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COMMENTARY

Bleeding risk assessment in atrial fibrillation: observations on the use and misuse of bleeding risk scores

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Stroke prevention is central to the management of atrial fibrillation (AF), and effective thromboprophylaxis requires oral anticoagulation. Even a single stroke risk factor confers excess risk, and the net clinical benefit (NCB) of treatment is positive for oral anticoagulation as compared with no treatment or aspirin, whereas aspirin confers a neutral or negative NCB [1].

AF patients are at higher intrinsic risk of bleeding [2], and the use of oral anticoagulants (OACs) or aspirin increases the risk, with intracranial hemorrhage (ICH) being the most serious form of bleeding related to antithrombotic therapy [3]. The risks of ICH are similar with vitamin K antagonists (VKAs) (e.g. warfarin) and aspirin, especially in the elderly [4]. The non-VKA OACs (NOACs) confer a significantly lower risk of ICH than VKAs [5].

Bleeding risk assessment when oral anticoagulation is started is not a new phenomenon,. For many years, clinicians used 'clinical assessment', whereby the presence of, for example, uncontrolled hypertension, concomitant non-steroidal anti-inflammatory drug (NSAID) use, or alcohol excess was used to estimate (or guess) a patient's bleeding risk. More recently, bleeding risk stratification scores incorporating some of the factors associated with excess bleeding have also been proposed, but, until recently, they have had limited uptake in the management of AF patients, owing to their complexity or because they are not AF-specific.

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In 2010, the HAS-BLED score was proposed [6]; this incorporated the more common bleeding risk factors in AF patients, and has since been recommended by guidelines. Importantly, HAS-BLED draws attention to the reversible bleeding risk factors (e.g. uncontrolled hypertension [H], labile International Normalized Ratios [INRs; this criterion only applies to a patient taking VKAs] [L], concomitant use of NSAIDs, or excess alcohol [D]) to be addressed by the responsible clinician during the follow-up. Risk is not static, and, particularly for bleeding, many risk factors can be modified.

Although stroke and bleeding risks track each other, it has been conclusively shown that HAS-BLED outperforms stroke scores such as $CHADS_2$ or CHA_2DS_2-VASc in predicting bleeding [7]. A high risk of bleeding (e.g. HAS-BLED score of ≥ 3) is not a reason to withhold oral anticoagulation; instead, such patients should be 'flagged up' for more careful review and follow-up [8]. This is increasingly important in an era of electronic health records with 'electronic alerts' that identify patients requiring review.

HAS-BLED has also been shown to be predictive of serious bleeding in patients receiving oral anticoagulation (whether with a VKA or a non-VKA OAC), aspirin, or no antithrombotic therapy (thus being applicable for the full spectrum of AF patients), and in AF and non-AF populations. HAS-BLED is also the only bleeding risk score that has been shown to be predictive of ICH.

Other bleeding risk scores have been proposed for AF patients, such as the ATRIA and ORBIT scores, and, more recently, the ABC bleeding score [9–11]. All of these scores focus on identifying 'high-risk' patients, and some have added complexity by the use of weighted scoring (ATRIA [9]) or including biomarkers (ABC [11]), or have opted for even greater simplicity and supposed applicability to any OAC type, whether a VKA or an NOAC (ORBIT [10]). Although some of the validation studies imply improved prediction (at least statistically) as compared with other scores (including HAS-BLED), the

crucial question for everyday clinical use concerns the simplicity and practical applicability of these new scores.

In this issue of the *Journal of Thrombosis and Haemostasis*, Focks *et al*. [12] compare the performance of HAS-BLED, ATRIA and HEMORR2HAGES for major bleeding in a random sample ($N = 1157$) of VKA-anticoagulated AF patients aged ≥ 80 years. They report a statistically significant association for these three scores with major bleeding, but poor predictive ability (C-statistics < 0.60). Only two (anemia and antiplatelet therapy) of the classic risk factors were associated with bleeding. It is of note that ATRIA categorized ~ 60% of this cohort as 'low risk'.

These findings are highly relevant to the ongoing use (and misuse) of bleeding risk scores. As highlighted above, bleeding risk scores are increasingly being used to 'flag up' those patients at high risk for bleeding for review, and risk scores that inappropriately categorize patients as 'low risk' may mean that such patients are ignored or that no action is taken.

Also, the focus on the identification of 'high-risk' patients who actually experience events neglects one of the fundamental purposes of bleeding risk assessment, i.e. drawing attention to, and correcting, the reversible risk factors. For easy use in a busy clinic or ward, practical scores require the inclusion of routinely recorded clinical factors. However, any risk scores based on clinical factors have only a modest predictive value for predicting high-risk patients who will experience events. The addition of any biomarker – whether blood-based, urine-based, or imaging-based – would clearly improve the predictive value of a clinical score, although the treating clinician would have to wait for the results of the biomarker test(s) [13].

The addition of a biomarker to improve risk prediction is not a new concept [14]. More recent validation studies have used biomarkers in highly selected anticoagulated clinical trial cohorts, and have demonstrated a modest, but statistically significant, predictive improvement over the risk scores based on clinical factors alone [15]. Also, many biomarkers have important interlaboratory and interassay variability, as well as diurnal and temporal variation, which need to be considered.

As shown recently, adding 'labile INR' (percentage time in therapeutic INR range [TTR] of $< 65\%$) to ORBIT, ATRIA and HEMORR2HAGES scores significantly improved their reclassification and discriminatory performances for patients with major bleeding while receiving VKAs, suggesting that these scores do perform suboptimally in identifying serious bleeding risk in a patient receiving warfarin, unless they were recalibrated with labile INRs (or TTRs) being taken into

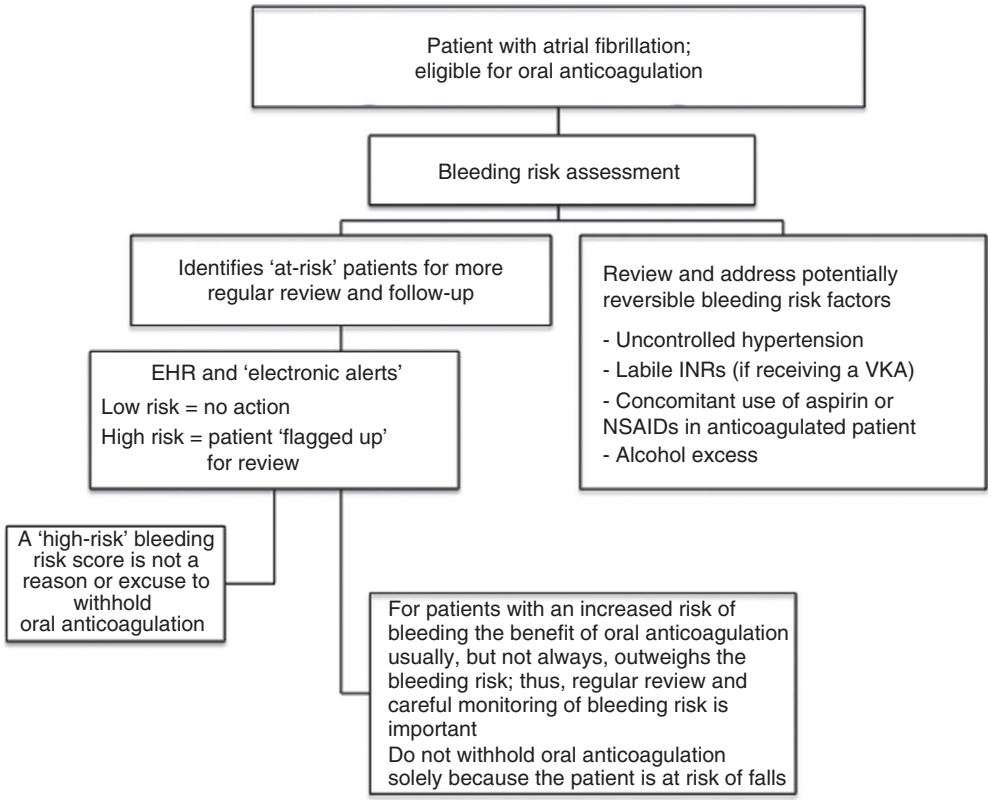

Fig. 1. Appropriate use of bleeding risk assessment in patients with atrial fibrillation. EHR, electronic health record; INR, International Normalized Ratio; NSAID, non-steroidal anti-inflammatory drug; VKA, vitamin K antagonist.

consideration [16,17]. In contrast, HAS-BLED categorized adjudicated major bleeding events in low-risk and high-risk patients appropriately, whereas ORBIT and ATRIA classified most patients experiencing major bleeds into their respective 'low-risk' categories [16].

Another clear misuse of bleeding risk scores is as an excuse to withhold oral anticoagulation. Focks *et al.* [12] clearly show a favorable trade-off for oral anticoagulation in this elderly cohort, consistent with the broad literature showing that the NCB is even greater among the elderly, because, in most cases, the magnitude of gain from stroke prevention far outweighs the smaller risk of serious bleeding even at high HAS-BLED scores [18].

Bleeding risk scores should thus be applied appropriately and not misused (Fig. 1). The continued preoccupation with trying to improve prediction of 'high-risk' patients with ever more complex scores (and often multiple biomarkers), with only marginal improvement in predictive performance, at the cost of simplicity and practicality, would seem to be counterintuitive for everyday clinical management. Risk is also a continuum, and AF patients often do not fall neatly into three artificially defined (i.e. low, moderate, and high) risk categories. Risk is also not a static 'one-off' assessment, and, because AF patients are often elderly with multiple comorbidities, risk assessment has to be dynamic, with regular review and reassessment – with particular attention being paid to reversible risk factors, whether for bleeding or stroke.

The continued misuse of these scores will ultimately be to the detriment of AF patient management, and greater awareness and understanding of appropriate practical use is needed. Ultimately, patients place greater value on stroke prevention, and, even to avoid one stroke (regarded by some as a fate worse than death), patients may be prepared to experience four major bleeds [19,20]. Surely we can do better.

Addendum

G. Y. H. Lip wrote the first draft and performed critical revision. D. Lane commented on and revised the article.

Disclosure of Conflict of Interests

G. Y. H. Lip has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, Bristol-Myers Squib/Pfizer, Biotronik, Portola, and Boehringer Ingelheim; and has been on speakers' bureau for Bayer, Bristol-Meyers Squibb/Pfizer, Boehringer Ingelheim, and Sanofi Aventis. D. Lane reports receiving investigator-initated educational grants from Boehringer Ingelheim and Bristol-Myers Squibb; personal fees from Boehringer Ingelheim, Bristol Myers Squibb, and Pfizer; and non-financial support from Boehringer Ingelheim, outside the submitted work.

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