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

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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[1] and, therefore, the primary focus for the management of patients with AF is stroke prevention with oral anticoagulation.[2–8] Major clinical guidelines advocate an integrated approach to the management of AF patients, with contemporary guidelines,[6,8] recommending the Atrial Fibrillation Better Care (ABC) pathway[9] (*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.[9]

Risk of stroke is heterogeneous, dependent on the presence of risk factors and risk modifiers.[6,8] 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

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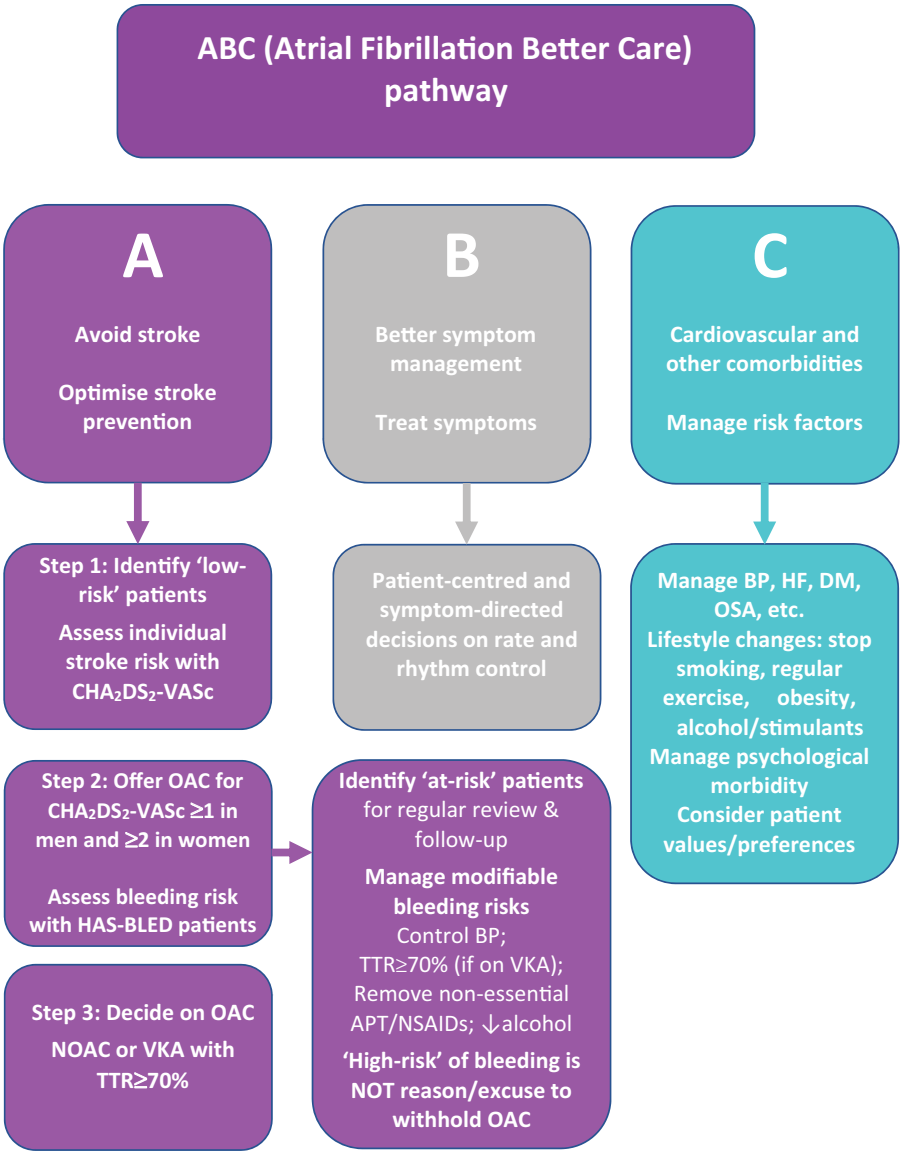

Figure 1 Atrial fibrillation better care pathway. ABC, atrial fibrillation better care; APT, antiplatelet therapy; BP, blood pressure; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years (2 points), diabetes, stroke/TIA/thromboembolism (2 points), vascular disease, age 65–74 years, sex category (female); 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. ↓, reduced/decreased. Adapted from Ref.[8]

was the $CHADS_2$,[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] CHA_2DS_2-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 score[14] to eight in the GARFIELD-AF[15] and ATRIA-Stroke[13] 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 CHA_2DS_2-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 CHA_2DS_2-VASc, Framingham, and $CHADS_2$ scores, including routinely available demographic and clinical variables, while the others[13-15] also include urine (renal function[13,15] proteinuria[13]) and blood[14] 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 CHA_2DS_2-VASc score has been previously summarized.[16]

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†[12]	ATRIA-Stroke[13]	ABC-Stroke‡[14]	GARFIELD-AF[15]	Framingham*[11]	$CHADS_2$[10]
Age	Age[a] ≥75 Age[a] 65-74	Age[b]	Age	Age at AF diagnosis	Age≥55	Age ≥75
Sex	Female	Female			Female	
Race/Ethnicity				Afro-Caribbean, mixed race (other) vs. Caucasian, Hispanic/Latino, Asian)		
Stroke	Previous stroke, TIA or thromboembolism		Stroke/TIA	Previous stroke	Stroke/TIA	Stroke or TIA
Hypertension	Hypertension or on antihypertensive therapy				SBP	
Diabetes mellitus						
Congestive heart failure	Clinical HF or LVEF<40%			History of HF and/or LVEF<40%		
Vascular disease	Previous MI, PAD, or aortic plaque					
Renal disease		eGFR<45ml/min/1.73m^2 or ESRD		CKD Stage III-V		
Proteinuria						
Previous bleed				History of bleeding		
OAC use				At enrolment, patient started on or already on OAC		
Biomarkers			High-sensitivity Troponin I and T (hs-cTnI/hs-cTnT) NT-proBNP			
World region						
Total number of risk factors	7[a]	8*	4[a]	8	5	5
Range of scores	0-9	0-12 for those without previous stroke and 7-15 for those with previous stroke	NR[a]	NR[c]	0-31[d]	6

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[14]

*score for each variable in the Framingham score is based on 6-steps[11]

[a]CHA_2DS_2-VASc stroke risk score awards age ≥75 (2 points) and age 65-74 (1 point)

[b]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

[c]GARFIELD-AF scoring system for each risk factor not reported

[d]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

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
CHA_2DS_2-VASc[a,46]	CHF (1), hypertension (1), age ≥ 75 (2), diabetes (1), stroke/TIA (2), vascular disease (1), age 65-74 (1), female (1)	0[a] 0 in men; 1 in women[6]	1[a] ≥1 in men ≥2 in women[6]	≥2[a]	0%[a]	0.6%[a]	3.0%[a]
ATRIA[b,13]	Female (1); diabetes (1), CHF (1), hypertension (1); proteinuria (1); eGFR <45 mL/min/1.73 m^2 or ESRD (1) Age in those with previous stroke: ≥85 (9), 75-84 (7), 65-74 (7), <65 (8) years Age in patients without previous stroke: ≥85 (6), 75-84 (5), 65-74 (3), <65 (0) years Scores range 0-12 for those without previous stroke and 7-15 for those with previous stroke	0-5	6	7-15	<1%	1 to <2%	≥2%
ABC[d,14]	Age[e], biomarkers[e] (troponin I, NT-proBNP), stroke/TIA[e]	<1%	1-2%	>2%	0.56	1.29	3.22
GARFIELD-AF[e,15]	World region, age, race, previous stroke, bleeding history, CHF, renal disease, OAC use	Very low to low risk: CHA_2DS_2-VASc score 0 or 1 in men and 1 or 2 in women		CHA_2DS_2-VASc ≥2 in men and ≥3 in women	CHA_2DS_2-VASc 0-2 (men) or 1-3 (women) 0.8 CHA_2DS_2-VASc ≥3 (men) and ≥4 (women) 1.7 (stroke/SE)		
Framingham[f,11]	Age (0-6); female (6); SBP (0-4), diabetes (5); stroke/TIA (6)	Not categorized into low/moderate/high risk[f]			Five-year actual risk of stroke was 8%, 9%, 13%, 20%, and 29%, respectively across quintiles		
$CHADS_2$ [10]	CHF (1), hypertension (1), age ≥75 (1), diabetes (1), stroke/TIA (2)	0-1	2-3	4-6	1.2-2.8	3.6-6.4	≥8.0

ABC, age, biomarkers, clinical history; ATRIA, anticoagulation and risk factors in atrial fibrillation; $CHADS_2$, 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); CHF, congestive heart failure; CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; NT-proBNP, n-terminal pro-B-type brain natriuretic peptide; OAC, oral anticoagulation; ORBIT-AF, Outcomes Registry for Better Informed Treatment of Atrial Fibrillation; TIA, transient ischaemic attack.

[a]Risk categories and stroke event rate in the validation cohort are taken from the original CHA_2DS_2-VASc paper.[12] Cut-off given below original categories are based on European Society of Cardiology 2020 guidelines reference.[6]

[b]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.

[c]Score for each variable in ABC score is based on a nonogram.[14]

[d]Score for each variable in the Framingham score is based on six steps.[11]

[e]GARFIELD-AF scoring system for each risk factor not reported.

[f]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.

Table 3 Stroke risk factors in patients with atrial fibrillation

Most common clinical risk factors[59]	Other clinical risk factors[60]
Stroke/TIA/thromboembolism	Impaired renal function/CKD
Hypertension	Obstructive sleep apnoea
Increasing age	Hypertrophic cardiomyopathy
Structural heart disease	Smoking
Diabetes mellitus	Malignancy
Vascular disease	Metabolic syndrome (ref 333)
Congestive heart failure/LV dysfunction	Hyperlipidaemia
Sex category (female)	Amyloidosis in degenerative cerebral and heart diseases

Imaging biomarkers[27-29]	Blood/urine biomarkers[30-33]
Echocardiography	Cardiac troponin T and I
LA dilatation	Natriuretic peptides
Spontaneous contrast or thrombus in LA	Cystatin C
Low LAA velocities	Proteinuria
Complex aortic plaque	CrCl/ eGFR
	CRP
Cerebral imaging	IL-6
Small vessel disease	GDF-15
	von Willebrand factor
	D-dimer

Adapted from Ref.[6]
CKD, chronic kidney disease; CrCl, creatinine clearance; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; GDF-15, growth differentiation factor-15; IL-6, interlukin-6; LA, left atrial; LAA, left atrial appendage; LV, left ventricular; TIA, transient ischaemic attack.

Age threshold

The age cut-off criteria among the stroke risk scores vary although most[10,12-14] use $\geq$65 years to indicate greater risk. Two recent analyses, one in the Korean National Insurance Service database [$n = 426\,650$ OAC-naïve AF patients with $\leq$2 non-sex-related CHA_2DS_2-VASc risk factors (CHA_2DS_2-VASc 0-2 in men and 1-3 in women)][17] and the other in the Taiwan National Insurance Research Database [non-anticoagulated AF patients: 9416 men (CHA_2DS_2-VASc score of 0) and 6390 women (CHA_2DS_2-VASc score of 1)],[18] suggest that among Asian patients a lower age (<65 years) threshold should be considered to indicate elevated stroke risk. In the Korean cohort,[17] although older age (65-74 or $\geq$75 years) was the most important risk factor for ischaemic stroke, patients aged 55-59 years with no risk factors had a similar risk of ischaemic 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.[19-24] An analysis using the Danish nationwide cohort examined the risk of thromboembolism among men and women with CHA_2DS_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[20] *per se* and is dependent on age.[19,21,24] In the Swedish national dataset, women with no other risk factors (CHA_2DS_2-VASc score of 1) had a low stroke risk, similar to men with a CHA_2DS_2-VASc score of 0.[25] Although utilizing the simplified 'CHA_2DS_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.[19,21] 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_2DS_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.[26] Women with AF with >1

Table 4 CHA_2DS_2-VASc score: risk factors, definitions, and score per criterion

Risk factors	C	H	A	D	S	V	A	Sc
	Congestive heart failure	Hypertension	Age 75 years and older	Diabetes mellitus	Stroke	Vascular disease	Age 65 years and older	Sex category
Definition	Clinical heart failure or objective evidence of moderate-to-severe LV dysfunction, or HCM	Hypertension or receiving antihypertensive therapy		Treatment with oral hypoglycaemic drugs and/or insulin or fasting blood glucose >125 mg/dL (7 mmol/L)	Previous stroke, TIA or thromboembolism	Angiographically significant CAD, previous MI, PAD, or aortic plaque		Female
Score	1	1	2	1	2	1	1	1

Adapted from Ref.[6]
CAD, coronary artery disease; HCM, hypertrophic cardiomyopathy; LV, left ventricular; MI, myocardial infarction; PAD, peripheral artery disease; TIA, transient ischaemic attack.

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,[22,27-29] and numerous urine and blood biomarkers[30-33] [von Willebrand factor, growth differentiation factor (GDF)-15, troponin, etc.] have been associated with increased stroke risk. Indeed, the biomarker, vWF,[34] and renal dysfunction[35] have been added to the CHA_2DS_2-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 CHA_2DS_2-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 CHA_2DS_2-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 (CHA_2DS_2-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 is 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 it 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 CHA_2DS_2-VASc and HAS-BLED scores. Indeed, a recent European Heart Rhythm Association and Young Electrophysiologist survey on the utility of the CHA_2DS_2-VASc score demonstrated that most physicians calculated the CHA_2DS_2-VASc score from memory.[36]

Combining the CHA_2DS_2-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

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[6]	CHA_2DS_2-VASc	HAS-BLED
2019 AHA/ACC/HRS[7]	CHA_2DS_2-VASc	No specific risk score specified
2018 American College of Chest Physicians[8]	CHA_2DS_2-VASc	HAS-BLED
2018 Cardiac Society of Australia and New Zealand[3]	CHA_2DS_2-VA(Sc)	No specific risk score specified
2017 Asia Pacific Heart Rhythm Society[5]	CHA_2DS_2-VASc	HAS-BLED
2015 Canadian Cardiovascular Society[4]	CHA_2DS_2-VA	No specific risk score specified
2014 National Institute of Clinical Excellence[2]	CHA_2DS_2-VASc	HAS-BLED

ACC, American College of Cardiology; AHA, American Heart Association; 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); HAS-BLED, (uncontrolled) hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs/drink (alcohol); HRS, Heart Rhythm Society.

and BMP) improved the prediction of stroke (and mortality), in a cohort of 10 077 AF patients undergoing AF cardiac catheterization[37]; a four-fold separation between low and high risk in those with a CHA_2DS_2-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 CHA_2DS_2-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.[38,39] 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.[27] Also many biomarkers are non-specific, and abnormal levels are likely to reflect a 'sicker' patient or concomitant comorbidities.[40]

A meta-analysis of studies comparing just the CHA_2DS_2-VASc and ATRIA stroke scores demonstrated that the ATRIA-stroke score performed better for stroke risk prediction but that the CHA_2DS_2-VASc was superior to ATRIA for identifying truly low-risk patients.[41] A Patient Centred Outcomes Research Institute (PCORI) systematic review[42] evaluated the prognostic precision of CHA_2DS_2-VASc, $CHADS_2$ Framingham, and ABC stroke risk stratification tools, identifying 61 studies, and assessed the strength of evidence. This independent review demonstrated that CHA_2DS_2-VASc, $CHADS_2$, 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 CHA_2DS_2-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,[14,15,43,44] 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.

Table 6 Risk factors incorporated into the risk stratification scores for assessing bleeding risk in patients with atrial fibrillation

	Bleeding risk scores					
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 ≥75	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
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	Hct<30% during hospitalisation
Renal disease		Severe (eGFR<30ml/min or dialysis dependent)	Dialysis, transplant, serum creatinine>200 μmol/L		eGFR <60mg/dL/1.73m^2	
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 antiplatelet 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				Including neuropsychiatric disease		
Genetic factors				CYP 2C9 single nucleotide polymorphisms		
Reduced platelet count			Severe thrombocytopenia*	Reduced platelet count or function		

(continued)

Table 6 Continued

Risk factor and definition	Bleeding risk scores						
	ABC-Bleeding[†43]	ATRIA[47]	HAS-BLED[46]	HEMORR$_2$HAGES[‡49]	ORBIT[48]	Shireman[44]
Total number of risk factors	3	5	9	12	5	8
Range of scores	NR[†]	0-10	0-9	0-12	0-7	0-4.17

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); HEMORR$_2$HAGES, 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] where data for definitions available it has been specified

*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

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

There may be a role for biomarkers in differentiating low risk and those with 1 (non-sex) risk factors,[45] 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,[11-13,15,46-48] non-vitamin K antagonist oral anticoagulant (NOAC) clinical trials,[14,43] and retrospective cohorts,[10,44,49] 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,[46] ATRIA,[47] ABC,[43] ORBIT,[48] HEMORR$_2$HAGES,[49] and Shireman.[44] As shown in *Table 6*, the number of risk factors within each score is variable, ranging from 12 in HEMORR$_2$HAGES[49] to 3 in the ABC-bleeding score,[43] with inconsistency in the definitions of risk factors. All the scores include age and previous bleeding history/bleeding predisposition, although the age threshold for increased risk varies, with ABC-Bleeding[43] using a cut-off of 50 years and older, compared to $\geq$65 for HAS-BLED, $\geq$70 for Shireman,[44] and 75 years[49] and older[47,48] for the others. With regard to bleeding, some include any previous bleeding history,[43,44,47,49] HAS-BLED[46] incorporates previous major haemorrhage only, while ORBIT[48] combines gastrointestinal and intracranial bleeds and haemorrhagic stroke. Further, some scores also assess separately factors, such as anaemia[44,46-49] and reduced platelet count,[49] while HAS-BLED[46] incorporates bleeding

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)		
		Low	Intermediate	High	Low	Intermediate	High
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
HEMORR$_2$HAGES[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	≥4	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]

Taken from Refs.[8,61]

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); HEMORR$_2$HAGES, 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); HEMORR$_2$HAGES, 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.

*Bleeding event in original derivation cohort;

[a]At 3 months; ↓ reduced/decreased; ↑ elevated/increased;

†Score for each variable in ABC score is based on a nonogram (see Ref.[4]).

predisposition (i.e. anaemia or severe thrombocytopenia) together with previous major bleeding. Renal dysfunction,[46–49] (uncontrolled)[46,49] hypertension,[47] concomitant APT,[44,46,48] and alcohol excess[44,46,49] were included in at least half of the scores. Risk factors, such as hepatic disease,[46,49] female sex,[44] diabetes,[44] cancer,[49] labile International Normalised Ratio (INR),[46] excessive falls risk,[49] biomarkers,[43] and genetic factors[49] 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.

A systematic review and meta-analysis[50] compared the sensitivity, specificity, and diagnostic odds ratio of HAS-BLED to ATRIA (four studies) and HEMORR$_2$HAGES (five

Table 8 Risk factors for bleeding with oral anticoagulation or antiplatelet therapy

Modifiable	Potentially modifiable
Hypertension/elevated SBP	Anaemia
Concomitant antiplatelet/NSAID	Severe frailty ± excessive risk of falls
Excessive alcohol intake	Reduced platelet count or function
Non-adherence to OAC	Renal impairment with CrCl <60 mL/min
Hazardous hobbies/occupations	VKA management strategy
Bridging therapy with heparin	
INR control (target 2.0–3.0), target TTR >70%	
Appropriate choice of OAC and correct dosing	
Non-modifiable	**Biomarkers**
Age >65 years	GDF-15
Previous major bleeding	Cystatin C/CKD-EPI/ cTnT-hs
Severe renal impairment (on dialysis or renal transplant)	von Willebrand factor (and other coagulation markers)
Severe hepatic dysfunction (cirrhosis)	
Malignancy	
Genetic factors (e.g. CYP 2C9 polymorphisms)	
Previous stroke, small-vessel disease, amyloid angiopathy, etc.	
Diabetes mellitus	
Cognitive impairment/dementia	

Adapted from Ref.[8]

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CrCl, creatinine clearance; cTnT-hs, high-sensitivity cardiac troponin T; CYP 2C9, cytochrome P450 2C9; GDF-15, growth differentiation factor-15; INR, international normalized ratio; NSAID, non-steroidal anti-inflammatory drugs; OAC, oral anticoagulation; SBP, systolic blood pressure; TTR, time in the therapeutic range.

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 HEMORR$_2$HAGES [0.41 (0.35–0.48) vs. 0.23 (0.17–0.29), respectively]. Another systematic review and meta-analysis[51] compared the predictive ability of HAS-BLED to assess risk of major bleeding on OAC in patients with AF to HEMORR$_2$HAGES, ATRIA (with 11 studies comparing the 3 bleeding risk scores), CHADS$_2$, and CHA$_2$DS$_2$-VASc. All three bleeding risk scores had similar predictive ability [pooled c-statistics (95% CI) for HAS-BLED 0.65 (0.61–0.69), HEMORR$_2$HAGES 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 HEMORR$_2$HAGES and ATRIA.[51] More recently a PCORI systematic review[42] identified 38 studies relating to bleeding risk in AF which compared HEMORR$_2$HAGES, 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.[42]

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.[52] 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.[53]

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,[54] although to date most were conducted in Asian populations (Taiwan and South Korea).[55–57] Two[56,57] studies have examined the dynamic change in CHA_2DS_2-VASc score over time. Chao *et al.*[56] utilized the Taiwanese National Health Insurance Research Database cohort of 31 039 AF patients whose only risk CHA_2DS_2-VASc stroke risk factors were their age and/or sex, who were not receiving antithrombotic therapy at baseline. During follow-up, 64.4% patients developed $\geq$1 new comorbidities; the mean change in CHA_2DS_2-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 CHA_2DS_2-VASc score of $\geq$1 compared to those without ischaemic stroke (89.4% vs. 54.6%, respectively). Change in the CHA_2DS_2-VASc score predicted incident ischaemic stroke better than baseline or follow-up CHA_2DS_2-VASc score. The analysis of the Korean National Health Insurance Service database ($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 CHA_2DS_2-VASc score and follow-up CHA_2DS_2-VASc score were better predictors of incident ischaemic stroke than baseline CHA_2DS_2-VASc score.[57] Similar observations were evident from a European cohort.[58]

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 $\leq$2.[55] 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). Change 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 CHA_2DS_2-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 nonograms/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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