

# Current approaches to the management of atrial fibrillation

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**Atrial fibrillation is increasingly common in older age groups and is associated with a high risk of stroke. Our Drug review considers today's recommended management of AF and thromboprophylaxis, followed by sources of further information.**

**A**trial fibrillation (AF) is an increasingly common arrhythmia as the population gets older. The overall incidence of AF is 11.5 per 1000 person-years in males and 8.9 per 1000 person-years in females, and it affects about 5 per cent of individuals over 65 years and almost 10 per cent of those over 80.<sup>1</sup> However, AF may be less common in the Afro-Caribbean and south Asian (Indian subcontinent) populations. The lifetime risk of developing AF is 23.8 and 22.2 per cent in a 55-year-old man and woman respectively.<sup>2</sup> The presence of AF increases the risk of mortality, and in addition confers an increased risk of stroke and thromboembolism, as well as a reduction in left ventricular ejection fraction by 15-20 per cent.

Much of the attention on AF is a consequence of the association of AF with a high risk of stroke and throm-

boembolism. AF confers an at least five-fold increased risk of embolic stroke, with as many as 15 per cent of all strokes directly attributable to the arrhythmia.<sup>1,2</sup> Of note, AF-related strokes bear worse prognosis for recovery, higher mortality, greater disability and longer hospitalisations.<sup>1</sup> About 1 per cent of all NHS expenditure in the UK is attributable to AF, thus reflecting the huge public health burden of this arrhythmia.<sup>3</sup>

Several guidelines for the management of AF are available. The National Institute for Health and Clinical Excellence (NICE) guideline on the management of AF was published in June 2006 and serves to provide an evidence-based framework to guide AF management.<sup>4</sup> A modern approach to the management of AF has recently been provided by the new *continued on page 28*



**CPD questions available for this article. See page 42**

Terminology	Clinical features	Pattern
<i>Initial event (first detected episode)</i>	symptomatic asymptomatic (first detected) onset unknown (first detected)	may or may not reoccur
<i>Paroxysmal</i>	spontaneous termination <7 days, most often <48 hours	recurrent
<i>Persistent</i>	not self-terminating, lasting >7 days or prior cardioversion	recurrent
<i>Permanent ('accepted')</i>	not terminated terminated but relapsed no cardioversion attempt	established

**Table 1.** Classification of atrial fibrillation<sup>1</sup>

2010 European Society of Cardiology (ESC) guidelines for the management of AF.<sup>5</sup>

**Causes and mechanisms of A**

AF often accompanies common cardiovascular disorders, such as hypertension, coronary artery disease (CAD) and heart failure. The prevalence of AF in the heart failure population is related to the severity of heart failure; overall, AF is present in one-third of heart failure patients and even half of those with NYHA class IV heart failure. AF can also be secondary to various systemic or respiratory illnesses and chronic alcohol excess, as well as to some reversible conditions such as thyrotoxicosis and acute poisoning with alcohol or illicit drugs. Where AF is secondary to a precipitant, management of the precipitating problem can prevent AF relapses. Alcohol and illicit drugs are especially common as AF precipitants in younger patients.

Drug	Interactions	Side-effects/caution
<i>Class Ia</i> quinidine	increased serum digoxin levels; potentiates anticoagulant effect of warfarin	dosage reduced in hepatic and renal dysfunction; QTc interval prolonged
procainamide	increased levels in patients taking H <sub>2</sub> -antagonists, beta-blockers, amiodarone, trimethoprim and quinidine; may increase effect of skeletal muscle relaxants and neuromuscular blockers; ofloxacin inhibits renal tubular secretion of procainamide	caution in patients with reduced LV function
<i>Class Ic</i> propafenone	rifampicin decreases plasma levels; quinidine increases drug effects; increases levels of beta-blockers, ciclosporin, warfarin and digoxin; CYP4502D6 inhibitors may cause cardiotoxicity	renal and hepatic dysfunction; increased mortality seen in those with underlying LV dysfunction or CHF; rarely positive ANA titres; reversible
flecainide	may increase toxicity of other rate-limiting drugs due to additive inotropic effects; CYP4502D6 inhibitors increase serum levels and cardiotoxicity	caution in pre-existing sinus node dysfunction; underlying cardiac disease; increases endocardial pacing thresholds; renal or hepatic impairment
<i>Class III</i> amiodarone	increased levels of theophylline, methotrexate, digoxin, ciclosporin, beta-blockers and anticoagulants; additive effect with calcium-channel blockers; cimetidine may increase levels	photosensitivity; pulmonary toxicity (3-7%), rare with doses <400mg daily; thyroid and liver dysfunction; pulmonary fibrosis; caution in patients with severe pulmonary disease; rare optic neuritis
sotalol	class Ia and other class III agents can enhance K channel-blocking effect	

**Table 2.** Interactions and side-effects of drugs used for pharmacological cardioversion to sinus rhythm

Co-morbid condition	Drug options for rate control	Comments
<i>Hypertension</i>	beta-blockers, calcium-channel blockers	these agents also help in controlling blood pressure
<i>Ischaemic heart disease</i>	beta-blockers, calcium-channel blockers	provide IHD symptom relief
<i>COPD/bronchospasm</i>	calcium-channel blockers, amiodarone	beta-blockers are avoided in the presence of evidence of hyper-reactive airways: this is tested by performing lung function tests; underlying interstitial disease could worsen with amiodarone: this needs to be ruled out and pulmonary functions monitored regularly if necessary
<i>Thyrotoxicosis</i>	nonspecific beta-blocker	helps control thyrotoxic symptoms
<i>Post-MI</i>	beta-blockers amiodarone	prognostic benefits in MI patients minimal negative inotropic effects, especially in patients with acute heart failure
<i>Heart failure (stable, chronic)</i>	digoxin amiodarone beta-blockers dronedarone	reduced morbidity and rehospitalisations; however, no prognostic benefits minimal negative inotropic effect beneficial in chronic stable heart failure due to systolic dysfunction, after optimisation on standard heart failure therapies in nonpermanent AF in NYHA class I–II heart failure; should not be used in patients with NYHA class III–IV or unstable heart failure (may exacerbate heart failure)

**Table 3.** Rate control agents of choice in patients with atrial fibrillation and associated co-morbidities

Precise details of the pathogenesis of AF are still not completely understood but it apparently reflects complex changes in the atrial tissue substrate. Myocardial fibrosis with formation of ectopic sites of spontaneous electrical activity, atrial dilation and remodelling, perturbations of cardiac haemodynamics (*eg* pressure overload), excessive production of thyroid hormones and toxic factors (*eg* alcohol) promote the development of the arrhythmia.

### Diagnosis and investigations

AF can usually be detected by palpation of an irregular pulse, which should always be performed in patients with palpitations, dyspnoea, dizziness/syncope,

stroke/transient ischaemic attack or chest discomfort. However, an ECG should be performed in all patients where a diagnosis of AF is suspected, where the arrhythmia manifests as rapid, irregular fibrillatory waves and an irregular ventricular response. Holter ECG monitoring is useful in patients with suspected spontaneously cardioverted paroxysmal AF and daily symptoms, while longer periods of monitoring are required in those with less frequent episodes. In patients with previous AF paroxysms, ECG monitoring is also useful for the detection of asymptomatic AF episodes, not an uncommon finding.<sup>6</sup>

A detailed history and previous ECG can help estimate duration of the arrhythmia. A transthoracic

echocardiogram should be performed in most patients, and the NICE guidelines recommend this when (a) it may be important for planning long-term management (*eg* in younger patients), (b) a rhythm control strategy, including electrical or pharmacological cardioversion, is being considered, (c) there is a high risk or suspicion of underlying structural/functional heart disease, such as heart failure or heart murmur, that influences management, *eg* choice of antiarrhythmic drug, or (d) where refinement of clinical risk stratification for antithrombotic therapy is needed.

A detailed clinical history should reveal possible co-morbidities, such as hypertension, CAD or sub-clinical thyroid dysfunction. Investigations should include routine blood tests, including parameters of thyroid and renal function – indeed, renal impairment has been associated with a higher risk of stroke in AF. Assessment of liver and thyroid function and their consequent monitoring are especially important before prescribing antiarrhythmic agents such as amiodarone. A chest X-ray is useful where thoracic pathology is suspected as a cause of AF.

### Types of AF

New-onset AF characterises the first episode of the disorder (see Table 1). Recurrent AF describes repeated episodes of the arrhythmia and is classified as paroxysmal or persistent. Paroxysmal AF defines the episodes that terminate spontaneously within seven days, while the arrhythmia should be regarded as persistent if it lasts longer and electrical or pharmacological cardioversion is required to terminate it. Permanent AF is diagnosed in patients who have the arrhythmia despite attempted cardioversion or when the cardioversion is deemed inappropriate (*eg* due to contraindications to anticoagulation, structural heart disease or maintenance of sinus rhythm is unlikely).<sup>2</sup>

### Management

Although subtypes of AF can define the objectives and preferable approach to management of AF, it is often led by symptoms. In the presence of clinical signs of haemodynamic compromise in acute-onset AF the patient should be referred for urgent cardioversion. Treatment of the AF episode itself should parallel the management of hypoxia, acute ischaemia, electrolyte abnormalities and left ventricular failure, which may commonly occur. For haemodynamically stable patients the choice of optimal strategy, aiming at either rate or rhythm control, should be made on the basis of both cardiac and extracardiac pathology (*eg* heart failure, thyrotoxicosis, *etc*). About two-thirds of patients

Letter	Clinical characteristics	Points awarded
<i>The CHA<sub>2</sub>DS<sub>2</sub>-VASc schema for stroke risk assessment</i>		
C	congestive heart failure/LV dysfunction	1
H	hypertension	1
A	age ≥75	2
D	diabetes mellitus	1
S	stroke/TIA/TE	2
V	vascular disease	1
A	age 65–74	1
Sc	sex category ( <i>ie</i> female gender)	1
		maximum 9 points
<i>The HAS-BLED bleeding risk score*</i>		
H	hypertension	1
A	abnormal renal and liver function (1 point each)	1 or 2
S	stroke	1
B	bleeding	1
L	labile INRs	1
E	elderly (age >65)	1
D	drugs or alcohol (1 point each)	1 or 2
		maximum 9 points
<p>In patients with thyrotoxicosis, antithrombotic therapy should be chosen based on the presence of other stroke risk factors, as listed above. ‘Vascular disease’ refers to MI, complex aortic plaque and peripheral artery disease (PAD), including prior revascularisation, amputation due to PAD or angiographic evidence of PAD, <i>etc.</i> LV: left ventricular, TE: thromboembolic event, TIA: transient ischaemic attack.</p> <p>*Hypertension is defined as systolic blood pressure &gt;160mmHg. Abnormal kidney function is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥200mmol per litre. Abnormal liver function is defined as chronic hepatic disease (<i>eg</i> cirrhosis) or biochemical evidence of significant hepatic derangement (<i>eg</i> bilirubin &gt;2 × upper limit of normal, in association with AST/ALT/ALP &gt;3 × upper limit normal, <i>etc.</i>). Bleeding refers to previous bleeding history and/or predisposition to bleeding, <i>eg</i> bleeding diathesis, anaemia, <i>etc.</i> Labile INRs refers to unstable/high INRs or poor time in therapeutic range (<i>eg</i> &lt;60%). Drugs/alcohol use also refers to concomitant use of drugs, such as antiplatelet agents, NSAIDs, <i>etc.</i></p>		

**Table 4.** Stroke and bleeding risk assessment using CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED

presenting with acute AF will revert spontaneously back to sinus rhythm within 48 hours.

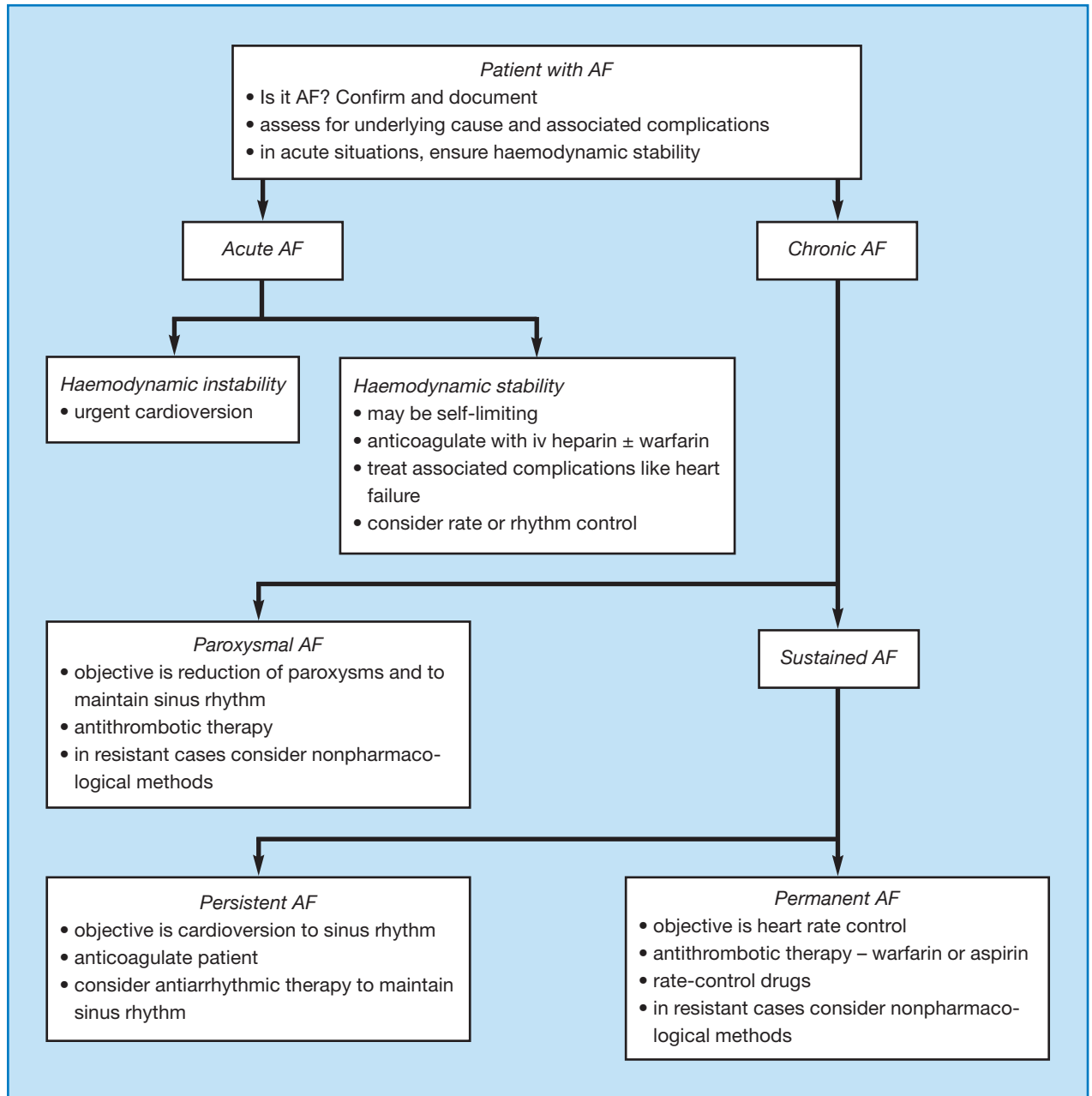
In paroxysmal AF, a rhythm control strategy is often a preferable choice and would require administration of antiarrhythmic drugs (or an electrophysiological procedure) to maintain sinus rhythm (see Figure 1 and Table 2). In persistent AF, the treatment objective is cardioversion to sinus rhythm in a hospital setting and its long-term maintenance. Pharmacological cardioversion is usually achieved by class Ic or class III antiarrhythmic drugs. Electrical cardioversion is usually performed using synchronised DC shock under anaesthesia or sedation.

Beta-blockers are typically considered the first option for pharmacological prevention of AF relapses. When beta-blockers are ineffective or contraindicated, class Ic (*eg* flecainide) or class III (*eg* amiodarone) agents can be recommended. However, even despite optimal management aiming to maintain sinus rhythm, only about half of patients are free of AF relapses at 12 months. Moreover, antiarrhythmic therapy is hampered by restriction of class Ic drugs to patients without structural heart disease and they are usually used in younger symptomatic patients. The recognised efficacy of amiodarone is limited by numerous side-effects.

More recently a novel class III agent, dronedarone (Multaq), has been licensed for the prevention of AF recurrences. The EURIDIS (European Trial in Atrial Fibrillation Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm) and ADONIS (American-Australian-African Trial with Dronedarone in Atrial Fibrillation Patients for the Maintenance of Sinus Rhythm) trials have shown that dronedarone was significantly more effective than placebo in the maintenance of sinus rhythm in AF patients, with no difference in lung and thyroid function in the short term.<sup>7</sup> In the large ATHENA trial (A Placebo-controlled, Double-blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400mg bid for the Prevention

Risk category	CHA <sub>2</sub> DS <sub>2</sub> -VASc score	Recommended antithrombotic therapy
1 ‘major’ risk factor or >2 ‘clinically relevant nonmajor’ risk factors	>2	oral anticoagulation with INR 2.0–3.0 (target 2.5)
1 ‘clinically relevant nonmajor’ risk factor	1	either oral anticoagulation or aspirin 75–325mg daily; preferred: oral anticoagulation rather than aspirin
no risk factors	0	either aspirin 75–325mg daily or no antithrombotic therapy; preferred: no antithrombotic therapy rather than aspirin

**Table 5.** Approach to thromboprophylaxis in patients with atrial fibrillation based on the 2010 ESC guidelines<sup>5</sup>



**Figure 1.** Recommended management of atrial fibrillation

of Cardiovascular Hospitalization or Death From Any Cause in Patients with Atrial Fibrillation/Atrial Flutter), dronedarone significantly reduced the composite end-point of first hospitalisation due to cardiovascular events or death (but not in all-cause death).<sup>8</sup>

However, in one study (ANDROMEDA – Antiarrhythmic Trial with Dronedarone in Moderate-to-severe Congestive Heart Failure Evaluating Morbidity Decrease) the drug doubled the death rate compared to placebo in decompensated congestive heart failure and thus should not be used in these patients.<sup>9</sup>

Compared to amiodarone, dronedarone is less effective in the prevention of AF recurrences but has fewer side-effects.<sup>10</sup>

In permanent AF, the objective of management is rate control and thromboprophylaxis. Rate-control drugs, such as beta-blockers or rate-limiting calcium-channel blockers (verapamil or diltiazem) are used initially (see Table 3). If needed, digoxin is added to optimise rate control.

Importantly, even though the restoration and maintenance of sinus rhythm is often perceived as the

first-line approach to achieve the relief of symptoms, avoidance of tachycardia-induced cardiomyopathy and a reduction of thromboembolic risk, the results of controlled clinical trials suggest the contrary.<sup>11,12</sup> The large randomised trials show that a rate-control strategy is noninferior to a rhythm control approach for mortality. The latter appears to be less cost-effective and tends to be associated with more thromboembolism, hospital admissions and adverse drug effects.<sup>13,14</sup>

### Thromboprophylaxis

The prevention of thromboembolism is an essential and crucial part of management in all patients. The risk of stroke in AF is not homogeneous, and risk factors can help identify patients with AF who are at low, intermediate or high risk. Patients with paroxysmal and persistent AF have a risk of stroke similar to patients with permanent AF, and those without symptoms similar to symptomatic patients.<sup>15</sup>

Adequate antithrombotic therapy with an adjusted dose of warfarin (INR 2-3) prevents two-thirds of cases of ischaemic stroke or systemic thromboembolism and significantly reduces all-cause mortality.<sup>16</sup> Of note, warfarin is superior to aspirin in reducing the risk of ischaemic stroke by approximately 40 per cent.<sup>16</sup> Unfortunately, numerous drug interactions and side-effects (particularly bleeding complications) of warfarin result in a large proportion of patients not receiving optimal antithrombotic therapy. Promising results of recent clinical trials with novel anticoagulants, *eg* dabigatran etexilate (Pradaxa), give hope of more effective and safer thromboprophylaxis in AF without the need for regular blood monitoring.<sup>17</sup>

Stroke prevention in AF will be optimised by better assessment of the risk, including the risk of bleeding. In order to improve selection of truly 'low-risk' patients, updated ESC guidelines on AF include a new stroke risk stratification schema, the CHA<sub>2</sub>DS<sub>2</sub>-VASc score (see Tables 4 and 5).<sup>18,19</sup> This score complements the commonly used CHADS<sub>2</sub> schema by inclusion of additional stroke risk factors. Oral anticoagulation therapy is indicated in 'high-risk' AF patients (score  $\geq 2$ ), while for those who are truly 'low risk' (CHA<sub>2</sub>DS<sub>2</sub>-VASc score = 0), no antithrombotic therapy is recommended. For those with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score = 1, 'oral anticoagulation or aspirin' may be used, with a preference for oral anticoagulation.

Additionally, the new ESC guidelines include a new validated bleeding risk score scheme called HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol – one point for each factor if present, see Table 4).<sup>20-24</sup> The HAS-BLED score

predicts those with a 'high risk' of bleeding, *ie* HAS-BLED score  $\geq 3$ , who require extra caution (rather than contraindication) following initiation of antithrombotic therapy, given that both warfarin and aspirin have the same rates of major bleeding, especially in older people.

### Conclusion

It is important to highlight that as both current pharmacological and electrophysiological approaches remain unsatisfactory, appropriate antithrombotic therapy is crucial to prevent thromboembolic complications. Trials of novel antiarrhythmic and antithrombotic drugs are ongoing, and hopefully these will improve the management of AF.

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## Resources

### Further reading

*Guidelines for the management of atrial fibrillation*. Camm AJ, *et al.*; The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 29 Aug 2010. [Epub ahead of print]

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### Groups and organisations

National Heart Forum, Website: [www.heartforum.org.uk](http://www.heartforum.org.uk). Produces policy documents, reports, teaching resources and a catalogue of key resources on coronary heart disease prevention.

AntiCoagulation Europe. Website: [www.anticoagulationeurope.org](http://www.anticoagulationeurope.org). Information on all aspects of anticoagulation therapy for patients and professionals.

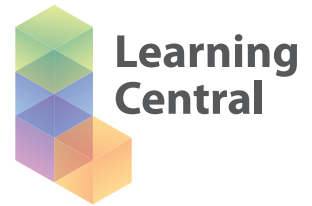
Atrial Fibrillation Association. Website: [www.atrial-fibrillation.org.uk](http://www.atrial-fibrillation.org.uk). Information and support for patients and professionals.

British Heart Foundation. Website: [www.bhf.org.uk](http://www.bhf.org.uk). Produces books, pamphlets, videos, posters and fact-sheets for patients and health professionals.

Primary Care Cardiovascular Society. Website: [www.pccs.org.uk](http://www.pccs.org.uk). Provides meetings and a newsletter for general practitioners.

## CPD: Atrial fibrillation management

Answer these questions online at [Prescriber.co.uk](http://Prescriber.co.uk) and receive a certificate of completion for your CPD portfolio. Utilise the Learning into Practice form to record how your learning has contributed to your professional development.



**1. Which one of these statements about the epidemiology of AF is false?**

- a. It affects about 20 per cent of people aged 80 or older
- b. It appears to be less common among people of Afro-Caribbean or Asian origin than the rest of the population
- c. It is associated with a five-fold increased risk of embolic stroke
- d. Strokes associated with AF carry a higher mortality than other strokes

**2. Which of these statements is false?**

- a. AF is associated with common cardiovascular disorders such as hypertension
- b. AF may be secondary to excessive alcohol consumption
- c. Myocardial fibrosis promotes the development of arrhythmias
- d. AF is a rare complication of heart failure

**3. One of these statements about the diagnosis and investigation of AF is false – which is it?**

- a. Holter ECG monitoring is useful in patients with suspected spontaneously cardioverted paroxysmal AF and daily symptoms
- b. Asymptomatic AF episodes are not uncommon in patients with previous AF paroxysms, who should undergo ECG monitoring
- c. A transthoracic echocardiogram is seldom useful in the assessment of younger patients
- d. Renal function should be checked because renal impairment is associated with an increased risk of stroke in patients with AF

**4. Which one of these statements is false?**

- a. Recurrent AF describes repeated episodes of arrhythmia
- b. Recurrent AF may be paroxysmal or persistent
- c. Permanent AF includes arrhythmia despite attempted cardioversion
- d. Paroxysmal AF episodes terminate spontaneously within three days

**5. Considering the management of AF, which one of these statements is false?**

- a. It is often symptom led
- b. Fewer than 1 in 10 patients presenting with acute AF revert spontaneously to sinus rhythm within 48 hours
- c. Patients with acute-onset AF and haemodynamic compromise should be referred for urgent cardioversion
- d. The optimal strategy for haemodynamically stable patients depends partly on extracardiac pathology

**6. Which one of these statement about the drug treatment of AF is false?**

- a. In persistent AF, pharmacological cardioversion is usually achieved by class Ic or class III antiarrhythmic drugs

- b. Beta-blockers are the drugs of first choice for prevention of AF relapses
- c. With optimal management to maintain sinus rhythm, 90 per cent of patients are free of AF relapses at 12 months
- d. The use of class Ic antiarrhythmic drugs should be restricted to patients without structural heart disease

**7. Considering antiarrhythmic drugs used to treat AF, which one of these statements is false?**

- a. Flecainide is a class III antiarrhythmic
- b. A CYP450D6 inhibitor may cause cardiotoxicity if co-administered with flecainide or propafenone
- c. Quinidine potentiates the anticoagulant effect of warfarin
- d. Amiodarone is a rate-control agent of choice for patients with COPD or bronchospasm unless they have underlying interstitial disease

**8. Which one of these statements is false?**

- a. Dronedarone is licensed for the prevention of AF recurrences
- b. The ANDROMEDA trial showed that dronedarone halved mortality in patients with decompensated congestive heart failure
- c. Dronedarone is less effective than amiodarone in preventing AF recurrences but has fewer side-effects
- d. In the ATHENA trial, dronedarone significantly reduced the composite end-point of first hospitalisation due to cardiovascular events or death, but not all-cause death

**9. One of these statements is false – which one?**

- a. Large randomised trials show that a rate-control strategy is non-inferior to a rhythm-control approach for mortality
- b. Digoxin reduces mortality and admissions in patients with AF and stable chronic heart failure
- c. Compared with a rate-control strategy, a rhythm-control strategy is associated with more thromboembolism
- d. In patients with heart failure, or after myocardial infarction, amiodarone is contraindicated due to its negative inotropic effects

**10. Which one of these statements about thromboprophylaxis in patients with AF is false?**

- a. Adequate antithrombotic therapy with an adjusted dose of warfarin (INR 2–3) significantly reduces all-cause mortality
- b. Compared with aspirin, warfarin is associated with a higher rate of major bleeding in older people
- c. Most patients don't receive the optimal dose of warfarin because of drug interactions and bleeding complications
- d. According to new European Society of Cardiology guidelines, oral anticoagulation or aspirin may be used in patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1, though oral anticoagulation is preferred