Management of atrial fibrillation

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Atrial fibrillation is the most common sustained cardiac rhythm disorder, and confers a substantial mortality and morbidity from stroke, thromboembolism, heart failure, and impaired quality of life. With the increasingly elderly population in the developed world, as well as improvements in the management of myocardial infarction and heart failure, the prevalence of atrial fibrillation is increasing, resulting in a major public-health problem. This Review aims to provide an overview on the modern management of atrial fibrillation, with particular emphasis on pharmacological and non-pharmacological approaches. Irrespective of a rate-control or rhythm-control strategy, stroke prevention with appropriate thromboprophylaxis still remains central to the management of this common arrhythmia. Electrophysiological approaches could hold some promise for a curative approach in atrial fibrillation.

Atrial fibrillation is the commonest sustained cardiac rhythm disorder, which results in a substantial mortality and morbidity from stroke, thromboembolism, heart failure, and impaired quality of life.[1,2] With the population in developed countries becoming increasingly elderly, as well as improvements in the management of myocardial infarction and heart failure, the prevalence of atrial fibrillation is substantially increasing.

What is our risk of developing atrial fibrillation? In the Framingham study,[3] the lifetime risks at age 40 years for developing the disorder were 26% (95% CI 24–27%) for men and 23% (21–24%) for women. In patients without prior or concurrent congestive heart failure or myocardial infarction, lifetime risks for atrial fibrillation were about 16%. Similar estimates of the epidemiology and lifetime risk of developing atrial fibrillation have been reported from the Rotterdam study,[4] in which the overall prevalence was 6%, rising from 1% in the age group 55–59 years to 18% in individuals aged 85 years and older. Incidence in individuals aged 55–59 years was 1·1 per 1000 person-years, rising to 20·7 per 1000 person-years in those aged 80–84 years. The lifetime risk of developing atrial fibrillation at age 55 years was 25% in men and 22% in women. Thus, the lifetime risks for the development of the disorder are about one in four for men and women aged 40 years and older. Furthermore, community surveys[5] have shown a rising occurrence of atrial fibrillation by 13% during the past two decades, and project that 15·9 million people in the USA will have the disease by 2050.

With such a common problem, a screening programme for atrial fibrillation has been advocated. The largest contemporary screening study for this condition is the Screening for Atrial Fibrillation in the Elderly (SAFE) study.[6] In this multicentre, randomised controlled trial, researchers investigated the role of systematic or opportunistic screening for atrial fibrillation. Baseline prevalence of this condition was 7%, with an increased prevalence in men (8%) and patients aged 75 years and older (10%). The only strategy that improved on routine practice was opportunistic screening, which was the most effective and cost-efficient method.

The clinical epidemiology of atrial fibrillation has been reported from population-based and hospital-based series.[1] Atrial fibrillation is common among admissions, being present in 3–6% of acute medical admissions and accounts for a third of admissions for cardiac arrhythmias. In the postoperative setting (especially after cardiothoracic surgery), the disorder can be present in about a third of patients, leading to more complications (eg, heart failure, thromboembolism) and extended hospital stay.[1,7] Only a third of patients with atrial fibrillation have presented to hospital,[8] and thus, epidemiological studies based on hospital series might not indicate the true picture of the epidemiology of the disorder.

This difference in clinical epidemiology is evident by the common associated medical conditions with atrial fibrillation, for example, hypertension being the most common causal factor associated with the disease on a population basis, whereas in hospital series, coronary artery disease and heart failure are the most common associated features.[1,8] Also, much of the epidemiology of atrial fibrillation is based on studies in white populations, and the scarce data available suggests a reduced prevalence of the disorder in black Afro-Caribbeans (in whom hypertension is the main causal factor) and south Asians (in whom coronary artery disease is the most common causal factor).[9]

This Review aims to provide an overview of management of atrial fibrillation, focusing on pharmacological and non-pharmacological approaches to manage this common arrhythmia. Many detailed management guidelines for atrial fibrillation have been published, such as the updated expert consensus-based 2006 guidelines for the management of patients with atrial fibrillation, from the American College of Cardiology (ACC), American Heart Foundation (AHA), and European Society of Cardiology (ESC).[10] In the UK, the evidence-based NICE (National Institute for Health and Clinical Excellence) Guidelines on atrial fibrillation management were formally published in June, 2006, and the full version provides systematic reviews and critical appraisal of the evidence behind the guideline recommendations.[11] The American College of Chest Physicians (ACCP) has published consensus guidelines on antithrombotic treatment for atrial fibrillation.[12] The American Academy of Family Physicians and the American College of Physicians have also published clinical practice guidelines for the management of newly detected atrial fibrillation.[13] Furthermore, extensive work

For the **NICE Guidelines on atrial fibrillation management** see http://www.nice.org.uk/page.aspx?o=cg36

has been done on the underlying pathophysiology of atrial fibrillation, including haemodynamic considerations and electrophysiology of the disorder.[14–16]

Management strategies for atrial fibrillation

In most patients, atrial fibrillation can be easily recognised from the surface electrocardiogram with the presence of rapid, irregular fibrillatory waves, and irregular ventricular response. However, electrocardiogram appearances between atrial fibrillation, atrial flutter, and atrial tachycardia greatly overlap.

The clinical presentation of atrial fibrillation can be classified on the basis of the temporal pattern of the arrhythmia.[10,11] Recurrent atrial fibrillation occurs when a patient develops two or more episodes of the disorder, which could be paroxysmal or persistent in nature. Paroxysmal atrial fibrillation is diagnosed if the episodes stop spontaneously within 7 days, but is regarded as persistent if electrical or pharmacological cardioversion is needed to stop the arrhythmia. Permanent atrial fibrillation occurs when the patient remains in the arrythmia, when the cardioversion is not successful or deemed inappropriate. An inappropriate cardioversion would be, for example, due to contraindications to anticoagulation, structural heart disease (eg, large left atrium >5·5 cm, mitral stenosis) that precludes long-term maintenance of sinus rhythm, a long duration of atrial fibrillation (usually >12 months), a history of many failed attempts at cardioversion or relapses (or both) even with concomitant use of antiarrhythmic drugs or non-pharmacological approaches, and a continuing but reversible cause of atrial fibrillation (eg, thyrotoxicosis).[11]

Irrespective of the temporal classification, the management of patients with atrial fibrillation should broadly be guided by symptoms, the presence or absence of haemodynamic compromise, and associated comorbidities.[17] The clinical subtypes of atrial fibrillation and patients' symptoms help define the objectives of management and therapeutic strategies (figure 1).[11,17] Irrespective of clinical subtype of atrial fibrillation, appropriate antithrombotic treatment is mandatory, based on risk factors for stroke and thromboembolism. In paroxysmal and persistent atrial fibrillation, either rhythm-control or rate-control approaches can be initially applied, and a large proportion of patients will need both. In patients given a rate-control strategy, the objective is heart rate control of the ventricular response, and hence, drugs (or non-pharmacological approaches) are used. For rhythm control in patients with paroxysmal atrial fibrillation, the objective of management is the reduction of paroxysms and the long-term maintenance of sinus rhythm, and thus, antiarrhythmic drugs (AADs), or non-pharmacological approaches are used. In persistent atrial fibrillation, the management objective is sinus rhythm restoration, and hence, cardioversion (either pharmacological or electrical) is attempted.

Nevertheless, this subdivision is a simplistic (and arguably, artificial) one, since even permanent atrial fibrillation can be successfully eliminated by catheter and surgical ablation, even in the setting of pronounced structural heart disease, especially with concomitant antiarrhythmic drug treatment. This classification system merely gives an idea of the time course of atrial fibrillation, but not the ultimate clinical outcome, and re-emphasises that management of the disorder should be guided by symptoms. Notably, many patients with atrial fibrillation progress to permanent atrial fibrillation, and older age at diagnosis is an independent predictor of progression on multivariate analysis.[18]

New onset of atrial fibrillation

Many patients with atrial fibrillation of recent onset convert spontaneously to sinus rhythm at presentation. Patients who remain in atrial fibrillation and develop haemodynamic unstability due to rapid ventricular rates should undergo emergency cardioversion. These patients usually have pre-excitation syndrome or have a very quick ventricular rate or pronounced structural heart disease, such as severe valvular heart disease, congestive heart failure, or acute myocardial ischemia. Figure 2 summarises a treatment strategy for acute atrial fibrillation.

Acute ventricular rate control

Acute ventricular rate control is needed to improve haemodynamic status and relieve symptoms. Based on a pooled analysis from Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) and RACE (RAte Control *vs* Electrical cardioversion),[19] a target resting heart rate of less than 100 beats per min should be achieved by intravenous or oral use of atrioventricular (AV) nodal blocking drugs (verapamil and diltiazem, β blockers, and digoxin). Webtable 1 lists the dosage, side-effects, and indications for different AV nodal blocking drugs. When rapid control of ventricular rate is needed or oral use of medication is not feasible, intravenous drugs are needed.

See Online for webtable 1

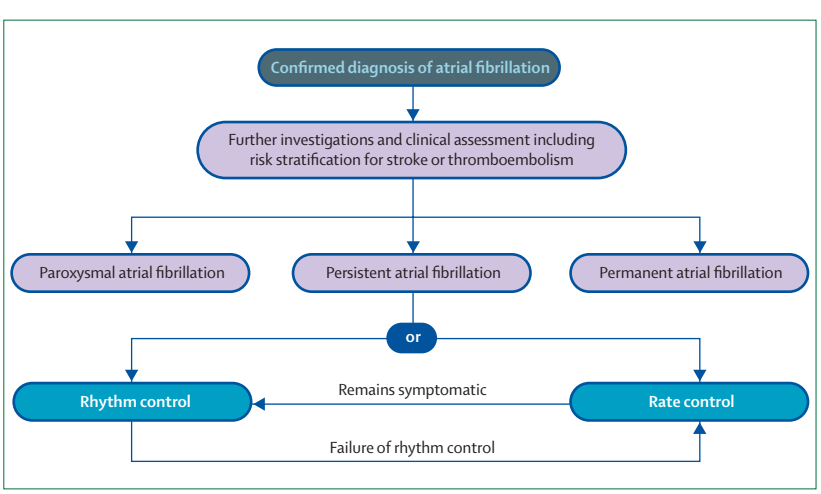

Figure 1: **Treatment strategy for atrial fibrillation**
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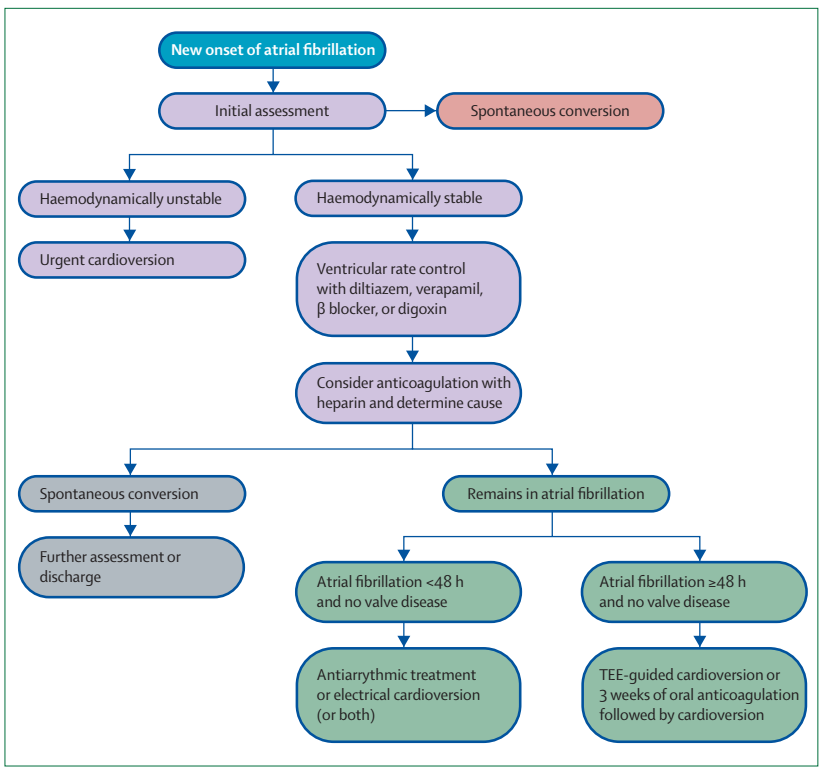

Figure 2: **Management of new onset of atrial fibrillation**
TEE=transoesophageal echocardiography.

See Online for webtable 2

The non-dihydropyridine (or rate-limiting) calcium-channel blockers, verapamil and diltiazem, extend the AV nodal refractory period to slow AV nodal conduction, and are effective agents for ventricular rate control during atrial fibrillation. Since intravenous verapamil has more potent negative inotropic and peripheral vasodilator effects, intravenous diltiazem has became more popular for the control of acute ventricular rate during atrial fibrillation, especially in patients with mild left-ventricular (LV) dysfunction or hypotension. Intravenous β blockers (esmolol, metoprolol, or propranolol) are also effective AV nodal blocking drugs through their sympatholytic properties. The β blockers are especially effective in conditions in which the rapid ventricular rate is due to heightened adrenergic tone, such as in the postoperative periods. Apart from esmolol, all the β blockers have a slower onset of action than diltiazem. Intravenous esmolol has a very short half-life that needs careful monitoring and titration of dose. Both β blockers and calcium-channel blockers should be used with caution in patients with hypotension or heart failure.

In patients with acute heart failure and atrial fibrillation, relief of pulmonary congestion by diuretics and vasodilators could aid in decreasing the heart rate. Digoxin has both negative chronotropic and positive inotropic effects and therefore is an appropriate first-line drug in patients with heart failure and atrial fibrillation.[20] In patients with hypotension, digoxin is a useful alternative to β blockers or calcium-channel blockers that might further reduce blood pressure. Since the effect of digoxin on ventricular rate is mediated by its vagotonic effect on the AV node, the onset of action could take several hours. For the same reason, digoxin is usually ineffective during acute settings with high catecholamines status, such as postoperative status, acute sepsis, myocardial ischemia, and pulmonary diseases.[20] In patients in whom monotherapy is adequate, different combinations of therapy with digoxin, β blockers, and rate-limiting calcium-channel blockers might be needed to achieve acute or chronic ventricular rate control. However, a combination of β blocker with verapamil should be avoided, because of a risk of ventricular asystole. Furthermore, permanent pacing might be needed in some patients who develop symptomatic bradycardia after rate-control drug treatment.

Intravenous use of digoxin, β blockers, and calcium-channel blockers is contraindicated for atrial fibrillation associated with pre-excitation, such as in Wolff-Parkinson-White syndrome. In haemodynamically stable patients with Wolff-Parkinson-White syndrome and atrial fibrillation, intravenous use of the AADs, flecainide or amiodarone, can be used. In critically ill patients with severe heart failure or hypotension in whom other drugs are ineffective or contraindicated for ventricular rate control, intravenous amiodarone is a safe and effective alternative. For use of intravenous amiodarone, an initial loading dose followed by a maintaining dose of infusion (webtable 2) should be given via a central venous line to avoid thrombophlebitis. The potential side-effects of intravenous amiodarone include hypotension and bradycardia.

In patients with acute atrial fibrillation who have no contraindications and are not receiving therapeutic anticoagulation, heparin should be initiated if medical or electrical cardioversion is planned. Patients should then receive detailed assessment for the need of long-term antithrombotic treatment based on stroke risk stratification, as described later.

Cardioversion

Within the first 24 h, up to 50% of patients with new onset of atrial fibrillation convert back to sinus rhythm.[21] If the patient does not convert spontaneously, pharmacological or electrical cardioversion should be attempted. Generally, in patients with non-valvular atrial fibrillation lasting less than 48 h, cardioversion can be safely done with a low risk of thromboembolism after anticoagulation with heparin. Care is needed to determine the precise onset of atrial fibrillation, since some patients could develop their current episode asymptomatically, and might only present when symptoms develop,

In patients with atrial fibrillation lasting more than 48 h or in those with a raised risk of thromboembolism due to underlying heart disease, 3 weeks of oral anticoagulation with an INR (international normalised ratio) of 2·0 or more before cardioversion is recommended. Alternatively,

transoesophageal echocardiography to exclude atrial thrombi allows immediate cardioversion with intravenous unfractionated heparin or low-molecular-weight heparin cover.[10–12,22] Use of low-molecular-weight heparin could simplify the treatment regimen, and allow early hospital discharge after cardioversion.[23] When the left atrial appendage cannot be adequately seen, cardioversion should be done after 3 weeks of therapeutic anticoagulation. Anticoagulation with warfarin should then be continued for a minimum of 4 weeks' postcardioversion to prevent thrombi formation due to atrial stunning in the postcardioversion period. Anticoagulation pericardioversion decreases the overall risk of stroke from 6–7% to less than 1%. Current clinical practice recommends that anticoagulation should be continued for life in patients at high risk of thromboembolism or with risk factors for atrial fibrillation recurrence. Risk factors for recurrence include: a history of unsuccessful cardioversion, structural heart disease (mitral valve disease, LV dysfunction, or an enlarged left atrium), a history of atrial fibrillation of more than 12 months, and previous recurrences of atrial fibrillation.[10–12]

If the episode of atrial fibrillation lasts for more than 7 days, the chance of spontaneous cardioversion is greatly reduced. In such cases, persistent restoration of sinus rhythm can almost always be achieved by electrical or pharmacological cardioversion. In episodes of recent onset (<48 h), either pharmacological or electrical cardioversion can be used as the initial strategy, since they have a similar effectiveness, but cardioversion of atrial fibrillation episodes of longer duration might be best done with electrical cardioversion. The potential advantage of pharmacological cardioversion is avoidance of anaesthetics and can prevent early recurrence of AF. The disadvantage of the procedure is that effectiveness of pharmacological methods is low if atrial fibrillation is 48 h or longer, and proarrhythmia during cardioversion could occur. Electrical cardioversion has an acute success rate of 90%, but will need sedation or general anaesthesia.

Several AADs can be used for pharmacological cardioversion with variable success (webtable 2). For atrial fibrillation lasting less than 48 h, oral or intravenous use of class I or III AADs can achieve conversion to sinus rhythm in 47–84% of patients within 24 h.[21] For atrial fibrillation episodes of longer duration, only 15–30% of patients convert to sinus rhythm with pharmacological cardioversion.[10,11] The choice of AAD is based on the presence or absence of underlying structural heart disease (figure 3). In patients with structural heart disease, such as coronary artery disease and LV dysfunction, class I AADs are contraindicated because of a perceived increase in proarrhythmia risk. However, the only strong evidence for the adverse effects of class 1 AADs is in patients with myocardial infarction, but this result has been interpreted as being due to myocardial scarring and the proarrhythmic tendency of these drugs.[24]

If pharmacological cardioversion fails, external electrical cardioversion can still be done to restore sinus rhythm. The two approaches can also be combined: an initial trial of AADs, followed by external cardioversion if the drug fails. Furthermore, pretreatment with class IC (flecainide, propaferone) and class III AADs (amiodarone, ibutilide, sotalol) can help electrical cardioversion and prevent recurrent atrial fibrillation.[10,11,25] In the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) trial,[25] for example, amiodarone and sotalol were equally efficacious in converting atrial fibrillation to sinus rhythm. Amiodarone was better at maintaining sinus rhythm than sotalol, but both drugs had a similar efficacy in patients with ischaemic heart disease.

Patients have a small risk of bradycardia after electrical cardioversion, if AADs are used. Thus, drugs such as digoxin (if used) are stopped the day before an elective electrical cardioversion procedure. In SAFE-T,[25] sustained sinus rhythm was associated with an improved quality of life and improved exercise performance.[26]

Rate control versus rhythm control

Several clinical trials[27–30] comparing the strategies of rhythm control with rate control for atrial fibrillation, as well as meta-analyses,[31–34] have shown no significant differences between the two strategies with respect to mortality, major bleeding, and thromboembolic events, at least on an intention-to-treat analysis. A non-significant trend was seen for excess mortality with a rhythm-control strategy in the AFFIRM trial.[29] For functional endpoints, four trials

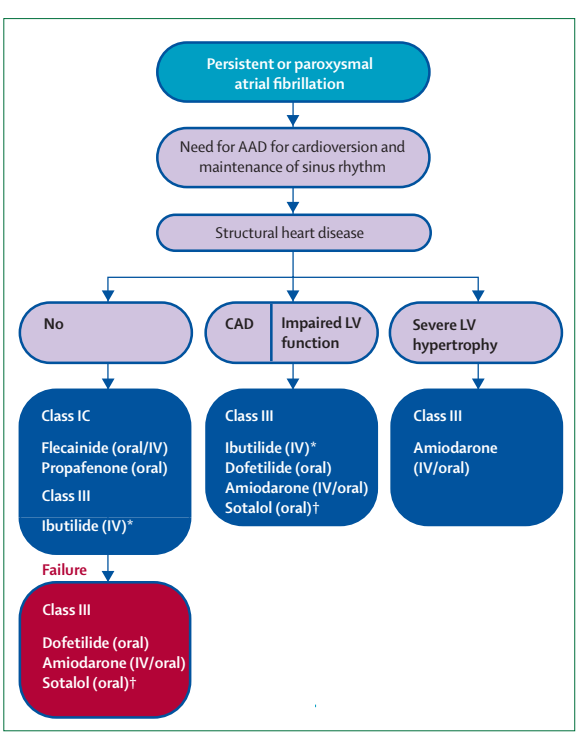

Figure 3: **Algorithm for AAD choice for cardioversion of atrial fibrillation and maintenance of sinus rhythm**
IV=intravenous. *For acute chemical cardioversion only. †For maintenance of sinus rhythm in patients with normal LV function.

have shown some improvement in exercise capacity in the rhythm-control group,[27–30,35] which is reinforced by the SAFE-T trial,[26] in which restoration and maintenance of sinus rhythm in patients with persistent atrial fibrillation was associated with improvements in quality-of-life measures and exercise performance. However, a recent systematic review[2] on quality of life in atrial fibrillation concluded that the published data were frequently compromised by various procedural weaknesses, but although patients with atrial fibrillation generally have impaired quality-of-life measures, this result could be improved greatly by both rate control or rhythm control, although the benefit of either strategy was unclear. Notably, the costs, need for hospital care, and adverse drug effects have been shown to be have much improved effect with a rhythm-control strategy.[36]

Nevertheless, these studies have highlighted the low clinical efficacy and potential adverse effects of current AADs to maintain sinus rhythm, which probably contributes to the stroke risk associated with rhythm control. Indeed, an on-treatment analysis[37] of AFFIRM showed that the presence of sinus rhythm (with or without AADs) was associated with a significant reduction in the risk for death, but AAD use was associated with increased mortality. Indeed, the availability of AADs that are more effective and safe would probably improve outcomes in atrial fibrillation. In AFFIRM, the risk of ischaemic stroke was strongly related to the absence of or suboptimum anticoagulation treatment.[38] Therefore, independent of the use of rate-control or rhythm-control strategies, anticoagulation treatment is still important to the management of patients with atrial fibrillation and stroke risk factors.

However, some caution should be given before the data from trials comparing rate control and rhythm control are extrapolated to all individuals with atrial fibrillation. In these trials, many patients in the rhythm-control groups did not maintain rhythm control, but were analysed on an intention-to-treat basis. Most participants were older patients (eg, age 60–70 years) with risk factors for stroke and other comorbidities also, or had previous failed attempts at rhythm control. Only a small proportion had valvular heart disease, heart failure, and symptomatic paroxysmal atrial fibrillation. Treatment crossover from rhythm control to rate control was also common. Indeed, a group of younger patients (eg, age <40 years) with valvular heart disease and atrial fibrillation showed a significant benefit of rhythm control with respect to reduction in mortality and improvement in functional class, quality of life, and exercise time.[39] Therefore, different subsets of patients with atrial fibrillation, both young and old, are potential candidates for maintenance of sinus rhythm. Also, some patients with persistent atrial fibrillation will satisfy criteria for either an initial rate-control or rhythm-control strategy, but the high prevalence of the disorder, inadequate capacity for catheter or surgical ablation procedures, and paucity of conclusive evidence for maintaining sinus rhythm in the long-term and toxic effects associated with AADs, could prompt pragmatic choices favouring either one or the other management strategy, depending on patients' attributes and choices. The NICE guidelines[11] suggest that a rate-control strategy should be the preferred initial option in patients with persistent atrial fibrillation with the following characteristics: older than 65 years with coronary artery disease, with contraindications to AADs, with no congestive heart failure, and unsuitable for cardioversion. By contrast, a rhythm-control strategy should be the preferred initial option for persistent atrial fibrillation in: symptomatic patients, younger patients (eg, age <65 years); those presenting for the first time with lone atrial fibrillation; and those with the disorder that is secondary to a treated or corrected precipitant. These categories are not mutually exclusive, and the strategy to adopt should account for any comorbidities, symptoms, and preferences by the patient.

In appropriate circumstances, the possibility to restore sinus rhythm (eg, by catheter ablation) can be considered, especially in symptomatic patients.

Restoration and maintenance of sinus rhythm

Restoration of sinus rhythm can be achieved by either pharmacological or electrical cardioversion. As already discussed, if atrial fibrillation persists (eg, for >7 days), the effectiveness of pharmacological cardioversion is low and electrical cardioversion is usually needed to restore sinus rhythm. Electrical cardioversion delivers external transthoracic synchronised electrical shock. Its success in atrial fibrillation varies with underlying heart disease (eg, mitral-valve disease, which could lower success rates) and methods of cardioversion. With recent advances of biphasic defibrillation, up to 90% success of restoring sinus rhythm can be achieved in selected patients with atrial fibrillation.[40] As previously discussed, all patients with persistent atrial fibrillation should receive appropriate anticoagulation treatment before and after cardioversion.

A more difficult task is to maintain sinus rhythm after successful cardioversion. Some patients might not have recurrence after one episode of atrial fibrillation, especially in those with clear precipitant of the disorder (which has been corrected or treated—eg, chest infection) and in whom no chronic form of drug treatment is needed after cardioversion. However, in most patients cardioverted from chronic atrial fibrillation, early and later recurrence of the disorder without AAD treatment is high. The efficacy of different AADs are similar and only about 50% of patients remain in sinus rhythm, with the possible exception of amiodarone. Use of sequential AADs and repeated cardioversion has been suggested to increase the proportion of patients successfully treated and maintained in sinus rhythm,[41] although whether sinus rhythm is maintained by repeated defibrillation or by differing drug efficacy is unclear. Furthermore, some caution is needed for potential adverse effects if AADs

are used to suppress atrial fibrillation, and the choice of long-term drug depends on the underlying comorbidities (figure 3). For example, class I AADs should be avoided in patients with structural heart disease, and the long-term adverse effects of AADs should be considered (webtable 2). Risk for drug-induced torsades de pointes (Tdp) is enhanced by metabolic disturbances (hypokalaemia, hypomagnesaemia), LV dysfunction, history of ventricular tachycardia, prolongation of QT interval, and bradycardia.

In patients with systolic heart failure, amiodarone and dofetilide have proven to be safe and effective for maintenance of sinus rhythm.[42,43] However, the use of dofetilide needs in-hospital initiation and monitoring for QT prolongation. Amiodarone seems to have a lower risk of proarrhythmia (<1%) than other AADs, but has serious extracardiac adverse effects, such as pulmonary fibrosis, hepatic and thyroid dysfunction, and neurological and dermatological effects, especially at high doses and after extended long-term use. Furthermore, amiodarone increases plasma amounts of warfarin, digoxin, and many other drugs, and their doses should be reviewed.[44] Because of its unfavourable long-term side-effect profile, amiodarone should be used in patients with clinically significant heart disease as a last resort, after failure with other drugs. Dronedarone is a non-iodinated amiodarone derivative that has a similar profile, but has more potent electrophysiological properties and lower extracardiac toxicity than amiodarone. Preliminary data suggest that dronedarone is more effective than placebo for maintenance of sinus rhythm and control of ventricular rate in patients with atrial fibrillation.[45] Continuing randomised controlled trials will address the long-term safety and efficacy of dronedarone for treatment of atrial fibrillation.

Patients with self-terminating, recurrent atrial fibrillation often pose a management problem. In the major clinical trials comparing rate control and rhythm control, only about 25% of patients had paroxysmal atrial fibrillation and highly symptomatic patients were excluded. Therefore, little data are available in guiding the treatment in those patients. In patients with infrequent paroxysmal atrial fibrillation and without structural heart disease, a pill-in-the-pocket strategy with the use of class IC AADs (single oral dose of 600 mg propafenone or 300 mg flecainide) during the acute attack of atrial fibrillation could be considered in patients in whom this strategy has proven safe in hospital.[46] Use of concomitant β blockers, non-dihydropyridine calcium-channel blockers, or digoxin are also recommended to avoid rapid AV conduction in the event of atrial flutter.

Nevertheless, many treated patients will continue to have symptomatic arrhythmia, and suppression of symptomatic episodes of atrial fibrillation might not abolish the arrhythmia itself, since many of these patients still have asymptomatic episodes that could be associated with an increased risk of thromboembolism.[47]

Concomitant disease

In patients with concomitant diseases, including hypertension, diabetes mellitus, thyroid disease, heart failure, and coronary artery disease, medical treatment should be at its best. Furthermore, specific treatment in some of these conditions might further prevent atrial fibrillation, or even reduce recurrence after cardioversion. For example, in patients with LV hypertrophy or heart failure, blockade of the renin-angiotensin-aldosterone system (RAAS) with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers have shown to prevent atrial fibrillation.[48,49] In patients with coronary artery disease or LV dysfunction, recent studies[50,51] have also suggested that statin treatment might also prevent atrial fibrillation. Patients with hypertension need good blood pressure control, and one recent analysis[52] in anticoagulated patients with atrial fibrillation showed that the event rates for stroke and systemic embolism substantially increase at a mean systolic blood pressure of more than 140 mm Hg.

Thyroid disease is closely associated with atrial fibrillation, and hyperthyroidism could be an unrecognised cause of the arrhythmia in elderly patients. In population studies, low amounts of serum thyroid-stimulating hormone are associated with subsequent development of atrial fibrillation,[53] and where thyroid disease is present, the abnormality must be corrected before use of cardioversion to sinus rhythm.

Non-pharmacological approaches

The limited efficacy and proarrhythmic risks of AADs have led the exploration of a wide range of alternative non-pharmacological treatments to treat atrial fibrillation. Furthermore, recent observations on the mechanisms of atrial fibrillation have resulted in the development of different non-pharmacological treatment directed to eliminate the triggers and to modify the electrophysiological substrate for the prevention and treatment of the disorder. Table 1 summarises the indications and potential adverse effects of such non-pharmacological treatments. In some patients, combined pharmacological and non-pharmacological treatments (hybrid therapy) could be needed for successful rhythm control.[54]

Surgical maze procedure

This surgical approach was designed to create conduction barriers at the critical area and reduce the critical mass within the left and right atria to prevent maintenance of atrial fibrillation. Based on animal and human mapping studies, Cox[55] described the surgical maze procedure, which involved encircling the pulmonary veins and multiple linear atrial incisions over both atria using either the classic cut-and-sew technique or different energy probes (radiofrequency, microwave, ultrasound, cryoablation, or laser) for curative ablation of atrial fibrillation. The reported success rate of surgical maze procedure ranges from 85% to 95%, and no significant difference was seen between different techniques.[56] Furthermore, with the removal or

closure of the left atrial appendage together with maintenance of sinus rhythm, the long-term stroke rate after the surgical maze procedure is low (<1%).[55–57] The potential adverse effects of surgical procedures include sinus node dysfunction needing permanent pacing (about 6%), postoperative bleeding needing reoperation (about 5%), stroke (about 0·5%), atrial arrhythmias (30%) and atrioesophageal fistula (<1%) and operative mortality (2–4%), especially in elderly patients.[55–57] Currently, most surgical maze procedures are done in patients with atrial fibrillation undergoing concomitant open-heart surgery such as mitral valve surgery or bypass surgery.[55] Recent modification of the surgical procedure with the use of thoracoscopic techniques and different energy ablation probes to a less invasive and simplified approach, including a shortened procedure time and improved safety, are more acceptable alternatives for a wider population of patients with atrial fibrillation.

Device therapies—atrial pacing and defibrillation

The use of permanent atrial pacing to treat paroxysmal atrial fibrillation in patients without conventional indications for pacing has not been proven.[58] In patients with conventional indications for pacemaker implantations—such as sinus node disease, symptomatic bradycardia, and chronotropic incompetence—the use of a physiological pacemaker (dual-chamber or atrial) rather than a single-chamber ventricular pacemaker has been shown to prevent atrial fibrillation.[59] Although many of the more recent pacemakers and implantable ventricular defibrillators have incorporated different features (overdrive pacing, antitachycardia atrial pacing, and atrial defibrillation) designed to prevent and stop atrial fibrillation, no consistent data from large randomised trials support their use. Some of these new devices are also not mainly directed towards the atrial fibrillation itself, but towards bradycardias and ventricular arrhythmias. Alternative single-site atrial pacing, multisite right atrial pacing, and biatrial pacing have also been tested for treatment and prevention of atrial fibrillation, but no studies have convincingly shown a substantial benefit on long-term clinical outcomes.[60]

Currently, stand-alone atrial defibrillators have no role in the treatment of atrial fibrillation. In patients implanted with an implantable cardioverter defibrillator for primary or secondary prevention of ventricular tachyarrhythmias, the appropriate use of a physician-activated or patient-activated shock-therapy device could effectively stop atrial fibrillation and reduce the burden of the disease.[61]

Catheter ablation

Ablation of AV node and permanent pacing is effective for symptomatic relief or rate control (or both) in patients with medically refractory atrial fibrillation or who are unable to tolerate pharmacological treatment. In a meta-analysis of 21 studies,[62] significant improvements were recorded after ablation and pacing therapy in quality-of-life and clinical outcome measures (apart from fractional shortening), and the total and sudden death mortality rates at 1 year were calculated as 6·3% and 2·0%, respectively. However, this approach creates pacemaker dependency, needs lifelong anticoagulation treatment, and is associated with proarrhythmia. The loss of AV synchrony could adversely affect the haemodynamics and symptoms in patients with associated diastolic dysfunction. However, such ablation procedures are commonly considered in patients with atrial fibrillation in whom other therapies failed to achieve either rate control or rhythm control and in those who already have an implanted pacemaker or defibrillator. In patients with symptomatic heart failure after right ventricular pacing or irreversible LV systolic function, biventricular devices after AV nodal ablation seems to improve functional capacity and LV function.[63]

	Current indications	Adverse effects
Surgical maze procedures	Patients with atrial fibrillation undergoing concomitant open-heart surgery such as mitral valve surgery or bypass surgery	Sinus-node dysfunction needing permanent pacing (about 6%) Postoperative bleeding (about 5%) Stroke (about 0·5%) Postoperative arrhythmias (about 30%) Operative mortality (2–4%)
Device therapies		
Atrial pacing	In patients with conventional indications for pacemaker implantations	..
Defibrillator	In patients with conventional indications for implantable cardioverter defibrillator	Shock discomfort Early reinitiation of atrial fibrillation
AV nodal ablation and permanent pacing	Symptomatic patients refractory to other rate-control and rhythm-control treatments Patients who already have an implanted pacemaker or defibrillator	Pacemaker dependence Sudden death early after ablation (<0·1%)
Catheter ablation	Symptomatic patients refractory to AADs Younger patients (eg, age <60 years) with lone atrial fibrillation Patients unable or unwilling to take long-term AADs	Vascular access complications (1%) Stroke and transient ischaemic attack (1%) Pronounced pulmonary-vein stenosis (0·5–1%) Proarrhythmia (10–20%) Rare: valvular, phrenic-nerve injury, and oesophagus injury

Table 1: **Non-pharmacological treatment for atrial fibrillation**

Based on the success of the surgical approach and the recognition that pulmonary veins are a common source of rapidly depolarising arrhythmogenic foci that induce paroxysmal atrial fibrillation,[64] catheter ablation strategies to treat atrial fibrillation aim to eliminate the triggers that initiate or perpetuate the disease and to modify atrial substrate that sustain the disease. In patients with paroxysmal atrial fibrillation, arrhythmogenic foci from the pulmonary veins, or less commonly from other atrial sites (superior vena cava, coronary sinus, left atrial posterior wall, vein of Marshall, and interatrial septum), could be important in the mechanism of the disease. Therefore, elimination of these arrhythmogenic foci can achieve a highly successful rate (80–90%) in patients with paroxysmal atrial fibrillation.[65,66] In patients with persistent atrial fibrillation, the substrate for arrhythmia and changes in the substrate due to electrical remodelling induced by the disease become more important. Therefore, compared with paroxysmal atrial fibrillation, a curative ablation approach for persistent atrial fibrillation needs to target both additional triggers as well as linear or focal ablation over the atrial substrates outside the pulmonary veins.[67] Currently, different catheter ablation techniques to isolate electrically the pulmonary veins from the left atrium (segmental ostial isolation) or to modify the left atrial substrate around the pulmonary veins (circumferential ablation) are used by most investigators for curative ablation of atrial fibrillation. Two randomised trials[68,69] have directly compared the clinical efficacy of segmental pulmonary-vein ostial isolation with circumferential left atrial ablations, with conflicting results. These data suggest that the experience of the operators on the types of ablation procedure, rather than the type of procedure itself, could determine clinical success. In specialised centres with extensive experience in atrial fibrillation ablation, the success of different catheter ablation techniques seems to be comparable (roughly 80%), especially if a tailored approach is used.[70]

In a small randomised trial,[71] segmental pulmonary-vein isolation with radiofrequency ablation was compared with AADs as initial treatment for symptomatic paroxysmal atrial fibrillation, and after 1 year of follow-up, the ablation group had a significantly lower rate of recurrence of symptomatic atrial fibrillation and admissions, as well as an improved quality of life at 6 months. Similarly, Oral and colleagues[72] did a randomised controlled trial of circumferential pulmonary-vein ablation for the treatment of chronic atrial fibrillation. They found that 74% of patients in the ablation group and 58% of controls were free of recurrent atrial fibrillation or atrial flutter without antiarrhythmic-drug therapy at 1 year. Maintenance of sinus rhythm was associated with a significant reduction in both the severity of symptoms and the left atrial diameter. Even in patients with heart failure and impaired LV ejection fraction, atrial fibrillation ablation restored sinus rhythm without AADs in 70% of patients and substantially improved LV function.[73]

Despite the success reported with atrial fibrillation ablation, these procedures are associated with a risk of serious and life-threatening complications. Major complications have been reported in 6% of such procedures, including complications secondary to vascular access, stroke, and transient ischaemic attack; pronounced pulmonary-vein stenosis; proarrhythmia; and valvular, phrenic nerve, oesophagus, and tracheal injury in rare instances.[74] Furthermore, ablation procedures for atrial fibrillation remain technically difficult, operator-dependent, labour-intensive, and lengthy—indeed, the real-life experience of most centres shows a much lower success rate than series reported from high-volume centres.[74] Additionally, a large proportion of patients have asymptomatic recurrence of atrial fibrillation, and a repeat procedure is needed in 10–40% of patients to achieve the high rate of success reported. Currently, scarce data exists on long-term (>2 years) clinical outcome after catheter ablation of atrial fibrillation. Notably, during long-term follow-up after radiofrequency ablation for AV nodal re-entrant tachycardia (AVNRT), one study[75] reported no AVNRT recurrences, but 24% of patients had new arrhythmias or late AV block. Finally, little data are available on the long-term risk of stroke and thromboembolism after ablation.

For now, atrial fibrillation ablation could be considered in symptomatic patients who have been resistant or intolerant to pharmacological treatment, or as an alternative to amiodarone treatment, especially those who are younger, have lone atrial fibrillation, and with congestive heart failure. Future development of catheter ablation techniques, such as integration with different imaging methods and magnetic navigation systems could further improve the success and safety of the procedure. Curative procedures of catheter ablation could become a first-line treatment in more patients if proven to be safer and more effective than pharmacological treatment during long-term follow-up.

A joint consensus statement on catheter and surgical ablation of atrial fibrillation, with recommendations for personnel, policy, procedures, and follow-up has recently been issued by the Heart Rhythm Society, European Heart Rhythm Association, and European Cardiac Arrhythmia Society.[76] In addition, the Venice Chart international consensus document on atrial fibrillation ablation has also been published, providing international consensus on ablation techniques; procedural endpoints; management before, during, and after ablation; training requirements or competences; the prevention and treatment of complications; and the definition of success and long-term results.[77]

Cardiac resynchronisation treatment

The role of cardiac resynchronisation therapy (CRT) in patients with atrial fibrillation who have heart failure is gaining prominence.[78,79] Kies and colleagues[80] reported a short-term study of CRT in chronic atrial fibrillation, in which New York Heart Association (NYHA) class,

quality-of-life score, 6-min walk test, and LV ejection fraction had improved significantly after 6 months of CRT. End-diastolic and end-systolic diameters of the left ventricle and left atrium also decreased, but despite 90% of patients with persistent atrial fibrillation being cardioverted to sinus rhythm at implantation, 72% had relapsed to atrial fibrillation at 6 months' follow-up. Similarly, the Cardiac Resynchronization in Heart Failure (CARE-HF) study[81] reported that in patients with new onset of atrial fibrillation and severe heart failure, CRT significantly reduced the risk for all-cause mortality and all other predefined endpoints and improved ejection fraction and symptoms. In another study,[82] patients with heart failure who had ventricular conduction disturbance and permanent atrial fibrillation were treated with CRT and showed large and sustained long-term (up to 4 years) improvements of LV function and functional capacity, similar to patients in sinus rhythm, only if AV nodal ablation was done.

Antithrombotic treatment: risk stratification and the patient's perspective

The risk of stroke and thromboembolism is increased 4–5-fold by non-valvular atrial fibrillation, which is similar in patients with either paroxysmal or permanent atrial fibrillation.[83] Asymptomatic cerebrovascular events could contribute to vascular dementia and impaired cognitive function in patients with atrial fibrillation. Little evidence links the burden of atrial fibrillation paroxysms to stroke risk, but results from one study[84] suggested that the risk of thromboembolism, adjusted for known risk factors, was 3·1-fold increased (95% CI 1·1–10·5, p=0·044) in patients with device-detected episodes of atrial fibrillation longer than 1 day during follow-up.[84] Thus, a strategy of rhythm control does not necessarily reduce stroke risk, and current recommendations suggest that in the presence of stroke risk factors or if risk of recurrence of atrial fibrillation is high, lifelong anticoagulation should be considered after cardioversion. Patients with atrial flutter should be managed with antithrombotic treatment in a similar manner to those with atrial fibrillation, depending on the coexistence of stroke risk factors. Patients with asymptomatic atrial fibrillation have less serious heart disease but more cerebrovascular disease, but their long-term prognosis seems no better than those with symptomatic disease.[85]

In a meta-analysis[86] of 13 trials (n=14423), adjusted-dose of warfarin significantly reduced the risk of ischaemic stroke or systemic thromboembolism compared with placebo (relative risk [RR] 0·33 [95% CI 0·2–0·45]).[86] No significant difference was seen in the rate of intracranial haemorrhage between the anticoagulation group and controls (0·3% *vs* 0·1% per year); furthermore, oral anticoagulation treatment reduced all-cause mortality (RR 0·69 [95% CI 0·53–0·89]). Warfarin was again more effective than aspirin in reducing the risk of ischaemic stroke or systemic embolism (0·59 [0·40–0·86]).

An updated meta-analysis[87] of 29 trials (n=28 044, mean age 71 years, mean follow-up 1·5 years) concluded that compared with controls, adjusted-dose warfarin (six trials, n=2900) and antiplatelet agents (eight, n=4876) reduced stroke by 64% (95% CI 49–74) and 22% (6–35), respectively. Adjusted-dose warfarin was substantially more efficacious than antiplatelet treatment (RR reduction 39% [95% CI 22–52]; 12 trials, n=12 963).

The benefits of anticoagulation over aspirin were recently confirmed in the Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA).[88] Anticoagulation (INR 2–3) was more effective than 75 mg aspirin for stroke prevention in elderly patients (age >75 years) with atrial fibrillation, in a primary-care setting. No significant difference in major bleeding events was seen between the anticoagulation and aspirin groups. In view of the effectiveness of anticoagulation in this elderly population, and being at very high risk of stroke, there is a strong argument to use anticoagulation more often in the absence of contraindication.

Compared with placebo, aspirin alone reduces the risk of stroke by about 22%, which is similar to the effect of antiplatelet treatment on stroke prevention in patients at high risk for vascular disease.[89] An updated Cochrane review[90] on antiplatelet treatment for stroke prevention in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischaemic attack (three trials, n=1965) showed that aspirin was associated with non-significant reduced risks of all stroke (odds ratio 0·70 [95% CI 0·47–1·07]), ischaemic stroke (0·70 [0·46–1·07]), all disabling or fatal stroke (0·86 [0·50–1·49]), and all-cause death (0·75 [0·54–1·04]). The combination of stroke, myocardial infarction, or vascular death was significantly reduced (0·71 [0·51–0·97]). No increase in intracranial haemorrhage or major extracranial haemorrhage was recorded.

Indeed, much of the evidence favouring aspirin emanates from the Stroke Prevention in Atrial Fibrillation (SPAF) I clinical trial,[91] composed of two separately randomised cohorts—one consisting of individuals who could not be assigned warfarin (aspirin *vs* placebo) and another for those who could be assigned to warfarin (the trial also included a warfarin group). The RR reduction afforded by aspirin was 94% in the first cohort (p<0·001) but 8% in the second (p=0·75)—the pooled analysis of events in these two cohorts (with the inconsistency between the two groups) gives the 42% risk reduction with aspirin for the entire SPAF I trial (p=0·02). Thus, aspirin should be not be regarded as an adequate substitute for warfarin with respect to stroke prevention in high-risk patients with atrial fibrillation. Since atrial fibrillation commonly coexists with vascular disease, aspirin probably has an effect on vascular disease rather than on atrial fibrillation specifically for stroke prevention.

The dose of aspirin in atrial fibrillation has also generated some debate. The only clinical trial to show a benefit of aspirin was the SPAF-I trial,[91] which used

	Usual strategy recommended	Perceived potential bleeding risk	Presentation of acute coronary syndrome	Management after PCI
Patients at low risk for stroke	Aspirin	..	..	Bare metal stent: aspirin plus clopidogrel for 4 weeks, then aspirin DES: aspirin plus clopidogrel for 6–12 months, then aspirin
Patients at high risk for stroke	Warfarin	Low	No	Use bare metal stent if possible Bare metal stent—triple therapy with warfarin, aspirin, and clopidogrel for 2–4 weeks, then change to warfarin plus clopidogrel for up to month 12, then warfarin alone. DES: triple therapy with warfarin, aspirin. and clopidogrel for 3–6 (or more) months, then warfarin plus clopidogrel for up to month 12, then warfarin alone
		Low	Yes	Bare metal stent or DES: triple therapy with warfarin, aspirin, and clopidogrel for 3–6 (or more) months, then warfarin plus clopidogrel for up to month 12, then warfarin alone
		High*	No	Use bare metal stent if possible Bare metal stent: triple therapy with warfarin, aspirin, and clopidogrel for 4 weeks, then change to warfarin alone DES: triple therapy with warfarin, aspirin, and clopidogrel for 4 weeks, then warfarin plus clopidogrel for up to month 12, then warfarin alone
		High*	Yes	Bare metal stent or DES: triple therapy with warfarin, aspirin, and clopidogrel for 4 weeks, then warfarin plus clopidogrel for up to month 12, then warfarin alone

DES=drug-eluting stent. Doses: aspirin 75 mg/day, clopidogrel 75 mg/day, warfarin adjusted to target INR 2·0–2·5. *Particular attention paid to following risk factors: age older than 75 years; antiplatelet drugs (eg, aspirin or clopidogrel) or non-steroidal anti-inflammatory drugs; more than one drug treatment (polypharmacy); uncontrolled hypertension; history of bleeding (eg, peptic ulcer or cerebral haemorrhage); and history of poorly controlled anticoagulation treatment.

Table 2: **Suggested management strategy for patients with non-valvular atrial fibrillation needing anticoagulation and PCI with stenting**

	High	Intermediate	Low
Atrial Fibrillation Investigators (AFI; 1994)[99]	Age >65 years; history of hypertension, CAD, or diabetes mellitus		Age <65 years; no high-risk features
SPAF Investigators trial (1995)[85]	Women aged >75 years; Systolic blood pressure >160 mm Hg; LV dysfunction (on echocardiogram or clinically)	History of hypertension; no high-risk features	No history of hypertension; no high-risk features
$CHADS_2$ scheme (2001)[93]	Score 3–6	Score 1–2	Score 0
Framingham study (2003)[3]	Weighted point scoring system (low risk, 0–7; intermediate risk, 8–13; high risk, 14–31)—points given for following risk factors: old age (max score <10); sex (women=6, men=0); high blood pressure (<4); and diabetes (6). Total score (maximum 31 points) correspond to predicted 5-year stroke risk		
ACCP guidelines (2004)[12]	Previous stroke, TIA, or systemic embolic event; age >75 years; moderately or severely impaired LV function with or without congestive cardiac failure; hypertension or diabetes	Age 65–75 years with no other risk factors	Age <65 years with no risk factors
NICE guidelines (2006)[11]	Previous ischaemic stroke, TIA, or thromboembolic event; age ≥75 years with hypertension, diabetes, or vascular disease; clinical evidence of valve disease or heart failure, or impaired left ventricular function on echocardiography	Age ≥65 years with no high risk factors; age <75 years with hypertension, diabetes, or vascular disease	Age <65 years with no history of embolism, hypertension, diabetes, or other clinical risk factors
ACC/AHA/ESC guidelines (2006)[10]	Previous thromboembolism (stroke, TIA, systemic embolism); valve disease; more than one of following: age ≥75 years, hypertension, heart failure, impaired LV systolic function, or diabetes mellitus	Age ≥75 years, hypertension, heart failure, impaired LV systolic function, or diabetes mellitus	Atrial fibrillation only (no other risk factors)

TIA=transient ischaemic attack.

Table 3: **Main stroke-risk stratification schemes for patients with atrial fibrillation**

325 mg/day. The AFASAK (Atrial Fibrillation Aspirin Antikoagulation) trial[92] tested aspirin at 75 mg/day, which showed no significant difference to placebo.[92] In the BAATAF (Boston Area Anticoagulation Trial for Atrial Fibrillation) trial,[93] aspirin (mostly at 325 mg/day) was used in a non-randomised manner, and showed no difference to placebo for stroke prevention. In the Japan Atrial Fibrillation Stroke trial,[94] patients with low-risk atrial fibrillation were randomly assigned 150–200 mg of aspirin per day or no treatment, and the primary endpoint events were 3·1% and 2·4% per year, respectively, with an increased bleeding rate with aspirin. Based on the Antithrombotic Trialists' Collaboration,[95] trials of higher daily doses of aspirin compared with no aspirin showed that no particular range of aspirin dose was preferable for prevention of serious vascular events, and the proportional reduction in vascular events was 19% (3%) with 500–1500 mg/day, 26% (3%) with 160–325 mg/day, and 32% (6%) with 75–150 mg/day.[66] Thus, current ACC/AHA/ESC guidelines[10] have recommended aspirin use at 81–325 mg/day; whereas NICE[11] recommends 75–300 mg/day, reflecting the formulations available in

North America and the UK. The seventh set of ACCP guidelines recommends a dose of 325 mg/day.[12]

Anticoagulation use in the pericardioversion period, and in atrial fibrillation and acute stroke, has recently been reviewed by Lip and Boos.[83] In patients who need to have oral anticoagulation discontinued temporarily for surgery or other invasive procedures, bridging treatment with unfractionated or low-molecular-weight heparin should be considered, especially for patients at high risk of thromboembolism, such as those with prosthetic heart valves or previous thromboembolism.[96]

A more pressing problem is the management of antithrombotic treatment in patients with atrial fibrillation undergoing percutaneous coronary intervention with coronary stenting, as well as the management of those admitted with acute coronary syndromes, in view of the increasing trend to use aspirin plus clopidogrel, and early invasive investigations in such patients (often with percutaneous coronary intervention) as part of current management guidelines. The consensus-based ACC/AHA/ESC guidelines in 2006[10] recommended that after PCI, low-dose aspirin (<100 mg/day) or clopidogrel (75 mg/day), or both, can be given concurrently with anticoagulation to prevent myocardial ischaemic events, but states that these strategies have not been thoroughly investigated and are associated with an increased risk of bleeding. The guidelines recommend that the maintenance regimen should then consist of clopidogrel (75 mg/day) plus warfarin (INR 2·0–3·0). Clopidogrel should be given at least 1 month after implantation of a bare metal stent, at least 3 months for a sirolimus-eluting stent, at least 6 months for a paclitaxel-eluting stent, and at least 12 months in selected patients, after which warfarin can be continued as monotherapy in the absence of a subsequent coronary event.[10] When warfarin is given in combination with clopidogrel or low-dose aspirin, the anticoagulation intensity should be carefully regulated. In view of the high risk of early stent thrombosis and recurrent ischaemia after a acute coronary syndrome, calls have been made for a more aggressive strategy of early antithrombotic treatment based on balancing stroke risk against the perceived bleeding risk, as well as the presentation of acute coronary syndromes in individual patients and type of stent used (table 2),[97] especially since in the real-life setting where the bleeding risk might be low.[98]

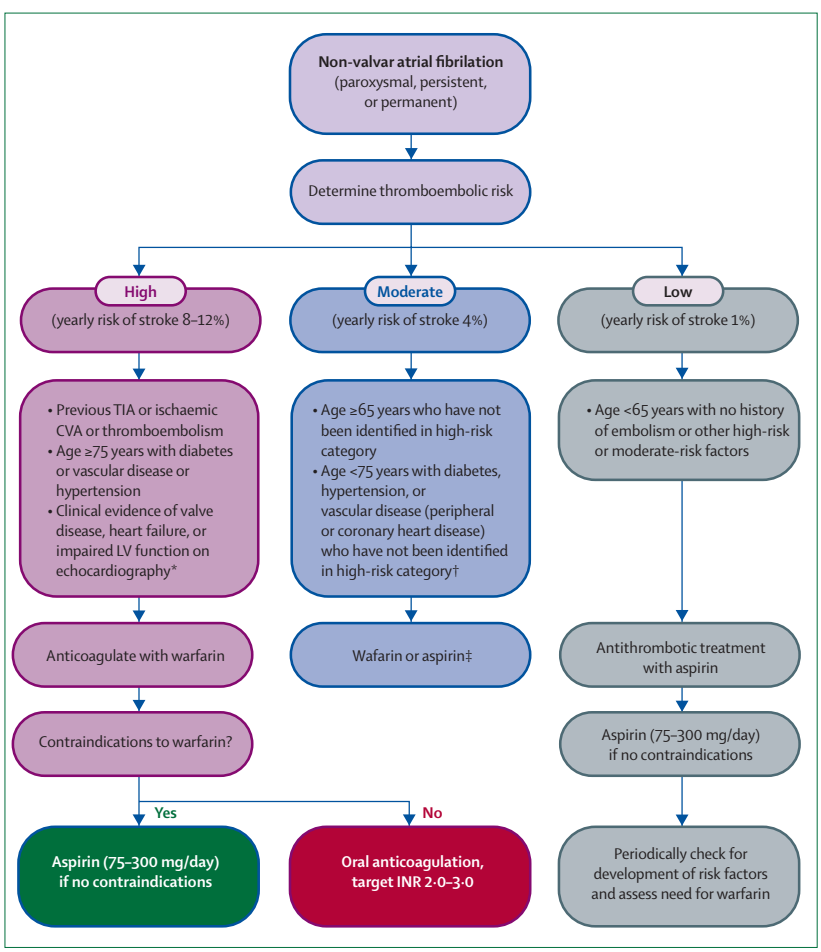

Figure 4: **Practical guidelines for antithrombotic treatment in non-valvular atrial fibrillation**
CVA=cerebrovascular accident. TIA=transient ischaemic attack. Assess risk and reassess regularly. Risk factors are not mutually exclusive, and are additive to each other in producing a composite risk. *Echocardiograms are not needed for routine risk assessment but refine clinical risk stratification in case of moderate or severe LV dysfunction and valve disease. †Owing to lack of clear evidence, treatment may be decided on an individual basis, and physicians should balance risks and benefits of warfarin versus aspirin; since stroke risk factors are cumulative, warfarin may (for example) be used in the presence of two or more risk factors. Referral and echocardiography could help in uncertain cases. ‡Since the incidence of stroke and thromboembolic events in patients with thyrotoxicosis seems similar to other causes of atrial fibrillation, antithrombotic treatments should be chosen on the basis of validated stroke risk factors. Figure reproduced from reference 11. Copyright 2006 Royal College of Physicians. Reproduced with permission.

The risk of stroke in atrial fibrillation is not homogeneous, and clinical factors associated with atrial fibrillation contribute to this risk. High-risk factors include previous stroke or transient ischaemic attack; age 75 years or more; presence of structural heart disease, hypertension, diabetes mellitus or vascular disease; or presence of moderate–severe LV systolic dysfunction on two-dimensional echocardiography. These clinical and echocardiographic criteria have informed the development of several risk stratification models with differing complexities (table 3).[83] Of the various published risk stratification criteria, $CHADS_2$ (Congestive heart failure, Hypertension, Age >75 years, Diabetes mellitus, and previous Stroke or transient ischaemic attack) is the most popular and well-validated scheme, having successfully identified primary prevention patients at high risk of stroke (5·3 strokes per 100 patient-years).[100] The $CHADS_2$ scheme clearly emphasises the cumulative nature of stroke risk factors. A practical algorithm-based risk stratification schema for antithrombotic treatment in atrial fibrillation—which is used in the NICE guideline—offers a balance between evidence and practical applicability (figure 4). The NICE clinical stratification defines patients into low-risk, moderate-risk, and high-risk categories, which has been shown to be similar to the $CHADS_2$ scheme for predicting stroke and vascular event rates.[101]

The assessment of bleeding risk is part of the clinical assessment of patients with atrial fibrillation before

beginning anticoagulation therapy, focusing on some high-risk categories of patients, such as those who are elderly, or those with concomitant use of antiplatelet drugs (aspirin, clopidogrel) or non-steroidal anti-inflammatory drugs, polypharmacy, uncontrolled hypertension, a history of bleeding (eg, peptic ulcer, cerebral haemorrhage), or poorly controlled anti-coagulation therapy.[102] In a recent analysis,[103] the cumulative incidence of major haemorrhage for patients aged 80 years or more was 13·1 per 100 person-years and 4·7 for those younger than 80 years. On initiation of warfarin treatment, age of 80 years or more and INR of 4·0 or more were associated with increased bleeding risk; notably, 26% of elderly patients stopped taking warfarin within the first year. The role of the available bleeding risk stratification schemes for predicting outcomes in anticoagulated patients with atrial fibrillation needs further prospective data.[104]

Recent data from the Euro Heart Survey[105] have shown that oral anticoagulation is still grossly underused in patients with atrial fibrillation and high risk of stroke. Furthermore, some patients will still refuse treatment with warfarin despite discussion of the risks and benefits of antithrombotic treatment (so-called informed dissent), for various patient-related reasons, including the inconvenience of dosing adjustments and regular blood tests to monitor INR levels; dietary restrictions; the risk of minor and major bleeding; under-appreciation or lack of knowledge regarding the risk of stroke; or poor adherence to the treatment regimen. Also, many patients with atrial fibrillation possess very little knowledge of the disease itself, its consequences and treatment, and few thought that their doctor had given enough information about their anticoagulation treatment.[106,107] With the right training, education, and support, the use of self-monitoring of oral anticoagulation in selected patients can further improve the quality of treatment to reduce thromboembolic events and mortality.[108]

The future

Increasing interest has been given to the role of the RAAS in atrial fibrillation. Various studies also show that RAAS blockade with angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers (ARB) could have a role in the prevention of atrial fibrillation recurrence and the maintenance of sinus rhythm after ca rdioversion,[48,49,109,110] and have been advocated as upstream treatments.

Atrial fibrillation is associated with a prothrombotic state, with abnormalities of haemostasis, platelets, and endothelial damage or dysfunction, which could contribute to an increased risk of stroke and thromboembolism.[111] Abnormalities of the prothrombotic state are not greatly altered by the presence of structural heart disease, and can be altered by cardioversion to sinus rhythm and antithrombotic treatment. More recently, prothrombotic indices, such as plasma von Willebrand factor and fibrin D-dimer, have been related to stroke and vascular events in atrial fibrillation.[112,113] Indeed, such indices could potentially complement clinical risk factors in refining stroke risk stratification in atrial fibrillation, especially in moderate-risk groups.[101]

Inflammation could also be important in the patho-physiology of atrial fibrillation.[114] In a recent analysis[115] of patients with atrial fibrillation, C-reactive protein (CRP, a marker of inflammation) was positively correlated to stroke risk strata and related to stroke-risk factors, as well as prognosis (mortality, vascular events) at follow-up. Inflammation seems to precede the development of atrial fibrillation and contribute to its persistence, as well as drive the prothrombotic or hypercoagulable state in the disease. The n-3 polyunsaturated fatty acids (PUFAs) and statins are thought to have anti-inflammatory effects that lead to their putative antiarrhythmic properties. Epidemio-logical data suggesting that increased PUFA intake decreases atrial fibrillation is less convincing,[116,117] but intervention trials suggest a reduction in postoperative atrial fibrillation by use of PUFAs[118] or statins (which also have anti-inflammatory pleotropic effects)[119] after coronary-artery bypass surgery.

In addition to dronedarone, new AADs for atrial fibrillation—such as azimilide, tedisamile, and vernakalant are currently in early clinical trials, which could overcome some limitations of existing drugs (especially proarrhythmia).[120] The uptake of these new drugs in clinical practice will ultimately depend on their efficacy as AADs as well as their safety.

With respect to thromboprophylaxis, new anticoagulants—such as the oral direct thrombin inhibitors and oral factor Xa inhibitors—show promise as alternatives to vitamin K antagonists. In general, these new drugs have few drug or food interactions and most importantly, do not need anticoagulation monitoring. For patients needing an alternative to anticoagulant treatments, closure of the left-atrial appendage with a percutaneous left-atrial appendage occluder and LAPTONI (laproscopic percutaneous transthoracic atrial appendage occluder) could become a feasible alternative, with encouraging initial results.[121]

Conflict of interest statement

GYHL has received funding for research, educational symposia, consultancy, and lecturing from different manufacturers of drugs used for the treatment of atrial fibrillation and thrombosis. He was the clinical adviser to the Guideline Development Group writing the UK NICE Guidelines on atrial fibrillation management and is on the writing group for the ACCP Consensus Guidelines on Antithrombotic Therapy for Atrial Fibrillation. HFT has received funding for research, educational symposia, consultancy, and lecturing from different manufacturers of drugs and devices used for the treatment of atrial fibrillation and thrombosis.

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