Atrial fibrillation (AF) is the most common serious chronic heart rhythm disorder, with an estimated prevalence in the general population of approximately 1% (1). The arrhythmia affects approximately 2.2 million persons in the U.S. and 4.5 million in the European Union. Because of the advancing age of the population, the prevalence of AF is likely to increase even further (2). Atrial fibrillation is associated with major morbidity and mortality, particularly due to thromboembolic complications. In patients older than 80 years of age, approximately 15% of all strokes are attributable to AF. Moreover, AF-related strokes are known to be associated with higher mortality and more disability than strokes of other origins (3).

Solid evidence exists that anticoagulation therapy with vitamin K antagonists reduces AF-related stroke risk by two-thirds compared to placebo (relative risk reduction [RRR]: 62%, 95% confidence interval [CI]: 48% to 72%), whereas aspirin decreases stroke risk only by 22% (RRR: 22%, 95% CI: 3% to 38%) (4). Vitamin K antagonists are clearly superior even in patients >75 years of age, as demonstrated in the BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged) study (5). Vitamin K antagonists also reduce the risk of stroke by one-third compared with the combination of acetylsalicylic acid and clopidogrel, as recently shown in the ACTIVE W (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) trial (RRR: 42%, 95% CI: 19% to 58%) (6).

The most serious side effect associated with the use of vitamin K antagonists is hemorrhage, with intracranial bleeding representing the most feared complication. Vitamin K antagonists compared with acetylsalicylic acid significantly increase the risk of major bleeding (2.2 vs. 1.3 events per 100 patient-years; p = 0.02) (7). Vitamin K antagonists have numerous other limitations, such as slow onset and offset kinetics and a narrow therapeutic window, and their metabolism is affected by diet, drugs, and genetic polymorphisms. However, the fear of iatrogenic hemorrhage is almost certainly one of the most important reasons why physicians do not prescribe warfarin for a substantial number of AF patients who are likely to benefit from it (8).

In contrast to current guideline recommendations, contemporary surveys of practice patterns, for instance, stemming from administrative databases, demonstrate that 40% to 50% of patients with AF who are at substantial risk for stroke are not treated with vitamin K antagonists (8–13). A recent study from the Canadian Stroke Network, for instance, showed that among 597 patients with known AF who had no contraindications for warfarin and who were admitted to hospital with acute ischemic stroke, only 10% received therapeutic anticoagulation (international normalized ratio [INR] ≥2.0) at the time of stroke admission (14). Even among a subset of AF patients with a prior history of stroke or transient ischemic attack, only 18% were taking warfarin with a therapeutic INR at the time of admission for stroke. When anticoagulation therapy with vitamin K antagonists is applied, the quality of anticoagulation treatment is less than optimal. A recent survey from the U.S. found that, on average, patients only spent a mean of 55% of their time in the therapeutic INR range (15). There were significant differences in quality of therapy, with standard community care giving 11% less time in the therapeutic range compared to anticoagulation clinic services. Similarly, the discontinuation rate of warfarin is high, particularly by elderly AF patients. A recent study reported that within the first year of therapy, 26% of patients ≥80 years of age stopped taking warfarin. Perceived safety issues, particularly concerns about bleeding, accounted for 81% of them (16). Even among patients who were prescribed vitamin K antagonists for secondary prevention after having suffered a first AF-related stroke, there was a high discontinuation rate of warfarin therapy, with only 45% of patients continuing on this treatment after 2 years (17). Thus, anticoagulation therapy is underused, is suboptimally applied, and is often inappropriately discontinued. All of this is driven for a good part by the perceived bleeding risk associated with vitamin K antagonists therapy.

Both the risk for stroke and the risk for bleeding are not homogenous in AF. Accordingly, there have been numerous attempts to stratify AF patients for their individual risk. The CHADS2 (Cardiac failure, Hypertension, Age ≥75 years, Diabetes, Stroke, the latter scoring 2 points) score has
evolved over recent years as being an easily applicable, useful tool to subdivide patients into those at low, intermediate, or high risk for AF-related stroke (18). However, it has been increasingly recognized that many risk factors for stroke are also associated with a higher risk for anticoagulation-associated hemorrhage. In fact, bleeding risk increases with increasing CHADS2 scores (17). Therefore, attempts have been made to develop separate scoring systems to identify clinical risk factors associated with incremental risk for hemorrhage (19–22). However, some of these risk scores employ complex scoring systems (19,22) that significantly limit their clinical applicability. Others have not been thoroughly validated in AF populations but rather in general anticoagulated populations, likely with fewer comorbidities than observed in AF patients (21,22). As a consequence, none of these risk scores has gained widespread acceptance in clinical practice.

In this issue of the Journal, Lip et al. (23) present a thorough validation of a new risk score, called HAS-BLED (an acronym for hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly [≥65 years of age], drugs/alcohol concomitantly), for predicting bleeding risk in anticoagulated AF patients. This score has been recently derived from an European AF population (24) and is now validated using a database separate from that in which it was developed. In addition, the authors performed a head-to-head comparison with previous risk prediction scores. Data from 2 large randomized phase III trials of ximelagatran versus warfarin for stroke prevention in AF comprising >11,000 patient-years of oral anticoagulation exposure were utilized. The validation of the HAS-BLED score in an AF population different from the inception population confirmed the predictive power of this score. Upon comparison with previous risk scores, evidence indicated that the HAS-BLED score may be associated with better predictive accuracy than its predecessors: The c statistics for this score were somewhat higher than those of previous scores, although they were not markedly higher. Importantly, hazard ratios for distinction among low, moderate, and high bleeding risks were greater for the HAS-BLED score than for any other scoring system. Finally, upon multivariate Cox regression analysis, the new score added significantly to those models that already incorporated the old models. In contrast, none of the older models significantly contributed when inserted in a model already incorporating the HAS-BLED score. For these reasons, the new score may indeed prove to be an important clinical tool to assess bleeding risk in AF patients, and the authors should be congratulated for their careful analyses.

As potential limitations, it should be mentioned that data from randomized clinical trials do not necessarily reflect daily clinical practice. Because the HAS-BLED score has been validated using trial data, it remains to be seen how it will perform in daily routine practice. Furthermore, new antithrombotic agents, such as dabigatran (25) or apixaban (26), are likely to be approved for clinical use. Whether the bleeding risk scores developed from data on patients receiving vitamin K antagonists apply to new anticoagulants that may have lesser bleeding risk (particularly with respect to intracranial bleeds [25]) remains to be seen. More efforts are clearly needed for better prediction of individual stroke and bleeding risk, with subsequent improved tailoring of therapy to the patients who will derive benefit from anticoagulation therapy. The development of the HAS-BLED score may turn out to be an important step in that direction.

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