Stroke and bleeding risk stratification in atrial fibrillation: a critical appraisal

Deirdre A. Lane 1,2* and Gregory Y.H. Lip1,2

1Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, William Henry Duncan Building, Liverpool L7 8TX, UK
2Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

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Atrial fibrillation (AF) significantly increases the risk of stroke and, therefore, stroke prevention is an essential component of the management for patients with AF. This requires formal assessment of the individual risk of stroke to determine if the patient is eligible for oral anticoagulation (OAC), and if so, their risk of bleeding on OAC, before a treatment decision regarding stroke prevention is made. Risk of stroke is not homogenous; it depends on the presence or absence of risk factors. A plethora of stroke and bleeding risk factors has been identified, including common and less-well established clinical risk factors, plus imaging, urine, and blood biomarkers. Consequently, there are several stroke and bleeding risk stratification scores available and this article provides an overview of them, the risk factors included and how they are scored, and provides a critical appraisal of them. The review also discusses the debate regarding whether female sex is a risk factor or a risk modifier, and highlights the dynamic nature of both stroke and bleeding risk and the need to re-assess these risks periodically to ensure treatment is optimal to reduce the risk of adverse outcomes. This review also summarizes the recommended stroke and bleeding risk stratification scores from all current major international guidelines.

Introduction

Atrial fibrillation (AF) increases the risk of stroke five-fold independently of other risk factors and, therefore, the primary focus for the management of patients with AF is stroke prevention with oral anticoagulation. Major clinical guidelines advocate an integrated approach to the management of AF patients, with contemporary guidelines recommending the Atrial Fibrillation Better Care (ABC) pathway (Figure 1).

The ‘A’ criterion represents ‘Avoiding stroke with Anticoagulation’ and outlines three steps in the decision-making process. Firstly, to identify patients at low risk who do not require oral anticoagulation (OAC), with the remainder being offered appropriate OAC (Step 2), and the final step deciding on the choice of OAC.

Risk of stroke is heterogeneous, dependent on the presence of risk factors and risk modifiers. Therefore, the initial stage requires assessment of the individual patients’ risk of stroke to identify those who require stroke prevention therapy, followed by an assessment of their individual risk of major bleeding on OAC, and an assimilation of the synergistic effect of both stroke and bleeding risk factors to determine the most appropriate OAC and the correct dose. There are several stroke and bleeding risk stratification scores available and the aim of this article is to provide an overview and critical appraisal of these and to discuss the evolution of the concept of risk in this population.

Stroke risk assessment

There are many stroke risk factors and the more common and validated ones have been used to formulate stroke risk stratification schema. The first of the popular risk scores...
was the CHADS2,10 which was a simple clinical score based on five stroke risk factors from the AF Investigators and the Stroke Prevention in AF trial, derived and validated in a registry of hospitalized AF patients. Since then, several new stroke risk stratification tools have been proposed, Framingham,11 CHA2DS2-VASc,12 ATRIA,13 ABC,14 and GARFIELD-AF,15 with the majority emerging over the last 10 years (Tables 1 and 2). The number of risk factors included in these schemas varies considerably, from four in the ABC-Stroke score14 to eight in the GARFIELD-AF15 and ATRIA-Stroke13 scores, with all stroke risk scores including age and previous stroke/transient ischaemic attack (TIA) and/or thromboembolism. Not all risk factors for stroke confer equal risk; age and previous stroke are independently associated with a greater risk of stroke; the CHA2DS2-VASc score acknowledges this increased risk by awarding each of these risk factors two points. However, the combination of other risk factors differs between the risk scores with only the CHA2DS2-VASc, Framingham, and CHADS2 scores, including routinely available demographic and clinical variables, while the others13–15 also include urine (renal function13,15 proteinuria13) and blood14 biomarkers. Further, the definitions of mutual risk factors differ between risk scores (Table 1) and the complexity and ease of calculation also varies markedly (Table 2), with the latter limiting the clinical applicability of some scores.11,13–15 The evolution of the CHA2DS2-VASc score has been previously summarized.16

Figure 1 Atrial fibrillation better care pathway. ABC, atrial fibrillation better care; APT, antiplatelet therapy; BP, blood pressure; CHA2DS2-VASc, congestive heart failure, hypertension, age >75 years (2 points), diabetes, stroke/TIA/thromboembolism (2 points), vascular disease, age 65-74 years, sex category (female); DM, diabetes mellitus; HAS-BLED, (uncontrolled) hypertension, abnormal renal, or liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs/drink (alcohol); HF, heart failure; NOAC, non-vitamin K antagonist oral anticoagulant; NSAIDs, non-steroidal anti-inflammatory drugs; OAC, oral anticoagulation; OSA, obstructive sleep apnoea; TTR, time in the therapeutic range; VKA, vitamin K antagonist. 
Table 1  Risk factors incorporated into the risk scores for assessing stroke risk in patients with atrial fibrillation and risk factor definitions

| Risk factor and definition | Stroke risk stratification scores |
|---------------------------|----------------------------------|
|                           | CHA^2DS^2-VASc†                |
|                           | ATRIA-Stroke‡                   |
|                           | ABC-Stroke^1^4                 |
|                           | GARFIELD-AF^1^5                |
|                           | Framingham*^11                 |
|                           | CHADS^2^10                     |
| Age                       | Age^a ≥ 75                     |
|                           | Age^a 65-74                    |
| Race/Ethnicity            | Female                         |
| Race/Ethnicity            | Afro-Caribbean, mixed race     |
|                           | (other) vs. Caucasian, Hispanic,|
|                           | Latins, Asian)                 |
| Stroke                    | Previous stroke, TIA or        |
|                           | thromboembolism                |
| Hypertension              | Hypertension or on antihypertensive therapy |
| Congestive heart failure  | Clinical HF or LVEF < 40%      |
| Vascular disease          | Previous MI, PAD, or aortic plaque |
| Renal disease             | eGFR < 45 ml/min/1.73 m^2 or ESRD |
| Proteinuria               | CKD Stage III-V                |
| Previous bleed            | History of bleeding            |
| OAC use                   | High-sensitivity               |
|                           | Troponin I and T (hs-cTnI/hs-cTnT) |
|                           | NT-proBNP                      |
| World region              |                                  |
| Total number of risk factors | 7^a                   |
| Range of scores           | 0-9                             |
|                           | 0-12 for those without         |
|                           | previous stroke and            |
|                           | 7-15 for those with            |
|                           | previous stroke                |

Shaded square indicates the risk factor is included in the stroke risk stratification score

ABC, Age, biomarkers, clinical history; ATRIA, Anticoagulation and Risk Factors in Atrial fibrillation; BP, CKD, chronic kidney disease; CHADS^2^, congestive heart failure, hypertension, age ≥ 75 years, diabetes, stroke/TIA/thromboembolism [2 points]; CHA^2DS^2-VASc, congestive heart failure, hypertension, age ≥ 75 years [2 points], diabetes, stroke/TIA/thromboembolism [2 points], vascular disease, age 65-74 years, sex category (female); CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; cTnI-hs, high-sensitivity cardiac troponin I; cTnT-hs, high-sensitivity cardiac troponin T; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HF, heart failure; GARFIELD-AF, Global Anticoagulant Registry in the FIELD- Atrial Fibrillation; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NR, not reported; NT-proBNP, n-terminal pro B-type brain natriuretic peptide; OAC, oral anticoagulation; PAD, peripheral artery disease; SBP, systolic blood pressure; TIA, transient ischaemic attack

†see Table 4 for current definitions of each risk factor in the CHA^2DS^2-VASc score

*score for each variable in ABC score is based on a nonogram

*score for each variable in the Framingham score is based on 6-steps

^CHA^2DS^2-VASc stroke risk score awards age ≥ 75 (2 points) and age 65-74 (1 point)

‡ATRIA stroke risk score awards different points for age depending on whether the patient has experienced a previous stroke. With previous stroke: ≥ 85 (9), 75-84 (7), 65-74 (7), < 65 (8) years; without previous stroke: ≥ 85 (6), 75-84 (5), 65-74 (3), < 65 (0) years

^GARFIELD-AF scoring system for each risk factor not reported

^Framingham score gives predicted 5-year risk of stroke ranging from 5% with a score of 0-1 to 75% with a score on 31

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| Table 2 | Risk stratification scores for assessing stroke in patients with atrial fibrillation |
|---------|---------------------------------------------------------------------------------------------------------------------------------|
| **Risk score** | **Risk factors (score for each factor)** | **Risk categories** | **Stroke events in validation cohort (per 100 patient years)** |
| | | | | **Low** | **Moderate** | **High** | **Low** | **Intermediate** | **High** |
| **CHA2DS2-VASc** | CHF (1), hypertension (1), age ≥ 75 (2), diabetes (1), stroke/TIA (2), vascular disease (1), age 65-74 (1), female (1) | 0<sup>a</sup> | 1<sup>b</sup> | ≥ 2<sup>a</sup> | 0%<sup>a</sup> | 0.6%<sup>a</sup> | 3.0%<sup>a</sup> |
| **ATRIA** | Female (1); diabetes (1); CHF (1); hypertension (1); proteinuria (1); eGFR < 45 mL/min/1.73 m<sup>2</sup> or ESRD (1) | 0-5 | 6 | 7-15 | <1% | 1 to <2% | ≥2% |
| **ABC** | Age<sup>e</sup>, biomarkers<sup>e</sup> (troponin I, NT-proBNP), stroke/TIA<sup>e</sup> | <1% | 1-2% | >2% | 0.56 | 1.29 | 3.22 |
| **GARFIELD-AF** | World region, age, race, previous stroke, bleeding history, CHF, renal disease, OAC use | Very low to low risk: CHA2DS2-VASc score 0 or 1 in men and 1 or 2 in women | CHA2DS2-VASc ≥ 2 in men and ≥ 3 in women | CHA2DS2-VASc 0-2 (men) or 1-3 (women) 0.8 | CHA2DS2-VASc ≥ 3 (men) and ≥ 4 (women) 1.7 (stroke/SE) |
| **Framingham** | Age (0-6), female (6), SBP (0-4), diabetes (5), stroke/TIA (6) | Not categorized into low/moderate/high risk<sup>f</sup> | | Five-year actual risk of stroke was 8%, 9%, 13%, 20%, and 29%, respectively across quintiles | 1.2-2.8 | 3.6-6.4 | ≥8.0 |
| **CHADS2** | CHF (1), hypertension (1), age ≥ 75 (1), diabetes (1), stroke/TIA (2) | 0-1 | 2-3 | 4-6 | | | |

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<sup>a</sup>Risk categories and stroke event rate in the validation cohort are taken from the original CHA2DS2-VASc paper.12 Cut-off given below original categories are based on European Society of Cardiology 2020 guidelines reference.6

<sup>b</sup>ATRIA stroke risk score awards different points for age depending on whether the patient has experienced a previous stroke. With previous stroke: ≥85 (9), 75-84 (7), 65-74 (3), <65 (0) years; without previous stroke: ≥85 (6), 75-84 (5), 65-74 (3), <65 (0) years.

<sup>c</sup>Score for each variable in ABC score is based on a nonogram.14

<sup>d</sup>Score for each variable in the Framingham score is based on six steps.11

<sup>e</sup>GARFIELD-AF scoring system for each risk factor not reported.

<sup>f</sup>Framingham score gives predicted 5-year risk of stroke ranging from 5% with a score of 0-1 to 75% with a score on 31.
Age threshold

The age cut-off criteria among the stroke risk scores vary although most\textsuperscript{10,12–14} use \(\geq 65\) years to indicate greater risk. Two recent analyses, one in the Korean National Insurance Service database [\(n = 426650\) OAC-naïve AF patients with \(\leq 2\) non-sex-related CHA\(_2\)DS\(_2\)-VASc risk factors (CHA\(_2\)DS\(_2\)-VASc 0-2 in men and 1-3 in women)]\textsuperscript{17} and the other in the Taiwan National Insurance Research Database [non-anticoagulated AF patients: 9416 men (CHA\(_2\)DS\(_2\)-VASc score of 0) and 6390 women (CHA\(_2\)DS\(_2\)-VASc score of 1)],\textsuperscript{18} suggest that among Asian patients a lower age (<65 years) threshold should be considered to indicate elevated stroke risk. In the Korean cohort,\textsuperscript{17} although older age (65-74 or \(\geq 75\) years) was the most important risk factor for ischemic stroke, patients aged 55-59 years with no risk factors had a similar risk of ischemic stroke when compared with AF patients with one non-sex-related risk factor. In the Taiwanese cohort, the annual risk of stroke was 1.78\% among those aged 50-64 years which exceeds the ‘normal’ treatment threshold to prevent stroke of 1\%, and thus a lower age threshold may be appropriate in Asian patients with AF. It is important to investigate if the current convention of age \(\geq 65\) years remains the appropriate age cut-off to indicate greater stroke risk in all populations.

Sex—is it a risk modifier or a risk factor for stroke in AF patients?

There has also been some debate over whether female sex is a risk factor for stroke or a risk modified.\textsuperscript{19–24} An analysis using the Danish nationwide cohort examined the risk of thromboembolism among men and women with CHA\(_2\)DS\(_2\)-VA score of 0 and demonstrated that female sex was a risk modifier for stroke in patients with AF rather than a risk factor\textsuperscript{20} per se and is dependent on age.\textsuperscript{19,21,24} In the Swedish national dataset, women with no other risk factors (CHA\(_2\)DS\(_2\)-VASc score of 1) had a low stroke risk, similar to men with a CHA\(_2\)DS\(_2\)-VASc score of 0.\textsuperscript{25} Although utilizing the simplified ‘CHA\(_2\)DS\(_2\)-VA score’ could potentially help to aid the initial decision about OAC in AF patients, ignoring the sex component completely would undervalue the risk of stroke among women with AF. Women have a higher risk of stroke per se than their male peers, therefore to disregard this, places female patients at risk and could lead to deleterious outcomes; women stand to gain the greatest benefit in terms of the largest absolute reduction in stroke. Also, women with AF tend to under-treated with oral anticoagulation; hence ignoring the female sex criterion with an (as yet non-validated) CHA\(_2\)DS\(_2\)-VA score could potentially lead to under-recognition of female sex as a factor that may affect stroke risk and further increase the sex differences in OAC prescribing.\textsuperscript{26} Women with AF with \(>1\)
non-sex stroke risk factor, have a consistently significantly higher stroke risk than men.20,23

Table 3 summarizes the multitude of stroke risk factors which have been shown to increase the risk of stroke in AF patients, including other clinical risk factors not incorporated into any of the published tools, such as obstructive sleep apnoea, amyloidosis, and smoking. In addition, cerebral and cardiac imaging (left atrial function and volume, left atrial fibrosis, left atrial appendage morphology,22,27 and numerous urine and blood biomarkers30–33 [von Willebrand factor, growth differentiation factor (GDF)-15, troponin, etc.] have been associated with increased stroke risk. Indeed, the biomarker, vWF,34 and renal dysfunction35 have been added to the CHA2DS2-VASc score, with mixed results. von Willebrand factor added to what was then called the ‘Birmingham risk score’34 modestly improved the c-statistic for predicting ischaemic stroke [0.640, 95% confidence interval (CI) 0.563–0.713 vs. 0.679, 95% CI 0.591–0.756] and vascular events [0.670, 95% CI 0.603–0.726 vs. 0.716, 95% CI 0.643–0.779] in the Stroke Prevention in AF (SPAF) III cohort. However, adding chronic kidney disease (CKD) to the CHA2DS2-VASc score in a Spanish cohort of 978 AF patients on OAC did not improve the prediction of stroke or systemic embolism, thromboembolic events or all-cause mortality.35

The most recent tool proposed is the GARFIELD-AF,15 a web-based risk score that allows simultaneous calculation of stroke/systemic embolism (SE) risk, major bleeding, and all-cause mortality. This score was derived from prospectively collected data from the GARFIELD-AF registry (March 2010 and July 2015; 35 countries in adults with recently diagnosed AF) and includes different risk factors for the calculation of stroke (Table 2) and bleeding (age, vascular disease, and kidney disease), although the exact scoring of each risk factor is not published. The GARFIELD-AF tool demonstrated better predictive value (evidenced by c-statistics) when compared with the CHA2DS2-VASc score for predicting stroke/systemic embolism [0.69 (95% CI 0.67–0.71) vs. 0.64 (0.61–0.66), respectively] and haemorrhagic stroke/major bleeding using the HAS-BLED score [0.66 (0.62–0.69 vs. 0.64 (0.61–0.68), respectively] among those on OAC and also among lower risk patients (CHA2DS2-VASc score 0 or 1 in men and 1 or 2 in women) [0.65, 0.56–0.73 vs. 0.59, 0.50–0.67; for stroke/SE and 0.60, 0.47–0.73 vs. 0.55, 0.53–0.56; for haemorrhagic stroke/major bleeding].15 The GARFIELD-AF tool is advantageous in that it offers simultaneous calculation of stroke/SE, major bleeding and all-cause mortality risk, but it requires a computer or smartphone to enable calculation thus limiting its clinical utility, and it offers only modest but statistically significant improvement in the c-statistics compared to the simple (able to be calculated at the bedside from memory) scores, such as the CHA2DS2-VASc and HAS-BLED scores. Indeed, a recent European Heart Rhythm Association and Young Electrophysiologist survey on the utility of the CHA2DS2-VASc score demonstrated that most physicians calculated the CHA2DS2-VASc score from memory.36

Combining the CHA2DS2-VASc score with the Intermountain Mortality Risk Score (IMRS),37 which consists of age, sex, complete blood count (CBC), and basic metabolic profile (BMP) (with sex-specific weighting for CBC
and BMP) improved the prediction of stroke (and mortality), in a cohort of 10 077 AF patients undergoing AF cardiac catheterization, a four-fold separation between low and high risk in those with a CHA2DS2-VASc score of 2.

The purpose of a risk assessment tool is to be reductionist, to simplify the information required to identify an ‘at high-risk group’ and to aid treatment decision making. They are necessarily an over-simplification. All clinical risk scores have at best, modest predictive power to identify those at risk of the outcome of interest; the CHA2DS2-VASc score and other stroke and bleeding risk scores are no exceptions. The addition of more clinical factors may lead to slight improvements in the overall predictive accuracy of the score, evidenced by an improvement in the c-statistic, but this statistically significant increase may not translate into a meaningful clinical difference, especially in real-world cohorts. Supplementing extra biomarkers into risk scores slightly increases the prognostic ability of risk scores over and above clinical risk factors alone but in the majority of patients is unlikely to change the fundamental decision regarding whether or not to prescribe anticoagulation, yet adds to the complexity and reduces clinical utility. Also many biomarkers are non-specific, and abnormal levels are likely to reflect a ‘sicker’ patient or concomitant comorbidities.

A meta-analysis of studies comparing just the CHA2DS2-VASc and ATRIA stroke scores demonstrated that the ATRIA-stroke score performed better for stroke risk prediction but that the CHA2DS2-VASc was superior to ATRIA for identifying truly low-risk patients. A Patient Centred Outcomes Research Institute (PCORI) systematic review evaluated the prognostic precision of CHA2DS2-VASc, CHADS2 Framingham, and ABC stroke risk stratification tools, identifying 61 studies, and assessed the strength of evidence. This independent review demonstrated that CHA2DS2-VASc, CHADS2, and the ABC-stroke scores had the best predictive ability (based on the c-statistic) for stroke. Consequently, the most commonly utilized stroke risk score is the CHA2DS2-VASc score and is recommended by all the major international clinical guidelines for assessing stroke risk in AF patients (Tables 4 and 5).

**Benefits/limitations of adding biomarkers to risk stratification scores**

As alluded to previously, incorporating imaging, urine, and blood biomarkers into risk stratification scores can improve their predictive ability, but the incremental benefit over a clinical risk factor-based score is often negligible. Biomarkers increases healthcare costs, can delay treatment decisions, and may lead to inequitable care due to their availability. Some biomarkers, such as cardiac troponins (T and I), NT-proBNP, D-dimer, and eGFR, are readily available in clinical practice, whereas many of the others are not (IL-6, GDF-15, and vWF), and there may be intra- and inter-assay variation. Biomarkers are non-specific and tend to predict increased risk per se (hospitalization, death, stroke, etc.) and therefore they may simply be markers of ‘sicker’ patients. We do not currently have contemporary data on the risk of stroke associated with biomarkers among non-anticoagulated patients with AF nor unequivocal evidence that OAC is advantageous/favourable in patients designated as ‘low-risk’ based on biomarker(s) risk factors. The patient pathway would include newly diagnosed and often non-anticoagulated patients who may or may not be on aspirin; a biomarker-based score would need to show data in these groups to aid decision-making in all steps of the AF patient journey. In addition, the current complex algorithms/nonograms required to compute some risk scores, particularly those incorporating biomarkers, severely limits their use in routine clinical practice. Greater widespread implementation of electronic health records may permit automated calculation of stroke and bleeding risk in AF patients using any pre-programmed risk scores, thereby negating their complexity and permitting greater clinical application. However, eliminating the need for the physician/healthcare professional to complete the risk assessment themselves by providing an automated score, removes the opportunity to consider the individual risk factors, many of which may need to be addressed and managed (blood pressure, heart failure, diabetes, etc.) in order to reduce risk.

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**Table 5 Summary of stroke and bleeding risk scores recommended for use in current major international guidelines for the management of AF**

| Clinical guideline for AF management | Recommended stroke risk score | Recommended bleeding risk score |
|-------------------------------------|-------------------------------|--------------------------------|
| 2020 European Society of Cardiology  | CHA2DS2-VASc                  | HAS-BLED                       |
| 2019 AHA/ACC/HRS                    | CHA2DS2-VASc                  | No specific risk score specified |
| 2018 American College of Chest Physicians | CHA2DS2-VASc                  | HAS-BLED                       |
| 2018 Cardiac Society of Australia and New Zealand | CHA2DS2-VASc                  | No specific risk score specified |
| 2017 Asia Pacific Heart Rhythm Society | CHA2DS2-VASc                  | HAS-BLED                       |
| 2015 Canadian Cardiovascular Society | CHA2DS2-VA                    | No specific risk score specified |
| 2014 National Institute of Clinical Excellence | CHA2DS2-VASc                  | HAS-BLED                       |

ACC, American College of Cardiology; AHA, American Heart Association; CHA2DS2-VASc, congestive heart failure, hypertension, age ≥75 years (2 points), diabetes, stroke/TIA/thromboembolism (2 points), vascular disease, age 65–74 years, sex category (female); HAS-BLED, (uncontrolled) hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs/drink (alcohol); HRS, Heart Rhythm Society.
## Table 6  Risk factors incorporated into the risk stratification scores for assessing bleeding risk in patients with atrial fibrillation

| Risk factor and definition | ABC-Bleeding\(^{43}\) | ATRIA\(^{47}\) | HAS-BLED\(^{46}\) | HEMORR\(^{2}\)HAGES\(^{49}\) | ORBIT\(^{48}\) | Shireman\(^{44}\) |
|---------------------------|------------------------|----------------|-------------------|------------------------|----------------|----------------|
| **Age**                   | Age ≥50                | Age ≥75        | Age ≥65           | Age ≥75                | Age ≥70        | Age ≥70        |
| **Sex**                   |                        |                |                   |                        |                | Female         |
| **Biomarkers**            | GDF-15                 |                |                   |                        |                |                |
|                           | cystatin C/CKD-EPI      |                |                   |                        |                |                |
|                           | cTnT-hs                 |                |                   |                        |                |                |
| **Previous bleed**        | Any                    |                | Previous major haemorrhage | Any previous GI, intracranial or haemorrhagic stroke | Remote and recent Hct <30% during hospitalisation |
| **Anaemia**               | Hb <13g/dl in men and <12g/dl in women |                   |                   | Reduced Hb (<13g/dl in men and <12g/dl in women), reduced Hct (<40% in men and 36% in women) or history of anaemia |                |
|                           | Dialysis, transplant, serum creatinine >200 μmol/L |                   |                   | eGFR <60mg/dL/1.73m² |                |
| **Renal disease**         | Severe (eGFR <30ml/min or dialysis dependent) |                   |                   |                        |                |                |
| **Hepatic disease**       | Cirrhosis, bilirubin > x2 ULN, AST/ALT/ALP > x3 ULN |                   |                   |                        |                |                |
| **Hypertension**          | Uncontrolled hypertension |                   |                   |                        |                |                |
| **Diabetes mellitus**     |                        |                |                   |                        |                |                |
| **Malignancy**            |                        |                |                   |                        |                |                |
| **Stroke**                | Previous ischaemic or haemorrhagic\(^{a}\) stroke |                   |                   |                        |                |                |
| **Concomitant antiplatelet therapy** | Concomitant use of anti-platelet or NSAIDs |                   |                   |                        |                |                |
| **Labile INR**            | TTR <60% among patients on VKA\(^{b}\) |                   |                   |                        |                |                |
| **Alcohol excess**        | >8 units/week           | Alcohol abuse   |                   |                        | Alcohol or drug abuse |
| **Excessive falls risk**  |                        |                |                   |                        |                |                |
| **Genetic factors**       |                        |                |                   |                        |                |                |
| **Reduced platelet count**| Severe thrombocytopenia\(^{a}\) | Reduced platelet count or function |                   |                        |                |                |

(continued)
There may be a role for biomarkers in differentiating low risk and those with 1 (non-sex) risk factors, however, the basic premise of stroke risk stratification is to determine if someone requires OAC or not; this can be simply, quickly, and reliably done without adding biomarkers. Therefore, biomarkers currently have limited clinical application for stroke risk assessment but could be utilized to refine or personalize risk assessment in selected patients.

### Limitations of clinical risk scores

One of the major problems with assessing risk related to stroke prevention in AF patients is that there is considerable overlap between risk factors for stroke and risk factors for bleeding, namely age, previous stroke, uncontrolled hypertension, renal dysfunction, etc. The cohorts from which the stroke and bleeding risk scores were derived varied considerably, prospective registries, or cohorts, non-vitamin K antagonist oral anticoagulant (NOAC) clinical trials, and retrospective cohorts, with not all risk factors recorded, missing data, and in some studies, stroke and bleeding outcome events were not adjudicated, and this may have led to under- or over-reporting. Subsequent validations of stroke and bleeding risk scores have also been conducted in a variety of cohorts, mainly retrospective cohort studies or registries in a range of settings (in-hospital vs. community), with significant demographic and clinical heterogeneity in terms of age, ethnicity, geographical region, clinical risk factors, proportion receiving OAC, outcome(s) verification, etc. and methodological variation with the inclusion or exclusion of those subsequently receiving OAC affecting event rates.

### Bleeding risk assessment

A multitude of risk factors that increase the risk of bleeding in patients with AF have been identified (Table 6), some are modifiable (blood pressure, adherence to OAC, etc.) or potentially modifiable (falls risk, anaemia, etc.), while others, such as age and clinical history, are fixed. Different combinations of these risk factors have been incorporated into risk scores and there are currently six-validated risk scores available for the assessment of bleeding in patients with AF (Tables 6 and 7): HAS-BLED, ATRIA, ABC, ORBIT, HEMORR2HAGES, and Shireman. As shown in Table 6, the number of risk factors within each score is variable, ranging from 12 in HEMORR2HAGES to 3 in the ABC-bleeding score, with inconsistency in the definitions of risk factors. All the scores include age and previous bleeding history, some also assess separately, such as anaemia and reduced platelet count, while HAS-BLED incorporates bleeding

| Risk factor and definition | ABC-Blending | ATRIA | HAS-BLED | HEMORR2HAGES | ORBIT |
|----------------------------|--------------|-------|----------|--------------|-------|
| Bleeding risk scores      |              |       |          |              |       |
| Shireman                  | 8            | 5     | 9        | 12           | 5     |
| ORBIT                     | 0.7          | 0.9   | 0.1      | 0.1          | 0.7   |
| Number of risk factors    | 3            | 5     | 9        | 12           | 5     |
| Range of scores           | 0-10         | 0-12  | 0-4.17   | 0-9          | 0.15  |

Shaded square indicates the risk factor is included in the bleeding risk stratification score. Definition is given where available.

ABC: Age; biomarkers; clinical history; APT: antiplatelet therapy; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ATRIA: Anticoagulation and Risk Factors in Atrial fibrillation; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; cTnT-hs: high-sensitivity cardiac troponin T; CYP 2C9: cytochrome P450 2C9; eGFR: estimated glomerular filtration rate; GDF-15: growth differentiation factor-15; GI: gastrointestinal; HAS-BLED: uncontrolled hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalised ratio, elderly, drugs/drink (alcohol); HEMORR2HAGES: Hepatic/renal disease, ethanol abuse, malignancy, age, reduced platelet function, re-bleeding risk [2 points], (uncontrolled) hypertension, anaemia, genetic factors, falls risk, stroke; Hb: haemoglobin; Hct: haematocrit; INR: international normalised ratio; NSAIDs: non-steroidal anti-inflammatory drugs; ORBIT-AF: Outcomes Registry for Better Informed Treatment of Atrial Fibrillation; Plt: platelet count or function; SBP: systolic blood pressure; ULN: upper limit of normal; VKA: vitamin K antagonist.

†Score for each variable in ABC score is based on a nonogram (see reference 43).
‡Risk factors determined from hospital records; no further detail on the specific definitions given in the derivation paper.49
*In the HAS-BLED score, the ‘B’ criterion denotes previous major bleed or bleeding predisposition (anaemia and/or severe thrombocytopenia).

A haemorrhagic stroke would also score 1 point for the ‘B’ criterion

Only included in the HAS-BLED calculation if the patient is receiving a VKA

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predisposition (i.e. anaemia or severe thrombocytopenia) together with previous major bleeding. Renal dysfunction, hypertension, concomitant APT, and alcohol excess were included in at least half of the scores. Risk factors, such as hepatic disease, female sex, diabetes, cancer, labile International Normalised Ratio (INR), excessive falls risk, biomarkers, and genetic factors feature infrequently in the bleeding risk scores.

As seen with stroke risk scores, the bleeding risk scores also vary considerably in their complexity, ease of computation, and routine availability of each risk factor and the same associated limitations apply to bleeding risk scores as discussed earlier in relation to stroke risk scores.

### Table 7: Risk stratification scores for assessing bleeding risk in patients with atrial fibrillation and bleeding events in the validation cohorts

| Risk score | Risk factors (score for each factor) | Risk categories | Bleeding events in validation cohort (per 100 patient years) |
|------------|-------------------------------------|----------------|----------------------------------------------------------|
| ABC †,43   | Age(†); biomarkers (†) (GDF-15 or cystatin C/CKD-EPI, cTnT-hs, & Hb); Previous bleed (†) | <1% 1-2% >3% | 0.62 1.67 4.87 |
| ATRIA 47   | Anaemia (3); severe renal disease (3); Age ≥75 (2); prior bleed (1); hypertension (1) | 0–3 4 5–10| 0.83 2.41 5.32 |
| HAS-BLED 46| SBP (1); severe renal/hepatic disease (1 each); stroke (1); bleeding history or predisposition (1); labile INR (1); Age >65 (1); APT/NSAIDs (1); alcohol excess (1) | 0–1 2 ≥3| 1.02–1.13 1.88 ≥3.74 |
| HEMORR2HAGES 49 | Hepatic/renal disease (1); ethanol abuse (1); malignancy (1); age >75 (1); Plt (1); re-bleeding risk (2); BP (1); anaemia (1); genetic factors (1); falls risk (1); stroke (1) | 0–1 2 3 | 1.9–2.5 5.3 8.4 10.4–12.3 |
| ORBIT 48   | Age ≥75 (1); Hb/Hct/anaemia (2); Bleeding history (2); renal function (1); APT (1) | 0–2 3 ≥4 | 2.4 4.7 8.1 |
| Shireman 44 | Age >70 (0.49); female sex (0.31); previous bleed (0.58); recent bleed (0.62); alcohol/drug abuse (0.71); diabetes mellitus (0.27); anaemia (0.86); APT (0.32) | ≤1.07 >1.07/2.19 ≥2.19 | 0.9% a 2.0% a 5.4% a |

* Bleeding event in original derivation cohort; † at 3 months; † alternative; † elevated/increased; † reduced/decreased; † score for each variable in ABC score is based on a nonogram (see Ref.4).

Taken from Refs.8,41

ABC, Age, biomarkers, clinical history; APT, antiplatelet therapy; ATRIA, Anticoagulation and Risk Factors in Atrial fibrillation; BP, blood pressure; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; cTnT-hs, high-sensitivity cardiac troponin T; GDF-15 = growth differentiation factor-15; HAS-BLED, (uncontrolled) hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs/drink (alcohol); HEMORR2HAGES, Hepatic/renal disease, ethanol abuse, malignancy, age, reduced platelet function, re-bleeding risk [2 points], (uncontrolled) hypertension, anaemia, genetic factors, falls risk, stroke; Hb, haemoglobin; Hct, haematocrit; HAS-BLED, (uncontrolled) hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs/drink (alcohol); HEMORR2HAGES, Hepatic/renal disease, ethanol abuse, malignancy, age, reduced platelet function, re-bleeding risk [2 points], (uncontrolled) hypertension, anaemia, genetic factors, falls risk, stroke; INR, International normalized ratio; NSAIDs, non-steroidal anti-inflammatory drugs; ORBIT-AF, Outcomes Registry for Better Informed Treatment of Atrial Fibrillation; Plt, platelet count or function; SBP, systolic blood pressure.

As seen with stroke risk scores, the bleeding risk scores also vary considerably in their complexity, ease of computation, and routine availability of each risk factor and the same associated limitations apply to bleeding risk scores as discussed earlier in relation to stroke risk scores.

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studies). HAS-BLED was more sensitive in predicting major bleeding than ATRIA [0.53 (0.52–0.54) vs. 0.27 (0.26–0.27), respectively] or HEMORR2HAGES [0.41 (0.35–0.48) vs. 0.23 (0.17–0.29), respectively]. Another systematic review and meta-analysis compared the predictive ability of HAS-BLED to assess risk of major bleeding on OAC in patients with AF to HEMORR2HAGES, ATRIA (with 11 studies comparing the 3 bleeding risk scores), CHADS2, and CHA2DS2-VASc. All three bleeding risk scores had similar predictive ability [pooled c-statistics (95% CI) for HAS-BLED 0.65 (0.61–0.69), HEMORR2HAGES 0.63 (0.61–0.66) and ATRIA 0.63 (0.56–0.72)] in predicting major bleeding. Based on net reclassification improvement and integrated discrimination improvement analyses, the HAS-BLED score was superior in predicting major bleeding risk compared to HEMORR2HAGES and ATRIA. More recently a PCORI systematic review identified 38 studies relating to bleeding risk in AF which compared HEMORR2HAGES, HAS-BLED, ATRIA, ABC-Bleeding, and concluded that the HAS-BLED score was the best risk score for predicting major bleeding but with a modest strength of evidence.

The purpose of the assessing bleeding risk on OAC is to identify patients at high risk of bleeding, who may require more intensive follow-up and those with modifiable bleeding risk factors (Figure 1 and Table 8) which can be addressed to remove or reduce the risk to the patient (controlling blood pressure, cessation of non-essential APT/NSAIDs, improving INR control if patient is receiving a vitamin K antagonist, and reduction/cessation of alcohol intake; Figure 1). Assessing bleeding risk on OAC treatment permits frank discussion with the patient about their individual treatment benefit/risk, allows the patient to make a more informed decision about treatment, and discussion of the patient’s role in reducing their risk of harm and highlighting signs and symptoms of bleeding and appropriate management. An analysis has shown that utilizing a validated bleeding risk score to assess bleeding risk in AF patients is preferable to reliance on assessment using modifiable bleeding risk factors alone. In a prospective cluster-randomized trial, appropriate use of the HAS-BLED score as part of structured care, based on the ABC pathway, to address and mitigate modifiable bleeding risks, and scheduling follow-ups, was associated with lower bleeding rates and an increase in OAC use when compared with “usual care” managed patients.

### Dynamic nature of risk

Risk of stroke and bleeding are on a continuum and change temporally, with age being the biggest driver of risk, together with the accumulation of new risk factors over the life course, and treatment, affecting overall risk. However, often risk of stroke and bleeding is undertaken when the patient is first diagnosed and/or anticoagulation is initiated, whereas the dynamic nature of risk necessitates periodic re-assessment of both stroke and bleeding risk factors to ensure treatment is appropriate. This is important for all patients with AF, particularly for those initially considered ‘low-risk’ who may not be receiving OAC, but who will require it once they reach the requisite age threshold, or as
they develop new risk factors. Re-assessment of stroke and bleeding risk factors is also important to ensure that treatment is appropriate, particularly factors that might affect OAC safety (age, renal function, cognitive impairment, uncontrolled hypertension, medication adherence/poor time in the therapeutic range, drug interactions, concomitant antiplatelet, etc.).

Recently several studies have examined the dynamic nature of stroke and bleeding risk factors in AF patients, although to date most were conducted in Asian populations (Taiwan and South Korea). Two studies have examined the dynamic change in CHA2DS2-VASc score over time. Chao et al. utilized the Taiwanese National Health Insurance Research Database cohort of 31,039 AF patients whose only risk CHA2DS2-VASc stroke risk factors were age and/or sex, who were not receiving antithrombotic therapy at baseline. During follow-up, 64.4% patients developed ≥1 new comorbidities; the mean change in CHA2DS2-VASc score was 1.02 (1.29–2.31). Those who suffered an ischaemic stroke were significantly more likely to have a change in their CHA2DS2-VASc score of ≥1 compared to those without ischaemic stroke (89.4% vs. 54.6%, respectively). Change in the CHA2DS2-VASc score predicted incident ischaemic stroke better than baseline or follow-up CHA2DS2-VASc score. The analysis of the Korean National Health Insurance Service database (n = 167,262 OAC-naïve AF patients) followed up over 10 years revealed that 46.6% and 72.0% of ‘low-risk’ and ‘moderate-risk’, respectively, were re-classified to a high stroke-risk group. The change in CHA2DS2-VASc score and follow-up CHA2DS2-VASc score were better predictors of incident ischaemic stroke than baseline CHA2DS2-VASc score. Similar observations were evident from a European cohort.

The dynamic change in HAS-BLED score was also examined in a subgroup of the Taiwanese national cohort, among 19,566 AF patients receiving warfarin who had a baseline HAS-BLED score ≤2. HAS-BLED score remained unchanged in 38.2% during a follow-up of 93,783 person-years. Among those experiencing a major bleed, significantly more had a change in their HAS-BLED score of 1 or more compared to those who did not have a major bleed (76.6% vs. 59.0%, respectively). Changes in HAS-BLED score or follow-up HAS-BLED score was a better predictor of major bleeding than baseline HAS-BLED score.

These studies support the need to re-assess stroke and bleeding risk to ensure OAC treatment is appropriate and cardiovascular and other comorbidities are correctly managed to reduce the risk of ischaemic stroke and major bleeding and other adverse outcomes (death and hospitalization).

Conclusions

There are several validated stroke and bleeding risk stratification scores available; major international guidelines recommend the use of the CHA2DS2-VASc score to assess stroke risk and formal assessment of bleeding risk, with most favouring the HAS-BLED score. Biomarkers (cardiac and cerebral imaging, urine, and blood) can improve the predictive ability of risk scores but lack of routine availability to measure these in clinical practice, limited evidence on their sensitivity and specificity for stroke and bleeding in AF patients, and the added difficulty in calculating more complex risk scores based on nomograms/formulas, limits their clinical utility. It is important to remember that risk of stroke and bleeding changes over time and with acquiring more comorbidities, therefore regular reassessment of risk is essential to ensure appropriate AF management and to reduce the risk of adverse outcomes.

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