Review Article

Treatment of atrial fibrillation: a comprehensive review and practice guide

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Abstract

Atrial fibrillation (AF) is an ectopic rhythm originating in the atrium. AF is the most common sustained cardiac arrhythmia in clinical practice and it is an enormous burden worldwide because of the high rates of morbidity, disability and mortality. Treatment of AF has become a hot spot in the field of cardiovascular medicine. Recently, increasing evidence and advancements in medical technology have helped us gain a better understanding of AF. As a result, management of AF has evolved in the past few years, so that we can better prevent and control AF. Current therapy for AF mainly includes drug therapy, catheter ablation, cryoballoon ablation, left atrial appendage closure and the maze procedure. The goal of this article is to update current treatment options for AF. We hope that this article will help deliver good care to AF patients based on the current state-of-the-art evidence.

Keywords: atrial fibrillation, drug therapy, catheter ablation, cryoballoon ablation, left atrial appendage closure, maze procedure

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Atrial fibrillation (AF) is an ectopic rhythm originating in the atrium. An electrocardiogram (ECG) of AF shows the normal sinus P waves are replaced by f waves (350 to 600 beats per min) and the ventricular rate is often irregular, which is characterised by an uneven R-R interval.[1,2] The prevalence of AF is higher in men than in women and it has increased rapidly due to the ageing population.[3,4] AF is associated with an increased risk of stroke,[5] heart failure,[6] myocardial infarction[7] and chronic kidney disease,[8] which increases the burden on healthcare systems around the world. Treatment of AF has become a huge challenge in the field of cardiovascular diseases.

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Risk factors and upstream treatment of AF

Previous studies have confirmed that initiation and maintenance of AF result from atrial remodelling, including electrical and structural remodelling, atrial energy metabolic remodelling and autonomic neural remodelling,[9-11] which are associated with a variety of risk factors,[2,12] such as valvular diseases, hypertension, ischaemic heart diseases, heart failure, hyperthyroidism, lung diseases, diabetes, obstructive sleep apnoea syndrome and atrial fibrosis. In addition, obesity, smoking, alcohol abuse and negative emotions (anger, stress, impatience and anxiety) are also risk factors for AF. Potential reversible causes of AF should be identified and treated where possible. Identification, prevention and proper management of these risk factors could effectively reduce the incidence of AF.

Upstream therapy refers to the use of non-anti-arrhythmic drugs that target the mechanisms of AF to prevent or reduce the occurrence of AF.[13] Recent research has highlighted the beneficial effects of lifestyle and risk-factor management for AF as upstream therapy. Treatment with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) will delay or even reverse atrial remodelling of individuals with hypertension or left ventricular dysfunction, resulting in a reduction in new-onset AF.[14] Patients with cardiac surgery will achieve clinical benefits from preventing the occurrence of AF by using statins.[15] Long-chain 3-polyunsaturated fatty acids (n-3 PUFA) are considered to be able to prevent AF because of their multiple effects on cardiac electrophysiology, such as membrane stabilisation in the myocardial cell, and antifibrotic, anti-inflammatory and antioxidant characteristics, which may influence the mechanisms involved in the initiation and maintenance of AF.[16]

Prevention or treatment of AF-related risk factors and upstream treatment can effectively reduce the prevalence of AF and hospital admissions of AF patients.

Drug therapy for AF

The three major drug treatment strategies for AF are rhythm control, rate control and prevention of stroke. A guiding principle of therapy is to eliminate reversible conditions, such as hyperthyroidism or alcohol consumption, before treatment.

Table 1. Anti-arrhythmic drugs for the maintenance of sinus rhythm

Drug	*Route*	*Typical dose*	*Contra-indications*	*References*
Flecainide	Oral	50–150 mg, BID	Ischaemic or structural heart disease; sinus node dysfunction, second- or third-degree atrioventricular block or bundle branch disease without a pacemaker	20, 21
	IV	1.5–2.0 mg/ kg, over 10 min		
Propafenone	Oral	150–300 mg, TID	Ischaemic or structural heart disease; asthma; sinus node dysfunction, second- or third-degree atrioventricular block or bundle branch disease without a pacemaker	20, 21
	IV	1.5–2.0 mg/ kg, over 10 min		
Sotalol	Oral	80–160 mg, BID	Asthma; creatinine clearance < 40 ml/min; left ventricular dysfunction; QTc > 450 ms; sinus bradycardia < 50 bpm, second- or third-degree atrioventricular block without a pacemaker	20
Amiodarone	Oral	200 mg, TID for 1 week; 200 mg, BID for 1 week; then maintenance dose of 200 mg QD	Avoid in those with advanced lung disease, severe hepatic impairment, thyroid dysfunction	21
	IV	5.0–7.0 mg/kg		
Ibutilide	IV	1.0 mg over 10 min, the same dose after waiting for 10 min	Avoid in patients with QT prolongation, hypokalaemia, severe left ventricular hypertrophy or low ejection fraction	21
Dronedarone	Oral	400 mg, BID	Permanent atrial fibrillation; severe heart failure (NYHA class III–IV); QTc > 500 ms; severe hepatic impairment	17, 20

QD, once daily; BID, twice daily; TID, three times a day; IV, intravenous.

Rhythm-control therapy in AF

Maintenance of sinus rhythm is the primary goal, especially for patients younger than 65 years with severe symptoms or first-diagnosed AF.[17,18] For these individuals, restoration and maintenance of sinus rhythm may alleviate symptoms and improve the quality of life. Selection of the anti-arrhythmic drug for maintenance of sinus rhythm is based on the drug's safety and efficacy. Generally, class Ic and IIIc anti-arrhythmic drugs are mainly used for maintenance of sinus rhythm (Table 1).

Class Ic treatment with flecainide or propafenone is often preferred, which exerts its effects by blocking sodium channels to reduce the rate of rise of the action potential and reduce excitation of the cardiac tissue. Class Ic drugs are recommended for paroxysmal AF, but their use is contra-indicated for AF patients with underlying structural heart diseases due to increased risk of ventricular arrhythmias and atrial flutter.[19]

Class IIIc treatment with sotalol, amiodarone, ibutilide or dofetilide is often preferred, which exerts its effects by potassium channel blockade and prolonging action potential duration to delay conduction. Class IIIc drugs are recommended for persistent AF, and also benefit AF patients with structural heart diseases.[19,20]

For patients with infrequent episodes of AF (less than one per month), oral flecainide or propafenone can be self-administered by the patient at home ('pill in the pocket' therapy). In those patients with frequent episodes of AF, daily maintenance anti-arrhythmic drug therapy with propafenone, flecainide or sotalol is preferred as first line. Amiodarone is used for those patients with low left ventricular ejection fraction (LVEF) ischaemic heart disease. Interventional therapies or surgical treatments should be taken into consideration when anti-arrhythmic drugs are contra-indicated, have been ineffective, or cannot be tolerated.[18]

Rate-control therapy in AF

Rate-control therapy has been demonstrated to improve symptoms and reduce hospital admissions, which benefit patients older than 65 years with minimal symptoms.[17,19] According to the latest European Society of Cardiology (ESC) guidelines for the management of AF,[21] AF patients should target a resting heart rate of < 110 beats per minute (bpm); it can be reduced to 80 to 100 bpm if symptoms call for stricter rate control. Commonly used drugs to control ventricular rate are β-adrenergic receptor

Table 2. Drugs for rate control

Drug	*Route*	*Typical dose*	*Contra-indications*	*References*
β-blockers				
Metoprolol (tartrate)	Oral	25–100 mg, BID	Acute pulmonary oedema, heart failure, asthma, severe atrioventricular block and severely depressed patients	17, 28
Metoprolol (succinate)	Oral	50–400 mg, QD		
Bisoprolol	Oral	2.5–10 mg, QD		
Atenolol	Oral	25–100 mg, QD		
ND-CCBs				
Diltiazem	Oral	120–360 mg QD	Severe hypotension, cardiogenic shock, second- or third-degree atrioventricular block or sick sinus syndrome without a pacemaker, patients with left ventricular systolic dysfunction and decompensated heart failure owing to their negative inotropic effects	17, 21, 28
	IV	0.25 mg/kg IV bolus over 2 min, then 5–15 mg/h		
Verapamil	Oral	120–480 mg QD		
	IV	(0.075–0.15 mg/kg) IV bolus over 2 min, then 0.005 mg/kg/min infusion		
Digitalis glycosides				
Digoxin	Oral	0.125–0.25 mg QD	Ventricular tachycardia, hypertrophic obstructive cardiomyopathy and pre-excitation syndrome combined with AF	17, 21, 28
	IV	0.25 mg IV with repeat dosing to a maximum of 1.5 mg over 24 h		
Specific indications				
Amiodarone	Oral	100–200 mg QD	Severe sinus node dysfunction, second- or third-degree atrioventricular block or bundle branch disease, syncope caused by bradycardia and diffuse interstitial pulmonary fibrosis	21, 28
	IV	300 mg IV over 1 h, then 10–50 mg/h over 24 h		

QD, once daily; BID, twice daily; IV, intravenous.

blockers (β-blockers), non-dihydropyridine calcium channel blockers (ND-CCBs), digitalis and amiodarone (Table 2).

The choice of these drugs should be based on individual characteristics and a patient's preferences. β-blockers are the preferred first-line agents for rate control during AF owing to the efficacy (lower heart rates) as well as potential survival advantage.[18] The most commonly used β-blockers are metoprolol, bisoprolol and atenolol. Contra-indications should be considered before we use β-blockers; briefly, acute pulmonary oedema, heart failure, asthma, severe atrioventricular block and severely depressed patients cannot choose β-blockers.

Commonly used ND-CCBs include diltiazem and verapamil, which are recommended for AF combined with chronic obstructive pulmonary disease or asthma. Digitalis can slow ventricular rate through increasing vagus nerve tension, so it is a reasonable alternative for those patients in whom other treatments are ineffective or contra-indicated, especially in heart failure and hypotension. Amiodarone can reduce ventricular rate due to its short-term effect in blocking calcium channels and the sympathetic nervous system, but it is not used for long-term ventricular rate control. Amiodarone can be useful for rate control when other drugs are ineffective or contra-indicated and for acute symptoms.

The latest ESC guidelines[21] use LVEF = 40% as the dividing line. Patients with LVEF ≥ 40% can use β-blockers, ND-CCBs and digitalis to control ventricular rate (Class I, level of evidence B), while β-blockers should start from a low dose for patients with LVEF < 40%, and ND-CCBs should be avoided (Class I, level of evidence B).

Prevention of stroke

Patients with AF are five times more likely to have a stroke,[22] which has long attracted the attention of clinicians. Besides, cognitive impairment, silent cerebral infarcts, memory impairment, hippocampal atrophy, Alzheimer's disease and other forms of dementia have been demonstrated at a higher prevalence in AF compared with non-AF.[23]

Anticoagulant therapy is highly recommended in preventing strokes for AF patients. CHA_2DS_2-VASc (Table 3) and HAS-BLED (Table 4) scoring systems are recommended to be used before anticoagulant therapy. There is strong evidence that patients with a CHA_2DS_2-VASc risk score of two or more in men, and three or more in women, benefit from oral anticoagulants (Class I, level of evidence A). Oral anticoagulants should be considered for men with a CHA_2DS_2-VASc score of one and women with a score of two, balancing the expected stroke reduction, bleeding risk, and patient preference (Class IIa, level of evidence B). No antiplatelet or anticoagulant therapy is recommended for men with a CHA_2DS_2-VASc score of zero and women with a score of one (Class III, level of evidence B).[21]

Low bleeding risk refers to a HAS-BLED score of two or less, while a score of three or more puts the patient at high bleeding risk. HAS-BLED score is a tool for clinicians to objectively assess the risk of bleeding in AF patients, aiming to treat reversible risk factors, especially for high-risk bleeding patients. Choices of anticoagulant drugs are new oral anticoagulants (NOACs, including the direct thrombin inhibitor dabigatran and the factor Xa inhibitors apixaban, edoxaban and rivaroxaban) and oral anticoagulants (OACs, such as warfarin).

According to the latest ESC guidelines,[21] NOACs are the preferred therapy unless contra-indications exist in patients, and OACs are secondary choices (Class I, level of evidence A). A meta-analysis[24] of NOACs versus warfarin included 42 411 participants receiving NOACs and 29 272 participants receiving warfarin. It demonstrated that NOACs significantly reduced stroke or systemic embolic events by 19% compared with warfarin (RR 0.81, 95% CI 0.73–0.91; $p < 0.0001$). NOACs also reduced all-cause mortality by 10% (0.90, 0.85–0.95; $p < 0.0001$), while gastrointestinal bleeding events were more frequent (1.25, 1.01–1.55; $p = 0.04$). NOACs had a favourable risk–benefit profile, with significant reductions in stroke, intracranial haemorrhage and mortality rates, and with similar major bleeding events to warfarin. The efficacy and safety of NOACs over warfarin seem to be even greater in East Asians compared with non-Asians.[25] But in the latest ESC guidelines,[21] warfarin is recommended for stroke prevention in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves (Class I, level of evidence B).

Combinations of OACs and platelet inhibitors increase bleeding risk and should be avoided in AF patients without another indication for platelet inhibition (Class III, level of evidence B). Aspirin is neither effective nor safe as thromboprophylaxis for AF patients, even possibly increasing stroke risk in elderly patients.[26,27] During anticoagulant therapy, monitoring the coagulation function is necessary to ensure the efficacy and safety of anticoagulants.

Direct-current cardioversion (DCC)

DCC is an effective therapy for AF patients or AF with rapid ventricular response to restore sinus rhythm. If unsuccessful, repeat DCC attempts should be made after applying pressure over the electrodes or adjusting the location of the electrodes or combining with anti-arrhythmic drugs.[28] DCC is recommended for AF patients who do not respond to pharmacological therapies, combined with heart failure or haemodynamic instability.[21,28] A study of the effect of early DCC on the recurrence of AF

Table 3. CHA_2DS_2-VASc scoring system

Risk factor	*Score*
Chronic heart failure	1
Hypertension	1
Age ≥ 75 years	2
Diabetes	1
Previous stroke/transient ischaemic attack	2
Vascular disease	1
Age 65–74 years	1
Gender category (female)	1

Table 4. HAS-BLED scoring system

Risk factor	*Score*
Hypertension	1
Abnormal renal function	1
Abnormal liver function	1
Stroke	1
Bleeding history or predisposition	1
Labile INR	1
Elderly (> 65 years)	1
Drugs concomitantly	1
Alcohol concomitantly	1

demonstrated that patients with persistent AF for less than 60 days who received early DCC had a significant reduction in AF recurrence risk, while in those with persistent AF for more than 60 days, there was no benefit of early DCC.[29]

Conversion of AF to sinus rhythm is associated with an increased risk of stroke. Two strategies of anticoagulation are available for reducing thromboembolic risk. The first is warfarin for three weeks prior to DCC and continues for four weeks after cardioversion. The second is transoesophageal echocardiography and combination treatment with an anticoagulant using heparin, enoxaparin or one of the NOACs immediately before DCC and followed by warfarin or NOACs for four weeks after cardioversion.

Radiofrequency catheter ablation (RFCA)

An important mechanism of AF is abnormal electrical activity surrounding the vestibule of the pulmonary veins (PVs). RFCA is primarily a treatment outcome achieved through isolation of the PVs. A long-term follow up showed the rate of freedom from atrial arrhythmia with a single procedure was 54.1% in paroxysmal AF patients and 41.8% in patients with non-paroxysmal AF. With multiple procedures, the long-term success rate improved to 79.8%.[30] Collective data from a number of randomised clinical trials had demonstrated the superiority of RFCA over drug therapies in maintaining sinus rhythm, reducing cardiovascular events, and improving quality of life.[31,32]

RFCA is highly recommended for symptomatic paroxysmal AF patients aiming to prevent recurrent AF and improve symptoms, especially when anti-arrhythmic drug therapy is unsuccessful. It is also a reasonable alternative for those symptomatic AF patients with heart failure, low ejection fraction or AF-related bradycardia.

A worldwide survey of 85 institutions indicated a 4.5% rate of major complications of RFCA. Specifically, the rate of procedure-related deaths was 0.15%, stroke or transient ischaemic attack were 0.94%, cardiac tamponade was 1.31% and atrial–oesophageal fistula was 0.04%.[33] RFCA is a therapy that highly depends on clinicians' experience and skill, which are related to the success rate and incidence of complications. Individual characteristics, patient preferences, as well as experience and skill of the clinician should be taken into consideration before making a decision.

Cryoballoon ablation

Catheter ablation using technical requirements with three-dimensional mapping systems with a point-by-point ablation strategy is time-consuming, and clinical outcomes and complications depend on the operator's experience and skill. To overcome these limitations, cryoballoon ablation was developed.[34] As a single-shot device, cryoballoon ablation markedly simplifies the ablation procedure and shortens the procedure time.[35]

Cryoablation systems work by delivering liquid nitrous oxide under pressure through the catheter to its tip or within the balloon, where it changes to gas, resulting in cooling and damage to the surrounding tissue, thus resulting in a reduction in the risk of AF.[36] A first-generation cryoballoon (CB-1) was released in 2010 and the more developed second-generation cryoballoon (CB-2) was developed in 2012. The one-year success rate of CB-2 was improved from CB-1, and the complication rates decreased in the former.[36]

Data from recent studies have demonstrated the clinical benefit of cryoballoon ablation for paroxysmal AF patients.[35,37] It is a promising, effective and safe alternative technique for paroxysmal AF patients. However, cryoablation is specially designed for dissection of the pulmonary artery. Pulmonary vein isolation is the cornerstone of cryoablation and other treatments should be considered for AF that does not originate in the pulmonary veins.

Left atrial appendage closure (LAAC)

Studies have shown that 91% of strokes occur in the left atrial appendage of non-rheumatic AF patients and 57% in rheumatic AF patients.[38] This understanding has prompted the development of novel percutaneous strategies for LAAC as an alternative to anticoagulation therapy for AF patients. Briefly, LAAC is recommended for elderly patients and those who can tolerate short-term anticoagulation but are not optimal candidates for long-term anticoagulation.[39]

A meta-analysis that compared LAAC with warfarin for stroke prevention in AF included 2 406 patients with a mean follow up of 2.69 years. It found that Watchman LAAC had significantly fewer haemorrhagic strokes and better clinical outcomes compared with warfarin therapy.[40] A network meta-analysis found that Watchman LAAC and NOAC therapy were both superior to warfarin for preventing haemorrhagic strokes, and that there were no significant differences in clinical outcomes between Watchman LAAC and NOACs.[41] According to the latest ESC guidelines, LAAC is a good alternative for AF patients with contra-indications to OAC (Class IIB, level of evidence B).

Surgical management

The Cox maze I procedure, introduced by James Cox in 1987, interrupted the aberrant re-entrant circuits in the atrium by 'cutting and sewing'. After iterative improvements, Cox maze I was modified into the Cox maze III procedure.[42] But the Cox maze III did not gain widespread acceptance due to its complexity and technical demand. It is mainly used in AF patients undergoing open-heart surgical procedures. Development in technology led to shortening and simplification of the operation to the Cox maze IV, which utilises new ablation technologies to replace the 'cut-and-sew' technique, and has decreased morbidity and mortality rates.[43] Cox maze IV is currently the gold-standard surgical treatment for AF, with a 93% freedom from AF at one year, and a 78% freedom from AF at five years.[44]

The totally thoracoscopic maze procedure (TT-maze) was developed in 2003. It was a minimally invasive alternative for treating AF with limited complications and high success rates.[45] Future studies are needed to determine whether the high success rates after TT-maze are stable over time.

Conclusions

Management of AF has evolved greatly in the past few years and there have been substantial advances and developments, which help clinicians to deliver better care to AF patients (Fig. 1). Treatment of AF is an individual therapy and the characteristics and willingness of patients, as well as the experience and skill of

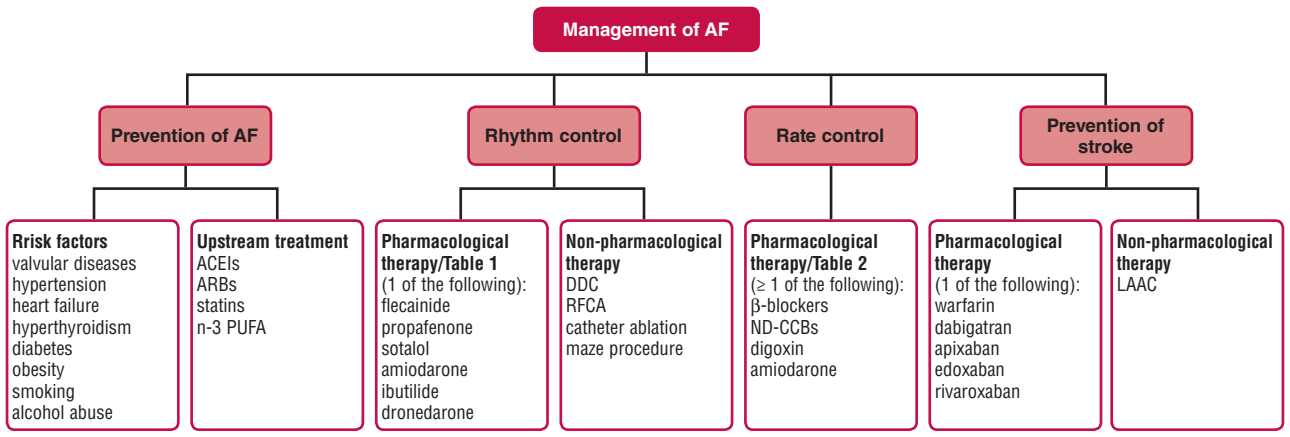

Fig. 1. Overview of management of AF.

the clinician should be taken into consideration before making a decision.

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