

STROKE PREVENTION IN ATRIAL FIBRILLATION: NOW AND THE FUTURE

David Russell, Dept of Neurology, Oslo University Hospital, Norway

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting approximately six million Europeans. The lifetime risk of developing AF is one in four men and women after the age of 40 years. The prevalence of AF increases dramatically with age, ranging from 1.5% in individuals aged 50–59 years to 23.5% in those aged 80–89 years. With an ageing population, the prevalence of AF is projected to double by 2030.

Stroke is the most devastating complication of AF. Atrial fibrillation causes 15–20% of ischemic strokes and the overall risk of stroke in patients with non-valvular AF is about 5% per year. Long-term studies have consistently shown that patients with AF have a 5-fold increased risk of stroke compared with individuals without AF. One-third of patients who have atrial fibrillation and stroke were not known to have atrial fibrillation until their stroke. Stroke in patients with AF is nearly twice as likely to be fatal compared with non-AF stroke. This is due to the development of large thrombi in the left atrial appendage which travel to the brain causing occlusion of the major intracranial arteries. This results in larger infarct volumes and more severe strokes. The costs of caring for patients with stroke associated with AF have been shown to be 33% greater for AF-related stroke than for non-AF stroke.

Risk stratification for stroke and thrombo-embolism

The European Society of Cardiology (ESC) has recently extended the CHADS₂ scheme by considering additional stroke risk factors that may influence a decision whether or not to anticoagulate. This risk factor-based approach for patients with non-valvular AF can also be expressed as an acronym, CHA₂DS₂-

VASc [congestive heart failure, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, and sex category (female)]. This scheme is based on a point system in which 2 points are assigned for a history of stroke or TIA, or age ≥ 75 ; and 1 point each is assigned for age 65–74 years, a history of hypertension, diabetes, recent cardiac failure, vascular disease (myocardial infarction, complex aortic plaque, and PAD, including prior revascularization, amputation due to PAD, or angiographic evidence of PAD, etc.), and female sex.

VKA treatment should be considered for patients with AF with ≥ 1 stroke risk factor(s) provided there are no contraindications, especially with careful assessment of the risk–benefit ratio and an appreciation of the patient's values and preferences. Patients with a CHA₂DS₂-VASc of 1 should be treated with either OAC or aspirin 75–325 mg daily (preferred: OAC rather than aspirin) and patients with a CHA₂DS₂-VASc of 0, either aspirin 75–325 mg daily or no antithrombotic therapy (preferred: no antithrombotic therapy rather than aspirin).

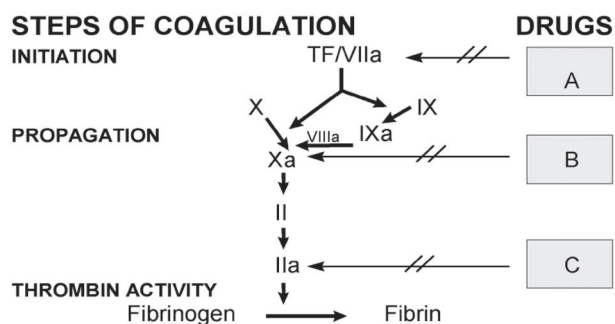
Antithrombotic management

The magnitude of stroke reduction from aspirin vs. placebo (19%) is broadly similar to that seen when aspirin is given to vascular disease subjects. The efficacy of warfarin in reducing the risk of stroke in patients with AF has been confirmed by randomized, placebo-controlled clinical trials. A meta-analysis of 6 major studies showed a 64% reduction in the risk of stroke in patients with nonrheumatic AF treated with warfarin compared with placebo. Survival following a stroke was also almost doubled in the patients who received anticoagulation treatment compared with those who received no treatment. However, 14–44% of patients with atrial fibrillation who are at risk of stroke are in-

eligible for anticoagulation therapy, primarily due to the risk of major bleeding. In patients who are eligible, the risk of bleeding, the need for frequent INR monitoring and dose adjustments, drug interactions, and restrictions on diet may explain why warfarin discontinuation rates are as high as 38% per year.

New anticoagulants

New anticoagulants that selectively block specific pathways of the coagulation cascade have demonstrated efficacy and safety. These drugs have a fast onset and anticoagulation does not need intensive monitoring (Figure).



Goals for new anticoagulants

- A Blockage of tissue factor VIIa pathway (example: rNAPc2)
- B Specific blockers of FXa (examples: rivaroxaban, apixaban and edoxaban)
- C Direct thrombin blockers (example: dabigatran)

RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy), evaluated 2 doses of the active direct thrombin inhibitor dabigatran (110 and 150 mg, twice daily) in 18,113 patients with nonvalvular AF. At a low dose (110 mg, twice daily) dabigatran was as effective as warfarin in reducing the primary outcome of stroke or systemic embolism, and at a high dose (150 mg twice daily) it was superior to warfarin. The primary outcome occurred at rates of 1.69% per year in patients receiving warfarin and 1.53 and 1.11% per year in patients receiving dabigatran 110 and 150 mg, respectively. The RRs compared with warfarin were 0.91 for 110 mg (95% CI = 0.74–1.11; $p < 0.001$ for noninferiority) and 0.66 for 150 mg (95% CI = 0.53–0.82; $p < 0.001$ for superiority). The rates of major bleeding were significantly lower for dabigatran

110 mg than warfarin (2.71 vs. 3.36% per year, $p = 0.003$) but similar to warfarin for the higher dose of dabigatran (3.11%, $p = 0.31$). Intracranial bleeding was significantly lower for both doses of dabigatran than for warfarin ($p < 0.001$ for each dose vs. warfarin).

The ROCKET AF study assessed the efficacy and safety of rivaroxaban (20 mg once-daily), a novel oral, direct Factor Xa inhibitor, compared to warfarin for the prevention of stroke and non-CNS systemic embolism in patients with AF. Rivaroxaban 20 mg was noninferior to warfarin in reducing all-cause stroke and non-central nervous system (CNS) embolism in AF patients, with a similar rate of major bleeding.

The AVERROES trial was terminated early because of demonstrated superiority of apixaban (5 mg twice daily) compared to aspirin (81–324 mg daily) alone in AF patients unsuited to warfarin, 40% because of prior problems with the drug. A large-scale trial against warfarin in AF (ARISTOTLE) is now under way. Other agents in late stage development in AF include edoxaban, TAK-442, betrixaban and dar-exaban.

In Canada, dabigatran has been approved for the stroke/AF indication in both the 110-mg and 150-mg doses studied in the RE-LY trial, whereas in the US, the FDA decided to approve only the 150-mg dose and an untested 75-mg dose for patients with severe renal impairment. In April, 2011 the European Medicines Agency (EMA) issued a “positive opinion” for dabigatran in the setting of atrial fibrillation, for prevention of stroke/systemic embolism. According to the proposed new indication, dabigatran, if granted final approval, would be marketed in the 110-mg and 150-mg strengths. It would be indicated for the primary prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more risk factors –namely, previous stroke, transient ischemic attack, or systemic embolism; left ventricular ejection fraction $< 40\%$; symptomatic heart failure (NYHA class 2); age > 75 years; and/or age > 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension.

Conclusion

Patients with atrial fibrillation have a high risk of stroke and an increased risk of stroke recurrence. Warfarin is currently the standard of care for high-risk AF

patients and in patients with AF who have had a stroke or TIA. However, warfarin is underutilized in patients with atrial fibrillation, at a cost of unnecessary strokes and disability. Fear of bleeding accounts for some of the underuse, but the difficulties of warfarin use (e.g., the

need for repeated INR monitoring and dietary restrictions) also play a role. New antithrombotic agents that can be given in fixed doses without coagulation monitoring offer new treatment possibilities for the prevention of stroke in patients with atrial fibrillation.