

Primary care management of atrial fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia seen in general practice. People with AF have two to seven times the risk of stroke as those in sinus rhythm.¹ If left uncontrolled, AF can lead to heart failure. However, many of the drugs used in AF are associated with clinically significant side effects and drug interactions.

This *Bulletin* discusses the drug treatment of AF in primary care, with particular attention to some important prescribing considerations.

What is atrial fibrillation?

AF is an arrhythmia caused by disorganised electrical activity in the atria leading to a rapid and irregular ventricular rate.² Although it can be asymptomatic, common symptoms include breathlessness, reduced exercise tolerance, angina, palpitations and dizziness.^{3,4} Patients often present with complications, such as heart failure from reduced cardiac output.^{1,5} Stasis of blood in the left atrium contributes to thrombus formation, increasing the risk of stroke.¹

The most common causes of AF in the UK are ischaemic heart disease (IHD) and hypertension. Other causes include heart failure, rheumatic heart disease, hyperthyroidism, excess alcohol intake and pneumonia.⁴

How should patients be assessed and managed?

The aims of treating AF are to reduce palpitations, symptoms of poor cardiac output, and the risk of stroke and thromboembolism.⁵

SUMMARY

- ❑ The aims of treating atrial fibrillation (AF) are to reduce palpitations, symptoms of poor cardiac output and the risk of stroke. This is achieved by controlling the ventricular rate or restoring sinus rhythm (cardioversion) and using aspirin or warfarin.
- ❑ Warfarin is considered to be underused in AF, even though most systematic reviews have shown that it is better than aspirin at reducing the risk of stroke. Drug choice should be based on regular assessment of each patient's stroke and bleeding risk.
- ❑ It is unclear whether restoring and maintaining sinus rhythm is preferable to just controlling the ventricular rate in AF.
- ❑ Cardioversion in secondary care is sometimes indicated in persistent AF. GPs have a role in identifying and referring patients suitable for cardioversion, including urgent referral of appropriate newly diagnosed patients. Early cardioversion is more likely to be successful initially, and sinus rhythm more likely to be maintained, in recent-onset AF.
- ❑ There is a moderate risk of thromboembolism with cardioversion. Therefore, patients who have had AF for more than two days or for an unknown duration should be anticoagulated for at least three weeks before and at least four weeks after cardioversion.
- ❑ Drugs that maintain rhythm should only be initiated under specialist supervision. Care should be taken to minimise the risk of life-threatening arrhythmias caused by these drugs by correcting metabolic disturbances (e.g. hypokalaemia) and avoiding combinations of drugs that prolong the QT interval.
- ❑ There are few good quality studies of drugs used to control the heart rate or rhythm in AF. Therefore, drug choice is usually based on individual factors, such as safety and concomitant disease.

Date of preparation: March 2002

The following treatment strategy has been suggested:⁶

- **Cause** — investigate the cause or triggers.
- **Coagulation** — address the need for warfarin or aspirin for thromboprophylaxis.
- **Control** — control the ventricular rate as necessary.
- **Conversion** — consider conversion to sinus rhythm (cardioversion), if appropriate and desirable.
- **Cure** — consider options for long-term maintenance of sinus rhythm, if appropriate and desirable for the patient.

The duration and pattern of AF (**Table 1**) can influence the general approach to treatment.¹ It is currently unclear whether restoring and maintaining sinus rhythm is preferable to just controlling ventricular rate.⁷ Drugs used to control heart rate are generally considered safer than antiarrhythmics, but cardioversion and maintenance of sinus rhythm may reduce the risk of stroke and the need for anti-coagulants.¹ A large ongoing study (the AFFIRM trial) may help to determine the best approach.¹

Although initial assessment and treatment may be carried out in secondary care, GPs have an important role in managing AF. Specific areas include monitoring treatment and identifying patients for referral (very symptomatic patients need immediate referral²), especially those suitable for cardioversion (see later).⁸ Every effort should be made to minimise the risk of toxicity from the drugs used and anticipate any clinically relevant drug interactions (**Table 2**).⁸

Investigations

A diagnosis of AF should be confirmed by electrocardiography. However, chest x-ray and echocardiography are necessary for further assessment (e.g. to determine left ventricular function).^{1,2} Additional investigation of patients with AF should include a full blood chemistry, haematology and coagulation profile, as well as thyroid function tests (TFTs) and liver function tests (LFTs).^{1,2} This should help to:²

Paroxysmal AF	Recurrent self-terminating episodes of AF. Episodes usually last less than seven days (most less than 24 hours).
Persistent AF	Sustained AF that does not terminate spontaneously without cardioversion.
Permanent AF	AF that is long-standing, in which cardioversion has failed or is not attempted.

Table 1. The different types of atrial fibrillation.¹

- Exclude causes and aggravating factors (e.g. hyperthyroidism or electrolyte disturbances).
- Assess suitability for warfarin.
- Identify factors that increase the toxicity of certain drugs.
- Check baseline values prior to treatment with potentially toxic drugs (e.g. amiodarone, which can alter LFTs and TFTs).

Cardioversion

Secondary care cardioversion of AF to sinus rhythm, using electrical direct current (DC) shocks or drugs, is sometimes indicated in persistent AF.¹ DC cardioversion is initially more effective than drugs, but requires sedation or anaesthesia.¹ Since cardioversion is more successful and sinus rhythm more likely to be maintained in AF of short duration, early referral of newly diagnosed patients (ideally within 48 hours of onset) is also important.² Indications for attempting cardioversion include:²

- AF of recent onset.
- No structural heart disease.
- Successful treatment of a precipitating cause.
- Young age (although old age is not an absolute contraindication).
- Acute AF with severe hypotension, acute heart failure, or unstable angina that does not respond promptly to treatment.

Cardioversion carries a moderate risk of thromboembolism in people who have been in AF for more than two days.¹¹ Therefore, such patients, or those with AF of unknown duration, should be anticoagulated (international normalised ratio [INR] 2–3) for at least three weeks before cardioversion.² Since the relapse rate is high (60–75%), warfarin should be continued for at least four weeks after cardioversion.² It is not clear whether patients should be anticoagulated for longer periods, but this may be considered, depending on the likelihood of AF recurrence and the thromboembolic risk.¹

Drugs used to control rate

Evidence for rate-controlling drugs is limited because most studies involved few patients.¹² Therefore, in practice, drug choice is based largely on each patient's requirements and concomitant disease. The target ventricular rate depends on the patient's age.¹

When used alone, **digoxin**, is most suitable for sedentary (e.g. older) patients with persistent or permanent AF, who do not have a sympathetic component to their arrhythmia.^{1,3,13} This is because digoxin controls ventricular rate at rest, but is less effective during exercise or in conditions of high sympathetic drive (e.g. hyperthyroidism).^{1,12,13} Because digoxin is an inotrope, it has a specific role in patients with heart failure.^{1,14} Digoxin does not convert AF to sinus rhythm and has no place in paroxysmal AF (it may even prolong paroxysmal attacks).^{1,2}

Digoxin has a narrow therapeutic index (1–2mcg/L) and lower doses should be used in renal impairment or if used with drugs that increase its plasma concentration (**Table 2**).² Concentrations (if required) must be measured at least six hours after a dose.² Toxicity should be suspected in any patient who develops nausea, vomiting, diarrhoea, confusion or blurred vision.² Elderly patients and people with metabolic disturbances (e.g. hypokalaemia) are particularly susceptible.^{2,13}

β -blockers or rate-limiting calcium channel blockers, verapamil and diltiazem, may be more useful than digoxin as they are better at controlling the rate during exercise,¹² (diltiazem is not licensed for AF in the UK.) They are also more suitable for people with hypertension or angina.

β -blockers are particularly suitable for patients with IHD as they increase survival¹⁵ (not specifically in AF). Similar benefits

Common drug interactions⁹

- **Digoxin with verapamil:** Digoxin concentration is increased (usually by 40–80%). Maximum effect seen in two weeks and depends on verapamil dose. If verapamil is started, reduce digoxin dose by one-third to one-half and monitor digoxin concentrations.
- **Digoxin with amiodarone*:** Digoxin concentration approximately doubles over one to four weeks. When amiodarone is started, reduce digoxin dose by one-third to one-half, with further adjustments as necessary. Monitor digoxin concentrations.
- **Amiodarone* with warfarin:** Anticoagulant effect of warfarin is increased (may take up to two weeks to develop). Reduce warfarin dose by one-third to two-thirds when amiodarone is added and monitor prothrombin time regularly.

* N.B. Effects of interaction can persist for several weeks or months after stopping amiodarone.

Drugs that prolong the QT interval¹⁰

Using more than one drug that prolongs the QT interval increases the risk of dangerous ventricular arrhythmias and should be avoided. The risk is also increased in patients with underlying cardiac disease and metabolic abnormalities (ensure potassium, calcium and magnesium are maintained within the normal range). Drugs that prolong the QT interval include: **quinidine, disopyramide, flecainide, amiodarone, sotalol, erythromycin, certain antihistamines, antipsychotics and antidepressants** (see also www.torsades.org).

N.B. This is not an exhaustive list. See *BNF* for details of other interactions.

Table 2. Some important interactions with drugs used in atrial fibrillation.

have been seen in heart failure.¹⁶ However, these drugs must be avoided in severe unstable heart failure, asthma and chronic obstructive pulmonary disease. Although β -blockers reduce the effects of increased sympathetic drive,¹ short-term studies show that exercise tolerance may be worsened and patients can develop bradycardia at rest.^{1,12}

Unlike β -blockers, **verapamil** and **diltiazem** usually improve exercise tolerance.¹² However, they should be avoided in heart failure because of their negative inotropic effects (greatest with verapamil). There is little evidence that they maintain sinus rhythm.¹

It is often necessary to use a combination of drugs to control heart rate in AF.¹ If one drug fails, it is worth referring the patient or trying a combination of digoxin with either a β -blocker or verapamil.² Small studies have found that both combinations are more effective than digoxin alone.¹² Particular care should be taken to avoid excessive bradycardia when more than one rate controlling drug is used.¹ In addition, verapamil increases digoxin concentrations (**Table 2**). **Verapamil should not be used with a β -blocker because there is a significant risk of bradycardia and reduced cardiac output.**²

Some of the drugs used to maintain rhythm can also control rate. Because of its side-effects (see later), amiodarone is only suitable for controlling rate when other treatments have failed.¹

Drugs used to maintain rhythm

Antiarrhythmic drugs are often prescribed to maintain rhythm, in patients with recurrences of AF after cardioversion, or in those with troublesome symptoms from paroxysmal AF.¹ Such drugs include the class I antiarrhythmics (flecainide, propafenone, disopyramide and quinidine); β -blockers (class II) including sotalol (class II/III); and amiodarone (class III).^{1,13} Treatment should only be initiated under specialist supervision.²

There are few good quality studies of drugs used to maintain rhythm in AF,^{1,17} so safety is an important determinant of choice.¹ GPs need to be familiar with the practical considerations around prescribing these drugs. Further details have been published elsewhere.^{1,13}

Amiodarone is considered to be the safest agent in heart failure, but it has the worst non-cardiac side effects.¹ These include corneal microdeposits, grey/blue skin discolouration, photosensitivity, hypo/hyperthyroidism (see *MeReC Bulletin* Vol. 12 No. 3), peripheral neuropathy, liver damage and pulmonary toxicity. To minimise these risks, all patients taking amiodarone should have their LFTs and TFTs checked every six months and their eyes checked annually (by slit examination). In addition, they should be advised to limit sunlight exposure and to use a sunscreen.¹⁸

Particular care is required when prescribing class I and class III

agents, as they can all worsen or cause life-threatening arrhythmias, especially in people with structural heart disease or heart failure.¹ To reduce this risk, metabolic abnormalities (e.g. hypokalaemia) should be corrected.¹ Many drugs prolong the QT interval (**Table 2**).

Drugs used to reduce the risk of thromboembolism

All patients with AF should be assessed regularly to determine whether they need to be offered long-term aspirin or warfarin to reduce the risk of stroke.¹ This includes people with paroxysmal AF, as stroke risk is as great as in those with sustained AF.¹⁹

Systematic reviews have shown that warfarin is more effective than aspirin at reducing stroke risk (with the greatest benefits in patients with higher baseline risks).^{20–22} A recent systematic review has questioned warfarin's superiority,²³ but it must be interpreted cautiously as not all trials were included.

Warfarin is more likely to cause bleeding than aspirin, although studies have found the risk to be low. In one meta-analysis, the annual rate of major bleeding with warfarin was 1.3% compared with 1.0% for aspirin and for placebo.¹⁹ The risk of bleeding may be increased with age (> 75 years), an INR greater than 3, fluctuating INRs, hypertension or other diseases such as peptic ulcer.^{2,24}

The decision to use aspirin or warfarin should be based on an assessment of the patient's overall risk of stroke in the context of their bleeding risk.^{1,11} Patient preference, compliance and facilities for INR monitoring should also be considered.¹¹ Many different risk stratification tables have been developed — **Table 3** gives one example.

The threshold for deciding what level of stroke risk warrants anticoagulation is controversial.¹ However, if there is a **high risk** of stroke (especially following ischaemic stroke or transient ischaemic attack²²) warfarin is preferred, as the benefits usually outweigh the risks (**Table 3**).¹

Risk group	Untreated	Aspirin	Warfarin
Very high Previous ischaemic stroke or transient ischaemic attack	12%	10%	5%
High Age over 65 and one other risk factor: • hypertension • diabetes mellitus • heart failure • left ventricular dysfunction	5–8%	4–6%	2–3%
Moderate • Age over 65, no other risk factors • Age under 65, other risk factors	3–5%	2–4%	1–2%
Low • Age under 65, no other risk factors	1.2%	1%	0.5%

Adapted with permission from the Scottish Intercollegiate Guidelines Network (SIGN)

Table 3. Annual risk of stroke with no treatment, or with aspirin or warfarin in high-, moderate- and low-risk patients with non-valvular atrial fibrillation.¹¹

Observational data suggest that patients with AF and heart valve disease or prostheses, thyrotoxicosis, intracardiac thrombus or non-cerebral thromboembolism are also at high risk of stroke.¹¹

Opinion on whether to use aspirin or warfarin is divided for patients with a **moderate risk** of stroke (3–5% per year¹¹),¹ although many would choose warfarin in this situation.^{1,11} Aspirin (75–300mg/day) should be considered when warfarin is not used or is contra-indicated.¹¹ There is a lack of consensus over the dose but most studies used about 300mg/day. The role of other antiplatelets in AF is still unclear.²

Patients aged under 65 years with no other risk factors have such a **low risk** of stroke that there is little benefit from using warfarin or aspirin (aspirin may be considered for other indications, such as IHD).¹¹ Patients under 60 years with lone AF (i.e. with no identifiable underlying cardiopulmonary disease¹) do not seem to be at increased risk of stroke.¹⁹

The INR for warfarin should be checked at least every other day initially, then at longer intervals (depending on the response), and then up to every 12 weeks, aiming for a target INR of 2.5 (range 2–3¹). It may be safer to aim for an INR of 2 in those aged over 75 years.^{1,2} Care should be taken when using drugs that

might interact with warfarin (e.g. amiodarone, **Table 2**).¹¹ Patients must be advised about bleeding risks and told to avoid interacting over-the-counter drugs (e.g. NSAIDs).

Warfarin is considered to be underused in AF.²⁵ This may be due to concern that the evidence from trials does not translate to clinical practice, as trial patients were young (at low risk of bleeding) and monitored more closely than would usually be expected. Also, the benefits of warfarin may have been either overestimated or underestimated in trials.^{24,25} However, a hospital outpatient study in 167 patients (considered representative of clinical practice) that tried to address these concerns, found stroke and bleeding rates similar to those reported in trials.²⁵

Conclusion

Because there are few good quality studies of drugs that control the rate or rhythm in AF, drug choice is usually based on safety and concomitant disease. Warfarin is considered underused in AF, even though the majority of evidence shows it is better than aspirin at reducing the risk of stroke. Prescribers should regularly assess the suitability of warfarin for each patient by considering their risk of stroke against the likelihood of bleeding.

References

- Fuster V, Rydén LE, *et al.* ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation. *Eur Heart J* 2001; **22**: 1852–1923
- Sowerby Centre for Health Informatics at Newcastle. Atrial Fibrillation. PRODIGY; June 2001. Available from: URL: <http://www.prodigy.nhs.uk>
- Falk RH. Atrial fibrillation. *N Engl J Med* 2001; **344**: 1067–1078
- Lip GYH, Beevers DG, *et al.* ABC of atrial fibrillation: aetiology, pathophysiology, and clinical features. *BMJ* 1995; **311**: 1425–1428
- Narayan SM, Cain ME, *et al.* Atrial fibrillation. *Lancet* 1997; **350**: 943–950
- Gilligan DM. Atrial fibrillation. *N Engl J Med* 2001; **345**: 620 [letter]
- Hohnloser SH, Kuck K-H, *et al.* Rhythm or rate control in atrial fibrillation — Pharmacological intervention in atrial fibrillation (PIAF): a randomised trial. *Lancet* 2000; **356**: 1789–1794
- Lip GYH, Beevers DG, *et al.* ABC of atrial fibrillation: atrial fibrillation in general and hospital practice. *BMJ* 1996; **312**: 175–178
- Stockley IH, editor. *Drug Interactions*. 5th ed. London: Pharmaceutical Press; 1999
- CSM/MCA. Drug-induced prolongation of the QT interval. *Curr Problems Pharmacovigilance* 1996; **22**: 2
- Scottish Intercollegiate Guidelines Network. Antithrombotic therapy (No. 36). Edinburgh: SIGN; 1999. Available from: URL: <http://www.sign.ac.uk>
- Segal JB, McNamara RL, *et al.* The evidence regarding the drugs used for ventricular rate control. *J Fam Pract* 2000; **49**: 47–59
- Lip GYH, Watson RDS, *et al.* ABC of atrial fibrillation: drugs for atrial fibrillation. *BMJ* 1995; **311**: 1631–1634
- The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997; **336**: 525–533
- Yusuf S, Peto R, *et al.* Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis* 1985; **27**: 335–371
- Brophy JM, Joseph L, *et al.* β -blockers in congestive heart failure: a Bayesian meta-analysis. *Ann Intern Med* 2001; **134**: 550–560
- Miller MR, McNamara RL, *et al.* Efficacy of agents for pharmacologic conversion of atrial fibrillation and subsequent maintenance of sinus rhythm. *J Fam Pract* 2000; **49**: 1033–1046
- Cordarone X. ABPI compendium of data sheets and summaries of product characteristics. January 2000. Available from: URL: <http://emc.vhn.net>
- Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomised controlled trials. *Arch Intern Med* 1994; **154**: 1449–1457
- Hart RG, Benavente O, *et al.* Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999; **131**: 492–501
- Segal JB, McNamara RL, *et al.* Anticoagulants or antiplatelet therapy for non-rheumatic atrial fibrillation and flutter. (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2002. Oxford: Update Software
- Koudstaal PJ. Anticoagulant versus antiplatelet therapy for preventing stroke in patients with non-rheumatic atrial fibrillation and a history of stroke or transient ischaemic attacks. (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2002. Oxford: Update Software
- Taylor FC, Cohen H, *et al.* Systematic review of long term anticoagulation or antiplatelet treatment in patients with non-rheumatic atrial fibrillation. *BMJ* 2001; **322**: 321–326
- Gubitz G, Sandercock P, *et al.* What are the effects of anticoagulant and antiplatelet treatment in people with atrial fibrillation? In: Barton S, editor. *Clinical Evidence*. Issue 6. London: BMJ Publishing Group; 2001. p.169–175
- Kalra L, Yu G, *et al.* Prospective cohort study to determine if trial efficacy of anticoagulation for stroke prevention in atrial fibrillation translates into clinical effectiveness. *BMJ* 2000; **320**: 1236–1239

The National Institute for Clinical Excellence (NICE) is associated with MeReC Publications published by the NPC through a funding contract. This arrangement provides NICE with the ability to secure value for money in the use of NHS funds invested in its work and enables it to influence topic selection, methodology and dissemination practice. NICE considers the work of this organisation to be of value to the NHS in England and Wales and recommends that it be used to inform decisions on service organisation and delivery. This publication represents the views of the authors and not necessarily those of the Institute.