Challenges of stroke prevention in patients with atrial fibrillation in clinical practice

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Summary

Strokes and transient ischaemic attacks in patients with atrial fibrillation (AF) can be largely prevented. Risk stratification and appropriate prophylactic regimens help to alleviate the burden of AF-related thromboembolism. Guidelines recommend routine anticoagulation with oral vitamin K antagonists (VKAs) for patients at moderate-to-high risk of stroke, and acetylsalicylic acid (ASA) for those at low risk of stroke. ASA is less effective at reducing the risk of stroke than VKAs; however, ASA does not require monitoring or dose adjustment. Trials of anticoagulants show consistent benefits of oral VKAs for primary and secondary stroke prevention in patients with AF. Nevertheless, VKAs do require frequent coagulation monitoring and dose adjustment because of their variable dose–response profile, narrow therapeutic window, increased risk for bleeding complications and numerous food and drug interactions. This review aims to provide an overview of the clinical challenges of anticoagulant therapy for the prevention of stroke in patients with AF.

Introduction

The risk of stroke or a transient ischaemic attack (TIA) in patients with atrial fibrillation (AF) can be reduced. Despite this, the rate of stroke remains high and results in substantial healthcare and patient burden costs. When stroke occurs in association with AF, there is higher risk of mortality and disability than in stroke patients without AF.1 One hypothesis for this is that stroke in patients with AF may be principally cardioembolic, thereby occluding larger cerebral arteries and being more severe.2 However, because the lethality of stroke is higher in the elderly, the difference in morbidity and mortality between people with and without AF is likely to become progressively more evident in an older population.3

The prevalence of AF increases with age, rising from 0.7% in people aged 55–59 years to 18% in those older than 85 years.4 Therapeutic strategies and optimal risk stratification offer the best hope for reducing the burden of AF-related thromboembolism.5 Guidelines for stroke prevention in patients with AF are based on risk stratification [e.g., guidelines from the American College of Cardiology (ACC)/American Heart Association (AHA)/European Society of Cardiology (ESC) and from the American College of Chest Physicians (ACCP), and the most recent guidelines published by the ESC] and assess the risk of stroke according to the presence of a
range of different risk factors.6–8 These risk factors include prior thromboembolism, age >75 years, hypertension, heart failure, impaired left ventricular systolic function and diabetes mellitus. Several stroke risk scores exist, most notably CHADS2 (Figure 1A) and CHA2DS2-VASc (Figure 1B).

Guidelines recommend routine anticoagulation with oral vitamin K antagonists (VKAs) for all patients at high risk of stroke, and for some at moderate risk, although the most recent ESC guidelines state that combination therapy with acetylsalicylic acid (ASA) plus clopidogrel may be considered in patients who refuse to take VKA therapy or where there is a clear contraindication to VKA use.8 ASA is only recommended for those at low risk of stroke.6,7 These treatment recommendations are mirrored in guidance from the UK’s National Institute for Health and Clinical Excellence (NICE) on the management of AF9 and Scotland’s Scottish Intercollegiate Guidelines Network (SIGN) guidance on antithrombotic therapy.10

Anticoagulation is highly effective in preventing stroke in patients with AF, but the risk of haemorrhage may be increased, particularly in older patients. Nevertheless, a patient-level meta-analysis of randomized controlled trials has shown that oral anticoagulation therapy safely prevents stroke in older patients (mean age 71 years) with AF.11 Moreover, direct trial data from the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study support the use of anticoagulation therapy for people aged >75 years who have AF, unless there are contraindications or the patient decides that the benefits are not worth the inconvenience.12

Primary prevention of stroke refers to patients without previous stroke or TIA; secondary prevention refers to patients with previous stroke or TIA. Trials of anticoagulants for primary prevention of stroke show a consistent benefit of oral VKAs for stroke prevention in patients with AF, with relative risk reductions ranging from 52% to 82%.5 In the European Atrial Fibrillation Trial (EAFT), the benefit of oral anticoagulation in secondary prevention was similar, with a relative risk reduction of 66%.5,13

Despite VKAs such as warfarin being effective in reducing the risk of stroke in patients with AF, their use can be particularly challenging in clinical practice. This review aims to provide an overview of the clinical challenges of anticoagulant therapy that may be encountered in the prevention of stroke in patients with AF.

**ASA**

The use of ASA in the secondary prevention of cardiovascular disease is now well established. Despite not requiring close monitoring, ASA, which is the only guideline-recommended platelet inhibitor for stroke prevention in AF, is less effective at reducing the risk of stroke than oral VKAs, especially in the elderly.14 In a meta-analysis of 16 trials, which included 9874 patients with AF, adjusted-dose warfarin (2900 patients, six trials) reduced stroke by 62%; absolute risk reduction (ARR) was 2.7% per year for primary prevention and 8.4% per year for secondary prevention. ASA (3119 patients, six trials) reduced stroke by 22% (ARR: 1.5% per year for primary prevention and 2.5% per year for secondary prevention).14

Moreover, as with warfarin, ASA increases major bleeding, particularly gastrointestinal bleeding.14,15 Even in an analysis of eight trials (49 927 participants) that used low doses (50–162.5 mg/day) of aspirin, gastrointestinal haemorrhage occurred in 2.30% of those taking aspirin compared with 1.45% taking placebo. Aspirin was associated with a significantly increased rate of gastrointestinal haemorrhage compared with placebo, with a pooled odds ratio of 1.59 (1.40 to 1.81; P<0.0001).15 Nevertheless, the EAFT study of secondary stroke prevention in patients with AF concluded that ASA was a safe, though less
effective, alternative when anticoagulation is contraindicated.13

**Oral vitamin K antagonists**

VKAs, which include the coumarins warfarin, phenprocoumon and acenocoumarol, are widely used anticoagulant agents that have been available for many years. By inhibiting the enzyme vitamin K epoxide reductase, VKAs prevent the regeneration of the reduced form of vitamin K, an essential cofactor in the synthesis of a number of factors in the coagulation cascade, including Factor II (prothrombin), Factor VII, Factor IX and Factor XI. Depletion of the reduced form of vitamin K ultimately impairs the ability to form thrombin, which subsequently inhibits the conversion of fibrinogen to fibrin.

Although effective in preventing stroke in patients with AF, oral VKAs have several limitations that make the routine, and acute, medical care of patients receiving long-term VKA therapy relatively complicated.

**Monitoring and bleeding risk of vitamin K antagonists**

VKAs have a variable dose–response profile and a narrow therapeutic window (Figure 2), which, combined with the increased risk for serious bleeding complications when the target international normalized ratio (INR) of prothrombin time is exceeded, means that patients require frequent coagulation monitoring. This need for sustained patient monitoring is not only inconvenient for the patient but also requires adequate healthcare infrastructure.16

Owing to their mechanism of action, VKAs have a slow onset of action, and their full effect only occurs after all currently active vitamin K-dependent coagulation factors have been cleared. Withdrawal of VKAs may also initially produce a hypercoagulable state, which means that, for individuals at a very high risk, concurrent therapy with heparin may be required.16

According to the ACCP evidence-based guidelines (8th edition), the long half-life of VKAs (36–42 h in the case of warfarin) and the resulting slow offset of action also represent limitations to optimal anticoagulation.17,18 When INR levels increase beyond the therapeutic range, warfarin therapy needs to be adjusted or stopped, depending on the circumstances, for a period to bring the INR back within range.17 In addition, vitamin K is also recommended in patients where reversal of the effects of warfarin is needed, with the expectation that a reduction of the INR will occur in 24 h.17

**Drug adverse events and interactions with vitamin K antagonists**

VKAs are also associated with a number of adverse reactions, the most clinically relevant of which is the risk of serious bleeding events, including gastrointestinal bleeding, haematomas and intracranial bleeding;16 bleeding risk increases substantially with the intensity of anticoagulation.19 The optimal INR range for effective anticoagulation with the lowest risk of bleeding is quite narrow (2.0–3.5), and requires regular coagulation monitoring of patients and frequent dose adjustments to maintain the therapeutic range.17 However, the optimal target range varies by indication and may also be dependent on patient characteristics.17 For example, in patients with AF receiving VKA prophylaxis, the recommended INR range is 2.0–3.0.7 The risk of bleeding is particularly increased for patients with prior stroke, renal impairment or anaemia, and these are the patient groups most in need of prophylaxis.20 The prior concerns that bleeding risk was greater in the elderly appear not to be the case.11

**Figure 2.** Therapeutic window for warfarin: risks versus benefits in relation to measurements of international normalized ratio.29
Moreover, VKAs are associated with a number of drug and food interactions, making effective treatment even more difficult. VKAs such as warfarin interact with a multitude of drugs, such as atorvastatin, esomeprazole, many antibiotics (chloramphenicol, clarithromycin, tetracycline, penicillin G, metronidazole), nonsteroidal anti-inflammatory agents and some of the most popular over-the-counter painkillers, including paracetamol (acetaminophen) and ASA. In addition, VKAs interact with a range of common foodstuffs, beverages and herbal remedies. Because of the mode of action of VKAs, subjects receiving long-term therapy will be sensitive to fluctuating dietary vitamin K. Eating large quantities of foods with high vitamin K content (such as broccoli, cabbage, kale, spinach and other green leafy vegetables, liver, green tea and some vegetable oils) should be avoided in patients on warfarin therapy.

These limitations of VKAs contribute to high levels of under-treatment with many eligible patients with AF at high risk of stroke not receiving any anticoagulant therapy. A retrospective study of a US cohort of inpatients with AF revealed that, despite 86% of patients having factors that stratified them at high risk of stroke, only 55% received warfarin and 21% of those at high risk of stroke received neither warfarin nor ASA. The study concluded that the risk stratification of a patient has little effect on warfarin use, but that age >80 years and AF classification (permanent/persistent) were factors that influenced the use of warfarin. Similarly, a report from the Euro Heart Survey on AF also confirmed that the patient’s risk profile was not a principal factor in the choice of antithrombotic therapy but that AF classification and the availability of an outpatient monitoring clinic were the most significant factors in influencing oral anticoagulation prescription.

Efficacy of vitamin K antagonists in clinical practice

Randomized trials have clearly shown the safety and efficacy of warfarin for the prevention of both primary and secondary stroke in patients with AF. The efficacy and safety of VKAs, which have been demonstrated in clinical trials, are perceived to be difficult to achieve in ‘real-world’ clinical practice because earlier randomized trials investigating VKA treatment enrolled highly selected patients, included few elderly patients (who commonly have AF) and monitored the INR more closely than in the usual care setting. Physicians have been concerned that the clinical trial results with VKAs cannot be duplicated in clinical practice where sicker patients are managed with less intensive anticoagulation monitoring; although more recent data, such as from the BAFTA trial, showed few patient exclusions while achieving good INR control in routine settings.

Several observational studies have evaluated antithrombotic therapy for prevention of stroke in patients with AF outside of randomized trials. However, many of these studies have been limited by the inclusion of patients from specific clinical settings (e.g. long-term care institutions, hospital clinics), modest sample sizes, and too few thromboembolic and bleeding events to generate accurate and precise event rates.

In two small observational studies in high-risk patients with AF who suffered an ischaemic stroke, warfarin was found to be significantly more effective than either ASA or no antithrombotic therapy for secondary prevention of stroke. Similarly, in two further studies of patients hospitalized with AF, prescription of warfarin therapy at discharge was associated with a lower risk of stroke and TIA compared with ASA or no antithrombotic therapy.

In the large AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) clinical practice trial, which studied 11,526 patients with non-valvular AF (mean age 71 years), warfarin was associated with a 51% lower risk of thromboembolism compared with no warfarin therapy, both in the presence and absence of risk factors for stroke. Warfarin was also associated with a reduced risk of all-cause mortality. Intracranial haemorrhage was uncommon; however, this event rate in patients on warfarin was moderately higher than in patients not on warfarin (0.46 versus 0.23 per 100 person-years, respectively; \( P = 0.003 \)). Warfarin therapy was not associated with an increased risk of non-intracranial major haemorrhage. In addition, this study has shown that anticoagulation to a therapeutic INR level of 2.0–3.0 can reduce the incidence of ischaemic stroke together with the severity and short-term risk of death in patients with AF.

Physicians’ concerns about the risk of major haemorrhage when warfarin is used outside of the clinical trial context, particularly in older patients, are therefore overstated, and present an educational challenge to healthcare systems. The use of warfarin can be maximized and its limitations minimized by using several strategies, including improvement of INR control through greater use of anticoagulation clinics or patient self-management, use of computerized INR decision support, greater adherence to relevant treatment guidelines and diligent avoidance of opportunities for food and drug interactions.
underused: inconvenience and physician’s fear of haemorrhage. The introduction of new oral agents with improved benefit–risk profiles and increased consistency and predictability compared with warfarin may offer a new approach in stroke prevention in AF that has the potential to improve therapeutic outcomes.

The future of anticoagulants for stroke prevention in AF

New oral anticoagulants, which avoid some of the disadvantages of VKAs, are being developed with improvements in specificity, more predictable pharmacokinetics, a better efficacy–safety balance and a more rapid onset of action. In addition, they have a wider therapeutic window with a lower potential for food and drug interactions. These drugs are being tested as once daily without the need for dose adjustment or routine coagulation monitoring, which offers convenience for both patients and physicians, thereby improving compliance. Although these new oral anticoagulants may be more expensive than warfarin, their ability to extend prophylaxis to more patients at risk of stroke may reduce overall costs.

Two main classes of anticoagulants are presently in clinical development for stroke prevention in AF: direct thrombin inhibitors and direct Factor Xa inhibitors. Dabigatran is the direct thrombin inhibitor furthest advanced in clinical development for stroke prevention in AF. The RE-LY study has shown that dabigatran 110 mg and 150 mg twice daily were non-inferior and superior, respectively, in terms of rates of stroke and systemic embolism, compared with warfarin. Dabigatran 110 mg has lower rates of major haemorrhage compared with warfarin, whereas dabigatran 150 mg was associated with similar rates of major haemorrhage to warfarin. The rate of myocardial infarction was higher with both doses of dabigatran than with warfarin, possibly a function of the effectiveness of warfarin in reducing myocardial infarction risk, and there was an increase in the rate of gastrointestinal bleeding with the higher dose of dabigatran due to its formulation increasing gastric acid levels. Lower rates of intracranial haemorrhage were noted with both doses of dabigatran compared with warfarin. Dabigatran is now licensed in the US for stroke prevention in atrial fibrillation at the 150 mg twice daily dose, with a 75 mg dose twice daily in renal impairment, whereas other countries are likely to license both the doses used in the RELY trial of 150 mg or 110 mg twice daily.

Results have recently been made available from the phase III, stroke prevention in AF, AVERROES trial, which compared the direct Factor Xa inhibitor, apixaban (5 mg twice daily) with ASA (81–324 mg/day) in patients unsuitable for vitamin K antagonists. The trial was terminated early because data from a predefined interim analysis demonstrated evidence of a clear superiority of apixaban over ASA. The annual rate of the primary outcome (stroke or systemic embolism) was 3.6% and 1.6% per year with ASA and apixaban, respectively ($P<0.001$), whereas major haemorrhage rates were 1.2% and 1.4% per year ($P=0.56$) and haemorrhagic stroke rates were 0.2% per year in both treatment groups.

Direct Factor Xa inhibitors currently being investigated in Phase III clinical trials for stroke prevention in AF include apixaban, edoxaban and rivaroxaban. Betrixaban and YM150 are currently in Phase II studies of patients with AF. Ongoing trials of the new, oral, direct Factor Xa inhibitors in stroke prevention in patients with AF include ARISTOTLE (apixaban vs. warfarin) and ENGAGE AF TIMI 48 (edoxaban vs. warfarin). Brief design details of these ongoing Phase III trials are shown in Table 1. Results for ARISTOTLE and ENGAGE AF TIMI 48 are expected in 2012.

Results for the recently completed ROCKET AF trial (rivaroxaban vs. warfarin) were reported at AHA (Chicago, 2010). ROCKET AF was a randomized, double-blind study that compared once daily rivaroxaban (20 mg, or 15 mg for patients with moderate renal impairment) with dose-adjusted warfarin for the prevention of stroke in 14 264 patients with AF. Rivaroxaban was superior to warfarin for the primary efficacy endpoint, showing a 21% relative risk reduction for stroke and non-central nervous system (CNS) systemic embolism in the pre-specified on-treatment population (1.7% vs. 2.2%, respectively, $P=0.015$). Additionally, in the intent to treat population, rivaroxaban showed comparable benefits to warfarin (2.1% vs. 2.4%, $P<0.001$ for non-inferiority).

### Box 1 Strategies for maximizing warfarin use.

**INR = international normalized ratio.**

- Improvement of INR control
  - Greater use of anticoagulation clinics
  - Patient self-management
  - Use of computerized INR decision support
- Improvement of INR control
- Greater adherence to treatment guidelines
- Diligent avoidance of opportunities for food and drug interactions
Rivaroxaban showed similar rates of major and non-major clinically relevant bleeding events, compared to warfarin (14.9% vs. 14.5%, \( P = 0.442 \)). Rates of major bleeding were also comparable between rivaroxaban and warfarin (3.6% vs. 3.5%, \( P = 0.576 \)).

Ongoing surveillance of thromboprophylaxis for AF in clinical practice

Registry-reported data, such as AFNET and EUROHEART can be used to provide insight into ‘real-world’ practice.\(^{23,32}\) These registries have shown that patients with AF are likely to have multiple comorbidities\(^ {23,32} \) and that current treatment guidelines (ACC/AHA/ESC) for stroke prevention in patients with AF are not being adhered to, with 28% of patients being untreated and 11% over treated with antithrombotic agents.\(^ {11} \) Data from new registries in AF are continually emerging and recent additions include GARFIELD, ORBIT AF and REALISE AF. GARFIELD is planned to be one of the largest registries to date and will provide data on ‘real-world’ treatment and use of anticoagulants in patients with AF who are at risk of stroke.

Conclusion

Guidelines currently recommend routine anticoagulation with oral VKAs for patients with AF at moderate-to-high risk of stroke. Despite a reasonable translation of the efficacy of VKAs for stroke prevention in patients with AF from clinical trials to clinical practice, their use remains challenging in clinical practice and requires frequent monitoring. The advent of new oral anticoagulants without the disadvantages seen with VKAs may enable even better outcomes for patients with AF, since these drugs exhibit improved pharmacokinetic profiles and reduced food/drug interactions. Clinical trials of these new oral anticoagulants in patients with AF are ongoing, and results are expected over the next couple of years. An increased focus on greater levels of warfarin initiation and careful INR monitoring are essential to ensure optimal patient care in preventing stroke in patients with AF. This is necessary even with the advent of newer agents without monitoring needs because warfarin is likely to continue to be used in a proportion of patients unless the new agents demonstrate strong cost-effectiveness over warfarin.

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