What is the most effective and safest delivery of thromboprophylaxis in atrial fibrillation?

GYH Lip

Professor of Cardiovascular Medicine, University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK

ABSTRACT The presence of atrial fibrillation (AF) increases the risk of stroke five-fold, but the risk is dependent upon the presence of stroke risk factors. The challenge is defining patients who would best benefit from thromboprophylaxis, and how to deliver it in the most effective and safe way. The objective of this brief overview is to address this question. Previously, attention has been directed towards identifying high-risk patients who could be subjected to an inconvenient (and potentially dangerous) drug, warfarin. Aspirin has been increasingly recognised as an inferior choice for stroke prevention, and may not be any safer than warfarin in terms of major bleeding, especially in the elderly. Thus, the focus more recently has been directed towards identifying truly low-risk patients who do not need any antithrombotic therapy, and all others with ≥ 1 stroke risk factors should be considered for oral anticoagulation therapy (whether as well-controlled warfarin or one of the new oral anticoagulant drugs), as the most effective means of reducing the risk of stroke and thromboembolism in AF.

Correspondence to GYH Lip,
University of Birmingham,
Centre for Cardiovascular Sciences,
City Hospital, Birmingham,
B18 7QH, England, UK

g.y.h.lip@bham.ac.uk

DECLARATION OF INTERESTS Professor Lip has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, Biotronik, Portola and Boehringer Ingelheim and has been on the speakers bureau for Bayer, BMS Pfizer, Boehringer Ingelheim and Sanofi-Aventis.

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder, and has attracted much attention due to the strong and consistent relationship to stroke and thromboembolism. The presence of AF increases the risk of stroke five-fold, but the risk is dependent upon the presence of stroke risk factors, such as hypertension, diabetes, heart failure, etc.¹

The challenge is in defining patients who would best benefit from thromboprophylaxis, and how to deliver it in the most effective and safe way. The objective of this brief overview is to address this question.

PATHOPHYSIOLOGY OF THROMBOEMBOLISM IN ATRIAL FIBRILLATION

AF fulfils components of Virchow's triad for thrombogenesis, with evidence of abnormalities of blood flow (atrial stasis), abnormalities of vessel wall (with structural heart disease, endothelial damage, etc.) and abnormalities of blood constituents (with abnormal coagulation and fibrinolysis).² Pathophysiologically, the composition of thrombus in AF is fibrin-rich (i.e. red clot) justifying oral anticoagulation (OAC) therapy, in contrast to thrombus in acute coronary syndromes (ACS) where the thrombus is platelet-rich (i.e. white clot), justifying antiplatelet therapy in the latter condition.

WHAT DO THE EARLY TRIALS TELL US?

Many clinical trials have shown the benefit of OAC therapy – essentially, the vitamin K antagonist (VKA) class of drugs (e.g. warfarin) for reducing stroke and thromboembolism in AF. In the meta-analysis by Hart et al,³ the use of OAC significantly reduces stroke by 64% and all-cause mortality by 26%, compared to placebo. When compared to antiplatelet therapy, OAC reduces stroke by nearly 50%. In many of the early trials, strokes in the patients randomised to OAC usually occurred when patients were either not taking assigned therapy or had suboptimal anticoagulation.

In contrast, antiplatelet therapy reduces stroke by 22% compared to placebo, a treatment effect size consistent with that seen for antiplatelet therapy in reducing stroke when given to patients with vascular disease.^{3,4} Given that AF commonly coexists with vascular disease, it is perhaps unsurprising that this small effect on stroke is seen. When confined to aspirin-only trials, aspirin non-significantly reduces stroke by 19%, and all-cause mortality by 14%, compared to placebo. This 19% risk reduction with aspirin compared to placebo is driven by data from one single positive trial, the SPAF-I trial,⁵ which compared aspirin 325 mg daily with placebo. There was an important internal inconsistency for the aspirin effect between anticoagulation-eligible (94% risk reduction) and anticoagulation-ineligible (8% risk reduction, not significant) patients, which was

pooled to give the 42% overall risk reduction with aspirin versus placebo in the SPAF-I trial.⁵ Also, the trial was stopped early, which may have exaggerated the effect size of aspirin, which did not prevent severe strokes nor show any significant effect in patients aged >75 years. In the European AF Trial,⁶ the first placebo-controlled secondary prevention trial, aspirin was ineffective for preventing strokes in this high-risk population. Thus, the evidence for aspirin as effective therapy for stroke prevention in AF is very weak, although it could be argued that there was no significant statistical heterogeneity between the trials.

In the early trials, there was a significant increase in major bleeding with OAC compared to placebo or aspirin.³ This was particularly evident in elderly patients (aged >75), where in one trial (SPAF-II), the beneficial reduction of ischaemic stroke was offset by a significant increase in major bleeding, including intracranial haemorrhage.⁷

These early trials have been criticised for their applicability to everyday clinical practice, given that only <10% of patients screened were randomised.⁸ These trials were also conducted nearly two decades ago, where standards of care (e.g. blood pressure control) and cardiovascular prevention strategies (e.g. the use of angiotensin converting enzyme [ACE] inhibitors, statins, etc.) were different from that seen in contemporary clinical practice. Indeed, more contemporary non-AF clinical trials for primary cardiovascular prevention in patients with vascular disease⁹ did not show any significant difference between aspirin and placebo for reducing mortality, stroke or cardiovascular events, at the cost of an increase in major bleeding events. This raises the possibility that the incremental benefit of aspirin over and above contemporary strategies for cardiovascular prevention (e.g. good blood pressure control, statins, etc.) may be small. Finally, OAC with warfarin was given with the measurement of the prothrombin time, an equivalent International Normalized Ratio (INR) ranging from 1.8 to 4.5, which differs from more contemporary clinical practice where the recommended INR range is 2–3.

Additional evidence comes from non-trial, 'real world' cohort studies. In a systematic review of such studies in AF cohorts, OAC-treated patients have an ischaemic stroke rate of 1.7 per 100 person years, compared to an average of 4.45 with antiplatelet therapy and 4.45 in untreated patients, while average major bleeding rates are only marginally increased with antithrombotic therapy (1.7 vs 1.4 vs 1.3, respectively).¹⁰

The elderly

Elderly patients (age >75) were under-represented in the early trials, and were perceived to do badly on warfarin as the reduction in ischaemic stroke rates would be offset by an increase in bleeding.

The BAFTA trial specifically addressed this point, and included elderly patients with AF (aged ≥75) in the primary care setting, who were randomised to warfarin (INR 2–3) or aspirin.¹¹ This trial showed that warfarin was clearly superior to aspirin, and the rate of major bleeding (and intracranial haemorrhage [ICH]) was not significantly different between them. This is supported by the small WASPO trial¹² in octogenarians, which showed significantly more adverse events in elderly patients treated with aspirin compared to warfarin.

The individual patient meta-analysis by van Walraven et al¹³ showed clearly that the risk of stroke starts to rise from age 65 onwards, and as patients got older, the absolute benefit of OAC increased while the absolute benefit of aspirin declined markedly. The risk of serious bleeding increased slightly with age, with a small absolute increase with antithrombotic therapy (either aspirin or warfarin) but the absolute increase in serious bleeding was far outweighed by the dramatic reduction in ischaemic stroke and cardiovascular events with warfarin.

Warfarin use may also be improving, with increasing awareness of the importance of good anticoagulation control, where well-controlled warfarin with time in therapeutic range (TTR) of >60% is the optimal strategy. Indeed, where TTR is poor (e.g. <50%) the stroke outcomes are worse than if the patient were untreated.^{15,16} The systematic review by Wan et al¹⁶ shows that poor TTR can be correlated to increased stroke and bleeding rates. Initiatives such as self-monitoring have been shown to improve outcomes.¹⁷

Low-risk patients

Patients with AF at low risk do not derive any benefit from OAC compared to aspirin, and in the Japanese AF Stroke trial,¹⁸ there was no significant difference between aspirin and control for the reduction of the primary endpoint (stroke, thromboembolism etc.), with a trend to more bleeding and ICH events with aspirin. Unsurprisingly, aspirin is not even recommended for low-risk patients in the Japanese treatment guidelines for AF.²⁰

ALTERNATIVE PHARMACOLOGICAL STRATEGIES TO THERAPEUTIC DOSE ADJUSTED VKA THERAPY

Despite the effectiveness of OAC, warfarin is inconvenient and requires regular monitoring and dose adjustment.²¹ The VKAs have significant drug interactions as well as diet and alcohol restrictions. Serial INRs are also poorly predictive of bleeding risk.²²

Thus, other alternative strategies to OAC therapy have been tested, with the use of fixed or low intensity warfarin with or without aspirin, or other antiplatelet drugs (e.g. indobufen, triflusal).

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The trials with fixed or low intensity OAC, whether in combination with aspirin or not showed that such a strategy was ineffective compared to therapeutic dose adjusted warfarin.²² One small trial (SIFA) suggested that the antiplatelet drug indobufen was associated with a similar rate of stroke to warfarin, but had less bleeding; however, this drug has never been tested in further trials in AF.²³

The antiplatelet drug triflusal was tested in combination with OAC in the NASPEAF trial, where combined antiplatelet plus moderate-intensity anticoagulation therapy significantly decreased the vascular events compared with OAC alone, with no significant difference in bleeding.²⁴ No further trials with triflusal in AF have been performed.

Aspirin-clopidogrel

Aspirin-clopidogrel combination therapy has been tested against warfarin in the ACTIVE-W trial,²⁶ and against aspirin monotherapy in the ACTIVE-A trial which was conducted in patients who were deemed unsuitable or had refused warfarin.²⁷ The ACTIVE-W trial was stopped early due to a clear superiority of warfarin over aspirin-clopidogrel combination therapy, although a posthoc analysis suggested that this benefit was largely seen in prior warfarin-experienced patients and the difference was non-significant among warfarin-naïve patients entering the trial.

In the ACTIVE-A trial, there was a significant 28% reduction in ischaemic stroke with combination therapy versus aspirin. However, aspirin-clopidogrel was associated with a rate of major bleeding that was broadly similar to that seen with warfarin (approximately 2%). Also, patients in ACTIVE-A were included on the basis of 'physician perception that the patient was unsuitable' for warfarin (50%) and patient preferences or refusal to take it in 26%, with contraindications at baseline (e.g. uncontrolled blood pressure) in 23% of patients.

New OACs

Given the various limitations of the VKA class of drugs, great efforts have been directed towards the development of new OACs that overcome the disutility of VKAs.²¹ These new OACs fall into two broad categories: the oral direct thrombin inhibitors (DTIs) and oral Factor Xa (FXa) inhibitors. Four large Phase 3 trials with new OACs have been published (RELY, ROCKET-AF, ARISTOTLE, AVERROES) and one is still ongoing (ENGAGE-AF, with edoxaban).

The first DTI, ximelagatran was tested against warfarin in the SPORTIF III and V trials, which showed non-inferiority of ximelagatran to warfarin.^{33,34} However, the drug has since been withdrawn due to liver toxicity. The next DTI, dabigatran was tested in two doses (110 mg twice a day [bid] and 150 mg bid) against warfarin in the huge RE-LY

trial.²⁸ The latter trial showed that dabigatran 110 mg bid was non-inferior to warfarin for the primary efficacy endpoint of reducing stroke and systemic embolism, with a significant 20% reduction in major bleeding events. Dabigatran 150 mg bid showed superiority (by 35%) over warfarin, with a similar rate of major bleeding events. Dabigatran 150 mg bid also resulted in significantly fewer ischaemic stroke events versus warfarin. Both doses of dabigatran were associated with significantly less haemorrhagic strokes and intracranial haemorrhage. There was a borderline reduction in all-cause mortality and a significant reduction in cardiovascular mortality. Total bleeding events (i.e. the composite of major plus minor bleeds) were significantly reduced with both doses of dabigatran, compared to warfarin. However, dabigatran 150 mg bid was associated with more gastrointestinal bleeds and both doses of dabigatran were associated with a non-significant numerical increase in myocardial infarction (MI) events. There was a significant excess of dyspepsia with dabigatran compared to warfarin.

The next new OAC with published Phase 3 data was the oral FXa inhibitor, rivaroxaban, tested against warfarin in the ROCKET-AF trial, which targeted high-risk patients with AF for inclusion.²⁸ In this trial, rivaroxaban was non-inferior to warfarin for the primary efficacy endpoint of stroke and systemic embolism, although there was a significant reduction in haemorrhagic strokes. When tested on a more conservative intention to treat analysis, rivaroxaban was not superior to warfarin, although an on-treatment analysis did suggest that superiority to warfarin was achieved (by 12%) for reducing stroke and systemic thromboembolism. Rivaroxaban was non-inferior to warfarin for the primary efficacy endpoint of major plus clinically relevant non-major bleeds, with no significant difference in major bleeds, but an increase in gastrointestinal bleeding events. There was no excess of MI events compared to warfarin, and no significant difference in all-cause mortality or cardiovascular mortality.

The FXa inhibitor apixaban was tested against warfarin in the ARISTOTLE trial,²⁹ which showed a superiority over warfarin in reducing stroke and systemic thromboembolism (by 21%), driven by a 50% reduction in haemorrhagic stroke and no significant difference in ischaemic stroke. Major bleeding was significantly less with apixaban (by 31%), as was total bleeding (major plus minor), with no excess of MI events. All-cause mortality was significantly reduced (by 11%) but there was no significant reduction in cardiovascular mortality. Apixaban was also tested against aspirin in a second Phase 3 trial, AVERROES, which included AF patients who had failed or refused VKA therapy.³⁰ This trial was stopped early, due to a clear superiority of apixaban over aspirin 81 mg – 324 mg daily), and the rate of major bleeding or ICH was not significantly different between apixaban and aspirin. Apixaban was also significantly better tolerated (as reflected by treatment discontinuations) compared to aspirin or warfarin.

Patients with severe renal failure, defined as a creatine clearance of <30 , were excluded from the trials with the new OACs. This is particularly relevant for dabigatran, which has a high renal excretion. In ROCKET-AF, there was a dose adjustment with a lower dose (15 mg once daily [od]) used in patients with moderate renal impairment, where outcomes have been shown to be broadly similar to that seen with the 20 mg od dose used for other patients.²⁸ In ARISTOTLE and AVERROES, there was a dose adjustment, with the use of the lower dose (2.5 mg bid) for patients with two out of three criteria (reduced BMI, age >80 and moderate renal impairment).

The new OACs have clearly changed the approach to thromboprophylaxis for stroke prevention in AF. Given the benefits of efficacy and safety, one Markov decision analysis model balancing the relative hazard of ischaemic stroke against the relative hazard of ICH concluded that the threshold for treatment with a new OAC (using the RELY data in the model) was an annual stroke rate of 0.9%, while the threshold for warfarin was 1.7%.³² Previously the strategy was to identify high-risk patients with AF so that these patients could be targeted for an inconvenient (and potentially dangerous) drug, warfarin. These new OACs offer convenience (no need for INR monitoring) and overcome the diet, drug and alcohol restrictions associated with warfarin. Various studies have also confirmed that these new drugs are cost-effective, given their safety and efficacy.^{34–36}

However, the fact still remains that these drugs are powerful anticoagulants and would work well if the patients are compliant and clinicians prescribe the drug correctly to appropriate patients. For example, elderly patients (age >80) are recommended dabigatran 110 mg bid given the significant age interaction with bleeding.³⁷ While there is no necessity for anticoagulation monitoring for dose adjustment (unlike warfarin), coagulation tests such as the activated partial thromboplastin time (aPTT), ecarin clotting time (ECT) and thromboplastin time (TT) can be used to test for an anticoagulation effect with (for example) dabigatran.^{38,39} As there is no specific antidote for dabigatran, measures to manage bleeding are still largely supportive although haemodialysis is a possibility. One recent study suggested that the anticoagulation effect of rivaroxaban can be reversed with prothrombin complex concentrates (PCC), although this was a study in relatively young healthy individuals where effects on various coagulation tests were studied, with no relation to bleeding per se.⁴⁰

Given the recent regulatory approval for dabigatran in Europe for stroke prevention in AF, a recent consensus document of the Italian Federation of Thrombosis Centers (FCSA) details questions and answers on the practical use of dabigatran and perspectives on the use of other new oral anticoagulants in everyday clinical practice.⁴¹

In summary, a paradigm shift has occurred to improve our ability to identify truly low-risk patients with AF who do not need any antithrombotic therapy, and those with one or more stroke risk factors who can be considered for OAC therapy, whether with well-controlled warfarin or one of the new OAC drugs.⁴² Hence, an important consideration is to improve our ability to comprehensively assess stroke risk in patients in AF.

STROKE RISK STRATIFICATION

While AF increased the risk of stroke five-fold, the risk is not homogeneous. The Stroke Risk in AF Working Group⁴³ performed a systematic review of stroke risk factors, largely driven by data from non-VKA arms of the early clinical trials, and showed that prior stroke, hypertension, diabetes and female gender were significant predictors of stroke, as was moderate-severe systolic dysfunction on echocardiography, while history of heart failure and coronary artery disease were not significant risk factors. However, risk factors based on data from early trials had some inconsistency in definitions of some stroke risk factors and not all were systematically looked for nor recorded. The trial data therefore needed to be supplemented by additional evidence from epidemiological and cohort studies.⁴⁴

The simple CHADS₂ score is the most commonly used stroke risk stratification scheme, and has been validated in many studies (Table 1). This score is an amalgamation of two risk schemes from trial cohorts (the AF Investigators and the SPAF scheme) derived from the original early trials.⁴⁵ As discussed above, the applicability of the early (now historical) trials to the general population has also been debated, given that only a minority of the patients screened ($<10\%$) were randomised. In a recent systematic review and meta-analysis, the pooled c statistic and calibration analysis suggested only minimal clinical utility of CHADS₂ in predicting ischaemic stroke across all risk strata, and even concluded that further validation of CHADS₂ should perhaps be undertaken.⁴⁶ While simple, the many advantages and disadvantages of the CHADS₂ score have been debated.⁴⁷

Various studies have shown that female patients with AF are at increased risk of stroke compared to men.^{48–50} Also, the presence of peripheral artery disease is a major risk factor for stroke and mortality, in the presence of AF.^{51,52} As mentioned above, the study by van Walraven et al¹³ clearly shows that age is an important driver for stroke risk, with the risk rising from age 65 upwards. Other cohort studies have clearly shown an increase in stroke risk at age 65–74 years,^{52–54} compared to younger subjects (age <65) and among these younger subjects, independent predictors of subsequent stroke were prior stroke, vascular disease and heart failure.⁵³

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TABLE 1 The CHADS₂, CHA₂DS₂-VASc and HAS-BLED scores for assessing stroke and bleeding risk (adapted from European Society of Cardiology Guidelines 2010).

CHADS₂	Score
Congestive cardiac failure (moderate to severe systolic left ventricular [LV] dysfunction, defined arbitrarily as left ventricular ejection fraction [LVEF] ≤40%)	1
Hypertension (blood pressure consistently >140/90 mmHg or treated hypertension on medication)	1
Age ≥75 years	1
Diabetes mellitus	1
Stroke/transient ischaemic attack/thromboembolism	2
Maximum score	6
CHA₂DS₂-VASc	
Congestive cardiac failure (moderate to severe systolic left ventricular [LV] dysfunction, defined arbitrarily as left ventricular ejection fraction [LVEF] ≤40%)	1
Hypertension	1
Age ≥75 years	2
Diabetes mellitus	1
Stroke/transient ischaemic attack/thromboembolism	2
Vascular disease (previous myocardial infarction [MI], peripheral arterial disease or aortic plaque)	1
Age 65–74 years	1
Sex category (i.e. female)	1
Maximum score	9
HAS-BLED	
Hypertension (e.g. systolic >160 mmHg)	1
Abnormal renal and liver function (1 point each)	1 or 2
Stroke	1
Bleeding tendency or predisposition	1
Labile International Normalized Ratio (INR) (only if on warfarin)	1
Elderly (e.g. age >65)	1
Drug (i.e. concomitant aspirin or non-steroidal anti-inflammatory drugs [NSAIDs]) or alcohol (1 point each)	1 or 2
Maximum score	9

Older guidelines have divided stroke risk into low, moderate and high-risk categories, whereby high-risk patients could be targeted for warfarin, low-risk patients given aspirin and moderate-risk patients given aspirin or warfarin.^{55,56} This was in the era prior to the availability of new OACs with demonstrable efficacy over warfarin, and even better safety (and possibly, tolerability) over aspirin and warfarin, as well as the increasing recognition that aspirin had minimal beneficial impact on stroke prevention and may not be any safer. As mentioned above, the Japanese guidelines have removed aspirin from their stroke prevention guidelines for AF.¹⁹

Stroke risk is a continuum, and numerous studies assessing the predictive value of categorising AF patients into low, moderate and high-risk strata have shown that such an artificial classification only has modest predictive value for high-risk patients who subsequently suffer strokes.^{57,58} Many physicians would prescribe antithrombotic therapy in broadly similar proportions irrespective of the three strata.^{59,60} Given the shift

towards getting better at identifying truly low-risk patients with AF (who do not need any antithrombotic therapy), rather than focusing on identifying high-risk patients, a major paradigm shift has been directed towards being more inclusive (rather than exclusive) of common stroke risk factors as part of any comprehensive stroke risk assessment.

The 2010 European Society of Cardiology (ESC) guidelines⁶¹ de-emphasises the artificial categorisation into low, moderate and high-risk strata, and recommends a risk factor based approach. The latter is based on defining major and clinically relevant non-major stroke risk factors (see Table 1) and these risk factors are within a new stroke risk score, CHA₂DS₂-VASc.⁶² This has consistently been shown to outperform the CHADS₂ score in identifying truly low-risk patients with AF, and is at least as good as, and possibly better^{53,63} than the CHADS₂ score in identifying high-risk patients who subsequently sustain a thromboembolic event. One recent analysis based on a large nationwide cohort dataset showed that there was a

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negative net clinical benefit analysis with warfarin, balancing ischaemic stroke against ICH only with a CHA₂DS₂-VASc score =0, reflecting the truly low-risk status of these patients.⁶⁴

The new ESC guidelines recommended use of the CHA₂DS₂-VASc score to complement the CHADS₂ score, since those with a CHADS₂ score of ≥ 2 were clearly high-risk and OAC is recommended (Table 2). In patients with a CHADS₂ score of 0–1, more comprehensive stroke risk assessment was necessary, so components of the CHA₂DS₂-VASc score should be taken into consideration. Once truly low-risk patients (defined as CHA₂DS₂-VASc score =0) were identified, no antithrombotic therapy is needed, and those patients with ≥ 1 stroke risk factors should have OAC as the preferred option, whether given as well-controlled warfarin or one of the new OAC drugs.

Given that guidelines should be applicable for >80% of the time, for >80% of the patients, the ESC guideline stroke risk assessment approach covers most of the patients we commonly see in everyday clinical practice, and considers the common stroke risk factors in such patients. The ESC guidelines⁶¹ also stress that antithrombotic therapy is necessary in all patients with AF unless they are age <65 and truly low-risk. Thus,

some patients with female gender only as a single risk factor (still a CHA₂DS₂-VASc score =1) would not need anticoagulation, if they fulfil the criteria of age <65 and lone AF.

BLEEDING RISK ASSESSMENT

Decision-making for thromboprophylaxis needs to balance the risk of stroke against the risk of major bleeding, especially ICH. Until recently, bleeding risk assessment tools were based on complex formulae and/or derived from cohorts of general anticoagulated patients, rather than specifically from AF patients. Also, many risk factors for bleeding are also risk factors for stroke.^{65–67} Hence, guidelines from 2006 did not recommend the use of any bleeding risk score, and many clinicians were simply informally assessing bleeding risk in their patients, although it has been shown that physician risk assessment is poor.⁶⁸

More recently, a simple bleeding risk score (HAS-BLED, Table 1) has been proposed⁶⁹ and used in the ESC⁶¹ and Canadian⁷⁰ guidelines. The latter guidelines recommend formal bleeding risk assessment, and in patients with a HAS-BLED score of ≥ 3 , caution and regular review is recommended. The HAS-BLED score allows clinicians to make an informed assessment of bleeding risk (rather

TABLE 2 Approach to thromboprophylaxis in patients with atrial fibrillation (adapted from European Society of Cardiology 2010 Guidelines).

Risk category	CHA ₂ DS ₂ -VASC score	Recommended
One major or ≥ 2 clinically relevant non-major risk factors	≥ 2	OAC, given as well-controlled VKA (INR 2.0–3.0) or dabigatran [*]
One clinically relevant non-major risk factor	1	OAC or antiplatelet therapy [†] Preferred: OAC [*]
No risk factors	0	Either antiplatelet therapy or no antithrombotic therapy Preferred: no antithrombotic therapy ^{**}
CHA₂DS₂-VASC: cardiac failure, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74 and sex category (female)		
OAC: oral anticoagulation, such as a vitamin K antagonist (VKA) dose-adjusted to an intensity range of INR 2.0–3.0 (target 2.5), or dabigatran		
VKA: vitamin K antagonist		
INR: international normalized ratio		
[*] Dabigatran 150 mg bd if a patient is at low risk of bleeding (e.g. HAS-BLED score of 0–2) or dabigatran 110 mg bd considered if a patient is age ≥ 80 , takes concurrent acting drugs (e.g. verapamil) or has a measurable risk of bleeding (e.g. HAS-BLED score of ≥ 3). When formally licensed, alternatives to dabigatran are as follows: (i) rivaroxaban 20 mg od, except in moderate renal impairment (creatinine clearance 30–49), 15 mg od; or (ii) apixaban 5 mg bid, except in patients with two of three criteria (BMI <20, age >80 and moderate renal impairment) whereby apixaban 2.5 mg bid should be used. The final labelling will determine the recommended doses of rivaroxaban and apixaban, when licensed.		
[†] Antiplatelet therapy is given as aspirin-clopidogrel (if not at high bleeding risk) or less effectively, aspirin 75–300 mg.		
[*] In patients with one clinically relevant non-major stroke risk factor (i.e. CHA ₂ DS ₂ -VASC score =1), dabigatran 110 mg bid may be considered (in view of a similar efficacy with VKA in the prevention of stroke and systemic embolism but lower rates of intracranial haemorrhage and major bleeding compared with the VKA and [probably] aspirin).		
^{**} Female patients with gender only as a single risk factor (i.e. CHA ₂ DS ₂ -VASC score =1) would not need anticoagulation, if they would otherwise clearly fulfil the criteria of 'age <65 and lone AF (i.e. truly low-risk)'.		

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FIGURE 1 An approach to using risk scores for stroke and bleeding in clinical practice.

***CHA₂DS₂-VASc**: cardiac failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74 and sex category (male).

**Female patients with gender only as a single risk factor (i.e. CHA₂DS₂-VASc score =1) would not need anticoagulation, if they would otherwise clearly fulfil the criteria of 'age <65 and lone AF (i.e. truly low-risk).'

†If HAS-BLED score ≥3, caution and regular review is recommended, including management of correctable risk factors for bleeding. Regular review of risk factors for stroke is essential.

***OAC**: oral anticoagulation

¶At time of publication, only dabigatran is licensed for this indication as a new oral anticoagulant.

‡Aspirin/clopidogrel combination or (less effectively for stroke prevention) aspirin.

than guesswork) and importantly, makes clinicians think of the correctable risk factors for bleeding, for example, uncontrolled blood pressure, concomitant use of aspirin/NSAIDs, labile INRs, etc.

In the net clinical benefit analysis by Olesen et al.,⁶⁴ patients with a high HAS-BLED score had a greater net clinical benefit with warfarin, given that higher risk individuals would have a much greater absolute reduction in stroke risk with warfarin, which would outweigh the small absolute increase in major bleeding events. This work has been extended by modelling these 'real world' data for net clinical benefit data balancing ischaemic stroke against intracranial haemorrhage in patients with non-valvular AF, for dabigatran, rivaroxaban and apixaban on the basis of recent clinical trial outcome data for these new OACs. This analysis showed that in patients with CHADS₂ =0 but at high bleeding risk, apixaban and dabigatran 110 mg bid had a positive net clinical benefit.

At CHA₂DS₂-VASc =1, apixaban and both doses of dabigatran (110 mg and 150 mg bid) had a positive net clinical benefit, while in patients with CHADS₂ score ≥1 or CHA₂DS₂-VASc ≥2, all three new OACs were superior to warfarin for net clinical benefit, irrespective of bleeding risk.⁷¹

CONCLUSION

What is the most effective and safest delivery of thromboprophylaxis in AF? Given recent developments in the field, the focus has been directed to improve our identification of truly low-risk patients who do not need any antithrombotic therapy, while those with one or more stroke risk factors should be recommended OAC, whether this is with well-controlled warfarin or one of the new OACs. Of the stroke risk schemes, the CHA₂DS₂-VASc consistently outperform the CHADS₂ score in identifying truly low-risk patients with AF, and is at least as good as, and possibly better than the CHADS₂ score in

identifying high-risk patients who subsequently sustain a thromboembolic event. Assessment of bleeding risk should also be mandated as part of the approach to thromboprophylaxis, and where relevant, the lower dose of new OACs (for example, dabigatran 110 mg bid), should be used. The HAS-BLED score is simple, well-validated and recommended in international guidelines. A suggested approach to stroke and bleeding risk assessment is shown in Figure 1.

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