Assessing bleeding risk in atrial fibrillation with the HAS-BLED and ORBIT scores: clinical application requires focus on the reversible bleeding risk factors

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This editorial refers to ‘The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation’†, by E.C. O’Brien et al., on page 3258.

Stroke prevention is central to the management of patients with atrial fibrillation (AF), and effective stroke prevention requires oral anticoagulation (OAC), delivered with either a vitamin K antagonist (VKA; e.g. warfarin) or a non-VKA oral anticoagulant (NOAC). If a VKA is used, good quality anticoagulation control, defined as a time in therapeutic range (TTR) >70%, is crucial, given that the efficacy and (particularly) safety of VKA is intimately related to TTR.1,2 Various clinical features are associated with a higher bleeding risk, and some have been used to derive various bleeding risk scores that have been proposed in the last decade.3 Until recently, these scores have not had much clinical use, given that many were derived or validated in non-AF patients. Of the various proposed bleeding risk scores, only the HEMORRHAGES, HAS-BLED, and ATRIA scores have been derived and/or validated in AF populations.

The HAS-BLED score has gained popularity, having been shown to be simple but yet as good as—and sometimes better than—other bleeding risk scores, in predicting bleeding risk.3–7 Various validation studies have examined HAS-BLED in predicting bleeding risk in AF whilst on OAC (both VKA and non-VKA anticoagulants), aspirin, or without any antithrombotic therapy. HAS-BLED is also the only score shown to be predictive of intracranial haemorrhage (ICH). The HAS-BLED score has also been validated in non-AF populations, including those with venous thrombo-embolism, acute coronary syndrome, or percutaneous coronary interventions, or those undergoing bridging therapy.9

Amongst AF patients, a high HAS-BLED score is not a reason to withhold OAC as such patients derive even greater net clinical benefit whilst on OAC. Instead, a high HAS-BLED score flags up those potentially at risk of bleeding, for more careful review and follow-up. Also, HAS-BLED draws attention to well-established potentially reversible bleeding risk factors, such as uncontrolled hypertension (the ‘H’ in HAS-BLED), labile international normalized ratios (INRs) (e.g. a TTR < 60%; only applies to a patient taking warfarin), and concomitant use of aspirin/non-steroidal anti-inflammatory drugs (NSAIDs) or alcohol excess (the ‘D’ criterion). In a patient who is not taking a VKA, the ‘L’ criterion is not scored when calculating the HAS-BLED score.

In this issue of the journal, O’Brien et al.11 propose the ORBIT bleeding risk score, which is comprised of Older age (1 point), Reduced Hb/HCT/anaemia (2 points), Bleeding history (2 points), Insufficient renal function (1 point), and Treatment with antiplatelets (1 point); thus, this score would perhaps be better abbreviated as OR2B2IT.

The authors suggest that this score is statistically better at predicting major bleeding than the HAS-BLED score, in both the derivation and validation cohorts. This score was derived from an observational registry (ORBIT-AF) and validated using the ROCKET-AF trial.12 The latter was a highly selected clinical trial patient cohort that only included high risk patients with AF (i.e. CHADS2 score of ≥2, with those with CHADS2 score 2 being capped at 10%) and excluded patients with significant renal impairment (creatinine clearance < 30 mL/min). Also, the warfarin-treated patients in ROCKET-AF had a poor TTR (55%), and the warfarin-treated patients in ORBIT-AF used as the derivation cohort were only those who remained on warfarin. They did...
conduct a sensitivity analysis (≥ 6 months of warfarin vs. < 6 months of warfarin), but only included the people who were still taking OAC.

Observation of the variables included in the ORBIT score also notes many similarities to the HAS-BLED score components, including elderly age, bleeding tendency, or predisposition [this encompasses reduced haemoglobin (Hb) or anaemia; given 1 point in HAS-BLED but can sum up to a maximum of 4 points in ORBIT, with 2 points from Reduced Hb/HCT/anaemia and 2 points from Bleeding history], abnormal renal function, and concomitant antiplatelets.

Notable differences include the different weighing for bleeding tendency or predisposition, and no consideration of uncontrolled hypertension, abnormal liver function, prior stroke, NSAIDs, and labile INRs in the ORBIT score. The latter parameter was not considered by O’Brien et al. as they wished for a ‘simple score that can be used for all types’ of OAC and stated that a TTR is ‘not easily available’.

Labile INR is one of the most powerful predictors of bleeding when on a VKA and, apart from a TTR < 65% by the Rosendaal method, ‘labile INR’ can also be easily defined using other simple (and easily accessible) parameters, such as the proportion of INR within range, INR variability, time above range, time above INT > 4, etc.; or, within the previous 6 months, INR > 5 twice, INR > 8 once, or INR < 2 twice.13,14

Thus, a 50-year-old man with uncontrolled hypertension (e.g. blood pressure > 180/110 mmHg), prior stroke, (very) labile INRs on warfarin (e.g. TTR 40%), concomitant use of NSAIDs (e.g. Cox-2 inhibitors), abnormal liver function, and excess alcohol intake would have an ORBIT score of 0 (i.e. low risk), but would have a HAS-BLED score of 5 (high risk). The responsible physician would certainly ‘flag up’ this patient with a high HAS-BLED score, and, in accordance with good clinical practice, would strive to control blood pressure, optimize the TTR (or swap to an NOAC), and reduce NSAID use or alcohol intake. The ORBIT score would not flag up such a patient or draw attention to the reversible bleeding risk factors (Figure 1).

Indeed in the paper by O’Brien et al., a ‘low risk’ category ORBIT score has a bleeding risk of 2.4 bleeds per 100 patient-years, whilst a ‘medium risk’ patient has a bleeding risk of 4.7 per 100 patient-years. Corresponding rates in the initial derivation cohort for HAS-BLED were <1.13 and 1.88 per 100 patient-years, respectively.4 Thus, a patient categorized as having a ‘low risk’ of bleeding by HAS-BLED has a low bleeding rate of 1 per 100 patient-years, but even a supposed ‘low risk’ patient using the ORBIT score has a bleeding rate of 2.4 per 100 patient-years. Indeed, even an ORBIT score of 1 has a bleeding rate of >2 per 100 patient-years.

O’Brien et al. report statistically significant better c-statistics and recalibration for the ORBIT score over HAS-BLED and ATRIA bleeding risk scores in predicting patients who sustain a bleeding event. All prediction scores based on clinical factors (whether CHADS2, CHA2DS2-VASc, HAS-BLED, ATRIA, ORBIT, etc.) have broadly similar c-statistics, ~0.6–0.7, and we suggest...
that statistical significance and clinical application should not be confused. Indeed, bleeding risk assessment is not a static phenomenon, and many common clinical factors that increase bleeding risk are potentially reversible. Undue oversimplification of bleeding risk scores with focus on statistical significances for c-statistics and recalibration neglects the clinical utility of applying the score in everyday clinical practice.

What are the clinical implications? The most important thing is to make sure we do assess bleeding risk in all patients initiating OAC and those already on it. Those at high bleeding risk with potentially reversible bleeding risk factors need to be flagged up and their bleeding risk factors addressed, an approach recommended (and emphasized) in contemporary guidelines.13 Also, clinicians will usually want to assess bleeding risk prior to starting OAC (of note, HAS-BLED has been validated in such AF patients); however, no-one in the derivation or validation cohort for the ORBIT score was not on OAC. Whilst proposing a score that can be used with ‘any OAC’, attention to labile INR amongst those taking a VKA is absolutely crucial given how closely related bleeding is to poor labile INRs—indeed, worldwide, VKAs are still widely used. A simple score such as HAS-BLED that flags up the reversible bleeding risk factors, that has been validated in a wide range of patients (AF and non-AF, VKA and non-VKA), and is predictive of ICH continues to retain many clinical and practical merits, far beyond the inappropriate focus on marginal statistical differences in predicting the occurrence of bleeding events. Common sense is sometimes needed.


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References