Stroke prevention in atrial fibrillation: Past, present and future
Comparing the guidelines and practical decision-making

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Summary
Concepts and our approaches to stroke prevention in atrial fibrillation (AF) have changed markedly over the last decade. There has been an evolution over the approach to stroke and bleeding risk assessment, as well as new treatment options. An increasing awareness of AF has led to calls to improve the detection of and population screening for AF. Stroke and bleeding risk assessment continues to evolve, and the ongoing debate on balance between simplicity and practicality, against precision medicine will continue. In this review article, we provide an overview of past, present and the (likely) future concepts and approaches to stroke prevention in AF. We propose three simple steps (the Birmingham ‘3-step’) that offers a practical management pathway to help streamline and simplify decision-making for stroke prevention in patients with AF.

Keywords
Atrial fibrillation, stroke prevention, non-vitamin K antagonist oral anticoagulants, warfarin

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Concepts and our approaches to stroke prevention in atrial fibrillation (AF) have changed markedly over the last decade. There has been an evolution over the approach to stroke and bleeding risk assessment, as well as new treatment options. An increasing awareness of AF has led to calls to improve the detection of and population screening for AF (1). As the public health impact of AF increases, there also is an urgent need to simplify and streamline patient management pathways, with attention to improving patient adherence and persistence with stroke prevention therapies (3), as this will optimise outcomes and reduce the burden of stroke associated with AF (4).

The past
The historical randomised controlled trials (RCTs) comparing warfarin to placebo or control, conducted two decades ago, clearly showed that warfarin reduced stroke/systemic embolism by 64% and all-cause mortality by 26% (5, 6). Of note, these trials included less than 8000 patients in comparison with either nothing or antiplatelet agents – mostly aspirin (5, 6). Clearly, warfarin (and the Vitamin K antagonists, VKA) became the standard of care when stroke prevention with OAC was needed.

Nonetheless, the use of VKA was problematic, requiring regular anticoagulation monitoring to keep within a relatively narrow therapeutic range, and furthermore, VKAs were subject to much inter- and intra-patient variability, as well as diet and drug interactions (7). Furthermore, oral anticoagulation (OAC) with the VKAs was associated with increased bleeding risk, the most serious being intracranial bleeding (ICH). Hence, initial stroke prevention efforts were particularly directed towards identifying the ‘high risk’ AF patients in whom stroke reduction benefits of OAC outweighed the bleeding risk.

Clinical characteristics of patients in the non-VKA treated or placebo arms of the historical RCTs were used to help identify clinical and echocardiographic risk factors for an increased risk of stroke, and the clinical features were used to formulate stroke risk stratification schemes, such as the CHADS2 score (8). Whilst the latter was simple, it had only modest predictive value, as reflected by a c-index of approximately 0.60 (a statistical measure of the predictive value, where a c-index of 1.0 is perfect prediction, and 0.5 is 50:50 prediction) (9), similar to most risk scores based on clinical features.
Attention was therefore directed towards echocardiographic parameters to refine stroke risk assessment, and the presence of moderate-severe left ventricular systolic impairment on two-dimensional echocardiography was independently predictive of stroke in AF (10). The availability of transoesophageal echocardiography allowed additional refinement, where the presence of spontaneous echo contrast, low left atrial appendage velocities and complex aortic plaques were independent predictors of thromboembolism (11), as was the presence of left atrial thrombus (12). The latter could be present asymptptomatically in approximately 10% of patients, even whilst on OAC (12).

Nonetheless, the historical RCTs have been debated as they only randomised <10% of patients screened, and many common risk factors associated with thromboembolism in AF were neither systematically recorded nor consistently defined. A systematic review by the Stroke in AF Working Group identified previous stroke (relative risk [RR] 2.5, 95% confidence interval [CI] 1.8–3.5), increasing age (RR 1.5 per decade, 95% CI 1.3–1.7) diabetes (1.7, 1.4–2.0), and history of hypertension (2.0, 1.6–2.5) as risk factors, whilst female sex was inconsistently associated with stroke – but heart failure and coronary artery disease were inconclusive as risk factors (13). Other systematic reviews by the National institute for Health and Care Excellence (NICE) and Pisters et al. found evidence for structural heart disease (including prior myocardial infarction or cardiac dysfunction) and female sex as risk factors (14, 15). Nonetheless, additional information on stroke risk factors has been obtained from large observational cohorts.

The present

Stroke risk stratification and treatment decisions

Currently, the CHA2DS2-VASc score (16) is commonly advocated in most guidelines (see Table 1), and extends the older CHADS2 score by recognising additional risk factors. For example, age is a powerful driver of stroke risk, so that age 65–74 gets one point, and age ≥75 gets 2 points; in Asian cohorts, where stroke risk seems higher than in non-Asian cohorts, stroke risk seems to rise from age of 50 upwards, such that a recalibration of CHA2DS2-VASc has been proposed with 1 point for age 50–74, with a significant improvement in stroke prediction over the conventional CHA2DS2-VASc score (17). The V in CHA2DS2-VASc refers to ‘complicated’ vascular disease, usually defined as myocardial infarction or revascularisation, peripheral artery disease or the presence of complex aortic plaque (18). The Sc (Sex category) criterion refers to female sex, which older literature suggested increased stroke risk (19), but it became apparent there was an age-dependency to this risk, such that females aged <65 in the absence of any additional stroke risk factors were at low risk (with stroke rates of <1% /year) (20). Also, the C criterion in CHA2DS2-VASc is broader than that in CHADS2, and also refers to recent decompen-sated heart failure (usually indicated by a hospitalisation) irrespective of the left ventricular ejection fraction (LVEF) (21), thus including heart failure with reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF), cardiomyopathy, etc., as well as asymptomatic or symptomatic moderate-severe LV systolic impairment on cardiac imaging.

Even a single stroke risk factor confers an accentuated risk of stroke and mortality, and the net clinical benefit (NCB) balancing stroke reduction against serious bleeding with OAC use is clearly positive in such patients, compared to aspirin or no treatment (22–24). In contrast, aspirin has a neutral or negative NCB, indicating no advantage even in patients with a CHA2DS2-VASc score of 1 (or 2 in females) (25).

Whilst CHA2DS2-VASc includes the common stroke risk factors seen in everyday clinical practice, it does not include every possible stroke risk factor especially since some have less supportive evidence as an independent predictor. For example, AF patients with chronic kidney disease (CKD) are at high risk for stroke, death, myocardial infarction and bleeding – but CKD does not appear to independently improve the predictive value of CHA2DS2-VASc, which is perhaps unsurprising since CKD is associated with the components of CHA2DS2-VASc such as age, heart failure, diabetes mellitus, vascular disease etc (26). As would be expected, the CHA2DS2-VASc score also predicts stroke and mortality in non-AF populations, given it is essentially a cluster of the common risk factors for stroke and mortality (27, 28).

The modest predictive value of CHA2DS2-VASc for identifying high risk patients can clearly be improved (at least statistically) by including substantially more clinical variables (QStroke, GARFIELD score), or the addition of biomarkers (29-31). With complicated clinical risk scores and multiple parameters, some refine-ment is possible, with a c-index statistically improved to approxi-mately 0.7, especially with machine learning methodology of large cohorts. Biomarkers can clearly improve stroke prediction (32), and addition of any biomarker (whether blood, urine or imaging based) will always improve on clinical risk prediction, at least statistically and changing the c-index to 0.65–0.70. This concept is not new, and even a decade ago (33), biomarkers were already shown to refine stroke risk stratification. The same biomarkers are also predictors of stroke, death, myocardial infarction and bleeding, and to weigh or balance these outcomes can only lead to treatment uncertainties and confusion in decision-making. Importantly, the predictive value of biomarkers should ideally be shown in non-anticoagulated general population cohorts, which is difficult, while recent studies proposing biomarkers have been conducted in highly selected anticoagulated RCT cohorts (31, 34).

Also, complicated scores and multiple biomarkers and/or im-aging simply add additional expense and reduce simplicity or practicality of widespread use in everyday clinical practice and busy clinics, especially since the default should be to offer stroke prevention (which is OAC) unless the patient is shown to be ‘low risk’.

Moreover, most of the increase in risk prediction in these studies is by improving prediction in mid to high risk range, where all will require anticoagulation regardless of actual risk. The real clinical unmet need is to improve separation of the low risk subset who do not need anticoagulation from the intermediate risk group who would benefit, not provided by addition of current bio-
Table 1: A comparison of the most recent (2014–2016) guidelines published in English on antithrombotic prophylaxis in atrial fibrillation.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Scoring system recommended</th>
<th>Recommendation for anti-coagulation in general</th>
<th>Recommendation for NOACs</th>
<th>Recommendation for intermediate-risk patients</th>
<th>Role of aspirin monotherapy</th>
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<tr>
<td>JCS 2013</td>
<td>CHA2DS2</td>
<td>Anticoagulation therapy based on risk assessment for cerebral infarction and bleeding is recommended. Class I – LOE A</td>
<td>NOACs should be considered, whenever indicated, as the first line therapy in patients with a CHADS2 score of ≥2. Class I – LOE A</td>
<td>Anticoagulation therapy with rivaroxaban, edoxaban or warfarin should be considered for intermediate-risk patients with a CHA2DS2 score of 1.</td>
<td>Antiplatelet drugs may be considered for patients who cannot use oral anticoagulants. Class Iib – LOE C</td>
</tr>
<tr>
<td>NICE 2014</td>
<td>CHA2DS2VASc</td>
<td>For most people the benefit of anticoagulation outweighs the bleeding risk.</td>
<td>Warfarin (Class I, LOE A) or a NOAC (dabigatran, rivaroxaban, or apixaban). Class I, LOE B</td>
<td>Consider anticoagulation for men with a CHA2DS2VASc score of 1. Take the bleeding risk into account.</td>
<td>Do not offer aspirin monotherapy solely for stroke prevention to people with AF</td>
</tr>
<tr>
<td>ACC/AHA 2014</td>
<td>CHA2DS2VASc</td>
<td>With prior stroke, TIA, or CHA2DS2VASc score 2, Class I, LOE A</td>
<td>When OAC is indicated, a NOAC is recommended in preference to a VKA for nonvalvular AF (NVAF) (also with concomitant CAD)</td>
<td>With nonvalvular AF and a CHA2DS2VASc score of 1, no anti-thrombotic therapy or treatment with oral anticoagulant or aspirin may be considered. Class Iib – LOE C</td>
<td>With nonvalvular AF and a CHA2DS2VASc score of 1, no anti-thrombotic therapy or treatment with oral anticoagulant or aspirin may be considered. Class Iib – LOE C</td>
</tr>
<tr>
<td>CCS 2016</td>
<td>CHADS-65</td>
<td>In general, oral anticoagulation (OAC) therapy is recommended for all patients with AF except those younger than 65 years of age with a Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke/TIA (CHADS2) score of 0.</td>
<td>Oral anticoagulation therapy to prevent thromboembolism is recommended for all male AF patients with a CHA2DS2VASc score of 2 or more. Class I – LOE A</td>
<td>In CHADS2 0 patients “aspirin (acetylsalicylic acid; ASA) is recommended in patients with CAD/vascular disease, and there is no indication for anti-thrombotic treatment in the absence of CAD/vascular disease”.</td>
<td>In CHADS2 0 patients “aspirin (acetylsalicylic acid; ASA) is recommended in patients with CAD/vascular disease, and there is no indication for anti-thrombotic treatment in the absence of CAD/vascular disease”.</td>
</tr>
<tr>
<td>ESC 2016</td>
<td>CHA2DS2VASc</td>
<td>Oral anticoagulation therapy to prevent thromboembolism is recommended in all female AF patients with a CHA2DS2VASc score of 3 or more. Class I – LOE A</td>
<td>Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA2DS2VASc score of 1, considering individual characteristics and patient preferences. Class IIa– LOE B</td>
<td>Oral anticoagulation therapy to prevent thromboembolism should be considered in female AF patients with a CHA2DS2VASc score of 2, considering individual characteristics and patient preferences. Class IIa– LOE B</td>
<td>Oral anticoagulation therapy to prevent stroke prevention in AF patients, regardless of stroke risk. Class III – LOE B</td>
</tr>
</tbody>
</table>

where low risk is defined as a CHA2DS2-VASc score 0 (or 1 in females), moderate risk is a CHA2DS2-VASc score 1 in males (or 2 in females), and high risk is ≥2 stroke risk factors based on CHA2DS2-VASc; in these guidelines, high risk patients are recom-
Combination therapy

Abbreviations: ACC/AHA = American College of Cardiology/American Heart Association; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; ESC = European Society of Cardiology; JCS = Japanese Cardiovascular Society; INR = International Normalised Ratio; LOE = Level of Evidence; NICE = National Institute for Health and Care Excellence (UK); NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; TIA = transient ischaemic attack.

Recommendations given

After coronary revascularisation in patients with CHA2DS2-VASc score 2, it may be reasonable to use clopidogrel concurrently with oral anticoagulants but without aspirin. Class Ib – LOE B

It is recommended that patients who refuse warranted OAC therapy should receive the combination of ASA and clopidogrel. When CAD is present, some expert clinicians prefer a combination of a NOAC and ASA rather than a NOAC alone in preference to warfarin alone for patients perceived to be at higher risk of coronary events and low risk of major bleeding and might choose a NOAC alone as a reasonable option in those with average to lower risk of coronary events and higher risk of bleeding. Combinations of oral anticoagulants and platelet inhibitors increase bleeding risk and should be avoided in AF patients without another indication for platelet inhibition. Class III – LOE B

Table 1: Continued

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<tr>
<td>A combination of antiplatelet and anticoagulant drugs may be considered for patients with CAD who undergo percutaneous coronary intervention (PCI) or surgical revascularisation. lib – LOE C</td>
<td>No specific recommendations given</td>
<td>After coronary revascularisation in patients with CHA2DS2-VASc score 2, it may be reasonable to use clopidogrel concurrently with oral anticoagulants but without aspirin. Class Ib – LOE B</td>
<td>It is recommended that patients who refuse warranted OAC therapy should receive the combination of ASA and clopidogrel. When CAD is present, some expert clinicians prefer a combination of a NOAC and ASA rather than a NOAC alone in preference to warfarin alone for patients perceived to be at higher risk of coronary events and low risk of major bleeding and might choose a NOAC alone as a reasonable option in those with average to lower risk of coronary events and higher risk of bleeding. Combinations of oral anticoagulants and platelet inhibitors increase bleeding risk and should be avoided in AF patients without another indication for platelet inhibition. Class III – LOE B</td>
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To simplify and improve clinical management, we should perhaps start by avoiding the obsession with trying to identify a particular event rate for a particular point on the CHA2DS2-VASc score. Unsurprisingly, there would be a wide variation in reported event rates for particular scores points in different cohorts (38, 39), as stroke rates are dependent on study population, clinical setting, ethnicity, etc. Indeed, hospitalised cohorts have higher rates than community based AF population cohorts, but AF patients have higher rates of hospitalisation – whilst individual AF patients may be in the community and ‘stable’ today, they may well be hospitalised next week, and even non-cardiovascular hospitalisations (e.g. from sepsis) increase the risk markedly.

The electrophysiological characteristics of AF (AF pattern, atrial flutter, AF with a reversible cause, AF efficiently treated with drugs or ablation, brady-tachy syndrome, etc) are not relevant predictors for a higher or a lower risk of stroke, and are not sufficiently robust to decide on antithrombotic strategies.

Also, with a single stroke risk factor, not all risk factors carry equal weight (40, 41). Of the CHA2DS2-VASc score factors, 1 point from age 65–74 is a powerful driver of stroke risk – but even in this category, the age of 65 is clearly lower risk than the age of 74 years. Also, well-controlled hypertension clearly has lower stroke risk compared to uncontrolled blood pressure, but what may be controlled hypertension today is not necessarily the case if patients do not take their antihypertensive medication.

Notwithstanding the fact that even one stroke risk factor confers an excess risk of stroke and death, and that OAC has a positive NCB with one or more stroke risk factors (25), the CHA2DS2-VASc score should be used in a stepwise approach to initially identify ‘low risk’ patients (Step 1), defined as a CHA2DS2-VASc score of 0 in males or 1 in females; such patients do not need any antithrombotic therapy.

Step 2 is then to offer stroke prevention (i.e. OAC) to those with ≥1 stroke risk factors – at this step it does not matter if the CHA2DS2-VASc score is 2, 3 or higher, or whether we have 1 or 10 biomarkers added, the patient merits stroke prevention to reduce the risk of a potentially fatal or severely disabling AF-related stroke. At Step 2, the decision with OAC these days is either a VKA with good quality anticoagulation control (as reflected by a good time in therapeutic range [TTR] >65–70 %), or a non-VKA oral anticoagulant (NOAC), now tested against warfarin in over 80,000 patients.

Despite the introduction of the NOACs, the VKAs are still widely used worldwide. However if VKAs are used, the challenge is how to identify those patients who are going to achieve a good TTR, as well as persistence with treatment, given that treatment discontinuations leads to more adverse outcomes (4).

Many common clinical and genetic factors have been associated with labile INRs (42). The more common clinical factors have been used to formulate the SATe-TT3R3 score (43), which is a simple score that has been validated to identify those patients likely to do well on VKA with a good TTR (score 0–2) or those less likely to achieve a good TTR (score >2) that can be flagged up for more regular review with INR checks or education/counselling.
(that has been shown to improve TTR) or these days, to be started on NOAC instead. The SAMe-TT$_2$R$_2$ score has now been validated in multiple independent cohorts (44, 45), and not only helps to identify those patients less likely to do well on VKA but is predictive of labile INRs and the adverse outcomes associated with labile INRs, e.g. thromboembolism, death and bleeding. The SAMe-TT$_2$R$_2$ score can therefore be incorporated into the patient pathway (Step 3).

These three simple steps (the Birmingham ‘3-step’) offers a management pathway to help streamline decision-making for stroke prevention in patients with AF, and is illustrated in Figure 1.

The NOACs have changed how we approach stroke prevention in AF, as they offer relative efficacy, safety and convenience compared to VKAs, in patients with AF, with an overall clear net clinical benefit (46, 47). The efficacy and safety of NOACs is even greater in Asians compared to non-Asians. With specific antidotes or reversal agents already licensed and available for dabigatran (specifically, idarucizumab [48, 49]), or in development for the Factor Xa inhibitors (eg. andexanet alpha [50]), we are also in the era where we can essentially ‘switch off’ any anticoagulation effect with the NOACs should the need arise, for example, following severe bleeding or the need for urgent surgery in a patient whilst on a NOAC (51, 52).

The large Phase 3 NOAC clinical trials have been complemented by large post-marketing observational ‘real world’ cohorts that augment and support the RCT data, showing effectiveness and safety with the NOACs versus warfarin – these perhaps contrast the broad use of the new drugs in the ‘real world’ against the artificial setting of a highly controlled protocol-based RCT cohort (53). The volume of these papers has largely reflected the sequence the individual NOACs were approved and marketed (54–57). Concerns about some adverse outcomes, such as myocardial infarction with some of the NOACs also seem unfounded (58).

In the Danish registries, Larsen et al. (59) reported that all NOACs seemed to be safe and effective alternatives to warfarin in a routine care setting, and no significant differences were found between ‘usual dose’ NOACs (dabigatran 150 mg bid, rivaroxaban 20 mg and apixaban 5 mg bid) and warfarin for ischaemic stroke. The risks of death, any bleeding, or major bleeding were significantly lower for apixaban and dabigatran compared with warfarin.

Comparative effectiveness or safety ‘real world’ cohorts are also been published, and subtle differences are emerging and providing differentiation between the different NOAC agents (60). For example, the independent FDA Medicare analysis by Graham et al. (61) reported that treatment with rivaroxaban 20 mg once daily was associated with similar risks of thromboembolic stroke but statistically significant increases in ICH and major extracranial bleeding, including major gastrointestinal bleeding, compared with dabigatran 150 mg twice daily.

Thus, apart from VKA (with good TTR), we have four NOACs licensed for AF stroke prevention – compared to five years ago when prescribers did not have a choice (VKA only, nothing else), we are now spoilt for choice, and can fit the NOAC drug to particular patient characteristics (62, 63). After all, AF patients are not homogeneous, and to assume ‘one drug fits all’ is simply unrealistic and misleading.

**Bleeding risk assessment**

The other side of the equation of thromboprophylaxis is bleeding risk assessment, which has been subject to many misconceptions and misuse (64). Unlike stroke risk factors, many bleeding risk factors can be modified – and bleeding risk assessment is a dynamic process that needs evaluation at regular review and follow-up.
Bleeding risk assessment is to ‘flag up’ the patients potentially at high risk of bleeding for more careful follow-up and most importantly, to address the reversible bleeding risk factors. A high bleeding risk score is not an excuse to withhold OAC, as the NCB in such patients is often greater given that the stroke and bleeding risk track each other – and the magnitude of gain from stroke reduction will far outweigh the small risk of serious bleeding. A history of falls is not a contraindication to OAC, and in a modelling analysis, the anticoagulated patient would need to fall 295 times per year, for the benefit of stroke reduction with OAC to be outweighed by the potential harm of serious bleeding (65). This is perhaps a simplification, as clearly a traumatic fall or uncontrolled epileptic seizures confers greater risk than less dangerous reasons for falls (e.g. syncope).

Many bleeding risk factors have been identified, and the more common ones have been used to formulate bleeding risk scores, of which the HEMORRHAGES, HAS-BLED, ATRIA, ORBIT and ABC-Bleeding scores have been derived for use in the AF population. The HAS-BLED score (66) has been popular, since it draws attention to the common reversible bleeding risk factors (uncontrolled blood pressure, labile INRs if on warfarin, excessive alcohol intake or concomitant use of aspirin or NSAIDs in an anticoagulated patient). The HAS-BLED has been validated in patients on no antithrombotic therapy, aspirin or anticoagulation (whether VKA or non-VKA anticoagulants), and is therefore applicable at all stages in the patient management pathway. HAS-BLED has also been validated in AF and non-AF populations, and is predictive of bleeding during bridging, acute coronary syndrome or percutaneous coronary interventions. Unlike other scores, HAS-BLED is also predictive of intracranial haemorrhage.

Last, the simple HAS-BLED score performs as well as, and often superior, to other bleeding risk scores (67). Indeed, newer simple bleeding risk scores would significantly underperform in predicting bleeding whilst on VKA, as they do not consider labile INR or TTR as a criterion, and TTR is a powerful determinant of bleeding risks (67, 68).

Figure 2: Thromboprophylaxis in AF – a summary of the principal steps recommended by selected international guidelines. VKA: Vitamin K Antagonists; OAC: Oral Anticoagulant; CAD: Coronary Artery Disease; ASA: Acetyl Salicylic Acid; NOAC: Non-VKA Oral Anticoagulants; TTR: Time in Therapeutic Range; SAMe-TT<sub>2</sub>R<sub>2</sub>: female sex, age of <60 years, history of two or more co-morbidities (hypertension, diabetes mellitus, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, and hepatic or renal disease) or treatment with drugs interacting with VKAs (e.g. amiodarone) 1 point each, tobacco use and non-Caucasian ethnicity 2 points each.
Adherence, CVD risk management, and multidisciplinary clinics

One of the major issues with current anticoagulant treatment is that it is not always offered to patients at increased stroke risk according to guideline recommendation, often because of an overestimate of falls or bleeding risk, and an underestimate of risk from paroxysmal AF (69). Once prescribed, reduced adherence to anticoagulant therapy results in subtherapeutic levels, and discontinuation of anticoagulant: even after just one year following initiation, only about 65% prescribed VKA, and 80% for NOACs are still taking the drugs (4). Multidisciplinary nurse-led clinics have been proposed as a way to increase guideline and medication adherence, and improve outcomes, including addressing cardiovascular risk factors. The results appear favourable and cost effective (70, 71).

What do the guidelines say?

Table 1 summarises the principal international guidelines from the Japanese Cardiology Society (JCS) (72), National Institute for Health and Care Excellence (NICE) (73), AHA/ACC/HRS (36), Canadian Cardiology Society (CCS) (74) and ESC (35). The principal decision steps have been summarised into Figure 2, where ‘the Birmingham 3-step’ pathway is also shown to put decision making into context.

The use of OAC in high-risk patients (that is, those with ≥2 stroke risk factors) and no therapy in AF patients without additional stroke risk factors is consistently recommended by all guidelines, whilst the recommendations for those at ‘intermediate’ stroke risk (i.e. single stroke risk factor) are heterogeneous and include no therapy, aspirin or (preferably) OAC (Table 1).

When recommend OAC, the ESC, CCS and JCS guidelines give a preference to NOACs, whilst the NICE and AHA/ACC/HRS guidelines do not specify any preference to NOACs or VKAs. Also, the JCS guidelines specify that the target INR range with VKAs in patients aged ≥70 years should be 1.6–2.6 (instead of 2.0–3.0 in all other AF patients or in all other AF guidelines).

Importantly, all guidelines make a distinction between so-called ‘valvular’ versus ‘non-valvular’ AF and recommend the use of NOAC only in patients with ‘non-valvular’ AF, based on the results of the Phase 2 RE-ALIGN trial (75) which showed higher rates of stroke, valve thrombosis and major bleeding with dabigatran compared to warfarin. ‘Valvular AF’, which is currently not a satisfying terminology, has been defined in recent years as AF in patients with mechanical prosthetic heart valves or moderate-to-severe mitral stenosis. All such patients should be given a VKA, whilst AF patients with any other heart valve abnormality may be given either NOACs or VKAs (76, 77). Stroke risk in such patients can also be assessed using the CHA2DS2-VASc score (78).

All guidelines highlight the importance of bleeding risk management by addressing the modifiable bleeding risk factors and scheduling AF patients at increased risk of bleeding for a more intense clinical follow-up during OAC treatment. The NICE and JCS guidelines explicitly recommend the HAS-BLED score for bleeding risk assessment, whilst the AHA/ACC/HRS guidelines mention several bleeding risk scores without any formal recommendation, but with the notion that the HAS-BLED score better discriminates bleeding risk in comparison to the HEMORRHAGES or ATRIA score. As discussed above, the ESC guidelines provide a long list of modifiable (uncontrolled hypertension, labile INR or TTR<60% with VKAs, concomitant aspirin or non-steroidal anti-inflammatory drug use, excessive alcohol use), potentially modifiable (anaemia, impaired renal or liver function, reduced platelet count or function) – most of which are included in the HAS-BLED score – and non-modifiable (age ≥65 years, previous bleeding, prior stroke, renal replacement therapy, liver cirrhosis, malignancy, genetic factors) or biomarker-based bleeding risk factors (e.g. high-sensitivity troponin). Whilst mentioning several bleeding risk scores (including the HAS-BLED, ORBIT and ABC scores), the ESC guidelines also do not provide any specific recommendation on the bleeding risk assessment tool or the definition of high-bleeding risk category, perhaps because a high-bleeding risk would not change the decision to initiate OAC, although this may be relevant with combination OAC and antiplatelet drugs in the setting of acute coronary syndrome or percutaneous coronary interventions.

All guidelines provide guidance on the optimal management of ‘special’ AF populations (e.g. elderly, patients with chronic kidney disease, etc.) or those presenting with an acute coronary syndrome, major bleeding or undergoing surgery or invasive procedures (79, 80). The ESC guidelines particularly extend on the management of acute stroke, major bleeding and the use of OAC post ICH, emphasising the role of integrated approach to AF management. Patient education and their values and preferences with respect to the management of stroke and bleeding risk are increasingly acknowledged in the formal AF guidelines.

Finally, the ESC, AHA/ACC/HRS and NICE guidelines emphasise that documentation of AF using an electrocardiographic (ECG) or monitor/device recording is necessary for the diagnosis of AF, which is required before initiating stroke prevention therapy. Along with recommending opportunistic screening for AF by manual pulse checking (and subsequent ECG recording in those
with palpated pulse irregularity) in all individuals aged >65 years (the ESC) or in individuals with symptoms suggestive of AF (the NICE), the ESC, NICE and AHA/ACC/HRS guidelines recommend prolonged screening for AF in post-stroke/TIA patients, using short-term ECG recording followed by continuous ECG monitoring for at least 72 hours. All three guidelines mention that long-term monitoring using non-invasive ECG monitors or implanted loop recorders should be considered for the detection of asymptomatic AF in post-stroke patients or to document AF in those with symptoms suggestive of paroxysmal AF.

The ESC guidelines further emphasise the significance of detecting asymptomatic (or silent) AF by suggesting that systematic ECG screening may be considered in all individuals aged >75 years or at high risk of stroke (81), and added an ECG rhythm strip to pulse palpation as a recommended way to undertake opportunistic screening. The ESC guidelines also recommended regular device interrogation in patients implanted with pacemakers or implantable cardioverter defibrillators (ICD) for AF or atrial high rate episodes (AHRE). At present, the detection of AHRE should trigger further ECG monitoring to document AF before initiating stroke prevention therapy.

The future

The last 10 years has been an exciting time in the field of stroke prevention in AF, and in a modelling analysis, our data point to a substantial increase in the human and economic cost burden of AF and so emphasize the need to reduce this burden (82). This may be achieved by the increased use of OACs, particularly with the NOACs.

Whilst we focus on stroke prevention in AF, many deaths in AF are actually not stroke related, and the majority are cardiovascular (83). OAC use is independently associated with a reduction in all cause, CV and non-CV mortality. Nonetheless, OAC use in patients with AF significantly reduces stroke to non-AF rates, but whilst mortality is reduced, there is still an excess compared to non-AF patients (84).

Unanswered questions remain, for example, the use of OACs in AF patients with a prior ICH (85), significant valvular heart disease (78), the very elderly (86) and those with severe kidney disease (87), given that such patients were excluded from RCTs. Also, when to re-initiate OAC in high risk patients after a recent acute ischaemic stroke or gastrointestinal bleed (88, 89).

In modelling the effect of the increasing use of NOACs in AF patients with a prior ICH (85), significant valvular heart disease (78), the very elderly (86) and those with severe kidney disease (87), given that such patients were excluded from RCTs. Also, when to re-initiate OAC in high risk patients after a recent acute ischaemic stroke or gastrointestinal bleed (88, 89).

Stoke and bleeding risk assessment continues to evolve, and the ongoing debate on balance between simplicity and practicality, against precision medicine will continue. As the NOACs are neither new nor novel anymore, new oral anticoagulants drugs targeting Factor IX, XI and other novel mechanisms are in development (90) as the quest for the holy grail of stroke prevention with no excess of bleeding continues.

Conflicts of interest

GYHL: Consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer-Ingelheim, Microlife and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo. No fees are received personally. BF: Grants, personal fees, non-commercial support from Bayer; Personal fees from BMS/Pfizer, Boehringer-Ingelheim, Servier, AstraZeneca, Gilead (not in the area of atrial fibrillation or stroke). TSP: Consultant and speaker fees from Bayer, Pfizer, and Boehringer Ingelheim. RDC: Lecture fees and honoraria from Boehringer-Ingelheim, Bayer, BMS/Pfizer, Daiichi-Sankyo, Lilly, and Novartis; Research grants from Boehringer-Ingelheim, Bayer, BMS/Pfizer.

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