Stroke and Bleeding Risk in Atrial Fibrillation: Navigating the Alphabet Soup of Risk-Score Acronyms (CHADS₂, CHA₂DS₂-VASc, R₂CHADS₂, HAS-BLED, ATRIA, and More)

Mikhail S. Dzeshka, MD; Deirdre A. Lane, PhD; Gregory Y. H. Lip, MD

University of Birmingham Centre for Cardiovascular Sciences (Dzeshka, Lane, Lip), City Hospital, Birmingham, United Kingdom; Grodno State Medical University (Dzeshka), Grodno, Belarus

Address for correspondence:

Gregory Y. H. Lip, MD,
University of Birmingham Centre for
Cardiovascular Sciences,
City Hospital, Birmingham B18 7QH,
United Kingdom,
g.y.h.lip@bham.ac.uk

ABSTRACT

Stroke prevention is central to the management of patients with atrial fibrillation (AF). As effective stroke prophylaxis essentially requires oral anticoagulants, an understanding of the risks and benefits of oral anticoagulant therapy is needed. Although AF increases stroke risk 5-fold, this risk is not homogeneous. Many stroke risk factors also confer an increased risk of bleeding. Various stroke and bleeding risk-stratification schemes have been developed to help inform clinical decision-making. These scores were derived and validated in different study cohorts, ranging from highly selected clinical-trial cohorts to real-world populations. Thus, their performance and classification accuracy vary depending on their derivation cohort(s). In the present review, we provide an overview of currently available stroke and bleeding risk-stratification schemes. We particularly focus on the CHA₂DS₂-VASc and HAS-BLED schemes, as these are recommended by the latest European guidelines on AF management. Other risk-stratification schemes (eg, CHADS₂, R₂CHADS₂, ATRIA, HEMORR₂HAGES, QStroke) and their place in the decision-making are also considered.

Introduction

The increasing prevalence of atrial fibrillation (AF) brings a high burden of arrhythmia-related complications, among which stroke is the most disabling and associated with high mortality and morbidity.^{1,2} Stroke prevention is central to the management of patients with AF. As effective stroke prophylaxis essentially requires oral anticoagulants (OAC), an understanding of the risks and benefits of OAC therapy is needed.^{3,4} Although AF increases stroke risk 5-fold, this risk is not homogeneous. Many stroke risk factors also confer an increased risk of bleeding. Various stroke and bleeding

risk-stratification schemes have been developed to help inform clinical decision-making. These scores were derived and validated in different study cohorts, ranging from highly selected clinical-trial cohorts to real-world populations. Thus, their performance and classification accuracy vary depending on their derivation cohort(s).⁵

In the present review article, we provide an overview and critique of currently available stroke and bleeding risk-stratification schemes. We particularly focus on the CHA₂DS₂-VASc and HAS-BLED schemes, as these are recommended by the latest European guidelines on AF management.^{3,6} Other risk-stratification schemes (CHADS₂, R₂CHADS₂, ATRIA, HEMORR₂HAGES, QStroke) and their place in the decision-making are also considered.

Stroke Risk

There is a large number of stroke risk factors identified among AF patients; hence, an individual patient's risk will depend largely on the combination of risk factors, rather than from simply being an AF patient. Permutations of these risk factors have been used to formulate stroke risk-stratification schemes, with the initial objective of identifying high-risk patients to be targeted for OAC using an "inconvenient" drug, warfarin.^{7,8}

The derivation of stroke risk-stratification schemes depends on identification of common risk factors, which importantly have been defined and recorded in derivation

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. D. A. L. has received investigator-initiated educational grants from Bayer Healthcare and Boehringer Ingelheim and served as a speaker for Boehringer Ingelheim, Bayer Healthcare, and BMS/Pfizer. In addition, D. A. L. is on the steering committee of a phase IV apixaban study (AEGEAN) and is a panelist on the ninth edition of the American College of Chest Physicians guidelines on antithrombotic therapy in AF. G. Y. H. L. and D. A. L. are coauthors of the CHA₂DS₂-VASc and HAS-BLED scores.

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cohorts.⁹ Some schemes are also simplistic in assuming each risk factor carries equal weight. In addition, the significance of some risk factors can change with effective treatment (eg, blood pressure). The (independent) impact of a particular stroke risk factor is also best tested in a nonanticoagulated cohort, preferably from a real-world setting with a broad range of stroke risk, rather than a selected clinical-trial cohort where intervention(s) may influence event rates.

The Stroke Risk in Atrial Fibrillation Working Group identified common predictors of stroke in AF from a systematic review of 7 studies: the Framingham Heart Study,¹⁰ Stroke Prevention in Atrial Fibrillation (SPAF),¹¹ AF Investigators (AFI),^{12,13} Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA),¹⁴ and others.^{15,16} This analysis found that history of stroke or transient ischemic attack (TIA; 2.5-fold higher risk), as well as advanced age (1.5-fold higher risk with each 10 years), arterial hypertension (either history of hypertension or systolic blood pressure [SBP], or SBP >160 mm Hg, depending on study; 2.0-fold higher risk), and diabetes mellitus (DM; irrespective of severity, duration, and quality of glycemic control; 1.7-fold higher risk) increased stroke risk.⁹ Both SPAF and AFI were part of the original historical trials of stroke prevention in patients with AF, and the stroke risk factors were derived from the nonwarfarin arms of these cohorts; however, these trials randomized <10% of patients screened, and many common stroke risk factors were not systematically looked for, nor recorded.

In the Stroke in AF Working Group, clinical heart failure (HF) was not found to be an independent risk factor for stroke development.⁹ One reason may be a discrepancy in definitions of HF between studies, whether defined as HF per se, recent congestive HF, severe-to-moderate systolic dysfunction, fractional shortening ≤25%, assessed via echocardiography, et al. Data about stroke risk associated with female sex and coronary heart diseases as potential risk factors were also not consistent between studies.⁹

A more recent systematic review of stroke risk factors in AF found that the best evidence was available for prior stroke or TIA (risk ratio [RR]: 2.86), hypertension (RR: 2.27), aging (RR: 1.46 per decade increase), structural heart disease (RR: 2.0), and DM (RR: 1.62). Female sex (RR: 1.67), vascular disease (RR: 2.61), and HF (RR: 1.85) were also independent predictors of stroke in about one-third of included studies.¹⁷

Other strong contemporary evidence comes from the Swedish Atrial Fibrillation cohort study (n = 90 490, approximately 1.5 years of follow-up, 7334 thromboembolic events), where peripheral artery disease (PAD; 22% risk increase), myocardial infarction (MI; 9% risk increase), coronary artery bypass graft (19% risk increase), any vascular disease (14% risk increase), female sex (17% risk increase), intracranial hemorrhage (49% risk increase), and kidney failure (16% risk increase) were identified as independent predictors of thromboembolic events (stroke, TIA, systemic emboli). The prognostic value of arterial hypertension, DM, age, and previous stroke was confirmed, whereas HF defined as only “history of” was not an independent stroke risk factor.¹⁸

Table 1. Stroke Risk Stratification With the CHADS₂ Score²⁰

Risk Factor	Score	CHADS ₂ Score	Stroke Rate, %
CHF (recent)	1	0	1.9
Hypertension (history of)	1	1	2.8
Age ≥75 years	1	2	4.0
DM	1	3	5.9
Stroke/TIA	2	4	8.5
		5	12.5
		6	18.2
Maximum score	6		
Abbreviations: CHF, congestive heart failure; DM, diabetes mellitus; TE, thromboembolism; TIA, transient ischemic attack. First letter of each row spells out the acronym.			

Of note, type of AF (paroxysmal or nonparoxysmal) still confers a similar risk for stroke. For example, in the Stockholm Cohort of Atrial Fibrillation, stroke incidence did not differ between paroxysmal and chronic AF (26 and 29 events per 1000 patient/years, respectively); however, the appearance of paroxysmal AF doubled stroke incidence in the general population.¹⁹

CHADS₂ Score

The CHADS₂ score (Table 1) is one of the simplest and commonly used stroke risk-stratification schemes. It was derived by the combination of stroke risk factors established in the AFI and SPAF studies.²⁰ Compared with the AFI and SPAF risk schemes, the original CHADS₂ score validation publication included “any history of hypertension,” instead of the SPAF trial definition of SBP >160 mm Hg; “age 75 years or older,” instead of combination of age 75 years or older plus female sex; and “recent heart failure exacerbation,” instead of any history of HF.²⁰ CHADS₂ is a point system in which 2 points are assigned to a history of prior cerebral ischemia and 1 point is assigned for the presence of each of the other risk factors, with a maximum of 6 points in total.

Initial validation of the CHADS₂ score was performed in the National Registry of Atrial Fibrillation (NRAF) participants who had nonrheumatic AF and were not taking anticoagulation therapy at hospital discharge (n = 1733).²⁰ A strong relationship was found between the CHADS₂ score and the adjusted stroke rate (Table 1).²⁰ The CHADS₂ score showed the highest performance comparatively to SPAF and AFI schemes.²⁰ The c-statistics (used to compare the goodness-of-fit of regression models with the range between 0.5 [model is not better than chance at making prediction] and 1.0 [perfect prediction with the model]) were 0.82, 0.74, and 0.68 for the 3 schemas, respectively.²⁰ Adjustment for aspirin therapy as well as subdivision into low (CHADS₂ 0–1), moderate (CHADS₂ 2–3), and high (CHADS₂ 4–6) risk strata did not significantly alter the c-statistic.²⁰

In the original validation, low-risk patients for whom antiplatelet treatment was recommended was defined as

CHADS₂ 0, whereas moderate risk was defined as CHADS₂ 1–2 and high risk as CHADS₂ > 2.²¹ This was problematic, because patients with a stroke as their only risk factor would be classed as moderate risk despite such patients being at the highest risk of further strokes. Subsequent treatment based on the CHADS₂ score was revised, with moderate risk being defined as CHADS₂ 1 and high risk as CHADS₂ ≥ 2.²² More recent guidelines even recommended OAC for those with CHADS₂ ≥ 1.²³

The predictive value of the CHADS₂ score was further analyzed in a cohort of 2580 patients with nonvalvular AF taking aspirin (207 ischemic strokes, 4887 patient-years), and compared with the AFI,^{12,13} SPAF,¹¹ Framingham,¹⁰ and American College of Chest Physicians²⁴ risk-stratification schemes.²⁵ The CHADS₂ score was best in identifying high-risk patients (5.3 strokes per 100 patient-years), whereas high-risk patients identified by other schemes had 3.0 to 4.2 strokes per 100 patient-years. Discrimination of the low-risk patients did not differ between stratification schemes (0.5–1.4 strokes per 100 patient-years of therapy).²⁵ A good performance of the CHADS₂ score in the identification of high-risk patients was also confirmed in the community-based cohort study from the Olmsted County (n = 2720, 4.4 years follow-up, 350 thromboembolic events).²⁶

In contrast, application of the 5 stratification schemes including CHADS₂ to the ATRIA cohort (n = 13 559, 6-year follow-up, 685 thromboembolic events) showed poor discriminative ability (c statistic: 0.58) with only a minor increase in thromboembolism (TE) rate with corresponding increase in the risk category. A significant proportion of patients without TE appeared within the high-risk category, and conversely, many patients with thromboembolic events were found in the low-risk stratum. Broadly similar c-statistics were obtained for other scores.²⁷ The latter was confirmed in the Swedish Atrial Fibrillation Cohort Study, where the CHADS₂ score had a c-statistic of 0.66 and other risk scores ranged from 0.58 to 0.67.¹⁸ Low performance of the CHADS₂ score was also seen in the systematic review of several studies, but wide heterogeneity was evident.²⁸

In summary, the CHADS₂ score manages well in identifying high-risk patients but provides ambiguous results in those at low or moderate stroke risk.²⁹ Thus, the CHADS₂ score has been subject to criticism for several reasons: first, its low discrimination ability for patients at low risk of stroke development; second, important independent stroke and TE risk factors were not included; and third, discrepancy between the original validation and further applications in guidelines and real-world cohorts.^{30,31}

CHA₂DS₂-VASc Score

To overcome some of the limitations of the CHADS₂ score, the CHA₂DS₂-VASc score (see Table 2 for acronym) has been proposed, giving extra weight to age ≥ 75 years, as this is a major driver of stroke risk, and including additional risk factors such as age 65 to 74 years, female sex, and vascular disease.^{6,32}

The CHA₂DS₂-VASc score was proposed as a risk-factor-based approach, which de-emphasized the artificial low-risk, moderate-risk, and high-risk classification. This score assigns 2 points to prior stroke, TIA, or TE, and

Table 2. Stroke Risk Stratification With the CHA₂DS₂-VASc Scheme³²

Risk Factor	Score	CHA ₂ DS ₂ -VASc Score	Thromboembolic Event Rate ⁴⁴
CHF/LV dysfunction	1	0	0
Hypertension	1	1	1.3
Age ≥ 75 years	2	2	2.2
DM	1	3	3.2
Stroke/TIA/TE	2	4	4.0
Vascular disease (prior MI, PAD, or aortic plaque)	1	5	6.7
Age 65–74 years	1	6	9.8
Sex category (ie, female sex)	1	7	9.6
		8	6.7
		9	15.2
Maximum score	9		

Abbreviations: CHF, congestive heart failure; DM, diabetes mellitus; F, female; LV, left ventricular; MI, myocardial infarction; PAD, peripheral artery disease; TE, thromboembolism; TIA, transient ischemic attack. First letter of each row (Sc for sex category) spells out the acronym.

older age (≥ 75 years), as the major risk factors. Other clinically relevant nonmajor risk factors are assigned 1 point each: HF (moderate to severe systolic left ventricular [LV] dysfunction, defined arbitrarily as left ventricular ejection fraction [LVEF] ≤ 40%, or recent decompensated HF requiring hospitalization), hypertension, DM, female sex, age 65 to 74 years, and vascular disease (eg, MI, complex aortic plaque, and PAD).^{6,32}

With the introduction of the CHA₂DS₂-VASc score, categorization of AF patients improved significantly with respect to selecting patients at low risk of stroke (essentially, a CHA₂DS₂-VASc of 0 in males or CHA₂DS₂-VASc of 1 in females).^{4,5,33} These are the patients with lone AF without structural heart disease and age < 65 years. Such “truly low-risk” patients do not need any antithrombotic therapy, and the subsequent step would be that all other AF patients, those with ≥ 1 stroke risk factor, require appropriate antithrombotic prophylaxis, which is essentially OAC.³

The advantages of the CHA₂DS₂-VASc score were clearly demonstrated in a retrospective analysis performed in the Danish nationwide cohort study, which involved 19 444 patients with CHADS₂ score 0 (ie, low-risk patients). When their stroke risk was substratified according to the CHA₂DS₂-VASc score, those with a CHADS₂ score of 0 had stroke rates ranging from 0.8% per year to 3.2% per year.³⁴ For the 28 132 subjects with the CHADS₂ score of 1, the stroke rate based on substratification according to the CHA₂DS₂-VASc score was as high as 8.18% at 1 year.³⁴

Because a CHADS₂ score of 0 (or 1) can confer significant stroke risk, the benefits of OAC in comparison with antiplatelet or no antithrombotic therapy in these patients are evident.^{35,36} Indeed, a lower stroke incidence was found

Table 3. Predictive Ability of Different Risk-Stratification Schemes Expressed by the C Statistic in Patients Without Anticoagulant Treatment

Study Cohort	No. of Patients	Stroke/TE Rate (Per 100 Patient-Years)	C Statistic (95% CI) ^a		
			CHA ₂ DS ₂ -VASc Score	CHADS ₂ Score (Revised)	CHADS ₂ Score (Classic)
Euro Heart Survey on Atrial Fibrillation ³²	1084	2.3	0.606 (0.513–0.699)	0.586 (0.477–0.695)	0.561 (0.450–0.672)
Swedish Atrial Fibrillation cohort study ¹⁸	90 490	6.2	0.56 (0.56–0.57)	0.61 (0.61–0.62)	0.64 (0.64–0.65)
United Kingdom General Practice Research Database ⁴⁸	79 844	0.5, low; 1.1, moderate; 4.6, high risk ^b	0.60 (0.59–0.61) ^c	0.63 (0.61–0.65) ^c	0.65 (0.63–0.67) ^c
Nationwide register of AF patients in Denmark ⁴⁷	73 538	1.67	0.850 (0.829–0.871) ^d	0.722 (0.694–0.748) ^d	—
Community-based cohort study from Olmsted County, MN ²⁶	2720	2.94	0.58 (0.57–0.58)	0.65 (0.63–0.67)	0.65 (0.63–0.68)
SPORTIF III and V cohorts ^{49e}	7329	1.63	0.647 (0.613–0.678)	0.637 (0.607–0.674)	0.637 (0.607–0.674)

Abbreviations: AF, atrial fibrillation; CI, confidence interval; SPORTIF, Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation; TE, thromboembolism.

^aFor categorization into 3 groups (low, moderate, and high risk) in all studies, apart from Swedish Atrial Fibrillation cohort study, in which low risk vs intermediate or high risk were analyzed. ^bAccording to the CHA₂DS₂-VASc score. ^cFor strokes recorded by the general practitioners or in hospital. ^dAt 1-year follow-up, rising to 0.888 (0.875–0.900) and 0.812 (0.796–0.827) at 10-year follow-up for the CHA₂DS₂-VASc and CHADS₂ scores, respectively.

^eAnticoagulated trial cohorts.

in patients taking warfarin compared with those taking aspirin (4.2% vs 12.9%), without any difference in the incidence of major bleeding.³⁵ This was consistent with another study by Gorin et al, who observed a 2.4-fold higher risk of stroke in the group of nonanticoagulated patients with CHADS₂ score of 1.³⁶

What is the impact of “non-CHADS₂” risk factors? Peripheral artery disease taken separately was associated with an even higher risk than MI (93% vs 12% increase in risk).³⁷ In the Loire Valley Atrial Fibrillation Project (n = 6438), vascular disease, when added to the CHADS₂ score, improved stratification of patients (net reclassification improvement, 0.4).³⁸ In a Taiwanese nationwide database analysis (n = 7920), there was a positive link between PAD and ischemic stroke development (odds ratio: 1.81).³⁹

The value of female sex as a risk factor for stroke in AF was reported previously.¹⁷ In the Swedish Atrial Fibrillation cohort, female sex remained an independent predictor (14% increase in risk).^{39,40} This was also evident in a population-based cohort from the Quebec, Canada (14% increase in risk)⁴¹ cohort and a Danish nationwide cohort (20% increase in risk).⁴² An age differential was evident, as differences in stroke rate with females became evident only if associated with other risk factors.

The risk of stroke increases from age 65 years upward, and each 10 years of aging results in a 1.5-fold increase in risk.⁴³ The stroke/thromboembolic rate increased significantly from 0.23 to 2.05 to 3.99 for patients age <65 years, age 65 to 74 years, and ≥75 years, respectively.³⁸ On average,

3-fold and 5-fold increases in stroke risk were observed for the latter 2 age categories when compared with age <65.¹⁸

The controversy of HF as risk factor of stroke has already been pointed out above. The CHA₂DS₂-VASc score uses HF defined as moderate to severe LV systolic dysfunction or recent HF exacerbation that requires hospitalization (independently of reduced or preserved systolic function).³ The distinction about preserved systolic function is of particular importance in patients with AF, as about half of such patients belong to this category.⁴⁴ Prognostic significance of HF with preserved systolic function in AF has limited evidence, but in the Loire Valley Atrial Fibrillation Project there were no differences in rates of stroke/TE between patients with HF with preserved LVEF, compared with those with HF with reduced LVEF.⁴⁵ Another study found a 3.3-fold higher rate of ischemic stroke (20.6% vs 6.7%) and a 5.5-fold higher rate of death (27.2% vs 2.0%) in patients with AF and HF with preserved LVEF, compared with those with AF only, after 3 years of follow-up.⁴⁶

Since the initial derivation and validation of the CHA₂DS₂-VASc score in the Euro Heart Survey on Atrial Fibrillation,³² its performance has also been confirmed in several cohorts, including large real-world cohorts (Table 3).^{18,26,47–49}

Interestingly, all contemporary risk-stratification schemes can be used for stroke prediction even in the non-AF population equally well (c statistics ranging from 0.658 to 0.728), as shown in the Chi-Shan Community Cohort Study (n = 3524, approximately 16 years of follow-up).⁵⁰

Table 4. Stroke Risk Stratification With the R₂CHADS₂ Scheme⁵³

Risk Factor	Score
Renal dysfunction (ie, CrCl <60 mL/min)	2
CHF (recent)	1
Hypertension	1
Age ≥75 years	1
DM	1
Stroke/TIA	2
Maximum score	8
Abbreviations: CHF, congestive heart failure; CrCl, creatinine clearance; DM, diabetes mellitus; TIA, transient ischemic attack. First letter of each row spells out the acronym.	

In summary, the performance of the CHA₂DS₂-VASC score for predicting those at high risk of stroke/TE was comparable with other contemporary risk-stratification schemes such as the Eighth American College of Chest Physicians Guidelines,⁵¹ National Institute for Health and Clinical Excellence (NICE),⁵² and modified CHADS₂.³² The CHA₂DS₂-VASC score is currently recommended by the European guidelines on AF management as the main scheme to assess patient stroke risk³ because of its ability to identify low-risk patients, as this was the principal group that does not need anticoagulation.³³

R₂CHADS₂ Score

The R₂CHADS₂ score (Table 4) was suggested based on an ancillary analysis of the ROCKET AF (Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) cohort (n = 14 264).⁵³ The score incorporates the components of the CHADS₂ score and also assigns 2 points for creatinine clearance <60 mL/min.⁵³

Development of the R₂CHADS₂ score was driven by the knowledge that AF and kidney dysfunction coexist commonly and both increase the risk of stroke. For example, in one cohort of stable anticoagulated AF patients (n = 978) during 2 years of follow-up, a low estimated glomerular filtration rate (eGFR) was associated with combined endpoint (stroke, acute coronary syndrome, acute HF); there was a 42% increase in risk with each 30-mL/min/1.73 m² decrease in eGFR.⁵⁴

The R₂CHADS₂ score had a c statistic of 0.587 and did not differ from the CHA₂DS₂-VASC and the CHADS₂ schemes (0.578 and 0.575, respectively) in the ROCKET AF cohort.⁵³ In addition, it was not better than the above-mentioned schemes in predicting thromboembolic events in patients after catheter ablation of AF in the cohort from the Leipzig Heart Center AF Ablation Registry (n = 2069, 1.5 years of follow-up).⁵⁵

The R₂CHADS₂ score has many limitations that may affect its performance; for example, derivation from a selected anticoagulated clinical-trial cohort that excluded patients with creatinine clearance <30 mL/min and included those

with a high risk of stroke development.⁵⁶ The latter is contradictory to current recommendations to first identify low-risk patients. Moreover, kidney dysfunction is known to be independently associated with female sex, advanced age, and HF (ie, components of CHADS₂), which eventually may lead to a reduction of the predictive value of the R₂CHADS₂ score.⁵⁷ Thus, as renal dysfunction in general results in poorer prognosis for AF patients, the independent predictive value of the R₂CHADS₂ score for stroke requires further validation with inclusion of patients with the full spectrum of stages of chronic kidney disease.

QStroke Score

The QStroke score was developed based on analysis of data from general practices in England and Wales (QResearch database, derivation cohort n = 3.5 million, 77 578 strokes; validation cohort n = 1.9 million, 38 404 strokes).⁵⁸ This score is relatively complex and includes 17 variables (Table 5). Importantly, patients with history of stroke or TIA were excluded from this study. Separate calculations for males and females are performed, and QStroke can be used in both AF and non-AF populations.⁵⁸ The QStroke score was composed of risk factors from the QRISK2 score, which was developed for the purpose of predicting cardiovascular disease risk.^{59,60}

In the validation cohort, the QStroke scheme did slightly better than the CHA₂DS₂-VASC and CHADS₂ scores in predicting stroke risk, but these differences were not significant. For example, c statistics for females were 0.65, 0.62, and 0.61 for the 3 schemes, respectively.⁵⁸ Thus, despite high representativeness, duration of the follow-up, size of derivation and validation cohorts, and general availability of data that are necessary for risk calculation, there are no major advantages in favor of the substantially more complex QStroke score. On the contrary, it represents a shift toward a more complex and less practical approach to individual stroke-risk calculation.

The ATRIA Stroke Risk Score

The ATRIA stroke risk score (ATRIA score) is the newest stroke risk-stratification scheme proposed. This score was derived from an ATRIA cohort.²⁷ Only those patients who were not on anticoagulation (median time out of warfarin, 2.4 years) were included in the current analysis (n = 10 927).⁶¹ The ATRIA score represents a point-based stratification scheme (Table 6) calculated separately for patients without prior stroke (ie, primary prevention) and those with history of stroke (ie, secondary prevention).⁶¹ An ATRIA score of 0 to 5 points corresponds to low risk (event rates of <1% per year); 6 points equates to moderate risk (1%–2% event rate); and 7 to 15 points indicates high risk (event rate ≥2% per year).

The ATRIA score was validated in the ATRIA–Cardiovascular Research Network (CVRN) cohort (n = 25 306, 496 thromboembolic events). C statistics were 0.70 for the ATRIA score, 0.66 for CHADS₂, and 0.68 for CHA₂DS₂-VASC, with net reclassification improvement of about 25% with the ATRIA score if all thromboembolic events were considered or 33% for severe thromboembolic events only. Of note, the ATRIA score particularly focused

Table 5. Stroke Risk Stratification With the QStroke^{ab}Scheme⁵⁸

Risk Factor	Score
Age (at entry), y	Range, 25–84
Sex	Separate models for M and F
Treated hypertension (diagnosis of hypertension and ≥ 1 current prescription for ≥ 1 antihypertensive)	Y/N
T1DM	Y/N
T2DM	Y/N
AF	Y/N
CHF	Y/N
CHD	Y/N
Self-assigned ethnicity (White/not recorded, Indian, Pakistani, Bangladeshi, other Asian, Black Caribbean, Black African, Chinese, other/mixed)	9 categories
Townsend Deprivation Score	Continuous
Smoking status (nonsmoker, ex-smoker, light smoker [<10 cigarettes/day], moderate smoker [$10\text{--}19$ cigarettes/day], heavy smoker [≥ 20 cigarettes/day])	5 categories
SBP	Continuous
TC:HDL-C ratio	Continuous
BMI	Continuous
Family history of coronary disease (in first-degree relative age <60 years)	Y/N
RA	Y/N
CKD	Y/N
Valvular heart disease	Y/N
Maximum score	99%
Abbreviations: AF, atrial fibrillation; BMI, body mass index; CHD, coronary heart disease; CHF, congestive heart failure; CKD, chronic kidney disease; F, female; HDL-C, high-density lipoprotein cholesterol; M, male; N, no; RA, rheumatoid arthritis; SBP, systolic blood pressure; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TIA, transient ischemic attack; Y, yes.	
^a Importantly previous stroke or TIA was not included. ^b Designed for use in primary care, as it requires an algorithm to calculate the QStroke score, which can be incorporated into existing software.	

on the severe thromboembolic events (defined as Rankin score ≥ 3 at discharge or death within 30 days after the event), as the predictive ability of the scheme was higher (c statistic up to 0.76) for this group than for all patients with thromboembolic events.⁶¹

In summary, the ATRIA score is more complex than both the CHA₂DS₂-VASc and the CHADS₂ scores and emphasizes the importance of severe thromboembolic conditions, leading to death or significant disability, and deemphasizes other events. Such an approach may result in

Table 6. Stroke Risk Stratification With the ATRIA Score⁶¹

Risk Factor	Score Without Prior Stroke	Score With Prior Stroke
Age, y		
≥ 85	6	9
75–84	5	7
65–74	3	7
<65	0	8
F sex	1	1
DM	1	1
CHF	1	1
Hypertension	1	1
Proteinuria	1	1
eGFR <45 mL/min/1.73 m ² or ESRD	1	1
Maximum score	12	15
Abbreviations: ATRIA, Anticoagulation and Risk Factors in Atrial Fibrillation; CHF, congestive heart failure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; F, female.		

undertreatment of AF patients with OACs, particularly those with nonsevere TE, with further much more devastating outcomes.

Bleeding Risk Assessment in Atrial Fibrillation

Increased risk of hemorrhage, particularly intracranial bleeding, is a downside of thromboprophylaxis with OAC. The annual incidence of anticoagulant-associated intracranial bleeding increased from 0.8 to 4.4 per 100 000 people during the 1990s, with increasing use of warfarin.⁶² A recent meta-analysis including 16 randomized controlled trials (61 563 patient-years of follow-up) and 31 observational studies (484 241 patient-years of the follow-up) confirmed the high rate of major bleeding in the anticoagulated population (approximately 2 per 100 patient-years).⁶³

An informed approach to assessing bleeding risk is needed. However, many risk factors for bleeding are also stroke risk factors. Many risk factors for bleeding are reversible; for example, uncontrolled blood pressure, labile international normalized ratios (if on warfarin), concomitant use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs), and alcohol excess. Various bleeding risk-assessment scores have been developed, but not all of them target the AF population and have been appropriately validated.⁶⁴

It is clear that bleeding risk is not equal in all patients taking OACs. Also, bleeding events may vary in severity. Many current bleeding-risk schemes evaluate major bleeding involving critical sites (eg, intracranial, retroperitoneal, intraspinal, intraocular, pericardial, atraumatic intra-articular hemorrhage), which may be potentially fatal. There are also laboratory indices of major bleeding, such as a drop

Table 7. Bleeding Risk Stratification With the HEMORR₂HAGES Score⁶⁹

Risk Factor	Score
Hepatic or renal disease	1
Ethanol abuse	1
Malignancy	1
Older age (≥ 75 years)	1
Reduced platelet count or function	1
Rebleeding risk	2
Hypertension (uncontrolled)	1
Anemia	1
Genetic factors (CYP2C9 single nucleotide polymorphism)	1
Excessive fall risk	1
Stroke	1
Maximum score	12
Abbreviation: CYP2C9, cytochrome P450 2C9. First letter of each row spells out the acronym.	

in hemoglobin of >2 g/dL or need to transfuse ≥ 2 units of packed red blood cells.⁶⁵

Some stroke and bleeding risk factors are broadly similar—advanced age, female sex, arterial hypertension, congestive HF—and these are usually nonmodifiable.⁶⁶ Of note, bleeding risk should not be considered as a contraindication or a reason to discontinue treatment with the OACs, as the reduction in stroke risk on anticoagulation usually far exceeds the elevation in bleeding risk. For example, in the cohort of 13 559 patients with nonvalvular AF, the net clinical benefit of warfarin, balancing stroke against serious bleeding, was 0.68% for the whole studied population, but even higher ($>2\%$) for patients with a history of stroke or in the elderly (ie, those with high stroke risk).⁶⁷ This was in line with the results from the Swedish Atrial Fibrillation cohort study, in which only the low-risk patients with a CHA₂DS₂-VASc of 0 were found not to benefit from warfarin therapy.⁶⁸

HEMORR₂HAGES Score

The HEMORR₂HAGES score (see Table 7 for acronym) was derived from known bleeding risk factors from the National Registry of Atrial Fibrillation ($n = 3791$, 162 events recorded).⁶⁹ It assigned 1 point for each risk factor but 2 points for previous bleeding, and denoted a score of ≥ 4 as high risk. Based on the original analysis, the HEMORR₂HAGES score had better predictive ability (*c* statistic: 0.67) than older prediction schemes.⁶⁹ However, this score is not easily applied to routine clinical practice, due in part to the necessity of genetic testing.

HAS-BLED Score

The HAS-BLED score (see Table 8 for acronym) was first derived and validated in the Euro Heart Survey in Atrial Fibrillation cohort ($n = 3978$, 1-year follow-up, 1.5% of major bleedings) with inclusion of previously established bleeding

Table 8. Bleeding Risk Stratification With the HAS-BLED Score⁷⁰

Risk Factors	Score
Hypertension (SBP >160 mm Hg)	1
Abnormal renal and/or liver function	1 or 2
Stroke	1
Bleeding tendency or predisposition	1
Labile INRs (if on warfarin)	1
Elderly (eg, age >65 years, frail condition)	1
Drugs (eg, concomitant antiplatelet or NSAIDs) or alcohol excess/abuse	1 or 2
Maximum score	9
Abbreviations: INR, international normalized ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; SBP, systolic blood pressure. First letter of each row spells out the acronym.	

risk factors.⁷⁰ Hypertension was defined as uncontrolled hypertension (SBP >160 mm Hg). Abnormal renal function refers to serum creatinine ≥ 200 μ mol/L, chronic dialysis or kidney transplantation; abnormal liver function refers to chronic liver disease or increase of biochemical indices of liver function (>2 -fold for bilirubin, >3 -fold for aminotransferases, alkaline phosphatase). Labile INR is defined as time in the therapeutic range of $<60\%$ and is only used if patient is taking warfarin or a vitamin K antagonist. The elderly criterion denotes age >65 years, although in reality this refers to “biological age”—that is, extreme frailty and poor physical state. Concomitant drugs include those that enhance bleeding risk with warfarin (eg, antiplatelets or NSAIDs). Alcohol abuse or excess implies for more than (say) 20 units per week. The resultant HAS-BLED score is a sum of 1 point for the presence of each risk factor (for kidney/liver dysfunction and drugs/alcohol separately), with a score of ≥ 3 used as criterion for high risk.⁷¹

Table 9 shows the performance of the simple HAS-BLED score vs other bleeding risk-assessment schemas in AF patients. The HAS-BLED score is also predictive of intracranial bleeding⁷² and has been used to predict bleeding with nonwarfarin anticoagulants.⁷³ HAS-BLED is also validated in AF and non-AF patients,⁷⁴ as well as for predicting bleeding in those undergoing bridging⁷⁵ and percutaneous coronary interventions.^{76–79}

The ATRIA Bleeding Risk Score

The ATRIA bleeding risk score (hereinafter, ATRIA bleeding score; see Table 10) defines high risk as score of 5 to 10 points.⁸⁰ The *c* statistic for predicting risk of major bleeding was 0.74 in the ATRIA cohort, and net reclassification improvement, when compared with the HEMORR₂HAGES score, was 28.9%.⁸⁰ The ATRIA score was derived from anticoagulated (and INR-stabilized) patients, whereas onset of treatment with OACs is known to be associated with higher risk of bleeding events.⁸¹ There was also concern about the definition employed for certain factors, used for generation of the ATRIA score, compared with other scores. For example, the ATRIA score

Table 9. Predictive Ability of Different Bleeding Risk-Stratification Schemes Expressed by the C Statistic in Patients With Anticoagulant Treatment

Study Cohort	No. of Anticoagulated Patients	Major Bleeding (Per 100 Patient-Years)	C Statistic (95% CI)		
			HAS-BLED Score	HEMORR ₂ HAGES Score	ATRIA Bleeding Score
Euro Heart Survey on Atrial Fibrillation ⁷⁰	1772	1.56	0.69 (0.59–0.80)	0.64 (0.53–0.75)	—
Swedish Atrial Fibrillation cohort study ¹⁸	48 599	1.9	0.61 (0.59–0.62)	0.63 (0.61–0.64)	—
Nationwide registry of AF patients in Denmark ⁷¹	44 771	5.27	0.795 (0.759–0.829)	0.771 (0.733–0.806)	—
ATRIA cohort ⁸⁰	3063	1.4	—	0.71 (0.69–0.73)	0.74 (0.72–0.76)
Roldán et al ⁸²	937	3.2	0.71 (0.68–0.74) ^a	—	0.68 (0.65–0.71)
AMADEUS trial cohort ^{72b}	2293	1.4	0.65 (0.56–0.73)	0.60 (0.51–0.69)	0.61 (0.51–0.70)

Abbreviations: AMADEUS, Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation; ATRIA, Anticoagulation and Risk Factors in Atrial Fibrillation; CI, confidence interval.
^aHAS-BLED score outperformed the ATRIA bleeding score when they were collapsed into binary groups (ie, high risk vs low plus moderate risk for major bleeding [c statistic, 0.68 (0.65–0.71) vs 0.59 (0.55–0.62), respectively]).

Table 10. Bleeding Risk Stratification With the ATRIA Score⁸⁰

Risk Factor	Score
Anemia ^a	3
Severe renal disease (eGFR <30 mL/min or dialysis dependent)	3
Age ≥75 years	2
Prior hemorrhage	1
Diagnosed hypertension	1
Maximum score	10

Abbreviations: ATRIA, Anticoagulation and Risk Factors in Atrial Fibrillation; eGFR, estimated glomerular filtration rate.
^aHemoglobin <13 g/dL in men and <12 g/dL in women and/or thrombocytopenia (platelet count <90 000).

included history of hypertension rather than uncontrolled hypertension, age cutoff of 75 years rather than 65 years, and, of particular note, concomitant aspirin use was not considered a risk factor for bleeding. The poorer performance of the ATRIA score and its inability to predict intracranial bleeding in comparison with the HAS-BLED scheme was observed in several validation cohorts (Table 9).^{72,82}

In summary, the HAS-BLED score is the best tool for bleeding prediction in patients with AF requiring or receiving anticoagulation to date, and current guidelines reflect this.³ There are a few other bleeding-risk schemes in addition to HAS-BLED, but they are less well validated or perform less well.⁶⁴

Combination Stroke and Bleeding Risk Assessment Scores

As many of the risk factors for stroke and bleeding in AF overlap, intentions to develop a combined stroke and bleeding risk-assessment tool look attractive and

Table 11. Composite Stroke and Bleeding Risk Scores⁸³

Composite Score 1	Composite Score 2
Combination of stroke/TE or major bleeding	Combination of stroke, systemic or venous embolism, MI, cardiovascular death, or major bleeding
$(\text{Age} \times 0.05) + (\text{previous stroke/TIA} \times 0.6) + (\text{concomitant ASA} \times 0.9) - (\text{TTR} \times 1.8)$	$(\text{Age} \times 0.05) + (\text{previous stroke/TIA} \times 0.6) + (\text{concomitant ASA} \times 0.7) + (\text{LV dysfunction} \times 0.6) - (\text{TTR} \times 1.4)$

Abbreviations: ASA, aspirin; LV, left ventricular; MI, myocardial infarction; TE, thromboembolism; TIA, transient ischemic attack; TTR, time in therapeutic range.

obvious. Two combined scores for stroke/TE/bleeding that offer good discriminatory and predictive performance were developed and validated in the vitamin K antagonist arm of the Evaluating the Use of Sr34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation (AMADEUS) trial (Table 11).⁸³ The composite endpoint “stroke/thromboembolism or major bleeding” was predicted by age, previous stroke/TIA, aspirin use, and time in therapeutic range. Predictors for another composite endpoint “stroke, systemic or venous embolism, myocardial infarction, cardiovascular death, or major bleeding” were the same but also included LV dysfunction.⁸³

In the recent Loire Valley Atrial Fibrillation Project analysis, their composite model included previous HF, age >75 years, age >65 years, DM, stroke, vascular disease, liver and/or renal impairment, previous bleeding, and labile INR (ie, risk factors from the HAS-BLED and CHA₂DS₂-VASc scores) and was tested for several endpoints.⁸⁴ Both studies failed to improve prediction of stroke and bleeding events beyond existing individual stroke or bleeding scores, and thereby currently recommended stroke and bleeding stratification schemes that allow greater usability and a more individualized balancing of risks should be continued.

Table 12. Quality of Anticoagulation Control Assessment With the SAME-TT₂R₂ Score⁹⁰

Risk Factors	Score
Sex category (ie, F sex)	1
Age <60 years	1
Medical history (≥2 of the following: hypertension, DM, CAD/MI, PAD, CHF, previous stroke, and pulmonary, hepatic or renal disease)	1
Treatment with interacting drugs (eg, amiodarone)	1
Tobacco use (within 2 years)	2
Race (ie, non-Caucasian)	2
Maximum score	8
Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; DM, diabetes mellitus; F, female; MI, myocardial infarction; PAD, peripheral artery disease. First letter of each row spells out the acronym.	

Other Scores

The importance of appropriate dose adjustment of warfarin with good INR control has been highlighted many times.^{3,5} Labile INR was found to be associated with both increased risk of stroke and major bleeding.^{64,70,85–88} The individual mean time in therapeutic range (TTR) is used to evaluate quality of warfarin-treatment management.

Overall survival in AF patients increases starting from a TTR of 40% compared with nonanticoagulated patients, but the risk of stroke is reduced only if TTR is above 70%.⁸⁵ In 27 458 patients taking warfarin from the UK General Practice Database, adhering to 70% threshold resulted in 79% reduction in risk of stroke when compared with patients with a TTR <30%.⁸⁶ With the increased use of novel OACs, the problem of poor anticoagulation control is likely to be partly solved,^{5,33,87} as they do not depend upon INR control; but high-quality anticoagulation control for warfarin patients remains of paramount importance⁸⁸ and is an important issue in the decision-making process regarding who is likely to fare well with being started on warfarin rather than a novel OAC.⁸⁹

The SAME-TT₂R₂ score (see Table 12 for acronym) was proposed based on an analysis of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, to help to identify which AF patients will achieve high TTR with the warfarin treatment (SAME-TT₂R₂ score 0–1), and those who are at risk of suboptimal anticoagulation control (SAME-TT₂R₂ score ≥2).⁹⁰ Additional validation of this score in a subsequent real-world validation cohort of AF patients, demonstrated that high SAME-TT₂R₂ scores (>2) were predictive of labile INRs, and consequently, serious bleeding and TE.⁹¹

Conclusion

Many stroke and bleeding risk-stratification scores are available for clinicians to use in everyday management of AF patients. A balance is needed between simplicity and practicality vs predictive value. For stroke risk, the CHA₂DS₂-VASc score has gained wide acceptance and

stratifies the majority of AF patients into high- (and moderate-) risk groups that require anticoagulation. The HAS-BLED score appears to be the best for bleeding risk assessment. Guidelines have evolved to reflect the new evidence base on how we can improve our individualized assessment of AF patients.

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