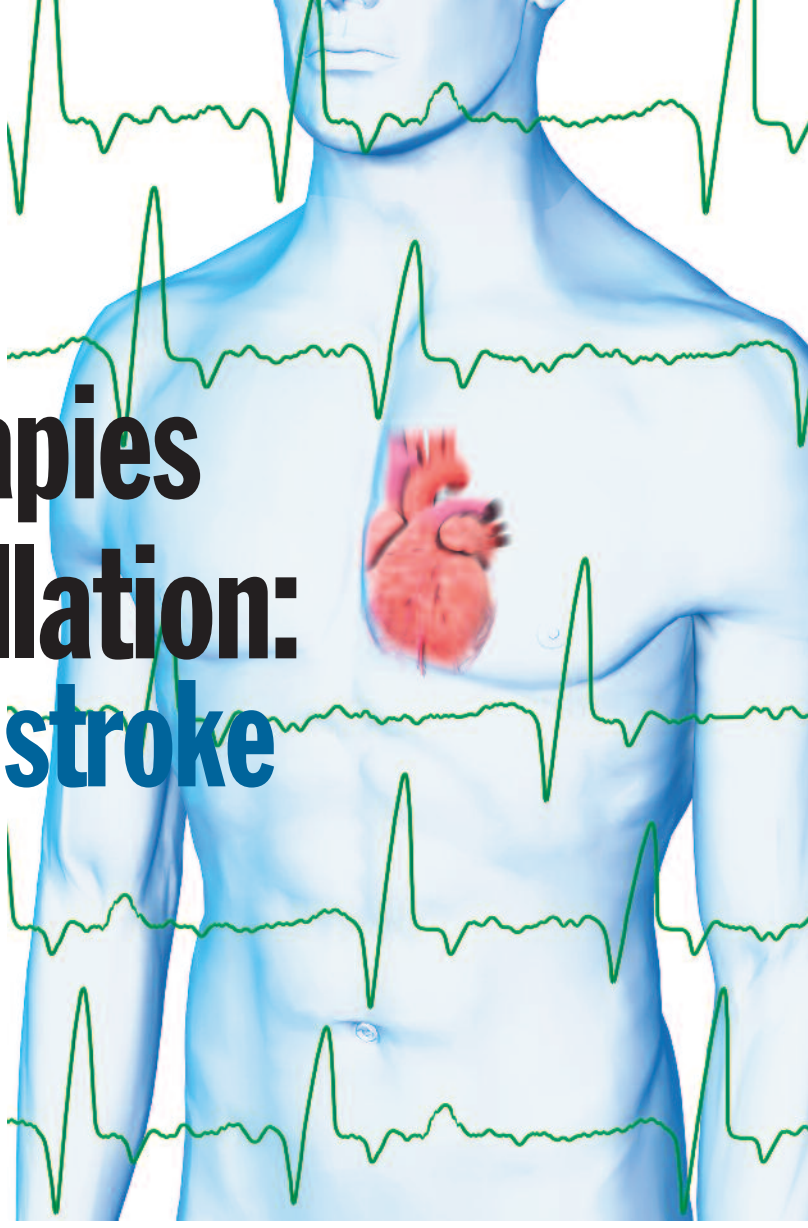
FEATURE



Evolving therapies for atrial fibrillation: focus on embolic stroke

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Oral anticoagulants are the treatment of choice for the prevention of stroke related to atrial fibrillation. Novel anticoagulants are now available and should be considered in suitable patients.

Key points

- **Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia.**
- **Strokes associated with AF often cause substantial neurological disability and mortality.**
- **Antithrombotic therapy is the mainstay for stroke prevention.**
- **Until recently, warfarin was the only effective oral anticoagulant available.**
- **Novel anticoagulants are safe and easy to use.**

CARDIOLOGY TODAY 2013; 3(1): 19-24

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Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia seen in clinical practice worldwide.[1] Recent data demonstrate an exponential rise in hospitalisations due to AF in Australia; currently, it is a more frequent cause of hospitalisation than chronic heart failure.[2] The importance of AF as a public health problem is underscored through its association with an increased risk of stroke,[3] heart failure and death,[4] and a reduced quality of life. The cost to the Australian economy in 2008-09 resulting from AF was conservatively estimated to be at least $1.25 billion.[5]

Objectives of the management of AF

The aim of the management of patients with AF is to reduce symptoms and prevent complications. The objectives of management are to:

- prevent AF-related stroke
- control ventricular rate
- treat concomitant cardiac diseases
- modify risk factors
- relieve symptoms with rhythm-control strategies.

Strokes associated with AF often cause substantial neurological disability and mortality and, consequently, primary rather than secondary

prevention is the most sensible approach.[6] Antithrombotic therapy is the mainstay for stroke prevention. However, despite good clinical evidence, many aspects of the use of antithrombotic therapy in patients with nonvalvular AF remain controversial. In this review, we address some of these issues and discuss the intricacies of the management of various patient subgroups.

Antithrombotic management

Optimal thromboprophylaxis for patients with nonvalvular AF should be individualised and requires an assessment of:

- the patient's risk of thromboembolism
- the patient's risk of bleeding
- the type of antithrombotic to be used
- patient preference.

Despite compelling evidence, use of antithrombotic therapy still lags behind requirement.[7] The reason for this underuse is multifactorial. Old age is the key deterrent in considering anticoagulation in some patients.[7] This is not surprising given the confusion in the literature. Most of the trials showing a benefit of antithrombotic therapy have excluded patients with advanced age. Whether the results of these studies can be generalised to an older population remains controversial;[8] however, recent studies have highlighted the importance of antithrombotic use in elderly patients.[9]

Risk stratification for stroke and thromboembolism

The incidence of ischaemic stroke among patients with AF who are not treated with antithrombotics averages 4.5% per year, and may be as high as 23% per year in certain high-risk groups.[3] The risk of stroke in patients with AF is not homogeneous, and various clinical and echocardiographic risk factors that accompany AF increase this risk exponentially. Several scoring systems have been developed to maximise the benefits of antithrombotic therapy in preventing first stroke in patients with nonvalvular AF. These scoring systems are described below:

- **$CHADS_2$ score.** This is based on a point system in which 1 point each is assigned for cardiac failure, a history of hypertension, age 75 years or over and diabetes, and 2 points are assigned for a history of stroke or transient ischaemic attack (TIA). This can be used as an initial and rapid means of assessing a patient's risk of stroke.[10] However, this scheme is based on older studies that did not adequately assess all the potential risk factors.[11] There are increasing data that other risk factors should be considered in refining stroke risk of patients with AF.[12]
- **CHA_2DS_2-VASc score.** This system has evolved from the $CHADS_2$ scoring system with an emphasis on age, vascular disease and sex. It is based on a point system in which 2 points are assigned for major risks (age 75 years or over and previous history of stroke), and 1 point each for minor risks (cardiac failure/left ventricular dysfunction, a history of hypertension, diabetes, vascular disease, age 65 to 74 years and female sex). This score is useful in detailed stroke risk assessment in patients with a $CHADS_2$ score of 0 to 1 (see the box on this page).[13,14] A particular benefit of the CHA_2DS_2-VASc score is in identifying the low-risk patient.

Current recommendations

The $CHADS_2$ score should be used initially for assessing stroke risk in patients with nonvalvular AF. In patients with a $CHADS_2$ score of 2 or more, long-term oral anticoagulant therapy is recommended. For those with a $CHADS_2$ score of 0 or 1, use of the CHA_2DS_2-VASc score is recommended to gain more detailed risk stratification.

A CHA_2DS_2-VASc score of 0 means the patient has an extremely low risk of stroke and does not warrant oral anticoagulant therapy. In those with a score of 1, use of an oral anticoagulant should be considered, but, if not suitable, combination therapy with aspirin and clopidogrel should be used. If a patient's score is 2 or more, then oral anticoagulant therapy is recommended.

CHA_2DS_2-VASc score: risk factors for stroke and thromboembolism in patients with nonvalvular atrial fibrillation[14]

Major risk factor (2 points for each)

- Previous stroke, TIA or systemic embolism
- Age ≥75 years

Clinically relevant nonmajor risk factor (1 point for each)

- Heart failure or moderate to severe left ventricular systolic dysfunction (e.g. left ventricular ejection fraction ≤40%)
- Hypertension
- Diabetes
- Female sex
- Age 65 to 74 years
- Vascular disease

Risk of bleeding

To assess the risk of bleeding in patients with AF taking anticoagulants, use of a simple tool called the HAS-BLED score has been suggested in the recent guidelines (Table 1).[14,15]

Pharmacological therapy

There is extensive evidence for the use of antithrombotic therapy in patients with AF. For most patients, the increased risk for major bleeding does not offset the benefit of these drugs. Current antithrombotic strategies for the prevention of stroke related to AF include oral anticoagulants (warfarin) and antiplatelet agents (aspirin and clopidogrel). Novel oral anticoagulant agents have become available recently.

When selecting antithrombotic therapy, it is imperative to have an individualised approach and determine the efficacy and safety of the available agents in contrast to the patient's thrombotic risk, comorbidities and bleeding risk before prescribing.

Table 1. Clinical characteristics comprising the HAS-BLED bleeding risk score[14]

	Clinical characteristic	Points awarded
H	Hypertension	1
A	Abnormal renal or liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

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Antiplatelet agents

Aspirin

In a meta-analysis by Hart and colleagues, it was concluded that aspirin reduces stroke by about 19% in patients with AF.[16] There was an absolute risk reduction of 0.8% per year for primary prevention using aspirin and 2.5% per year for secondary prevention. In comparison with oral anticoagulants, aspirin use reduces the patient's risk of major haemorrhage; however, this risk is not negligible, especially in the elderly population.[9,17]

Aspirin plus clopidogrel

In the atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events (ACTIVE-A), a 28% relative risk reduction in the rate of stroke in patients receiving aspirin and clopidogrel compared with those receiving aspirin monotherapy was reported.[18] However, major bleeding was significantly increased to 2% per year, similar to that seen with warfarin use. This dual therapy should be considered as an interim measure in patients for whom warfarin is unsuitable, but not as an alternative to warfarin in patients at high risk of bleeding. For patients, who choose not to take an oral anticoagulant (for reasons other than concerns about major bleeding), combination therapy with aspirin and clopidogrel is recommended.

Oral anticoagulants

Warfarin

A meta-analysis by Hart and colleagues showed that warfarin reduced the incidence of stroke by 64% compared with placebo and was 39% more effective than antiplatelet therapy.[16] Aspirin appears

to reduce the risk of noncardioembolic strokes, whereas adjusted-dose warfarin is much more effective for the prevention of cardioembolic events.[19]

However, warfarin requires frequent dose adjustments guided by laboratory measurements to increase the time in therapeutic range, and to achieve optimal thromboprophylaxis and an international normalised ratio (INR) between 2.0 and 3.0.[20] Additionally, the metabolism of warfarin is complicated by its significant pharmacological interactions. In elderly patients who are generally on polypharmacy this can be a major problem.

Table 2. Summary of pharmacokinetics of novel anticoagulant drugs

	Dabigatran	Rivaroxaban	Apixaban
Target	Thrombin	Factor Xa	Factor Xa
Dosing	Twice daily	Once daily	Twice daily
Half-life (hours)[24]	12 to 17	5 to 9	9 to 14
Time to maximum concentration (hours)	2 to 3	2 to 4	3 to 4
Renal excretion (%)	80	66	25

Novel oral anticoagulants

Due to the mentioned limitations of warfarin, the search for the 'ideal' anticoagulant is ongoing. Three novel oral anticoagulants (apixaban, dabigatran and rivaroxaban) have been evaluated in phase III randomised controlled trials. In contrast to warfarin, these novel oral anticoagulants interact less with food or drugs and have more predictable dose responses, obviating the need for routine coagulation monitoring (Table 2). Dabigatran and rivaroxaban are now TGA approved for the prevention of stroke and systemic embolism in patients with nonvalvular AF and at least one additional risk factor for stroke.

Dabigatran

Dabigatran is a potent competitive inhibitor of thrombin. Drugs that inhibit P-glycoprotein, such as amiodarone, can increase plasma levels of dabigatran by reducing its clearance.[21]

In the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial, dabigatran at a dose of 110 mg twice a day was found to be noninferior to warfarin in the prevention of stroke or systemic embolism, and to cause significantly less major bleeding.[22] In the same population, dabigatran 150 mg twice a day was found to be superior to warfarin in the prevention of stroke or systemic embolism, with no difference in the risk of major bleeding.[22] However, the study was designed to determine noninferiority and not superiority over warfarin.

Dabigatran is generally well tolerated, but it can cause some gastrointestinal side effects. It is predominantly cleared through the kidneys and is best avoided in patients with renal dysfunction and used cautiously in the elderly. Currently, acute reversal of the drug's effects relies on haemodialysis; however, due to its short half-life, 48 hours of drug cessation is adequate for most elective surgeries.

Rivaroxaban

Rivaroxaban is a factor Xa inhibitor. Due to its partial renal clearance it is not recommended in patients with a creatinine clearance of less than 15 mL/min.[23] The rivaroxaban once daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF) study showed that rivaroxaban was noninferior to warfarin in the prevention of stroke or systemic embolism, with no difference in the risk of major bleeding.[24] Rivaroxaban was studied as a single daily dose and is generally well tolerated.

Apixaban

Apixaban is a factor Xa inhibitor. About 25% of the drug is excreted unchanged in the urine, so it should be used with caution in patients with a creatinine clearance of 15 to 29 mL/min and is not recommended for patients with a creatinine clearance of less than 15 mL/min.[25] The apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation (ARISTOTLE) trial showed that apixaban administration in patients with nonvalvular AF with a mean $CHADS_2$ scores of 2.1 was superior to warfarin in the prevention of stroke or systemic embolism.[25] It also resulted in less bleeding and lower mortality.[25]

Summary of pharmacological therapy

Trials have shown no inferiority or superiority of novel oral anticoagulants over warfarin for the primary outcome of combined ischaemic stroke and systemic embolism. A head-to-head comparison of these novel oral anticoagulants requires a large number of patients, which would be expensive and therefore unlikely to be performed. However, many indirect comparisons and a meta-analysis of these novel oral anticoagulants has been published recently.[26] The findings can be summarised as:

- dabigatran (150 mg twice a day) and rivaroxaban have comparable risks of major bleeding with warfarin; however, dabigatran (110 mg twice a day) and apixaban demonstrated superiority for this outcome
- there is no significant difference in efficacy between dabigatran 150 mg twice a day and apixaban 5 mg twice a day for the prevention of thromboembolic events[26]
- dabigatran 150 mg twice a day is superior to dabigatran 110 mg twice a day and rivaroxaban for the prevention of systemic embolism.

Indirect comparison analysis has its own limitations and therefore should not be over-interpreted; however, it is a well-accepted method in the absence of head-to-head trials.

Limitations of novel oral anticoagulants

There are several limitations of novel oral anticoagulants, which are outlined below.

- Novel oral anticoagulants have been tested in patients with nonvalvular AF but efficacy and safety data in patients with valvular AF is lacking.
- Twice-daily dosing of some agents can increase noncompliance, and without regular monitoring drug adherence cannot be tested, therefore increasing the risk of bleeding or thrombosis.
- Given the short half-life of novel oral anticoagulants it is imperative that patients do not miss a dose.
- These drugs should be used with caution in elderly patients and those with renal impairment.
- There is no specific antidote available for reversal of the drugs' effects.

Nonpharmacological therapy

The left atrial appendage is considered an important site for atrial thrombogenesis.[27] Occlusion of the left atrial appendage orifice with occluders may reduce the development of atrial thrombi and stroke in patients with AF.

In the WATCHMAN left atrial appendage closure technology for embolic protection in patients with atrial fibrillation (PROTECT AF) trial, the WATCHMAN device (a left atrial appendage occluder) was found to be noninferior to warfarin in preventing thromboembolic events.[28] However, during follow up it was found that up to 40% of cases had incomplete occlusion, which itself is a risk factor for the occurrence of stroke. Also, a higher rate of adverse safety events was seen due to periprocedural complications.[29]

However, patients with contraindications to anticoagulation therapy may be considered as candidates for left atrial appendage occlusion. This is an area of ongoing research and further evidence is awaited.

Conclusion

AF is the most common clinical arrhythmia. Oral anticoagulation is the mainstay in the prevention of AF-related stroke. Risk stratification for stroke and risk assessment for bleeding are the two most important aspects in the management of patients with AF. Risk factor assessment should be a dynamic process. In the appropriate patients, novel anticoagulants are safe and better tolerated, and may be considered as an alternative to warfarin. **CT**

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COMPETING INTERESTS: Dr Pathak is supported by a Lions Medical Research Scholarship. Drs Pathak and Mahajan are supported by Leo J. Mahar Electrophysiology Scholarships from The University of Adelaide. Professor Sanders is supported by the National Heart Foundation of Australia and a Practitioner Fellowship from the National Health and Medical Research Council of Australia.