



## Stroke And Bleeding Risk Assessment: Where Are We Now?

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### Abstract

Atrial fibrillation (AF) is one of major problems of the contemporary cardiology. Ischaemic stroke is a common complication of the AF, and effective prophylaxis requires treatment with oral anticoagulants. The purpose of this current review article is to provide an overview of the various stroke and bleeding risk assessment scores that help decision making with respect to thromboprophylaxis.

Particular focus is made on the currently guideline-recommended stroke and bleeding risk scores, such as CHA<sub>2</sub>DS<sub>2</sub>-VASc (congestive heart failure or left ventricular dysfunction, hypertension, age  $\geq 75$ , diabetes, stroke, vascular disease, age 65–74 and sex category [female]) and HAS-BLED (uncontrolled hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly [e.g. age  $> 65$ , frail condition], drugs [e.g. aspirin, nonsteroidal anti-inflammatory drugs]/excessive alcohol) is made. Future directions for improvement of predictive ability of risk assessment with clinical factors and biomarkers are also discussed.

### Introduction

Atrial fibrillation (AF) is one of commonest cardiovascular conditions we deal with. The prevalence of AF is approximately 1–2% in the general population.<sup>1</sup> In a recent study population-based study, the prevalence of AF was 3.2% in subjects age  $\geq 20$  years old.<sup>2</sup> Ischaemic stroke is one of the major complications of AF, which has a high mortality and disability when strokes occur in association with AF.<sup>3</sup>

Effective thromboprophylaxis requires treatment with oral anticoagulants. Currently, two options, either the vitamin K antagonists (VKAs, eg. warfarin), or the non-VKA (previously referred to as novel or new) oral anticoagulants such as the oral direct thrombin inhibitor (dabigatran) or the oral factor Xa blockers [rivaroxaban, apixaban, edoxaban].<sup>4</sup> Whilst effective in reducing stroke and all cause mortality, oral anticoagulants result in an elevated risk of bleeding that can sometimes be life-threatening.<sup>5</sup> Intracranial bleeding is the most devastating example of major bleeding events, but is up to 9 times less common than ischaemic strokes.<sup>2</sup> Thus, the

net clinical benefit of oral anticoagulation (balancing ischaemic stroke versus major bleeding) was generally positive in AF with one or more stroke risk factors.<sup>6,7</sup>

The purpose of the current review article is to provide an overview of the various stroke and bleeding risk assessment tools. These are validated instruments which provide help in making decisions with respect to antithrombotic prophylaxis. Particular focus will be on the currently recommended risk scores as CHA<sub>2</sub>DS<sub>2</sub>-VASc (congestive heart failure or left ventricular dysfunction, hypertension, age  $\geq 75$ , diabetes, stroke/transient ischaemic attack [TIA], vascular disease, age 65–74 and sex category [female]), and HAS-BLED (uncontrolled hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly [e.g. age  $> 65$ , frail condition], drugs [e.g. antiplatelet, nonsteroidal anti-inflammatory drugs]/excessive alcohol). Future directions for improvement of predictive ability of risk assessment with clinical factors and biomarkers are also discussed.

### Stroke Risk Assessment In Atrial Fibrillation

There are various published stroke risk stratification schemes, amongst which the CHADS<sub>2</sub> score (congestive heart failure, hypertension, age  $\geq 75$ , diabetes mellitus, stroke/TIA) and the CHA<sub>2</sub>DS<sub>2</sub>-VASc scores are most commonly used, having been validated and compared in numerous clinical trial populations and 'real world' cohorts.<sup>8,9</sup>

Previous stroke risk scores from older guidelines<sup>10–12</sup> as well as the Framingham score,<sup>13</sup> and 'classical' CHADS<sub>2</sub> score<sup>14</sup> have all focused on stroke risk assessment by (artificially) categorizing patients into three risk categories: low, moderate and high. This was explained from the practical point of view, because thromboprophylaxis was

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### Disclosures:

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down to an inconvenient drug, warfarin – and if not, aspirin. Thus, old guidelines had focused on the identification of ‘high risk’ patients who could be targeted for warfarin.

First, such artificial categorization leads to more crude estimation and overall reduced discriminative ability of the risk stratification tools, that is, potential misclassification of patient’s stroke risk and following inappropriate treatment.<sup>15-17</sup> Second, risk assessment schemes are strongly dependent on the cohorts, from which they were derived and validated. These cohorts, particularly those from older clinical trials and epidemiological studies, can be extensively variable in terms of documentation of stroke risk factors and differences in definitions of stroke risk factors between cohorts. For example, ‘hypertension’ may stand for ‘history of hypertension’ [irrespective of stage or clinical course] or ‘uncontrolled hypertension’ [systolic blood pressure >160 mmHg].<sup>8,9</sup> Third, freedom to choose between drugs for antithrombotic prophylaxis is likely to be cause of undertreatment of patients with AF. Indeed, aspirin was erroneously perceived to be safer with lower rates of bleeding, and sufficiently effective to prevent thromboembolic events; also, aspirin more convenient as it did not require regular monitoring of the quality of anticoagulation.<sup>18,19</sup>

In the EuroHeart survey, patients with AF were often prescribed oral anticoagulation irrespective of stroke risk both in low (up to half of patients) and high risk strata, thus underscoring their low directive impact on the decision-making when prescribing oral anticoagulants.<sup>20</sup> Anticoagulation was also more commonly used in such circumstances as the first episode of AF, absence of significant comorbidity, and the availability of facilities for regular INR control. On the contrary, well known components of the CHADS<sub>2</sub> score (history of stroke/TIA, hypertension, age >75 years) were associated with the administration of aspirin.<sup>20</sup> Moreover, separate risk categories overlapped when different risk stratification schemes were applied.<sup>20</sup> Indeed, the relative complexity of the compared risk assessment tools (apart from the CHADS<sub>2</sub>) and inconsistency between guidelines were acknowledged as one of the reason for such ‘unexpected’ results.<sup>20</sup>

We now recognize that aspirin was is neither effective nor safe for stroke prevention. In the meta-analysis of antithrombotic therapy in patients with non-valvular A, warfarin was superior to antiplatelet therapy (39% relative risk reduction, 95% confidence interval [CI] 22-52%) and aspirin monotherapy did not significantly reduce the

incidence of stroke.<sup>21</sup> Furthermore, this aspirin was ineffective with increasing age.<sup>22</sup>

In the ‘real world’ Danish nationwide cohort study, significant reductions of stroke risk with warfarin in comparison with aspirin, as well as similarity of bleeding risk with warfarin and aspirin were confirmed.<sup>7</sup> Also, the significant value of warfarin was seen in patients with one stroke risk factor eg. CHADS<sub>2</sub> score=1.<sup>23,24</sup>

Clearly things may be improving, over the last decade, with about 80% of AF patients with ≥1 stroke risk factors now being prescribed oral anticoagulants, although the rate of administration of antiplatelet agents still remains high, particularly in patients with elevated bleeding risk.<sup>25</sup>

Basically, various stroke risk stratification schemes are based on various permutations of stroke risk predictors in AF. These include such independent risk factors as stroke/TIA, increasing age, history of hypertension, and diabetes mellitus. The predictive role of the female gender, heart failure, and vascular disease are supported by more recently available data.<sup>26,27</sup>

### The CHADS<sub>2</sub> Score

The CHADS<sub>2</sub> score is one of the simplest risk stratification schemes, and was derived by the combination of 2 stroke risk classification schemes from non-anticoagulated arms of AF Investigators (AFI) and Stroke Prevention and Atrial fibrillation (SPAF) datasets, including: prior cerebral ischemia, history of hypertension, diabetes mellitus, congestive heart failure and age ≥75 years.<sup>14</sup> Two points were assigned to a history of prior cerebral ischemia and 1 point was assigned for the presence of other risk factors.<sup>14</sup> One validation of CHADS<sub>2</sub> score was performed on an independent sample of National Registry of Atrial Fibrillation. participants and was highly correlated with the stroke rate: 1.9 (95% CI 1.2-3.0) for a score of 0; 2.8 (95% CI 2.0-3.8) for 1; 4.0 (95% CI 3.1-5.1) for 2; 5.9 (95% CI 4.6-7.3) for 3; 8.5 (95% CI 6.3-11.1) for 4; 12.5 (95% CI 8.2-17.5) for 5; and 18.2 (95% CI 10.5-27.4) for 6.<sup>14</sup>

The CHADS<sub>2</sub> score was further tested in 2580 participants with nonvalvular AF taking aspirin from several randomized trials (Atrial fibrillation, Aspirin, Anticoagulation I Study [AFASAK-1], AFASAK-2, European Atrial Fibrillation Trial, Primary Prevention of Arterial Thromboembolism in patients with nonrheumatic AF in primary care study and SPAF III) in comparison with the AFI, SPAF, ACCP and Framingham stratification criteria.<sup>28</sup> In this study, the CHADS<sub>2</sub> scheme identified successfully and better than other stratification schemes primary prevention patients who were at high-risk of stroke as well as low risk patients were identified equally by all schemes.<sup>28</sup> However, in the ATRIA (AnTicoagulation and Risk Factors In Atrial Fibrillation) cohort of 13559 adults with AF and 685 validated thromboembolic events during median follow-up of 6.0 years the CHADS<sub>2</sub> score was not superior to other stratification schemes (AFI, SPAF, Framingham, 7th ACCP) in prediction of stroke or other thromboembolic events, which all had c-statistics ranging from 0.56 to 0.62.<sup>29</sup>

There was a concern as for appropriateness of stratification with the CHADS<sub>2</sub> scheme, particularly in its ‘classical’ interpretation. As many as >60% AF patients could be categorized into the ‘moderate or intermediate risk’ stratum with the CHADS<sub>2</sub> scheme, where guidelines recommended ‘warfarin or aspirin’ which made decision-making difficult.<sup>29</sup> The most obvious example is a history of stroke or TIA in the absence of other CHADS<sub>2</sub> risk factor, where the CHADS<sub>2</sub>

**Table 1: Stroke and bleeding risk stratification with the CHA<sub>2</sub>DS<sub>2</sub>-VASC<sup>30</sup> and HAS-BLED<sup>56</sup> scores**

CHA <sub>2</sub> DS <sub>2</sub> -VASC	Score	HAS-BLED	Score
Congestive heart failure/LV dysfunction	1	Hypertension (systolic blood pressure >160 mmHg)	1
Hypertension	1	Abnormal renal or liver function	1 or 2
Age ≥75 years	2	Stroke	1
Diabetes mellitus	1	Bleeding tendency or predisposition	1
Stroke/TIA/TE	2	Labile INRs (if on warfarin)	1
Vascular disease (prior MI, PAD, or aortic plaque)	1	Age (e.g., >65, frail condition)	1
Aged 65–74 years	1	Drugs (e.g., concomitant antiplatelet or NSAIDs) or alcohol excess/abuse	1 or 2
Sex category (i.e. female gender)	1		
Maximum score	9		

INR, international normalized ratio; LV, left ventricular; MI, myocardial infarction; NSAIDs, non-steroidal anti-inflammatory drugs; TIA/TE, transient ischemic attack/thromboembolism; PAD, peripheral artery disease

score will be equal to 2, which will define patient's risk as 'moderate' although systematic reviews of stroke risk factors all consider history of prior cerebral ischaemia as the most powerful predictor of stroke recurrence (relative risk 2.5, 95% CI 1.8 to 3.5).<sup>26</sup> More recently, the low/moderate/high risk strata using the CHADS<sub>2</sub> score was defined in the following way: CHADS<sub>2</sub>=0 – low risk, CHADS<sub>2</sub>=1 – moderate risk, CHADS<sub>2</sub>≥2 – high risk.<sup>30</sup> Recommendations on initiation of anticoagulation therapy in several guidelines were revised correspondingly with the CHADS<sub>2</sub>≥1 as indication for oral anticoagulants.<sup>31,32</sup>

Nonetheless, the low risk stratum according to the CHADS<sub>2</sub> score still appears have an adjusted stroke rate of 1.9 (95% CI 1.2–3.0) per 100 patient-years.<sup>14</sup> In the Danish nationwide cohort study (total number of participants 47576), there were 19444 patients at low stroke risk using the CHADS<sub>2</sub> score (score=0). They developed 275 strokes during 1-year follow-up, with a stroke rate was 1.59 (1.41–1.79).<sup>33</sup> If these patients were substratified by the CHA<sub>2</sub>DS<sub>2</sub>-VASc score (see later), the stroke rate ranged from 0.84 (95% CI 0.65–1.08) if CHA<sub>2</sub>DS<sub>2</sub>-VASc=0 versus 3.2 (95% CI 1.60–6.40) if CHA<sub>2</sub>DS<sub>2</sub>-VASc=3.<sup>33</sup> In the United Kingdom General Practice Research Database, which included 79844 patients with AF during approximately 4 years follow-up, the average annual incidence rate in the CHADS<sub>2</sub>=0 was lower (1.0 per 100 person-years), but still more than 2-times higher when compared with the CHA<sub>2</sub>DS<sub>2</sub>-VASc=0.34

### The CHA<sub>2</sub>DS<sub>2</sub>-VASc Score

The CHA<sub>2</sub>DS<sub>2</sub>-VASc score was developed to refine stroke risk stratification of patients with particular emphasis on identifying those in the low risk category.<sup>30,35</sup> CHA<sub>2</sub>DS<sub>2</sub>-VASc score consists of 'major' risk factors (prior stroke or TIA, or thromboembolism, and older age ≥75 years) and 'clinically relevant non-major' risk factors (heart failure [moderate to severe left ventricular systolic dysfunction, defined as left ventricular ejection fraction ≤40% or recent decompensated heart failure requiring hospitalization], hypertension, diabetes, female sex, age 65–74 years, and vascular disease (specifically, myocardial infarction, complex aortic plaque and peripheral artery disease).

Improvement of stratification has been achieved in part by adding 'non-CHADS<sub>2</sub>': female gender, vascular disease, separation of age as a risk factor into two subcategories. The CHADS<sub>2</sub> score has been frequently criticized because of not including these important stroke factors.<sup>36,37</sup>

Support for the 'new' risk factors was derived from the Swedish Atrial Fibrillation cohort study, which included 182 678 patients with AF and followed-up for about 1.4 years.<sup>38</sup> The risk of stroke in this study was found to be increased from age ≥65 years, with even greater risk at age 75 years or older: hazard ratio (HR) 2.97 (95% CI 2.54–3.48) and HR 5.28 (95% CI 4.57–6.09), respectively, when compared with the 'reference' age <65 years.<sup>38</sup> Consistent results were reported from the Taiwanese nationwide cohort study: odds ratios (OR) of 1.34 (95% CI 1.06–1.69) and 1.65 (95% CI 1.31–2.08) were seen for age 65–74 and ≥75 years categories, respectively.<sup>39</sup> The stroke/thromboembolic event rate per 100 person-years in the Loire Valley Atrial Fibrillation Project was 0.23 (95% CI, 0.08–0.72) in patients <65 years old, 2.05 (95% CI 1.07–3.93) in those aged 65–74 years, and 3.99 (95% CI, 2.63–6.06) if ≥75 years.<sup>40</sup>

Female gender is a moderate risk factor for stroke in AF overall, but there is an age dependency. For example, HRs were 1.17 (95% CI 1.11–1.22) in the Swedish Atrial Fibrillation cohort study<sup>38</sup>; 1.14 (95% CI 1.07–1.22) in the population-based cohort study of

older patients with recently diagnosed AF in the Quebec, Canada;<sup>41</sup> and 1.20 (95% CI 1.12–1.28) in the Danish nationwide cohort study.<sup>42</sup> The age-dependancy of the female gender as a stroke risk factor was underscored throughout all studies, i.e., females with AF younger than 65 years were at low stroke risk and no antithrombotic prophylaxis was required.<sup>40–43</sup>

Finally, vascular disease was found to be an independent risk factor for stroke in AF (HR 1.14, 95% CI 1.06–1.23) in the Swedish Atrial Fibrillation cohort study, significantly improving the predictive ability of CHADS<sub>2</sub>.<sup>38</sup> Vascular disease remained significant even while peripheral artery disease (HR 1.22, 95% CI 1.12–1.32), myocardial infarction (HR 1.09, 95% CI 1.03–1.15), prior coronary artery bypass graft (HR 1.19, 95% CI 1.06–1.33) were considered separately.<sup>38</sup> Predictive value of vascular disease was confirmed in other cohorts.<sup>39,40,44</sup>

Some confusion in the description of some risk factors, specifically heart failure and arterial hypertension, has been raised. As heart failure is often defined as 'history of heart failure' irrespectively of functional class, left ventricular function, need for hospitalization was found to be not an independent risk factor for stroke both based on systematic literature reviews and analysis of contemporary data.<sup>26,38</sup> In the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, heart failure is used as 'left ventricular moderate to severe systolic dysfunction or recent heart failure exacerbation that requires hospitalization' (whether it is a heart failure with reduced or preserved ejection fraction).<sup>4</sup> Questions still remain about impact of the heart failure with the preserved ejection fraction on stroke development in AF. Indeed, this type of heart failure includes about half of heart failure patients and AF is particularly prevalent amongst them.<sup>45</sup> In the Loire Valley Atrial Fibrillation Project, there were no differences in rates of stroke and/or thromboembolism between patients with heart failure with preserved and those with heart failure and reduced ejection fraction.<sup>46</sup> Another study showed 3.3-fold higher rates (20.6% vs. 6.7%) of ischaemic stroke and 5.5-fold of deaths (27.2% vs. 2.0%) in patients with AF and heart failure with preserved ejection fraction compared to those with AF without heart failure at 3 years of follow-up.<sup>47</sup>

Hypertension in the CHA<sub>2</sub>DS<sub>2</sub>-VASc score is defined as a history of hypertension, assuming that prolonged history of hypertension even if well-controlled is associated with vascular changes, which predispose to stroke.<sup>8</sup> Clearly, uncontrolled blood pressure also increases stroke risk in AF.

The CHA<sub>2</sub>DS<sub>2</sub>-VASc score was found to be superior to other stratification schemes in selection of the 'truly low-risk' in several cohorts. Apart from Danish nationwide cohort and United Kingdom General Practice Research Databases<sup>33,34</sup> the CHA<sub>2</sub>DS<sub>2</sub>-VASc score did the best in the Belgrade Atrial Fibrillation study which targeted 'lone' AF patients as it was the only stratification scheme, in accordance to which low risk (i.e. CHA<sub>2</sub>DS<sub>2</sub>-VASc score=0) was associated with the absence of stroke (OR 5.1, 95% CI 1.5–16.8).<sup>48</sup> This was consistent with a small study by Abu-Assi et al.<sup>49</sup>

### Bleeding Risk Assessment In Atrial Fibrillation

Whilst prescribing oral anticoagulants for stroke prevention in AF patients, clinicians have to balance stroke prevention against the risk of bleeding, particularly major bleedings. Major bleeding is different from nonmajor by the following criteria: fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial,



or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cells.<sup>50</sup>

The reported rate of intracranial haemorrhage, which is the most devastating example of bleeding event, has increased markedly with spreading use of anticoagulants in older adults often with AF as the only indication.<sup>51</sup> A recent meta-analysis of data on major bleeding in oral anticoagulation found an overall incidence of 2.1 (ranged 0.9–3.4) for the randomized clinical trials and 2.0 (ranged 0.2–7.6) per 100 patient-years for observational studies.<sup>52</sup>

In line with stroke risk in AF bleeding risk in anticoagulation also is not homogeneous. Different bleeding risk stratification schemes to evaluate it were developed, however only three of them were derived and validated in AF populations.<sup>53</sup>

The HEMORR2HAGES score (hepatic or renal disease, ethanol abuse, malignancy, older [aged  $\geq 75$  years], reduced platelet count or function, rebleeding risk, hypertension [uncontrolled], anaemia, genetic factors [CYP2C9 single nucleotide polymorphism], excessive fall risk, and stroke) was derived based on known bleeding risk factors from the National Registry of Atrial Fibrillation.<sup>54</sup> Prediction of bleeding events was improved with the use of HEMORR2HAGES score, but its application to everyday clinical practice was limited because of necessity of genetic testing. In addition, genetic polymorphisms other than CYP2C9 gene, are also involved in warfarin metabolism have been shown, e.g., for example, VKORC1.<sup>55</sup>

The HAS-BLED score (hypertension, abnormal renal/liver function, previous stroke/TIA, bleeding history or predisposition, labile international normalized ratio, elderly [e.g. age  $\geq 65$ , frailty, etc.], drugs/alcohol concomitantly)<sup>56</sup> gained success as a very simple stratification scheme in comparison to the HEMORR2HAGES score performance, based on validations in various independent 'real world' cohorts.<sup>38,57</sup> It was associated with improvement of bleeding risk classification when compared with variety of bleeding risk stratification schemes, including the new ATRIA score (see below) in the Loire Valley Atrial Fibrillation Project.<sup>58</sup> Amongst major advantages of the HAS-BLED score its ability to predict intracranial haemorrhage, the high performance in both AF and non-AF populations, in patients taking warfarin or other anticoagulants, as well as for bridging therapy were highlighted.<sup>59,62</sup>

The ATRIA (anemia, severe renal disease [GFR $<30$  ml/min or dialysis-dependent], age $\geq 75$  years, previous bleed, hypertension) is the newest bleeding risk score proposed.<sup>63</sup> The ATRIA bleeding score defines elderly patients as aged  $\geq 75$  years (versus  $\geq 65$  in the HAS-BLED score) and hypertension is defined 'history of hypertension' versus 'uncontrolled hypertension' in the HAS-BLED score.<sup>63</sup> Thus, the predictive and discriminative ability ATRIA score was poorer when compared to HAS-BLED, including failure to predict intracranial haemorrhage.<sup>59,64</sup>

Current guidelines recommend to perform evaluation of bleeding risk in all patients with AF routinely but to focus on those with high bleeding risk (i.e. HAS-BLED score  $\geq 3$ ). This should be realized through regular follow-up and reduction of impact of potentially modifiable risk factors, e.g. achievement of blood pressure control, stable INR values, patients' education to avoid alcohol intake and minimize use of aspirin or non-steroidal anti-inflammatory drugs. The benefits of anticoagulation clearly outweigh hazard of bleeding, furthermore, with higher bleeding risk even greater net clinical benefit might be expected.<sup>67</sup> Indeed, anticoagulation therapy should

not to be discontinued on the grounds of a high HAS-BLED score.<sup>4</sup> It should be noted that the labile INR criterion in HAS-BLED is only considered only in case of vitamin K antagonist (e.g. warfarin) use. Stability of INR is very important, and only if patient spends more than 70% of time within therapeutic range (TTR), the best effectiveness and safety profiles can be expected; in contrast, low average TTR is associated with poor outcomes (stroke, bleeding mortality).<sup>65-68</sup>

Thus, efforts towards development of prediction tool for quality of INR control (as reflected by TTR) have been made. The SAME-TT2R2 score (female sex, age less than 60 years, medical history [2 of the following: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral artery disease, heart failure, previous stroke, pulmonary, hepatic or renal disease], treatment with interacting drugs [e.g. amiodarone], tobacco use (within 2 years), non-Caucasian race) was described from an analysis of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial in order to aid decision-making between vitamin K antagonists and novel oral anticoagulants by identifying those AF patients who would do well on VKA (SAME-TT2R2 score 0-1), and those who less likely reach target TTR (SAME-TT2R2 score  $\geq 2$ ).<sup>69,70</sup>

### Integrated Stroke And Bleeding Risk Assessment

As many of the risk factors for stroke and bleeding in AF are overlapped is it possible to use one stratification scheme to get simultaneously individuals' stroke and bleeding risk? This was tested in two ways. First, the predictive ability for major bleedings was assessed using the stroke risk stratification scores, that is, CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc. For example, in the AMADEUS (evaluating the use of sr34006 compared to warfarin or acenocoumarol in patients with atrial fibrillation) trial incidence of bleeding was found to rise with increasing of either HAS-BLED, CHADS<sub>2</sub>, or CHA<sub>2</sub>DS<sub>2</sub>-VASc scores, but statistical significance was achieved only for the HAS-BLED score. Also, only HAS-BLED demonstrated significant discriminatory performance and net reclassification improvement when compared with the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc as well.<sup>71</sup> Thus, stroke risk stratification schemes should not be applied for bleeding risk assessment instead of the HAS-BLED score.

Second, several composite scores for stroke and bleeding prediction have been developed.<sup>72,73</sup> For example, evaluation of 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 included left ventricular dysfunction as well.<sup>72</sup> Generally, regression models are likely to give more faithful conclusions on patient's stroke or bleeding risk as they include appropriate regression coefficients which characterize the real impact of risk factors on the studied outcome instead of assumption of equal weight (1 or 2 points) for the range of stroke predictors. However, both models actually allowed comparative discriminative ability in comparison to the CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores, but did not outperform them.<sup>72</sup> Thus, taking into account relative complexity of calculations with composite scores, the 'traditional' stroke and bleeding risk scores which are currently in use are more attractive in the aspect of usability, detailed assessment, individualized balancing of risks, and right decision making.

## Further Directions To Improve Risk Scores: Are More 'Non-Traditional' Clinical Factors And Biomarkers The Answer?

Clearly, there are a lot of clinical risk factors for thromboembolism and bleeding, which were not included into the current risk stratification schemes but had potential to improve their performance.

For example, a history of both arterial (HR 1.39, 95% CI 1.08-1.79) and venous (HR 1.26, 95% CI 1.02-1.54) retinal occlusions was found to be associated with an increased risk of stroke/thromboembolism/TIA in patients with non-valvular AF. As cerebral and retinal circulation are adjacent, it was suggested that retinal vascular occlusion could be considered as a previous thromboembolic event when evaluating stroke risk.<sup>74</sup> Despite that, AF in eye ischaemic events is much less prevalent than in cerebral ischaemia; indeed, the probability to diagnose AF in patient with stroke is about 3.6-fold higher than in patient with retinal artery occlusion. Hence, counterpoint view is that stroke and retinal thrombosis may represent pathophysiologically distinct patterns of vascular disease.<sup>75</sup>

Obesity apart from being a risk factor for development of new-onset AF<sup>76,77</sup> and stroke risk factor in the general population,<sup>78</sup> does have an independent predictive role for stroke development in patients with AF.<sup>79</sup> In the prospective Danish Diet, Cancer and Health study there was a 31% and 36% increase in risk of the composite end point of 'ischaemic stroke, thromboembolism, or death' in overweight and obese patients, respectively, even after adjustment for CHA<sub>2</sub>DS<sub>2</sub>-VASc score.<sup>79</sup>

Data derived from the same cohort was indicative for relation of alcohol intake. Men with an intake of >27 drinks/week were more prone to develop thromboembolism or death (HR 1.33, 95% CI 1.08-1.63) compared to men with an intake of <14 drinks/week. Women with an intake of >20 drinks/week also had a higher risk (HR 1.23, 95% CI 0.78-1.96) than women in the low intake category (adjusted for oral anticoagulation and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores).<sup>80</sup> Heavy smoking, was found to be independently associated with a higher risk of thromboembolism or death as well (HR 3.64 [95% CI 1.88-7.07] for females, and HR 2.17 [95% CI 1.59-2.95] for males).<sup>81</sup>

Ethnic differences are important for stroke prediction. Specifically, Asians represents large population with overall higher burden of AF than in Western countries.<sup>82,83</sup> Despite stroke risk factors being common for both populations, oral anticoagulation is underused and decision-making does not correspond to individual risk, assessed via modern stratification schemes. Based on data from the China National Stroke Registry, only about 15% of moderate and high risk patients according to the CHADS<sub>2</sub> score were taking warfarin.<sup>84</sup> Moreover, stroke scores were derived and validated in predominantly Caucasians and, hence, may have lower prediction strength when applied to population in the Far Eastern countries. For example, in the nationwide database of patients with nonvalvular AF from Taiwan, CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores had only modest predictive ability.<sup>39</sup>

The role of ethnicity as well as some aforementioned risk factors (e.g., smoking, obesity) was advocated in a new QStroke score, that was proposed based on England and Wales general practice data. The QStroke score was validated for AF patients without a prior stroke only. Besides 9 categories that included self-assigned ethnicity and a wide range of other risk factors that included age, sex, smoking

status, systolic blood pressure, ratio of total serum cholesterol to high density lipoprotein cholesterol concentrations, body mass index, family history of coronary heart disease in first degree relative under 60 years, Townsend deprivation score, treated hypertension, type 1 and type 2 diabetes, renal disease, rheumatoid arthritis, coronary heart disease, congestive heart failure, valvular heart disease, and AF. Incorporation of AF as a separate risk factor means that the QStroke score also can be used in non-AF patients. Unfortunately, the QStroke score did not outperform both the CHADS<sub>2</sub> and the CHA<sub>2</sub>DS<sub>2</sub>-VASc score in patients without a prior stroke.<sup>85</sup>

Also, future improvement of stroke risk stratification can be achieved by inclusion of biomarkers to complement clinical risk factors. Echocardiographic parameters (presence of spontaneous echocontrast, low left atrial appendage velocities, left atrial appendage thrombus, and complex aortic plaque on the descending aorta),<sup>86,87</sup> blood biomarkers of prothrombotic or hypercoagulable state (von Willebrand factor, D-dimer)<sup>88-91</sup>; left-ventricular overload (brain natriuretic peptide, galectin-3);<sup>92,93</sup> renal function (creatinine clearance, estimated glomerular filtration rate, proteinuria);<sup>94-96</sup> detailed cerebral imaging with computer tomography or magnetic resonance imaging (presence of small-vessel disease)<sup>3</sup> were shown to have prognostic implications in AF patients.

Of these, the impact of chronic kidney disease (CKD) in stroke stratification schemes is of particular importance as CKD is associated strongly with increased cardiovascular morbidity and mortality. The range of cardiovascular disorders associated with CKD is wide, with arterial stiffening causing heart failure, stroke, and arrhythmic sudden death and premature atherosclerosis causing vascular occlusive events.<sup>97</sup> The prevalence of AF was recognized to be higher in CKD and prognosis is known to be negative regarding both thromboembolic and bleeding risk in comparison to general population.<sup>97</sup> At the same time, there is relatively poor evidence for anticoagulation in the given cohort of patients as CKD was used as exclusion criterion in majority of studies (particularly if eGFR<30 ml/min/1.73 m<sup>2</sup>).

The R<sub>2</sub>CHADS<sub>2</sub> score was derived from 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. The score incorporated the components of the CHADS<sub>2</sub> score and also awarded 2 points for creatinine clearance <60 mL/min.<sup>98</sup> When validated in the ATRIA study, improvement of net reclassification index by 17.4% (95% CI 12.1-22.5) was seen, relative to CHADS<sub>2</sub>.<sup>98</sup> However, some methodological issues were underscored and discussed that might limit spread of the R<sub>2</sub>CHADS<sub>2</sub> score in clinical practice.<sup>99</sup>

## Conclusions:

Numerous risk stratifications schemes for stroke and bleeding prediction highlight the fact, that none is perfect and further research is needed to improve the individuals' risk assessment. Given the global burden associated with AF and its complication such as stroke, new treatment options could have a major impact on reducing this healthcare burden associated with AF-related stroke, as recently shown for Europe and China.<sup>100-102</sup> For now, the CHA<sub>2</sub>DS<sub>2</sub>-VASc and the HAS-BLED scores are currently superior to other prognostic tools in guiding anticoagulation in AF patients without losing simplicity and practicality for everyday use. With stroke risk, the focus now is the initial identification of 'low risk' patients



(CHA<sub>2</sub>DS<sub>2</sub>-VASc=0 if male, and 1 if female). Subsequent to this step, effective stroke prevention (which is oral anticoagulation) can be offered to patients with AF and ≥1 stroke risk factors. Thus, things can only improve.

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