative scores have been published with similar predictive ability but they have not caught on.3 Recently, the CHA2DS2-VASc score has been proposed as an alternative to the CHADS2 score and has been incorporated into the 2010 European Society of Cardiology (ESC) guidelines.1

Friberg and colleagues have evaluated risk factors and risk classification schemes for ischaemic stroke and bleeding in 182 678 patients with AF from the Swedish National Hospital Discharge Registry.4 After comparing the CHADS2 and CHA2DS2-VASc scores for the prediction of ischaemic stroke and thromboembolism, the authors found that discrimination for stroke events was minimally improved with CHA2DS2-VASc compared with CHADS2 (C-statistic 0.67 vs. 0.66). However, CHA2DS2-VASc did help identify a very low risk group of patients.

CHA2DS2-VASc adds three features to CHADS2, i.e. age 65–74, female sex, and vascular disease (defined as prior myocardial infarction, peripheral artery disease, or aortic plaque).1,4 In CHA2DS2-VASc, age ≥75 is now given a weight of 2 points, equal to a prior stroke or transient ischaemic attack. It is important to consider the added risk factors and their relative merit. The risk of stroke increases continuously with age. Addition of another category besides ≥75 years (the single age category in CHADS2) should provide further predictive information. Female sex has been found to be a risk factor in many, but not all cohorts.5,6 In contrast, the independent association of stroke risk with vascular disease is not well supported. In the report of Friberg et al., the presence of vascular disease raised the relative risk of stroke by only 7% [hazard ratio (HR) 1.07, 95% confidence interval (CI) 1.01–1.14]. In a prior analysis of nearly 80 000 individuals with AF in the UK, ischaemic heart disease (the main component of ‘vascular disease’) was not an independent risk factor for stroke, nor was it a risk factor in the analysis of the BAFTA trial in elderly AF patients.7,8 A systematic review found inconclusive evidence that coronary disease was an independent risk factor for stroke.8 Taken together, these data suggest that vascular disease contributes little to estimating stroke risk in AF.

What are the advantages of CHA2DS2-VASc? In effect, CHA2DS2-VASc expands the range of CHADS2 (Figure 1). The expanded risk score does appear to improve risk stratification for the lowest risk patients. The additional risk factors included in CHA2DS2-VASc, particularly age 65–74 years, can identify a smaller and lower risk group that has no risk factors. In those patients with a risk score of zero, the annualized stroke rate was

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0.2% for CHA₂DS₂-VASc vs. 0.6% for CHADS₂. It is likely that physicians and patients would be comfortable using aspirin monotherapy at either of these very low rates of stroke. However, at a point score of 1, the scoring systems diverge. Friberg et al.⁴ report an annualized stroke rate of 0.6% for CHA₂DS₂-VASc vs. 3.0% for CHADS₂. An expected stroke rate of 3.0% per year seems too high for antiplatelet therapy.

Recent ESC guidelines state that oral anticoagulation is ‘preferred’ in patients with ≥1 CHA₂DS₂-VASc risk factors.¹ In the Swedish registry, this approach results in recommending anticoagulation to 94% of the cohort (including all women). While CHA₂DS₂-VASc can identify a small percentage of patients with very low risk of stroke, it ends up characterizing nearly all the rest as high risk. Certainly, most CHA₂DS₂-VASc ≥2 patients merit anticoagulation, particularly given the lower risk of intracranial haemorrhage with novel oral anticoagulants. However, the annual stroke rate of 0.6% in patients with a CHA₂DS₂-VASc = 1 seems too low to justify anticoagulation. It is important to remember that patients who are CHADS₂ = 0 and CHA₂DS₂-VASc = 1 have largely been excluded from the major trials of novel oral anticoagulants. Additionally, Friberg et al. only included hospital-based patients, probably biasing towards higher stroke rates.⁴ Ultimately, an aggressive approach in low risk patients may be warranted, but we should appreciate that this strategy is not well supported by trial results.

We do need stroke risk prediction tools that are clearly better than the CHADS₂ score. Until they appear, clinicians should consider additional risk factors for patients where the anticoagulation decision is particularly troublesome. Such risk factors would include female gender, older age, and presence of renal dysfunction.⁹

What about bleeding scores? Many guidelines have cautioned against use of anticoagulants in patients at increased risk of bleeding, but failed to specify how to estimate bleeding risk. There are now several bleeding scores developed specifically for patients with AF.⁴,¹⁰ One of these scores, HAS-BLED, was incorporated into the recent ESC guidelines. Friberg et al. compared HAS-BLED with the HEMORR2HAGES score and concluded that they have ‘similar predictive value’, although the point estimate of the C-statistic was higher for HEMORR2HAGES (0.63 vs. 0.61). The comparison was hampered by the absence of several risk factors included in the original scores. The authors argue that HAS-BLED has the advantage of ‘simplicity’, but HAS-BLED strikes us as fairly complicated and unlikely to serve as a ‘simple’ bedside tool. It has seven categories of risk factors, a pair of subcategories (e.g. A = ‘abnormal’ renal and liver function), and multiple risk factors whose definitions are not intuitive. Both the HAS-BLED and HEMORR2HAGES scores would be difficult to use without formal scoring aids.

While it makes sense to incorporate bleeding risk scores into the anticoagulation decision, the process is not straightforward. First, bleeding risk scores need to be tested in multiple cohorts; their current track record is quite limited. Secondly, balancing stroke and bleeding risk is complex. The most common type of major bleeding is extracranial, such as gastrointestinal haemorrhage, which, on average, has much less clinical impact than ischaemic stroke. In contrast, intracranial haemorrhage is often fatal, yet bleeding scores lump these events together. As a result, withholding anticoagulation based simply on a bleeding risk score is a premature and potentially harmful recommendation. For example, if we take a hypothetical patient with a CHADS₂ score of 2 and a HASBLED score of 5, the estimated untreated annualized risk of

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**Figure 1** The rates of ischaemic stroke per 100 patient years in the Swedish Registry according to both the CHADS₂ and CHA₂DS₂-VASc scores. Immediately below the x-axis, the range of low, intermediate, and high risk scores are illustrated, as well as the frequency of each score in the overall registry population (% of cohort).
ischaemic stroke in the Swedish register is 4.7% and the absolute increase in the intracranial bleeding rate with oral anticoagulation is 0.4% (1.2–1.6%). It is hard to imagine this patient would benefit from avoidance of oral anticoagulation. Balancing stroke and bleed risk scores is even more difficult because bleeding risk and stroke risk are highly correlated such that those patients who are most likely to bleed often are also most likely to have a thrombo-embolic stroke.15 Simply avoiding anticoagulation in AF patients at high risk for bleeding could result in preventable strokes and increased mortality.

Ultimately, rational use of stroke prophylaxis should hinge on appropriately defined net clinical benefit.15 We need better prediction rules across the risk spectrum. The ultimate goal is to identify the restricted (but significant) number of AF patients who will have a stroke and limit anticoagulation to these patients. This very challenging goal will certainly not be approached with current models. Moving forward, application of risk models should be anchored in the prevention of ischaemic stroke, avoidance of devastating haemorrhage, particularly intracranial haemorrhage, and improved survival.

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