CLINICAL CARDIOLOGY

Author's accepted manuscript

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Clin Cardiol. 2014 Oct; 37(10):634-44.

DOI: 10.1002/clc.22294

Stroke and bleeding risk in atrial fibrillation – navigating the alphabet soup of risk score acronyms ($CHADS_2$, CHA_2DS_2-VASc, R_2CHADS_2, HAS-BLED, ATRIA and more)

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Abstract

Stroke prevention is central to the management of patients with atrial fibrillation (AF). As effective stroke prophylaxis essentially requires oral anticoagulants (OAC) an understanding of the risks and benefits of OAC therapy is needed. While 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 varies 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 CHA_2DS_2-VASc and HAS-BLED schemes, as these are recommended by the latest European guidelines on AF management. Other risk stratification schemes ($CHADS_2$, R_2CHADS_2, ATRIA, $HEMORR_2HAGES$, QStroke, etc.) and their place in the decision-making are also considered.

Key words: atrial fibrillation, stroke, bleeding, risk assessment.

Introduction

The increasing prevalence of atrial fibrillation (AF) brings 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] While 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 varies 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 CHA_2DS_2-VASc and HAS-BLED schemes, as these are recommended by the latest European guidelines on AF management.[3,6] Other risk stratification schemes ($CHADS_2$, R_2CHADS_2, ATRIA, $HEMORR_2HAGES$, QStroke, etc) and their place in the decision-making are also considered.

Stroke risk

There are 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 cohorts. 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, for example, blood pressure. The (independent) impact of a particular stroke risk factor is also best tested in a non-anticoagulated 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 seven studies (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 history of stroke or transient ischaemic 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 or systolic blood pressure >160 mmHg depending on study; 2.0-fold higher risk) and diabetes mellitus (irrespective of severity, duration and quality of glycemic control; 1.7-fold higher risk) increased stroke risk.[9] 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 non-warfarin 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 was not found to be an independent risk factor for stroke development.[9] One reason may be a discrepancy in definitions of heart failure between studies, whether defined as heart failure per se, recent congestive heart failure, severe-to-moderate systolic dysfunction, fractional shortening ≤25%, assessed via echocardiography, etc. Data about stroke risk associated with female gender 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 2.86), hypertension (risk ratio 2.27), ageing (risk ratio 1.46 per decade increase), structural heart disease (risk ratio 2.0) and diabetes (risk ratio 1.62). Female sex (risk ratio 1.67), vascular disease (risk ratio 2.61) and heart failure (risk ratio 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=90490, approximately 1.5 years follow-up, 7334 thromboembolic events), where peripheral artery disease (22% risk increase), myocardial infarction (9% risk increase), coronary artery bypass graft (19% risk increase), peripheral artery disease (22% risk increase), any vascular disease (14% risk increase), female gender (17% risk increase), intracranial haemorrhage (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, diabetes mellitus, age and previous stroke was confirmed, while heart failure defined as just 'history of' was not an independent stroke risk factor.[18]

Of note, type of AF (paroxysmal or non-paroxysmal) 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]

$CHADS_2$ score

The $CHADS_2$ score (Table 1) is one of the simplest and commonly used stroke risk stratification scheme. It was derived by the combination of stroke risk factors established in the AFI and SPAF studies.[20] Compared to the AFI and SPAF risk schemes, the original $CHADS_2$ score validation publication included 'any history of hypertension', instead of the SPAF trial definition of systolic blood pressure higher than 160 mmHg; '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 heart failure.[20] $CHADS_2$ is a point system where 2 points were assigned to a history of prior cerebral ischemia and 1 point was assigned for the presence of each of the other risk factors, with a maximum of 6 points in total.

Initial validation of the $CHADS_2$ score was performed in the National Registry of Atrial Fibrillation (NRAF) participants who had non-rheumatic AF and were not taking anticoagulation therapy at hospital discharge (n=1733).[20] A strong relationship was found between the $CHADS_2$ score and the adjusted stroke rate (Table 1).[20] The $CHADS_2$ score showed the highest performance comparatively to SPAF and AFI schemes.[20] 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]) was 0.82; 0.74 and 0.68 for the three schemas, respectively.[20] Adjustment for aspirin therapy as well as subdivision into low ($CHADS_2$ 0-1), moderate ($CHADS_2$ 2-3) and high ($CHADS_2$ 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 $CHADS_2$ 0, while 'moderate risk' was defined as $CHADS_2$ 1-2, and 'high risk' as $CHADS_2$>2.[21] This was problematic, since 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 stokes. Subsequent treatments based on the $CHADS_2$ score was revised with 'moderate risk' being defined as $CHADS_2$=1 and 'high risk' as $CHADS_2$ ≥2.[22] More recent guidelines even recommended oral anticoagulation for those with $CHADS_2$ ≥1.[23]

The predictive value of the $CHADS_2$ score was further analyzed in a cohort of 2580 patients with nonvalvular AF taking aspirin (207 ischaemic strokes, 4887 patient-years), and compared with the AFI[12,13], SPAF[11], Framingham[10] and ACCP (American College of Chest Physicians)[24] risk stratification schemes.[25] The $CHADS_2$ 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 to 1.4 strokes per 100 patient-years of therapy).[25] A good performance of the $CHADS_2$ 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 five stratification schemes including $CHADS_2$ to the ATRIA cohort (n=13559, six year follow-up, 685 thromboembolic events) showed poor discriminative ability (c-statistics 0.58) with only a minor increase in thromboembolism rate with corresponding increase in the risk category. A significant proportion of patients without thromboembolism 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 $CHADS_2$ score had a c-statistic of 0.66 and other risk scores ranged 0.58-0.67.[18] Low performance of the $CHADS_2$ score was also seen in the systematic review of several studies but wide heterogeneity was evident.[28]

In summary, the $CHADS_2$ score manages well in identifying high risk patients but provides, ambiguous results in those at low or moderate stroke risk.[29] Thus, the $CHADS_2$ 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 thromboembolism risk factors were not included; and third, discrepancy between the original validation and further applications in guidelines and 'real world' cohorts.[30,31]

CHA_2DS_2-VASc score

To overcome some of the limitations of the $CHADS_2$ score, the CHA_2DS_2-VASc (see Table 2 for acronym) score has been proposed, giving extra weight to age ≥75, since this is a major driver of stroke risk, and including additional risk factors such as age 65-74, female gender and vascular disease.[6,32]

The CHA_2DS_2-VASc score was proposed as a risk factor based approach, which de-emphasised the artificial low, moderate and high risk classification. This score assigns 2 points to prior stroke, TIA, or thromboembolism, and older age [≥75 years]), as the major risk factors. Other clinically relevant non-major risk factors are assigned 1 point each: heart failure (moderate to severe systolic left ventricular dysfunction, defined arbitrarily as left ventricular ejection fraction ≤40%, or recent decompensated heart failure requiring hospitalisation), hypertension, diabetes, female sex, age 65–74 years, and vascular disease (e.g., myocardial infarction, complex aortic plaque and peripheral artery disease).[6,32]

With the introduction of the CHA_2DS_2-VASc score, categorization of the AF patients improved significantly with respect to selecting patients at low risk of stroke (essentially, a CHA_2DS_2-VASc=0 in males or CHA_2DS_2-VASc=1 in females).[4,5,33] These are the patients with lone AF without structural heart disease and aged <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 oral anticoagulation.[3]

The advantages of the CHA_2DS_2-VASc score were clearly demonstrated in a retrospective analysis performed in the Danish nationwide cohort study which involved 19444 patients with $CHADS_2$ score=0, i.e., low risk patients. When their stroke risk was substratified according to the CHA_2DS_2-VASc score, those with a $CHADS_2$ score=0 had stroke rates ranging from 0.8%/year to 3.2%/year.[34] For the 28132 subjects with the $CHADS_2$ score=1, the stroke rate based on substratification according to the CHA_2DS_2-VASc score was as high as 8.18 % at one year.[34]

Since a $CHADS_2$ score=0 (or 1) can confer significant stroke risk, the benefits of oral anticoagulation in comparison to antiplatelet or no antithrombotic therapy in these patients are evident.[35,36] Indeed, a lower stroke incidence was found in patients taking warfarin compared to 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 higher risk of stroke in the group of non-anticoagulated patients with $CHADS_2$ score=1.[36]

What is the impact of 'non-$CHADS_2$' risk factors? Peripheral artery disease taken separately was associated with an even higher risk than myocardial infarction (93% vs. 12% increase in risk).[37] In the Loire Valley Atrial Fibrillation Project (n=6438), vascular disease when added to the $CHADS_2$ score improved stratification of patients (net reclassification improvement 0.4).[38] In a Taiwanese nationwide database analysis (n=7920) there was positive link between peripheral artery disease and ischaemic stroke development (odds ratio 1.81).[39]

The value of female gender as a risk factor for stroke in AF was reported previously.[17] In the Swedish Atrial Fibrillation cohort female gender remained an independent predictor (14% increase in risk).[39] This was also evident in a population-based cohort from the Quebec, Canada (14% increase in risk)[41] 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 rises from age 65 upwards, and each ten years of aging results in 1.5-fold increase in risk.[43] Stroke/thromboembolic rate increased significantly from 0.23 to 2.05 and 3.99 for <65, 65-74 and ≥75 age categories, respectively.[38] On average, a 3-fold and 5-fold increase in risk of stroke was observed for the latter two age categories when compared with those younger than 65.[18]

The controversy of heart failure as risk factor of stroke has already been pointed out above. The CHA_2DS_2-VASc score uses heart failure defined as moderate to severe left ventricular systolic dysfunction or recent heart failure 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 heart failure 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/thromboembolism between patients with heart failure with preserved ejection fraction, compared to those with heart failure and reduced ejection fraction.[45] Another study found a 3.3-fold higher rate (20.6% vs. 6.7%) of ischaemic stroke and 5.5-fold of death (27.2% vs. 2.0%) in patients with AF and heart failure with preserved ejection fraction compared to those with AF only after 3 years of follow-up.[46]

Since initial derivation and validation of the CHA_2DS_2-VASc score in the Euro Heart Survey on AF[32], its performance has also been confirmed in the 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 0.658 to 0.728) as shown in the Chi-Shan Community Cohort Study (n=3524, approximately 16 years of follow-up).[49]

In summary, the performance of the CHA_2DS_2-VASc score for predicting those at high risk of stroke/thromboembolism was comparable with other contemporary risk stratification schemes as the 8th ACCP[51], NICE[52] and modified $CHADS_2$[32]. The CHA_2DS_2-VASc score is currently recommended by the European guidelines on AF management as the main scheme to assess patient's stroke risk[3] because of its' ability to identify low risk patients as this was the principal group that do not need anticogulation.[33]

R_2CHADS_2 score

The R_2CHADS_2 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=14264).[53] The score incorporates the components of the $CHADS_2$ score and also assigns 2 points for creatinine clearance <60 mL/min.[53]

Development of the R_2CHADS_2 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 end-point (stroke, acute coronary syndrome, acute heart failure); there was a 42% increase in risk with each 30 $ml/min/1.73\ m^2$ eGFR decrease.[54]

The R_2CHADS_2 score had a c-statistic 0.587 and did not differ from the CHA_2DS_2-VASc and the $CHADS_2$ schemes (0.578 and 0.575, respectively) in the ROCKET AF cohort.[53] It was not better in predicting of thromboembolic events than the above-mentioned schemes 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) as well.[55]

The R_2CHADS_2 score has many limitations which may affect its performance, for example, derivation from a selected anticoagulated clinical trial cohort, which excluded patients with the creatinine clearance <30 mL/min and included those with a high risk of stroke development, etc.[56] The latter is contradictory to current recommendations to firstly identify low risk patients. Moreover, kidney dysfunction is known to be independently associated with female gender, advanced age, heart failure (i.e., components of $CHADS_2$), that eventually may lead to a reduction of the predictive value of the R_2CHADS_2 score.[57] Thus, as renal dysfunction in general results in poorer prognosis of AF patients, the independent predictive value of the R_2CHADS_2 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, 77578 strokes, validation cohort n=1.9 million, 38404 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 calculation 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 that was developed for the purpose of predicting cardiovascular disease risk.[59,60]

In the validation cohort, the QStroke scheme did slightly better than the CHA_2DS_2-VASc and $CHADS_2$ 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 three schemes, respectively.[58] Thus, despite high representativeness, duration of the follow-up, size of derivation and validation cohorts, and general availability of data which 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 towards a more complex and less practical approach to individual stroke risk calculation.

The ATRIA stroke risk score

The ATRIA stroke risk score (hereinafter referred to as the ATRIA score) is the newest stroke risk stratification scheme proposed. This score was derived from 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=10927).[61] The ATRIA score represents a point-based stratification scheme (Table 5) separately for patients without prior stroke (i.e., primary prevention) and those with history of stroke (i.e., 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=25306, 496 thromboembolic events). C-statistics were 0.70 for the ATRIA score, 0.66 for $CHADS_2$ and 0.68 for CHA_2DS_2-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 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 CHA_2DS_2-VASc and the $CHADS_2$ 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 under-treatment of AF patients with oral anticoagulants particularly those with non-severe thromboembolism with further much more devastating outcomes.

Bleeding risk assessment in atrial fibrillation

Increased risk of haemorrhage, particularly intracranial bleeding, is a downside of thromboprophylaxis with oral anticoagulation. The annual incidence of the anticoagulant-associated intracranial bleeding increased from 0.8 to 4.4 per 100,000 people during the nineties, 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 INRs (if on warfarin), concomitant use of aspirin or NSAIDs, alcohol excess, etc. 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 oral anticoagulants. Also, bleeding events may vary in severity. Many current bleeding risk schemes evaluate major bleeding, that is, those involving critical sites (intracranial, retroperitoneal, intraspinal, intraocular, pericardial, atraumatic intra-articular haemorrhage) which may be potentially fatal. There are also laboratory indices of major bleeding like a drop of hemoglobin more than 2 g/dl or need to transfuse 2 or more units of packed red blood cells.[65]

Some stroke and bleeding risk factors are broadly similar, for example, advanced age, female gender, arterial hypertension, congestive heart failure, etc. – and these are usually non-modifiable.[66] Of note, bleeding risk should not be considered as a contraindication or a reason to discontinue treatment with the oral anticoagulants, as the reduction in stroke risk on anticoagulation usually far exceeds the elevation in bleeding risk. For example, in the cohort of 13559 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, i.e., 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 CHA_2DS_2-VASc=0, were found not to benefit from warfarin therapy.[68]

$HEMORR_2HAGES$ score

The $HEMORR_2HAGES$ 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 one point for each risk factor but two points for previous bleeding, and denoted a score of ≥4 as high risk. Based on the original analysis, the $HEMORR_2HAGES$ 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 AF cohort (n=3978, 1-year follow-up, 1.5% of major bleedings) with inclusion of previously established bleeding risk factors.[70] Hypertension was defined as uncontrolled hypertension (systolic blood pressure >160 mmHg). Abnormal renal function refers to serum creatinine ≥200 µmol/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 (e.g., antiplatelets or non-steroidal anti-inflammatory drugs). Alcohol abuse or excess implies for more than (say) 20 units per week. The resultant HAS-BLED score is a sum of one 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.[70]

Table 9 shows the performance of the simple HAS-BLED score versus other bleeding risk assessment schemas in AF patients. The HAS-BLED score is also predictive of intracranial bleeding[72], and has been used to predict bleeding with non-warfarin anticoagulants[73]. HAS-BLED is also validated in AF and non-AF patients[74], as well as for predicting bleeding in those undergoing bridging[75] and percutaneous coronary interventions[76-79].

The ATRIA bleeding risk score

The ATRIA bleeding risk score (hereinafter referred to as 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 HEMORR$_2$HAGES score, was 28.9%.[80] The ATRIA score was derived from anticoagulated (and INR-stabilized) patients, whereas onset of treatment with oral anticoagulants 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 to other scores. For example, the ATRIA score included history of hypertension rather than uncontrolled hypertension, age cut-off 75 years rather 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 combined stroke and bleeding risk assessment tool look attractive and obvious. Two combined scores for stroke/thromboembolism/bleeding that offer good discriminatory and predictive performance were developed and validated in the vitamin K antagonist arm of the AMADEUS trial (Table 11).[83] The composite end point 'stroke/thromboembolism or major bleeding' was predicted by age, previous stroke/TIA, aspirin use, and time in therapeutic range. Predictors for another composite end point 'stroke, systemic or venous embolism, myocardial infarction, cardiovascular death, or major bleeding' were the same but also included left ventricular dysfunction.[83]

In the recent Loire Valley Atrial Fibrillation Project analysis, their composite model included previous heart failure, age >75, age >65, diabetes mellitus, stroke, vascular disease, liver and/or renal impairment, previous bleeding and labile INR (i.e. risk factors from the HAS-BLED and CHA_2DS_2-VASc scores) and was tested for several end-points.[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 which allow greater usability and a more individualized balancing of risks should be continued.

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 both with 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 to non-anticoagulated patients, but the risk of stroke is reduced only if TTR is above 70%.[85] In 27458 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 oral anticoagulants 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 importance[88] and an important issue in the decision making process of who's likely to fare well with being started on warfarin rather than a novel oral anticoagulant[89].

The SAMe-TT_2R_2 score (see Table 12 for acronym) was proposed based on an analysis of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, in order to help to identify which AF patients will achieve high TTR with the warfarin treatment (SAMe-TT_2R_2 score 0-1), and those who are at risk of suboptimal anticoagulation control (SAMe-TT_2R_2 score ≥2).[90] Additional validation of this score in a subsequent 'real world' validation cohort of AF patients, demonstrated that high SAMe-TT_2R_2 scores (>2) were predictive of labile INRs, and consequently, serious bleeding and thromboembolism.[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, versus predictive value. For stroke risk, the CHA_2DS_2-VASc score has gained wide acceptance, and stratifies the majority of AF patients into high (and moderate) risk group that requires 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 individualised assessment of AF patients.

Disclosure of conflict of interests.

G.Y.H.L. has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife and Daiichi-Sankyo and has been on the speakers bureau for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife and Daiichi-Sankyo.

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, BMS/Pfizer. In addition, DAL is on the Steering Committee of a Phase IV apixaban study (AEGEAN) and is a panellist on the 9th edition of the American College of Chest Physicians guidelines on antithrombotic therapy in AF.

G.Y.H.L. and D.A.L. are co-authors of the CHA_2DS_2-VASc and HAS-BLED scores.

M.S.D. has no conflicts of interest to declare.

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Table 1. Stroke risk stratification with the $CHADS_2$ score[20]

Risk factor	Score	$CHADS_2$ score	Stroke rate, %
Congestive heart failure (recent)	1	0	1.9
Hypertension(history of)	1	1	2.8
Age ≥75 years	1	2	4.0
Diabetes mellitus	1	3	5.9
Stroke/transient ischaemic attack (TIA)	2	4	8.5
		5	12.5
		6	18.2
Maximum score	6		

Table 2. Stroke risk stratification with the CHA_2DS_2-VASc scheme[32]

Risk factor	Score	CHA_2DS_2-VASc score	Thrombo-embolic event rate[44]
Congestive heart failure/LV dysfunction	1	0	0
Hypertension	1	1	1.3
Age ≥75 years	2	2	2.2
Diabetes mellitus	1	3	3.2
Stroke/TIA/TE	2	4	4.0
Vascular disease (prior MI, PAD, or aortic plaque)	1	5	6.7
Aged 65–74 years	1	6	9.8
Sex category (i.e. female gender)	1	7	9.6
		8	6.7
		9	15.2
Maximum score	9		

LV, left ventricular; MI, myocardial infarction; PAD, peripheral artery disease; TIA/TE, transient ischemic attack/thromboembolism

Table 3. Predictive ability of different risk stratification schemes, as expressed by the c-statistic, in patients without anticoagulant treatment

Study cohort	**No of patients**	**Stroke / thrombo-embolism rate (per 100 patient-years)**	**C-statistic (95% confidence interval)[a]**		
			CHA_2DS_2-VASc score	**$CHADS_2$ score (revised)**	**$CHADS_2$ score (classical)**
Euro Heart Survey on Atrial Fibrillation[32]	1 084	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 to 0.871) [d]	0.722 (0.694 to 0.748) [d]	
Community-based cohort study from Olmsted County, Minnesota[26]	2 720	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[49 e]	7329	1.63	0.647 (0.613, 0.678)	0.637 (0.607-0.674)	0.637 (0.607-0.674)

[a] for categorization into 3 groups (low, moderate and high risk) in all studies, apart from Swedish Atrial Fibrillation cohort study, in which ‘low risk’ versus ‘intermediate or high risk’ were analysed; [b] according to the CHA_2DS_2-VASc score; [c] for strokes recorded by the general practitioners or in hospital; [d] at 1 year follow-up, rising to 0.888 (0.875-0.900) and 0.812 (0.796-0.827) at 10 years follow-up for the CHA_2DS_2-VASc and $CHADS_2$ scores, respectively; [e] anticoagulated trial cohorts

Table 4. Stroke risk stratification with the R_2CHADS_2 scheme[53]

Risk factor	Score
Renal dysfunction (i.e. creatinine clearance <60 mL/min)	2
Congestive heart failure (recent)	1
Hypertension	1
Age ≥75 years	1
Diabetes mellitus	1
Stroke/transient ischaemic attack	2
Maximum score	8

Table 5. Stroke risk stratification with the QStroke[a,b] scheme[58]

Risk factor	Score
Age (at entry)	Range 25-84
Sex	Separate models for women and men
Treated hypertension (diagnosis of hypertension and ≥1 current prescription for ≥1 antihypertensive)	Yes/No
Type 1 diabetes	Yes/No
Type 2 diabetes	Yes/No
Atrial fibrillation	Yes/No
Congestive cardiac failure	Yes/No
Coronary heart disease	Yes/No
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(non-smoker, ex-smoker, light smoker (<10 cigarettes/day), moderate smoker (10-19 cigarettes/day), heavy smoker (≥20 cigarettes/day)	5 categories
Systolic blood pressure	Continuous
Cholesterol:HDL ratio	Continuous
Body mass index	Continuous
Family history of coronary disease (in first degree relative <60 years of age)	Yes/No
Rheumatoid arthritis	Yes/No
Chronic renal disease	Yes/No
Valvular heart disease	Yes/No
Maximum score	99%

[a] Importantly previous stroke or transient ischaemic attack 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

Table 6. Stroke risk stratification with the ATRIA score[61]

Risk factor	Score without prior stroke	Score with prior stroke
Age		
≥85	6	9
75 to 84	5	7
65 to 74	3	7
<65	0	8
Female	1	1
Diabetes	1	1
Congestive heart failure	1	1
Hypertension	1	1
Proteinuria	1	1
eGFR<45 or ESRD	1	1
Maximum score	12	15

eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease

Table 7. Bleeding risk stratification with the $HEMORR_2HAGES$ score[69]

Risk factor	Score
Hepatic or renal disease	1
Ethanol abuse	1
Malignancy	1
Older (aged ≥75 years)	1
Reduced platelet count or function	1
Rebleeding risk	2
Hypertension(uncontrolled)	1
Anaemia	1
Genetic factors (CYP2C9 single nucleotide polymorphism)	1
Excessive fall risk	1
Stroke	1
Maximum score	12

Table 8. Bleeding risk stratification with the HAS-BLED score[70]

Risk factors	**Score**
Hypertension (systolic blood pressure >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
Age (e.g.,>65, frail condition)	1
Drugs (e.g., concomitant antiplatelet or NSAIDs) or alcohol excess/abuse	1 or 2
Maximum score	9

INR, international normalized ratio; NSAIDs, non-steroidal anti-inflammatory drugs

Table 9. Predictive ability of different bleeding risk stratification schemes, as 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% confidence interval)**		
			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]	48599	1.9	0.61 (0.59–0.62)	0.63 (0.61–0.64)	-
Nationwide register of AF patients in Denmark[71]	44771	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[72] [b]	2293	1.4	0.65 (0.56–0.73)	0.60 (0.51–0.69)	0.61 (0.51–0.70)

AMADEUS, Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation

[a] HAS-BLED score outperformed the ATRIA bleeding score, when they were collapsed into binary groups, i.e. high risk vs. low plus moderate risk for major bleeding (c-statistic 0.68 [0.65-0.71] versus 0.59 [0.55-0.62], respectively).

Table 10. Bleeding risk stratification with the ATRIA score[80]

Risk factor	Score
Anaemia [a]	3
Severe renal disease (eGFR <30 ml/min or dialysis-dependent)	3
Age ≥75years	2
Prior haemorrhage	1
Diagnosed hypertension	1
Maximum score	10

[a] haemoglobin <13 g/dl in men and <12 g/dl in women and/or thrombocytopenia (platelet count <90,000)

Table 11. Composite stroke and bleeding risk scores[83]

Composite score 1	Composite score 2
Combination of stroke/thromboembolism or major bleeding	**Combination of stroke, systemic or venous embolism, myocardial infarction, cardiovascular death, or major bleeding**
(Age x 0.05) + (Previous stroke/TIA x 0.6) + (Concomitant aspirin x 0.9) – (TTR x 1.8)	**(Age x 0.05) + (Previous stroke/TIA x 0.6) + (Concomitant aspirin x 0.7) + (LV dysfunction x 0.6) – (TTR x 1.4)**

LV, left ventricular; TIA, transient ischemic attack; TTR, time in therapeutic range

Table 12. Quality of anticoagulation control assessment with the SAMe-TT_2R_2 score[90]

Risk factors	Score
Sex category (i.e. female gender)	1
Age <60 years	1
Medical history (≥2 of the following: hypertension, DM, CAD/MI, PAD, CHF, previous stroke, pulmonary, hepatic or renal disease)	1
Treatment with interacting drugs (e.g., amiodarone)	1
Tobacco use (within 2 years)	2
Race (i.e. non-caucasian)	2
Maximum score	8

CAD, coronary artery disease; CHF, congestive heart failure; DM, diabetes mellitus; MI, myocardial infarction; PAD, peripheral artery disease