

Anti-Arrhythmic Drugs for Atrial Fibrillation

Atrial Fibrillation Association: Summary of Drug Therapy Options 2012



An expert update summary report on anti-arrhythmic therapy in the UK

www.afa.org.uk
www.heartofaf.org

Providing information, support and access to established,
new or innovative treatments for Atrial Fibrillation

Report summary

The goals of medical treatment for individuals with atrial fibrillation (AF) are to maintain normal sinus rhythm of the heart, reduce the risk of complications of AF (especially thromboembolism and stroke) and to minimise the symptoms experienced by patients.

There are two classes of drugs available to achieve these goals — anticoagulants and anti-arrhythmic drugs (AADs). This document looks at AADs; we have produced a separate information leaflet on drugs for anticoagulation.

AADs generally fall in to two categories depending on the action they exhibit on the heart rate — rhythm control or rate control. Restoring and maintaining normal sinus rhythm can eliminate symptoms that affect many people with AF and improve patients' quality of life.

However, several trials have found serious adverse effects (including death, pro-arrhythmia and hospitalisation) from AADs in some patient groups. Therefore, safety rather than efficacy is an important consideration in deciding on the use of an AAD.

The largest study that compared both rhythm and rate control treatment strategies for patients with AF was the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial.

This large multi-centre randomised study demonstrated that a rhythm-control strategy was no better than a ventricular rate control strategy with regard to quality of life, incidence of stroke, or mortality at a follow-up of about 5 years. However, there were some weak areas in this trial. In patients who returned to normal rhythm, warfarin was often stopped leading to some strokes. Also, the patients studied were elderly, average age 77, and no account was taken of the burden of symptoms and quality of life.

Contents

- [Report summary](#)
- [About AF](#)
- [Rhythm control](#)
- [Rate control](#)
- [Summary](#)
- [References](#)

About AF

What is AF?

Atrial fibrillation (AF) is a common heart rhythm disorder associated with deadly and debilitating consequences including heart failure, stroke, poor mental health, reduced quality of life and death.¹ In AF, chaotic electrical activity develops in the walls of the atria, the heart's top two chambers, over-riding the heart's natural pacemaker. The normal, steady rhythm of the atria is disrupted and they instead begin to fibrillate – quivering with a shallow but very fast rhythm as their muscular walls fail to contract with regularity and coordination.

This disrupts the contraction of the heart's main pumping chambers, the ventricles. Consequently, the ventricles beat faster and their rhythm becomes irregular. This can be detected as an irregular pulse, a valuable yet simple test of AF. AF directly affects the rhythm of the heart, anti-arrhythmic drugs are a central treatment option. These drugs can alter the rate or rhythm of the heart to restore normal sinus rhythm and thus reduce the symptoms of AF.

Who is at risk of AF?

It is difficult to overstate just how big a problem AF presents. One recent authoritative study concluded for anyone aged 40 or above, the lifetime risk of AF exceeds 25% – meaning one in four adults can expect to develop AF.²

We now know that around 2% of the population in 2004 had AF, and it is predicted by 2050, over 4% of the population will have it.³ Consequently, it is very possible that for those aged 40 today, the lifetime risk of developing AF is in fact higher than one in four. AF is frequently asymptomatic and very commonly intermittent, further adding to the likelihood that current prevalence estimates are lower than the true figure. In the UK, approaching a million Britons are diagnosed with AF, yet experts suggest between one third and one half of all patients have not yet been detected.⁴

Given the number of people who have or will develop AF, it is not easy to define a typical AF patient. Men and women of all ages can be affected. In general terms, the likelihood of developing AF increases with age.⁵

However, some people appear to be at a higher genetic risk and this predisposition to AF is most often seen in young patients.⁶ In addition, some studies suggest the incidence of AF is higher than normal in athletes and others who engage in frequent, vigorous exercise regardless of age.^{7,8} For all these reasons, AF is not just a condition of the elderly. The most common underlying causes of AF are high blood pressure, thyroid disease and, to a lesser extent, coronary artery disease and diabetes.^{9,10}

Dietary, lifestyle and other factors that contribute to the risk of AF include emotional and physical stress and excessive caffeine, alcohol or illicit drug intake.¹¹

Signs and symptoms of AF

A simple and easily identifiable sign of AF is an irregular pulse. For this reason, many AF experts and patient advocacy groups are calling for regular pulse checks to become a free, swift and routine part of every GP visit. However, AF is frequently intermittent and many people with AF have no or non-specific symptoms.¹² These combine to make detection and diagnosis difficult; often AF is not apparent until a person goes to see their doctor with a serious complication such as stroke, a blood clot in the leg or heart failure.

Yet even patients who do experience symptoms of AF are not always diagnosed immediately. In a recent international survey, there was an average delay of 2.6 years between the onset of symptoms and the diagnosis of AF.¹³ In another piece of research it was found up to half of patients with documented chronic AF were unaware why they were being treated and more than a third were not aware of their diagnosis.¹⁴ This indicates many patients with AF are not being

detected or managed effectively, and many are at risk of serious long-term consequences.

Cost of AF to individuals

There are many negative consequences of AF frequently leading symptomatic patients into a life of confusion and despair. It has been found approximately one third of AF patients suffer persistent anxiety or depression.¹⁵ Regardless of symptoms, AF is associated with a significant increase in risk of stroke, heart failure and death. Approximately half of AF patients are symptomatic. Symptoms include palpitations, shortness of breath, light-headedness, fainting, fatigue and chest pain.¹⁶ For emergency admissions to hospital, AF most often presents as difficulty with breathing, chest pain and palpitations.¹¹

For many patients addressing the symptoms of AF represents a much greater concern than preventing long-term complications. AF is strongly associated with diminished quality of life (QOL) and can lead to a pronounced decline in mental health.

At diagnosis, it is common for a patient to have endured a considerable period of time living in fear of symptoms over which they had no control or understanding.

One study of the experiences of AF patients living with recurrent symptomatic AF found their quality of life was significantly affected with patients struggling to find the meaning of symptoms, feeling uninformed and unsupported and experiencing emotional distress.

Participants also reported experiencing delays in diagnosis, an absence of information and advice on the nature of AF and its management. Support for coping with the emotional burden of AF was also found to be lacking.¹⁷

Patients frequently find that their symptoms are dismissed following a clinical focus on the prevention

of stroke. Yet treatments that returning the heart to a normal rhythm offer resolution of these debilitating symptoms. Allowing patients to return to a normal life.

For these reasons, it is vital that the use of drugs and procedures that treat the underlying AF as assessed in appropriate patients as soon as possible.

Cost of AF to society

AF is a significant and growing drain on the NHS. During the past 20 years there has been a 60% increase in the number of patients being admitted to hospitals as a result of AF.¹⁸

In 2008, there were an estimated 850,000 GP visits because of AF in the UK.⁴ When including AF as a causative secondary diagnosis, the total cost of AF to the NHS has been calculated to be nearly £2.2 billion a year.⁴

AF patient days spent in hospital beds cost the NHS over £1.8 billion. Non-bed in-patient costs were £124 million, and outpatient costs completed the total at £205 million. Some authoritative estimates predict a three-fold increase in AF over the next 50 years.^{3, 19}

Together with loss of time in employment and contribution to the community of the patient, and most probably also to those providing informal care, this amounts to a significant burden on society and on thousands of individuals.

Rhythm-control therapies

Guidelines issued by the ESC in 2010 and 2012 make recommendations on the use of anti-arrhythmic drugs (AADs) for the conversion and maintenance of sinus rhythm in patients who suffer from AF.

- For patients with no evidence of structural heart disease, propafenone, flecainide and dronedarone are considered first-line agents.
- Amiodarone can be considered as an alternative second line choice. However, it is the drug of choice for patients with severe left ventricular hypertrophy.
- For patients with coronary artery disease, sotalol may be a first-line agent.

AADs can also be classified according to their effects on the electrical behaviour of myocardial cells during activity (the Vaughan Williams classification) although this classification is of less clinical significance:

- Class I: membrane stabilising drugs (e.g. flecainide, propafenone)
- Class II: anti-adrenergic drugs (e.g. beta-blockers)
- Class III: drugs which prolong the action potential (e.g. amiodarone, dronedarone, sotalol)
- Class IV: calcium-channel blockers (e.g. verapamil, diltiazem)

These drugs can have serious side effects and this must be carefully considered by clinicians prior to commencing treatment and all patients need to be monitored whilst taking them. Some of them have no rate controlling effects and are rarely prescribed without rate controlling drugs.

Flecainide

Flecainide is a Class Ic AAD that works by blocking sodium channels in the heart, causing prolongation of the cardiac action potential, thereby slowing conduction of the electrical impulse within the heart. Flecainide is commonly given to patients with paroxysmal AF and is generally well tolerated. It should not be used in patients with a history of

heart failure or myocardial infarction. Side effects include visual problems, oedema, and arrhythmias.

The British National Formulary recommends that flecainide is initiated under direction of a hospital consultant. Flecainide has a variable half-life and often causes PR and QRS prolongation and rarely Brugada type ST elevation in leads V₁-V₂. It can precipitate serious arrhythmias in a small minority of patients with otherwise normal hearts. ECGs therefore must be performed at, and monitored regularly following, initiation of flecainide. Additionally, in patients with renal failure, plasma levels also have to be monitored regularly.

Amiodarone

This Class III anti-arrhythmic has the greatest efficacy of any AAD and a low risk of pro-arrhythmia but carries a significant extra-cardiac adverse effect profile. It is therefore often used in patients with structural heart disease but should be used with caution in patients with moderate to severe heart failure because of an increased risk of death.

Amiodarone contains iodine and can commonly cause disorders of thyroid function. Laboratory tests (T₃, T₄, and TSH) should be performed before treatment and every six months whilst taking the drug. Regular assessment for pulmonary fibrosis is also required and should be suspected if new or progressive shortness of breath or cough develops in a patient taking amiodarone. As it is associated with hepatotoxicity this requires regular LFT monitoring with discontinuation if severe abnormalities develop. Almost all patients develop photosensitivity, and have to be careful of exposure to sunlight

Sotalol

Sotalol is a mixture of two chemical isoforms: l-Sotalol is a B-blocker only and d-Sotalol is a Class III anti-arrhythmic agent. At lower doses, the drug acts mainly as a B-blocker, but at higher doses more of

a Class III effect is seen. This effect prolongs the action potential and the recovery phase, such that QT prolongation is commonly seen. Sotalol is commonly used at doses of 40-80mg twice daily, at which level it usually has little or no true anti-arrhythmic action. Higher doses of 80-160 mg twice daily or more are needed to achieve a significant anti-arrhythmic effect though such doses commonly prove intolerable because of excessive B-blockade.

It is indicated for maintenance of normal sinus rhythm after conversion of AF. It was tested in patients with previous myocardial infarction and poor ventricular function in the SWORD Study, where it was found to be more dangerous than placebo in such patients. Because of this, it should be given with care in structural heart disease, especially heart failure.

As it can cause QT prolongation and torsade de pointes, Sotalol initiation and dose changes should be undertaken with medical evaluation. ECG monitoring with measurement of the corrected QT interval is required here and thereafter on a yearly basis.

Loss of potassium and magnesium, in such patients, greatly increases the risks of an arrhythmia related to QT prolongation. A number of sudden deaths have been reported in patients without structural heart disease, who are taking sotalol and develop gastroenteritis with nausea and vomiting.

Side effects related to its B-blocking properties include exacerbation of reactive airways disease, depression, and hypotension.

Dronedarone

Dronedarone is an AAD that has properties belonging to all the classes of anti-arrhythmics drugs. It is licensed for the maintenance of sinus rhythm after cardioversion in clinically stable patients with paroxysmal or persistent atrial

fibrillation. Therefore, dronedarone has a place in the treatment of non-permanent AF to provide options for clinicians and patients.^{25,26,27}

Dronedarone is associated with some risks that are off-set by benefits when the drug is helping to maintain sinus rhythm. Dronedarone should be given to patients either in sinus rhythm or prior to scheduled restoration of sinus rhythm. Pre-loading with dronedarone prior to cardioversion to increase the likelihood of maintaining sinus rhythm once restored by cardioversion may be appropriate.

Importantly, the PALLAS study (The Permanent Atrial fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy) was stopped when it found dronedarone to be associated with increased mortality in patients with permanent AF, as well as a two-fold increase in stroke and hospitalisation for heart failure. To avoid dronedarone being used by patients in permanent AF, dronedarone should be discontinued whenever the patient develops permanent AF.

Dronedarone should be initiated and monitored under "specialist" supervision (appropriate hospital consultant or specialist nurse practitioner). Liver function tests are required regularly and an ECG should be performed at least every six months to confirm sinus rhythm.

Dronedarone should not be given to patients with impaired left ventricular function, especially if they have NYHA Class III or IV heart failure, because mortality is increased. In the past 25 years, there has remained a need for effective anti-arrhythmics with reduced adverse effects.

An alternative strategy to rhythm control of AF is one of rate control. The ventricular response rate of the heart during AF may be rapid and therefore require slowing. This usually is accomplished with medications that slow conduction through the AV node. Medications that may be used for rate control in AF include B-Blockers, rate-limiting calcium channel blockers and digoxin.

Rate-control therapies

Calcium Channel Blockers (diltiazem, verapamil)

Non-dihydropyridine CCBs work by reducing the rate of AV nodal conduction, by selectively affecting nodal cells, and control ventricular response by inhibiting calcium ions entering the myocardium thus reducing the frequency of cardiac contractions. They control the rate at both rest and during activity. Side effects include worsening of heart failure in decompensated patients and fatigue.

Verapamil is a highly negatively inotropic calcium channel-blocker and it reduces cardiac output, slows the heart rate, and may impair atrioventricular conduction. It may precipitate heart failure, exacerbate conduction disorders, and cause hypotension at high doses and should not be used with n-blockers. This effect is because calcium flow in heart muscle cells stimulates contraction of the muscle cell.

Diltiazem has a less negative inotropic effect than verapamil and significant myocardial depression occurs rarely. It may be used in patients for whom B-blockers are contra-indicated or ineffective.

Beta-adrenergic Receptor Blockers (bisoprolol, propranolol, atenolol, metoprolol)

B-blockers exert an anti-arrhythmic effect principally by decreasing the effects of the sympathetic system on automaticity and conductivity within the heart (they slow the sinus rate of the heart and reduce AV nodal conduction). Blood pressure needs to be carefully monitored in patients taking a B-blocker, they may worsen heart failure in decompensated patients, and may exacerbate reactive airways disease e.g. asthma. Additionally, they can be used in conjunction with digoxin to control the ventricular response in atrial fibrillation.

Cardiac Glycosides (digoxin)

In relation to atrial fibrillation, digoxin is primarily used in patients with congestive heart failure in persistent or permanent AF. Close monitoring of drug levels and renal function is required for patients taking digoxin since it has a narrow therapeutic window. It doesn't control heart rate during periods of activity, because vagal tone is removed at that time. However, in elderly patients and patients who lead a sedentary life digoxin, perhaps combined with another AV nodal blocking agent, can be very effective for controlling heart rate. Side effects include nausea, vomiting, diarrhoea, arrhythmias, dizziness, and blurred or yellow vision.

Summary

AADs can reduce the duration and frequency of AF episodes and therefore improve symptoms and thus quality of life. However, all AADs carry risks that must be weighed against the benefits they may provide.

Particular caution is needed in patients with heart failure where a detrimental effect is seen with Class I and Class III AADs. Importantly, all AADs require monitoring at initiation and then regularly thereafter to ensure efficacy and ongoing safe use.

Consultation with an experienced clinician is therefore recommended prior to starting any of these drugs. Patients with AF should seek to establish with their doctors a strategy for rhythm control, or rate control. Both require anticoagulation if appropriate. Rhythm-control is likely to involve drug treatment alone or combined with cardioversion and/or ablation, but should also have a strategy for long-term maintenance of sinus rhythm.

Rate control implies accepting AF and using drugs to control AV nodal conduction. In some patients, with poor rate control on rate limiting drugs or who are experiencing unacceptable drug side-effects, an alternative option involves ablation of the AV node and subsequent pacemaker implantation. This “ablate & pace” strategy can relieve symptoms and allow these drugs to be stopped.

References

- Wyse, D. Waldo, A. DiMarco, J. et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *New England Journal of Medicine*. 2002; 347: 1825-1833.
- Hirsh J, Dalen J, Anderson DR et al. Oral anticoagulants: mechanism of action, clinical effectiveness and optimal therapeutic range. *Chest* 2001; 119:85-215
- Lloyd-Jones DM, Wang TJ, Leip EP et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation* 2004; 110: 1042-6
- Miyasaka Y, Barnes ME, Gersh BJ et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 2006; 114: 119-25
- The Office of Health Economics Estimating the direct costs of atrial fibrillation to the NHS in the constituent countries of the UK and at SHA level in England, 2008, November 2009, London
- Kannel WB, Wolf PA, Benjamin EJ et al. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol* 1998; 82:2N-9N
- Kirchhof P, Bax J, Blomstrom – Lundquist C et al. Early and comprehensive management of atrial fibrillation: executive summary of the proceedings from the 2nd AFNET-EHRA consensus conference 'research perspectives in AF'. *Eur Heart J* 2009;doi: 10.1093/eurheartj/ehp235
- Aizer A, Gaziano JM, Cook NR et al. Relation of vigorous exercise to risk of atrial fibrillation. *Am J Cardiol* 2009; 103: 1572-7
- Farrar MW, Bogart DB, Chapman SS et al. Atrial fibrillation in athletes. *Mo Med* 2006; 103:297-301
- Lip GY, Beevers DG, Singh SP et al. ABC of atrial fibrillation. Aetiology, pathophysiology, and clinical features. *BMJ* 1995;311:1425-8
- Iqbal MB, Taneja AK, Lip GY et al. Recent developments in atrial fibrillation. *BMJ* 2005;330:238-43
- Royal College of Physicians. Atrial fibrillation National clinical guideline for management in primary and secondary care. National Collaborating Centre for Chronic Conditions. <http://www.nice.org.uk/nicemedia/pdf/cg036fullguideline.pdf> Accessed March 2009
- Fuster V, Ryden LE, Cannom DS et al. ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation : a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society *Circulation* 2006; 114: e257-354
- AF AWARE. AF AWARE cardiology groups call for greater awareness and better education on atrial fibrillation. Press release 2009. <http://www.world-heart-federation.org/press/press-releases/news-details/article/af-aware-cardiology-groups-call-for-greater-awareness-and-better-education-on-atrial-fibrillation/> . Accessed 16 June 2009
- Lip GYH, Kamath S, Jafriet M al. Ethnic Differences in Patient Perceptions of Atrial Fibrillation and Anticoagulation Therapy. *Stroke* 2002;33;238-44
- Thrall G, Lip GY, Carroll D, Lane D. Depression, anxiety, and quality of life in patients with atrial fibrillation. *Chest*. 2007 Oct; 132 (4): 1259-64. Epub 2007 Jul 23
- National Institute for Health and Clinical Excellence. Understanding NICE guidance: Atrial fibrillation. <http://www.nice.org.uk/nicemedia/pdf/CG036publicinfo.pdf>. Accessed May 2009
- McCabe PJ, Schumacher K, Barnason SA. Living with atrial fibrillation: a qualitative study. *J Cardiovas Nurs*. 2011 Jul-Aug;26(4):336-44
- Friberg J, Buch P, Scharling H, et al. Rising rates of hospital admissions for atrial fibrillation. *Epidemiology* 2003;14:666-72
- Banach M, Mariscalco G, Urgulan M et al. The significance of preoperative atrial fibrillation in patients undergoing cardiac surgery: preoperative atrial fibrillation – still underestimated opponent. *Europace*. 2009; 10: 1266-70
- Fuster, V. Ryden, L, Cannom, D. et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology / American Heart Association Task Force on Practice Guideline and the European Society of Cardiology Committee for Practice Guidelines: developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*. 2006; 114 (7): 257-354.
- Guidelines for the management of atrial fibrillation, The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC) 2010
- Antonaccio M, Gomoll A. Pharmacologic basis of the antiarrhythmic and hemodynamic effects of sotalol. *American Journal of Cardiology*. 1993; 72: 27A-37A
- ESC Statement on Dronedaron 2011
- ESC Atrial Fibrillation Focused Update 2012 Focused update 2012 A. John Camm (Chairperson), Gregory Y.H. Lip, Dan Atar, Raffaele de Caterina, Gerhard Hindricks, Stefan Hohnloser, Paulus Kirchhof, Irina Savelieva
- The British Journal of Cardiology | July–September 2012 | Volume 19 Issue 3
- Connolly SJ, Camm AJ, Halperin JL, et al; PALLAS Investigators. Dronedaron in high-risk permanent atrial fibrillation. *N Engl J Med* 2011;365:2268–2276.

Pharmacological information from British National Formulary. Available at: <http://www.medicinescomplete.com/mc/bnf/current/>

Anti-Arrhythmic Drugs for Atrial Fibrillation

Atrial Fibrillation Association: Summary of Drug Therapy Options 2012



www.afa.org.uk



www.heartofaf.org