



# Current management of atrial fibrillation

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## Summary

**Atrial fibrillation is a common condition and carries the risk of cerebral thromboembolism. The CHADS<sub>2</sub> score is often used to stratify this risk. Anticoagulant therapy with warfarin significantly reduces this risk, but there are limitations to its use. This has prompted the use of antiplatelet drugs. Patients with mitral valve disease should always be considered for anticoagulant therapy. However for other patients with atrial fibrillation, the decision about which drug to use is based on the patient's risk of thromboembolism. In addition to stroke prevention, management is directed towards restoring and maintaining sinus rhythm or controlling the ventricular rate in those for whom permanent atrial fibrillation is accepted. For some patients percutaneous (catheter-directed) creation of lesions within the left atrium may be effective in maintaining sinus rhythm.**

Key words: anticoagulants, aspirin, clopidogrel, dabigatran, Pradaxa, rivaroxaban, thromboembolism, warfarin.

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## Introduction

Atrial fibrillation is the most common sustained cardiac arrhythmia, occurring in 1–2% of the population of the developed world.<sup>1</sup> Its prevalence increases with age so that around 8% of people over 80 years of age have atrial fibrillation.<sup>2</sup> It may occur in isolation or secondary to structural heart disease, hypertension, myocardial ischaemia and infarction, hyperthyroidism, obesity and sleep apnoea. It can also develop following cardiac surgery or excess consumption of alcohol.<sup>3–5</sup> Symptoms include palpitations, dizziness, dyspnoea, angina and worsening heart failure.<sup>1,3,5</sup>

Atrial fibrillation may be categorised according to its presentation (initial, paroxysmal or recurrent, persistent) and duration.<sup>1</sup> Its management depends on the assessment of thromboembolic risk and control of symptoms. In general, a decision is made to pursue either a rhythm or rate control strategy.<sup>1,2,6–8</sup> With rhythm control the aim is to maintain

the patient in sinus rhythm, while with rate control the aim is to control the ventricular rate with medication and accept permanent atrial fibrillation.

## Assessing stroke risk

Atrial fibrillation carries the risk of cerebral thromboembolism<sup>2</sup> and may be responsible for one in five of all strokes.<sup>1</sup> Systemic thromboembolism, leading to stroke, transient ischaemic attacks or embolisation to other sites, is the most dreaded complication of atrial fibrillation. Anticoagulant therapy reduces this risk. The decision to use anticoagulant or antiplatelet therapy is dictated by the patient's risk of these events. Those with mitral valve disease should always be considered for anticoagulant therapy.<sup>1,2</sup> The CHADS<sub>2</sub> score has been commonly used to stratify risk (see Box 1).<sup>1–3</sup> A score of 2 or more is generally taken to indicate a risk of thromboembolism which may warrant warfarin therapy, depending on the patient's haemorrhagic risk, although even those with only one risk factor (CHADS<sub>2</sub> score of 1) may benefit from oral anticoagulants (Fig. 1).<sup>1</sup>

The CHA<sub>2</sub>DS<sub>2</sub>-VASc score, introduced by the European Society of Cardiology, provides a more comprehensive stroke risk assessment. It extends the CHADS<sub>2</sub> score with points also being allotted for female sex, vascular disease and age 65–74 years.<sup>1</sup> The European guidelines also introduced the concept of assessing the bleeding risk (see Box 2). Any patient with a bleeding score of 3 or above is at high risk and regular review during antithrombotic therapy is recommended.

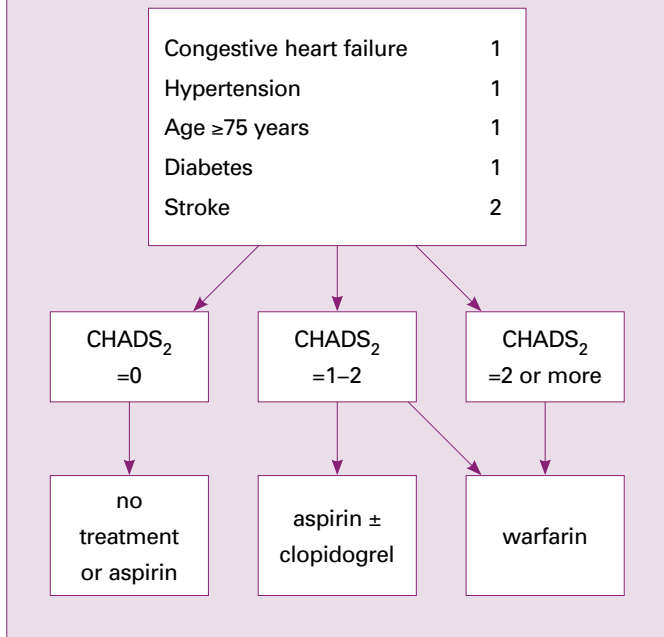
### Box 1

#### CHADS<sub>2</sub> score: stratifying risk of stroke in patients with atrial fibrillation

Congestive heart failure	1 point
Hypertension	1 point
Age ≥ 75 years	1 point
Diabetes	1 point
Systemic embolism, including Stroke (previous episode)	2 points

Fig. 1

**Treating patients with non-valvular atrial fibrillation depending on their CHADS<sub>2</sub> score**



There are other models for assessing stroke risk. These incorporate echocardiographic findings such as left atrial size, left ventricular systolic dysfunction and spontaneous echo contrast or thrombus in the left atrium.

**Drug therapies for preventing stroke**

For low-risk patients with atrial fibrillation, aspirin, or no treatment, may be sufficient. For higher-risk patients, treatment options include warfarin, aspirin and clopidogrel. Several studies have compared the efficacy of antiplatelet regimens to warfarin.<sup>9-11</sup> The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study showed that warfarin (target INR 2-3) was superior to aspirin 75 mg daily.<sup>10</sup> The ACTIVE-W trial showed that clopidogrel plus aspirin was associated with a 45% increase in the risk of stroke, non-central nervous system embolism, myocardial infarction or vascular death compared to oral anticoagulation (annual rates for events 5.60% vs 3.93% respectively, p=0.0002). However, the cumulative risk of major bleeding complications was nearly identical (2.4% vs 2.2% per year, p=0.67).<sup>11</sup> In summary, warfarin is more effective in preventing cerebrovascular events than dual antiplatelet therapy, although the danger of major bleeding is similar.<sup>11</sup> The INR is usually maintained between 2 and 3,<sup>12</sup> but a higher range may be appropriate in patients with prosthetic heart valves or rheumatic mitral valve disease. In patients unable to take warfarin, adding clopidogrel to aspirin reduces the risk of major vascular events by 11%, particularly stroke, but increases the risk of major haemorrhage by 57%.<sup>13</sup>

**Box 2**

**HASBLED score**

Hypertension	1 point
Abnormal liver or kidney function	1 point each
Stroke	1 point
Bleeding	1 point
Labile INRs	1 point
Elderly (e.g. >65 years)	1 point
Drugs or alcohol	1 point each

Hypertension = systolic blood pressure >160 mmHg

Abnormal renal function = dialysis/renal transplantation/serum creatinine ≥200 mmol/L

Abnormal liver function = chronic hepatic dysfunction (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin 2 x upper limit of normal in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase 3 x upper limit normal etc.)

Bleeding = history of bleeding or a bleeding diathesis

Drugs = concomitant use of antiplatelet or non-steroidal anti-inflammatory drugs

**Alternative oral anticoagulants**

Several effective substitutes for warfarin are used for stroke prevention in North America and Europe. These include the direct thrombin antagonist dabigatran and factor Xa inhibitors such as rivaroxaban, apixaban, betrixaban and edoxaban.<sup>14</sup> Dabigatran is the first drug to show non-inferiority to warfarin for stroke prevention in atrial fibrillation.<sup>4,14-16</sup> The 150 mg twice-daily dose was superior to warfarin in efficacy with a similar risk of major bleeding whereas 110 mg twice daily was non-inferior for efficacy with a reduced risk of major bleeding. The risk of intracranial haemorrhage was less with both doses of dabigatran than with warfarin.<sup>15-18</sup> Rivaroxaban is also an effective anticoagulant.<sup>19,20</sup> The main advantage of rivaroxaban and dabigatran over warfarin is they have more predictable pharmacokinetics, and routine anticoagulation monitoring is not needed. No interaction between cytochrome P450 enzymes and dabigatran has been observed, although P-glycoprotein inhibitors such as amiodarone and verapamil may increase plasma concentrations of dabigatran and lead to an increased bleeding risk. There is also a risk of dabigatran accumulation in renal impairment.<sup>14</sup> There is no antidote if bleeding occurs with dabigatran and rivaroxaban. These drugs may replace warfarin for thromboembolic prophylaxis in atrial fibrillation if their cost-effectiveness can

be shown.<sup>21</sup> However, for a condition that requires long-term prophylaxis there are no long-term data to suggest that they will be safe and effective alternatives.

### Device-based strategies for preventing stroke

Medical prophylaxis of stroke in patients with atrial fibrillation has been plagued by a high risk of bleeding complications, frequent drug interactions and a narrow therapeutic range of the drugs and hence poor compliance. Alternative approaches have been sought and a number of device-based treatments are becoming available or being evaluated.

Thrombi have been demonstrated in the left atrial appendage in up to 90% of patients with non-valvular atrial fibrillation.<sup>22</sup> For many years surgeons have combined mitral valve surgery with ligation of the left atrial appendage to try and reduce the risk of subsequent embolism.

The Watchman device is delivered by catheter to the left atrial appendage. It has been shown to be non-inferior to chronic warfarin therapy in patients with a CHADS<sub>2</sub> score of more than 1. This was despite a peri-procedural complication rate of 10.6% which included major bleeding, stroke and sequelae such as device or air embolism and pericardial effusion that may have

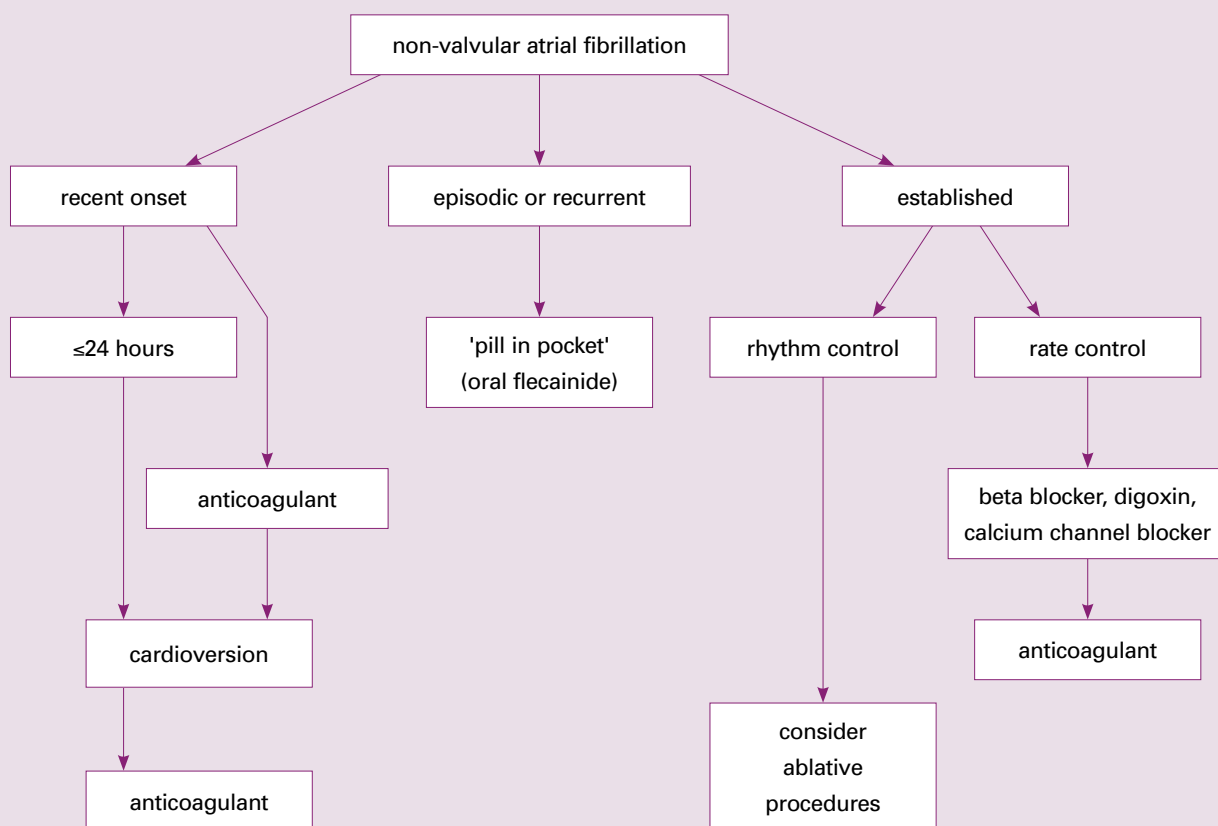
reflected operator inexperience. Most ischaemic strokes occurred at the time of the procedure – their subsequent incidence was less than in control patients treated with warfarin. These results support the hypothesis that thrombus in the left atrial appendage is the likely source of embolic stroke in patients with non-valvular atrial fibrillation, and appear to endorse a role for left atrial appendage closure.<sup>22,23</sup> Longer-term follow-up is necessary before the use of these devices can be generally recommended.

### Rate control

Most patients with atrial fibrillation are managed by controlling the ventricular rate. In patients with minimal symptoms, aggressive attempts to maintain sinus rhythm have not been shown to reduce mortality, improve quality of life, or prevent heart failure or thromboembolic complications.<sup>6-8</sup> The ventricular rate may be controlled using beta blockers, non-dihydropyridine calcium channel blockers (for example verapamil) or digoxin.<sup>1,3,5</sup> However, beta blockers should be avoided in patients with asthma, and digoxin and calcium channel blockers should be avoided in those with pre-excitation. Lenient control (resting heart rate less than 110 beats/minute) is as effective as strict rate control and is easier to achieve.<sup>6</sup> Anticoagulation should be continued in these patients (Fig. 2).

Fig. 2

### Proposed management of non-valvular atrial fibrillation



## Rhythm control

The severity of symptoms usually drives the decision to pursue a rhythm control strategy. In symptomatic patients it may be reasonable to attempt to restore sinus rhythm. For those without structural heart disease who present within 48 hours of the onset of atrial fibrillation, immediate cardioversion (electrical or drug) may be attempted under cover of unfractionated or low molecular weight heparin.<sup>1</sup> Those who present later should be presumed to have left atrial thrombus (unless this has been excluded with a trans-oesophageal echocardiogram) and cardioversion should be deferred until they have been effectively anticoagulated for at least three weeks.<sup>1,3,5</sup>

Anticoagulants should be continued for at least four weeks after successful cardioversion even if transoesophageal echo has excluded left atrial thrombus.<sup>2,3</sup>

Although amiodarone is the most effective antiarrhythmic drug for maintenance of sinus rhythm its long-term value is limited by adverse effects.<sup>2,3</sup> Sotalol combines beta blocking and antiarrhythmic properties but prolongs the QT interval and may provoke torsades de pointes and cardiac arrest,<sup>3,5</sup> particularly in patients with renal dysfunction and impaired drug clearance or hypokalaemia, which may occur with concomitant diuretic therapy.<sup>23</sup> Intravenous or oral flecainide ('pill in pocket')<sup>1,3,5</sup> may be effective but should be avoided in those with left ventricular dysfunction or ischaemia.<sup>24</sup>

Dronedarone cannot be recommended as a first-line drug.<sup>25</sup> Although it may not have the pulmonary and thyroid toxicity of amiodarone<sup>25-27</sup> and is more effective than placebo in maintaining sinus rhythm and reducing the ventricular rate during recurrent atrial fibrillation,<sup>26,28</sup> its use has been associated with worsening heart failure and increased mortality in patients with severe left ventricular systolic dysfunction.<sup>29</sup>

Catheter-directed creation of lesions within the left atrium has become an acceptable treatment for selected patients who have not responded to at least one antiarrhythmic drug. Most strategies depend on electrical isolation of the pulmonary veins, with successful maintenance of sinus rhythm for 12 months in excess of 80% for paroxysmal atrial fibrillation and 70% for persistent atrial fibrillation.<sup>28,30</sup> However, atrial fibrillation may recur and patients may need to remain on medications, including anticoagulants. In recent surveys the complication rate was 5.9% and included cardiac tamponade, pulmonary vein stenosis, stroke, phrenic nerve palsy, atrio-oesophageal fistula and death.<sup>31,32</sup> For those who are highly symptomatic with uncontrolled ventricular rates despite optimal medical therapy, atrio-ventricular node ablation and insertion of a permanent pacemaker may improve quality of life.

## Conclusion

The burden of atrial fibrillation will grow further as populations age. The major adverse outcome is embolic stroke. Newer

antithrombotic regimens offer an alternative to warfarin as do techniques for left atrial appendage occlusion.

If the management of atrial fibrillation is directed towards restoring and maintaining sinus rhythm, percutaneous (catheter-directed) creation of lesions within the left atrium may be warranted, but for most patients with permanent atrial fibrillation controlling the ventricular rate is the most practical strategy.

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*Conflict of interest: none declared*

### Self-test questions

*The following statements are either true or false (answers on page 123)*

3. A 76-year-old woman with atrial fibrillation, type 2 diabetes and hypertension should be considered for anticoagulation therapy.
4. Dual antiplatelet therapy is more effective than warfarin for stroke prevention.



The August issue of NPS RADAR reviews the evidence and place in therapy for:

- dabigatran for stroke prevention in patients with non-valvular atrial fibrillation
- sitagliptin, vildagliptin and saxagliptin – dipeptidyl peptidase-4 inhibitors ('gliptins') for type 2 diabetes mellitus (updated review available online)

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