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Editorial

**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 (OAC). Even a single stroke risk factor confers excess risk, and the net clinical benefit of treatment is positive for OAC compared to no treatment or aspirin, whilst aspirin confers a neutral or negative NCB¹.

Whilst AF patients are at higher intrinsic risk of bleeding², the use of OAC or aspirin increases risk, with intracranial haemorrhage (ICH) being the most serious form of bleeding related to antithrombotic therapy³. The risks of ICH are similar with vitamin K antagonists (VKA, e.g., warfarin) and aspirin, especially in the elderly⁴. The non-VKA OACs (NOACs) confer significantly lower risk of ICH compared to VKA⁵.

Bleeding risk assessment is not a new phenomenon. For many years, clinicians used 'clinical assessment', where the presence of, for example, uncontrolled hypertension, concomitant NSAID use, alcohol excess, etc.,- 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, have had limited uptake in the management of AF patients due to their complexity or being non-AF specific.

In 2010, the HAS-BLED score was proposed⁶ which 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 INRs (L), concomitant use of NSAIDs or excess alcohol (D), etc.) 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. Whilst stroke and bleeding risks track each other, it has been conclusively shown that the HAS-BLED score outperforms stroke scores such as CHADS₂ or CHA₂DS₂-VASc in predicting bleeding⁷. High risk of bleeding (e.g., HAS-BLED score ≥ 3) is not a reason to withhold OAC, instead such patients should be 'flagged-up' for more

careful review and follow-up⁸. 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 OAC (whether a VKA or non-VKA type), aspirin or no antithrombotic therapy [thus, applicable for the full spectrum of AF patients], and in AF and non-AF populations. HAS-BLED is also the only bleeding risk score 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 score⁹⁻¹¹. All these scores focus on identifying 'high risk' patients and some have added complexity by weighted scoring (ATRIA⁹) or including biomarkers (ABC¹¹), or opted for even greater simplicity and supposed applicability to any OAC, whether VKA or NOAC (ORBIT¹⁰). Whilst some of the validation studies imply improved prediction (at least statistically) compared to other scores (including HAS-BLED), the crucial question for everyday clinical use is the simplicity and practical applicability of these new scores.

In this issue of the *Journal of Thrombosis and Haemostasis*, Focks et al¹² compare the performance of the HAS-BLED, ATRIA and HEMORR2HAGES for major bleeding in a random sample (N=1,157) of VKA-anticoagulated AF-patients ≥80 years. They report a statistically significant association for these 3 scores with major bleeding, but poor predictive ability (C-statistics <0.60). Only two (anaemia, antiplatelet therapy) of the classical risk factors were associated with bleeding. Of note, use of the ATRIA bleeding score categorized approximately 60% of this cohort as 'low risk'.

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

Also, the focus on the identification of 'high risk' patients who actually sustain events

neglects one of the fundamental purposes of bleeding risk assessment, drawing attention to, and correcting, the reversible risk factors. For easy use in a busy clinic or ward, practical scores require 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 sustain events. Addition of any biomarker – whether blood, urine 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.

Addition of a biomarker to improve risk prediction is not a new concept¹⁴. More recent validation studies have used biomarkers in highly selected anticoagulated clinical trial cohorts and have demonstrated modest, yet statistically significant predictive improvement over the risk scores based on clinical factors alone¹⁵. Also, many biomarkers have important inter-laboratory and inter-assay variability, as well as diurnal and temporal variation which need to be considered.

As shown recently, adding 'labile INR' (TTR < 65%) to the ORBIT, ATRIA and HEMORR₂HAGES scores significantly improved their reclassification and discriminatory performances for major bleeding whilst on VKA, suggesting that these scores may perform sub-optimally in identifying serious bleeding risk in a patient on warfarin, unless they were re-calibrated taking labile INRs (or TTRs) into consideration^{16, 17}. In contrast, HAS-BLED categorised adjudicated major bleeding events in low-risk and high-risk patients appropriately, whilst ORBIT and ATRIA classified most major bleeds into their 'low-risk' categories¹⁶.

Another clear misuse of bleeding risk scores is as an excuse to withhold OAC. Focks et al¹² clearly show a favorable trade-off for OAC in this elderly cohort, consistent with the broad literature showing that the NCB is even greater among the elderly, since in most cases, the magnitude of gain from stroke prevention far outweighs the smaller risk of serious bleeding even at high HAS-BLED scores¹⁸.

Bleeding risk scores should thus be applied appropriately and not misused [FIGURE]. 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 counterintuitive for everyday clinical management. Risk is also a continuum, and patients often do not fall neatly into 3 artificially defined (i.e. low, moderate and high) risk categories. Risk is also not static 'one-off' assessment, and since AF patients are often elderly with multiple comorbidities, risk assessment has to be dynamic with regular review and reassessment – with particular attention 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 sustain 4 major bleeds^{19, 20}. Surely we can do better.

FIGURE 1

Appropriate use of bleeding risk assessment in patients with atrial fibrillation

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