New strategies

Stroke is a major complication of atrial fibrillation, prevention of which is a major challenge in the treatment of this common arrhythmia. The recently updated European Society of Cardiology guidelines emphasise a risk factor based strategy for decisions on antithrombotic drugs. Oral anticoagulation is the gold standard, although several challenges remain in its implementation. New alternative agents to warfarin are being developed and once available, they could be important therapeutic advances in the care of patients with atrial fibrillation.

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Atrial fibrillation (AF) is the most common arrhythmia, occurring in 1–2% of the general population with prevalence rising to 5% in those aged >65 years and approaching 10% in those over 80 years.[1] Due to a progressive ageing population, the worldwide health related burden of AF is expected to increase 2.5 fold in the next 50 years.[1] It is estimated that 1% of NHS expenditure is on atrial fibrillation.[2] About one sixth of strokes are related to the condition.[3]

AF is a major risk factor for stroke and thromboembolism. Moreover, when strokes occur in AF patients, the risk of mortality and disability is higher than in stroke patients without AF.[4] Patients with AF are five times more likely to suffer a disabling or fatal stroke than those without AF.[4]

Types of AF

The recently updated European Society of Cardiology (ESC) guidance for AF recommends that the condition, based upon its presentation and duration, is subdivided into five types rather than the traditional three (paroxysmal, persistent, and permanent).[5]

1. First diagnosed AF; ie, patient who presents with AF for the first time
2. Paroxysmal AF; lasts less than seven days, usually self-terminating within 48 hours
3. Persistent AF; lasts longer than seven days and requires termination with drugs or cardioversion
4. Longstanding persistent AF; lasts one year or more when rhythm control strategy is adopted
5. Permanent AF; when rhythm control intervention is not pursued.

Management

This includes:

- Ventricular rate control, acutely and long term
- Assessment for antithrombotic treatment
- Decision for rhythm control
- Treatment of underlying heart disease and associated conditions: hypertension; heart failure; valvular heart disease; cardiomyopathy; congenital heart defects; coronary heart disease; thyroid disease; obesity; diabetes; and chronic obstructive pulmonary disease.

Antithrombotic therapy

During the past decade, there have been several clear messages from trials of antiplatelet and oral anticoagulant (OAC) treatments to reduce the risk of cardiovascular mortality and morbidity in patients with rheumatic and non-rheumatic AF.

Warfarin and other Vitamin K antagonists (VKA) have been shown in randomised trials to be highly effective for the prevention of stroke in AF patients. In a meta-analysis of 29 trials, which included 28000 participants with a mean age of 71 years, warfarin and aspirin reduced stroke by 64% (95% CI; 49–74%) and 22% (95% CI; 6–35%) respectively when compared with controls.[6] This reduction in stroke risk with warfarin was similar for both primary and secondary prevention, and for both disabling and non disabling strokes. Also, mortality was significantly reduced (26%) by adjusted dose warfarin versus control. The magnitude of benefit of warfarin is underestimated as many participants in trials had

subtherapeutic International Normalised Ratios (INR).

Warfarin is particularly effective in those patients at higher risk for thromboembolism, such as older or female patients, or those with previous stroke/transient ischemic attack (TIA), hypertension and left ventricular dysfunction. Supported by results of trials, warfarin should be considered for patients with AF and more than one stroke risk factor (Box 1).[7]

Data concerning the efficacy of aspirin versus placebo in prevention of stroke in AF are less clear. In comparison with warfarin, aspirin is significantly less effective—especially for primary prevention.[8]

The ACTIVE A trial[9] showed that in patients unable or unwilling to tolerate warfarin, the combination of aspirin plus clopidogrel compared with aspirin alone reduced the risk of stroke by 28%, but the benefit was offset by an increased risk of bleeding. The combination of aspirin and clopidogrel therapy could perhaps be considered as an interim measure when warfarin is not suitable, but not as an alternative to warfarin in patients at high risk of bleeding.

The ACTIVE W study evaluated warfarin versus the combination of aspirin plus clopidogrel.[10] The trial was stopped early because the rate of primary endpoint (a composite of stroke, non-central nervous system embolism, myocardial infarction, and vascular death) was almost doubled in the group receiving aspirin and clopidogrel compared with the group receiving warfarin. This suggests that even two antithrombotic agents are not better than warfarin. There is no data for clopidogrel monotherapy in AF.

This strong evidence base has led to the development of evidence based guidelines from NICE[11] and joint recommendations from the American College of Cardiology, the American Heart Association, and the ESC[12] for the appropriate use of warfarin/aspirin in AF. The ESC has recently published separate guidelines on the management of AF.[5]

The $CHADS_2$ stroke risk stratification scheme is recommended by ESC guidelines[5] as an initial rapid assessment to estimate stroke risk. In patients with a $CHADS_2$ score of ≥2, long-term warfarin therapy is recommended to achieve a target INR of 2.5 (range 2–3) unless contraindicated. For a score of 0-1, a more comprehensive risk factor based approach, such as the CHA_2DS_2 VASc, score is recommended.[5]

Despite the availability of effective treatments and guidelines, the use of warfarin is under used especially in the elderly population, who are at the highest risk of stroke.[13,14] The under use of warfarin could be related to several factors, which can be categorised into drug related, patient preference or physician-related reasons.

Box 1: Risk factors for stroke in patients with AF

- Previous embolic event or stroke
- Age >65 years
- History of hypertension
- History of myocardial infarction
- Diabetes mellitus
- Left ventricular dysfunction or heart failure
- Enlarged left atrial size; left atrial thrombus
- Rheumatic mitral valve disease
- Prosthetic heart valve

One concern could be usage in elderly patients. The BAFTA (Birmingham Atrial Fibrillation treatment of Aged) study[15] was a randomised trial of AF patients aged older than 75 years in the primary care setting. This showed that warfarin was clearly superior to aspirin for stroke prevention without any significant difference in bleeding complications. This "real world" data showed that the absolute benefit of warfarin increases as patients get older while the relative efficacy of aspirin decreases. This suggests that warfarin should be the treatment of choice in elderly patients with AF unless contraindicated.

Another major concern to the clinician is the risk of bleeding with warfarin. Many factors affecting the risk of bleeding have been evaluated. If haemorrhagic complications are to be avoided, it is most important to maintain an INR range between 2 and 3 as INR >3 vastly increases risk of bleeding and INR <2 increases stroke risk. In all cases where warfarin is considered, evaluation of bleeding complications, a discussion of risks and benefits with patients, patients' ability to safely sustain chronic anticoagulation, and patient preference are necessary.

For certain situations, the ESC[5] has the following updated recommendations:

- In patients with mechanical heart valves, target INR should be at least 2.5 in mitral prosthetic valve and at least 2 for aortic valve prosthesis
- Patients with atrial flutter also need anticoagulation
- Anticoagulation for three weeks is recommended prior to elective cardioversion and continued for four weeks post procedure

Table 1: Emerging anticoagulants for atrial fibrillation

Drug	Mode of action	Dosing	Trial
Dabigatran	Direct thrombin inhibitor	Oral OD or BD	RELY
AZD0837	Direct thrombin inhibitor	Oral OD or BD	
Apixaban	Direct Factor Xa inhibitor	Oral BD	ARISTOTLE, AVERROES
Rivaroxaban	Direct Factor Xa inhibitor	Oral OD or BD	ROCKET-AF
Betrixaban	Direct Factor Xa inhibitor	Oral BD	EXPLORE Xa
Edoxaban	Direct Factor Xa inhibitor	Oral OD or BD	ENGAGE-AF TIMI48
Idrabiotaparinux	Direct Factor Xa inhibitor	Weekly sc injection	BOREALIS-AF

- Aspirin and clopidogrel combination therapy can be considered for patients unable to take warfarin and who have a low risk of bleeding
- In patients with AF and acute stroke/TIA, cerebral imaging should be performed to exclude haemorrhage and warfarin started two weeks later
- In patients with AF and acute TIA warfarin should be started as soon as possible
- Subcutaneous low molecular weight heparin can be considered when surgical procedures require interruption of warfarin
- In patients with AF who suffer thromboembolic episode during warfarin and INR 2–3, raising a target INR of 3–3.5 may be considered rather than adding an antiplatelet agent
- Following elective percutaneous coronary intervention (PCI) triple therapy (clopidogrel and aspirin and warfarin) should be considered short-term followed by long-term (one year) warfarin and clopidogrel or aspirin along with proton pump inhibitors (PPIs)
- Following acute coronary syndrome with or without PCI in AF patients, triple therapy should be considered short-term three to six months followed by long-term therapy with warfarin and clopidogrel or aspirin plus PPIs.

Limitations of warfarin

Despite recommendations, many eligible high-risk patients do not receive warfarin. Even if warfarin is appropriately prescribed, the quality of anticoagulation control is often suboptimal. Besides slow onset of action, maintaining therapeutic dose within the narrow margin of efficacy and safety with warfarin is challenging. Anticoagulant effect of warfarin is variable depending upon genetic variability and multiple drug and food interactions that require frequent monitoring and dose adjustments.

It has been observed that only 50% of patients with AF at high risk of stroke receive therapy with warfarin and of those who receive treatment, a substantial proportion do not benefit.[16] In a large systematic review of literature, including 36 studies amongst 35198 patient years follow-up, the overall meantime spent in therapeutic INR range was 61.3%.[17] Limitations of warfarin have prompted search for new, more effective, safer and convenient anticoagulant alternatives for use in AF.

New antithrombotic agents

Two broad classes of drugs have been being developed and include inhibition of Factor IIa (thrombin) and Factor Xa. The first oral direct thrombin inhibitor, ximelagatran, for stroke prevention was evaluated in the SPORTIF trial,[18] but it had to be withdrawn due to its association with liver toxicity.

Dabigatran, an oral direct thrombin inhibitor, was evaluated in a large non-inferiority trial—RELY (Randomised Evaluation of long term anticoagulant).[19] In this largest trial of antithrombotic therapy

References: 1. Boehringer Ingelheim. Pradaxa® 150mg SPC. August 2011. **2.** Boehringer Ingelheim. Pradaxa® 110mg SPC. August 2011. **3.** BMJ Risk Calculation. http://clinicalevidence.bmj.com/ceweb/resources/calculate_risk.jsp. Accessed April 2011. **4.** Connolly S, Ezekowitz M, et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med 2009; 361:1139-1151. **5.** Connolly S, Ezekowitz M, et al. Newly identified events in the RE-LY trial. N Engl J Med 2010; 363:1875-1876.

stroke prevention to date, more than 18,000 patients were randomised to one of two blinded doses of dabigatran 110mg or 150mg BD without laboratory monitoring and compared with warfarin with a mean follow-up of two years.

The higher dose was superior to warfarin while the lower dose showed similar efficacy to warfarin in stroke prevention. Rates of major bleeding were lower with the lower dose. Intracranial haemorrhage was more than halved with both doses of dabigatran versus warfarin.[19] There was no liver toxicity.

In practical terms, dabigatran offers several advantages (eg, no need for routine blood monitoring and no food/drug interactions) over warfarin, and the higher dose could be considered in patients at high stroke risk and the lower dose in patients at high bleeding risk.

The Apixaban VERsus acetylsalicylic acid to prevent stROkeS (AVERROES) study was stopped early due to clear evidence of reduction in stroke with apixaban 5mg BD compared with aspirin once daily in patients unsuitable for warfarin. It also had a good safety profile.[20] Ongoing studies of other agents (Table 1) will add more data and more options for healthcare professionals and patients for stroke prevention in AF.

For over half a century, warfarin has been the main anticoagulant available for long-term clinical use. New compounds have the potential to treat a wider population at risk. Moreover, a fixed dosing regimen without routine anticoagulation monitoring represents a landmark therapeutic advance.

Conclusion

Warfarin is highly effective for the prevention of stroke and systemic embolism in patients with AF and is the current gold standard treatment. Several trials are ongoing, comparing new anticoagulants with warfarin. The new anticoagulant agents have a predictable anticoagulant response that allows convenient fixed dose and unmonitored treatment. There

is substantial scope in increasing the proportion of eligible patients to receive treatment, thereby reducing the burden of stroke. So far, dabigatran and rivaroxaban are the most advanced and have been approved for the prevention of venous thromboembolism following major orthopaedic surgery. Dabigatran (Pradaxa®) is the first new oral anticoagulant in over 50 years licensed for the prevention of stroke and systemic embolism in adult patients with nonvalvular AF and one or more risk factors. Given the chronic nature of AF and indefinite treatment, long-term cost effectiveness and safety evaluation will be essential.

Conflict of interest: none

References

1. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implication for rhythm management and stroke prevention: the ATRIA study. *JAMA* 2001; **285:** 2370–75
2. Stewart S, Murphy N, Walker A, et al. Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK. *Heart* 2004; **90:** 286–92
3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke. The Framingham Study. *Stroke* 1991; **22**: 983–88
4. Dulli DA, Stanko H, Levine RL. Atrial fibrillation is associated with severe acute ischaemic stroke. *Neuroepidemiology* 2003; **22**: 118–23
5. ESC. Atrial Fibrillation (Management of) ESC Clinical Practice Guidelines. http://bit.ly/2xO5sj (Accessed 29 November 2010)
6. Hart RG, Pearce LA, Aguilar M. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007; **146:** 857–67
7. Levy S, Breithardt G, Campbell RW, et al. Atrial Fibrillation: current knowledge and recommendations for management. Working Group on Arrhythmias of the European Stroke Group. *Eur Heart J* 1998; **19**: 1294–20
8. EAFT. European Atrial Fibrillation Trial Study Group. Secondary prevention in non rheumatic atrial fibrillation after TIA or minor ischemic stroke. *Lancet* 1993; **342:** 1255–6
9. ACTIVE Investigators. Effect of Clopidogrel added to aspirin in patients with atrial fibrillation. *New Eng J Med* 2009; **360**: 2066–78
10. The ACTIVE writing group on behalf of the ACTIVE Investigators. Clopidogrel plus aspirin vs oral anticoagulation for atrial fibrillation in the atrial fibrillation Clopidogrel trial with Irbesartan for prevention of vascular events. ACTIVE W: a randomised controlled trial. *Lancet* 2006; **367:** 1903–12
11. National Collaborating Centre for chronic conditions. Atrial Fibrillation. National clinical guideline for management in primary and secondary care. London. Royal College of Physicians 2006
12. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for management of patients with atrial fibrillation. *Europace* 2006; **8**: 651–745
13. Go AS, Hylek EM, Chang Y, et al. Anticoagulant therapy for stroke prevention in atrial fibrillation: how well do randomised trials translate into clinical practice? *JAMA* 2003; **290**: 2685–92
14. Bradley BC, Perdue KS, Tisdell KA, et al. Frequency of anticoagulation for atrial fibrillation and reasons for its nonuse at a Veterans Affairs Medical Centre. *Am J cardiol* 2000; **85**: 568–72
15. Mant J, Hobbs R, Fletcher K, et al. Warfarin vs aspirin for atrial fibrillation. BAFTA. A randomised controlled trial. *Lancet* 2007; **370**: 493–03
16. Hylek EM, D Antonio J, Evans-Molina C, et al. Translating the results of randomised trials into clinical practice, the challenge of warfarin candidacy amongst hospitalised elderly patients with atrial fibrillation. *Stroke* 2006; **37:** 1075–80.
17. Dolan G, Smith LA, Collins S, et al. Effect of setting monitoring intensity and patient experience on anticoagulation control: a systematic review and meta-analysis of literature. *Curr Med Res Opin* 2008; **24:** 1459–72
18. SPORTIF Executive Steering Committee for the SPORTIF V Investigators. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomised trial. *JAMA* 2005; **293**: 690–98
19. Connolly SJ, Ezekowitz MD,Yusuf S, et al. Dabigatran vs warfarin in patients with atrial fibrillation. *N Eng J Med* 2009; **361**: 1139–51
20. Eikelbroom JW, O Donnell M, Yusuf S. Rationale and design of AVERROES : Apixaban vs acetyl salicylic acid to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment. *American Heart Journal* 2010; **159**: 348–53