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EDITORIAL

Specific risk scores for specific purposes: Use CHA_2DS_2-VASc for assessing stroke risk, and use HAS-BLED for assessing bleeding risk in atrial fibrillation

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Competing interests

G.Y.H.L. has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife and Daiichi-Sankyo and has been on the speakers bureau for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife and Daiichi-Sankyo. M.D. – none declared.

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia which is often asymptomatic AF. The detection of this arrhythmia is improved by population screening, detecting newly diagnosed (and untreated) cases that would have otherwise have presented with devastating complications such as stroke, heart failure, etc.[1,2] Indeed, AF accounts for a large proportion of cryptogenic strokes where prolonged ECG monitoring was used to reveal 'silent' AF cases. [3] Thus, stroke prevention is central to the management of AF, and oral anticoagulants (OACs) are recommended as the effective means of stroke prevention. Until recently, the only OAC available for use were the Vitamin K Antagonists (VKAs, eg. warfarin) and given the various limitations associated with these drugs, as well as the need for good quality anticoagulation control to reduce complications [4, 5], much of the focus of risk stratification was to identify 'high risk' patients to be targeted for these 'inconvenient' drugs. Hence, various risk stratification schemes were proposed, to aid clinical decision making for patients with AF.

For stroke risk stratification, the $CHADS_2$ and the CHA_2DS_2-VASc scores have had the most support and acceptance, as they include common stroke risk factors seen in daily clinical practice.[6] The CHA_2DS_2-VASc score is now the recommended stroke risk score in the major guidelines, from the 2012 European Society of Cardiology, 2013 Asia Pacific Heart Rhythm Society, 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society and the 2014 National Institute for Health and Care Excellence (NICE).

However, the OACs reduce risk of stroke and other thromboembolic events at cost of increased risk of haemorrhage. In a recent systematic review of 16 randomized controlled trials (61 563 patient-years of follow-up) and 31 observational studies (484 241 patient-

years of the follow-up), the overall incidence for major bleeding in the anticoagulated population appeared to be as high as 2.1 (ranging 0.9-3.4) for controlled trials and 2.0 (ranging 0.2-7.6) for observational studies. [7] Therefore, stroke risk assessment should also be accompanied with an appraisal of patient's bleeding risk. [2]

Nonetheless, stroke and bleeding risk track each other, and many risk factors for stroke are also risk factors for bleeding.[6] Amongst the different bleeding risk scores ,only three ($HEMORR_2HAGES$, HAS-BLED and ATRIA) were derived and validated in patients with AF. [6] The HAS-BLED score is recommended in the ESC, Canadian Cardiovascular Society and NICE guidelines for assessing bleeding risk in AF. An assessment of the net clinical benefit shows a positive net clinical benefit for OAC for most patients with ≥1 stroke risk factors given that the gain from reducing strokes outweighs the small increase in serious bleeding risk. [8]

In the current issue of *Thrombosis Research*, Barnes et al.[9] evaluated the applicability of stroke risk scores ($CHADS_2$ and CHA_2DS_2-VASc) for prediction of major bleeding events and compared their performance with current bleeding stratification scores ($HEMORR_2HAGES$, HAS-BLED and ATRIA) in a contemporary real-world cohort of AF patients anticoagulated with warfarin in the US. [9] Unsurprisingly, the frequency of haemorrhagic complications increased with higher stroke risk and vice versa, given the co-distribution of stroke and bleeding risk factors [10]. Barnes et al. found all specific bleeding scores had a higher performance in the prediction of major bleeding events, when compared to stroke risk scores: for example, the c statistic difference was 0.10-0.16 and net reclassification improvement (NRI) was 0.54-0.58 over the $CHADS_2$ and 0.36-0.54 - over the CHA_2DS_2-VASc scores. An advantage of the study by Barnes et al. is the analysis of data from a real-world

cohort of AF patients recruited from several anticoagulation clinics, making the data generalizable and applicable to everyday clinical practice.

These results are consistent with previous similar studies, showing that specific bleeding risk scores perform best in predicting bleeding, compared to using $CHADS_2$ or CHA_2DS_2-VASc. [10-12] In the post-hoc analysis of the AMADEUS trial cohort, the HAS-BLED score but not the $CHADS_2$ and CHA_2DS_2-VASc scoring systems demonstrated significant discriminatory performance for any clinically relevant bleeding (major and non-major). [11] Broadly similar data were obtained in the study of Roldán et al, who followed-up 1370 'real world' (ie. non-trial) AF patients in an outpatient anticoagulation clinic for median of 996 days. [12]

Barnes et al. also suggest considering an integration of both stroke and bleeding risk assessment schemes into a single risk assessment score [9]. Perhaps this is unwise. The current experience of the development of combination (or composite) stroke and bleeding risk assessment scores testifies to their complexity and only marginal comparative performance against the currently recommended individual stroke and bleeding stratification schemes.[13,14]

In one study from the AMADEUS trial cohort, regression models for composite end-points 'stroke/thromboembolism or major bleeding' and 'stroke, systemic or venous embolism, myocardial infarction, cardiovascular death, or major bleeding' included following predictors: age, previous stroke / transient ischaemic attack, aspirin use, time in therapeutic range and left ventricular dysfunction (the latter had predictive value for second end-point only), but despite good predictive value for the composite endpoint, did not offer significant

advantage over separate stroke and/or bleeding risk scores.[13] In the Loire Valley Atrial Fibrillation Project, a composite risk model included risk factors from the HAS-BLED and CHA_2DS_2-VASc scores (history of heart failure, age >75, age >65, diabetes mellitus, stroke, vascular disease, liver and/or renal impairment, history of bleeding and labile international normalized ratio) and was tested for four end-points, but also failed to outperform separate stroke and bleeding risk assessment scores. [14]

Nonetheless, another important aspect of study of Barnes et al. is a validation of the bleeding risk assessment schemes in their studied cohort. [9] They highlighted a modest predictive ability of existing bleeding scores as evaluated with the c-statistic, which is a statistical index used to compare performance of different prognostic tools with range between 0.5 (model is not better than chance at making prediction) and 1.0 (perfect prediction with the model).

For risk scores to be useful for everyday clinical practice, one has to reduce complexity and increase simple practicality of the risk assessment tools (importantly, without loss of their discriminative ability). Also, equal weighing is assigned for majority of risk factors (i.e., 1 point for each) for simplicity - despite the fact that in the derivation studies, the association of various risk factors with predicted outcomes varied in wide range. Thus, a c-statistic of 1.0 cannot be reached, without exceedingly complex and impractical risk stratification schemes that include a long list of clinical factors added to biomarkers, imaging etc.[6]

Nevertheless, previous studies have shown that the HAS-BLED score outperformed older bleeding risk scores and the newer ATRIA bleeding score, and HAS-BLED was the only score

that was predictive of risk of intracranial haemorrhage.[15-17] When Barnes et al. calculated the net reclassification index (NRI), the HAS-BLED score showed a 31% and 26% improvement over the HEMORR$_2$HAGES and ATRIA scores. [9] Also, the HAS-BLED score has been validated in multiple populations, even in AF and non-AF patients undergoing bridging therapy, percutaneous coronary interventions, etc – as well as those taking VKAs and non-VKA anticoagulants. [18, 19] Unsurprisingly HAS-BLED score is relatively simpler than the HEMORR$_2$HAGES score and more predictive than the other bleeding risk scores, and has been recommended in guidelines and consensus documents.

In conclusion, the study by Barnes et al. confirms what should really be common sense – use specific risk scores for specific purposes, and not use bleeding risk scores to assess stroke risk (or vice versa). In particular, use the CHA$_2$DS$_2$-VASc for assessing stroke risk, and use the HAS-BLED for assessing bleeding risk in patients with AF. Guidelines are there for a reason, and we should follow them.

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