

Review

Clinical review: Clinical management of atrial fibrillation – rate control versus rhythm control

Hoong Sern Lim¹, Ali Hamaad² and Gregory YH Lip³

¹Research Fellow, University Department of Medicine, City Hospital, Birmingham, UK

²Research Fellow, University Department of Medicine, City Hospital, Birmingham, UK

³Professor of Cardiovascular Medicine, University Department of Medicine, City Hospital, Birmingham, UK

Corresponding author: GYH Lip, G.Y.H.LIP@bham.ac.uk

Published online: 19 February 2004

Critical Care 2004, **8**:271-279 (DOI 10.1186/cc2827)

This article is online at <http://ccforum.com/content/8/4/271>

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Abstract

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the critically ill and is associated with adverse outcomes. Although there are plausible benefits from conversion and maintenance of sinus rhythm (the so-called 'rhythm-control' strategy), recent randomized trials have failed to demonstrate the superiority of this approach over the rate-control strategy. Regardless of approach, continuous therapeutic anticoagulation is crucial for stroke prevention. This review addresses the findings of these studies and their implications for clinical management of patients with atrial fibrillation.

Keywords atrial fibrillation, rate control, rhythm control

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the community [1]. It is characterized electrocardiographically by irregular fibrillatory waves, usually associated with an irregular ventricular response, which manifests clinically as an irregular pulse. The presence of rapid, uncontrolled AF may be associated with severe symptoms and haemodynamic compromise, necessitating urgent intervention. In addition to its direct haemodynamic effects, AF is associated with a prothrombotic state and is a major risk factor for stroke and thromboembolism [2]. Overall, this arrhythmia also appears to be an independent predictor for death [3].

In addition, AF is the most common arrhythmia in post-operative patients [4] (particularly following cardiac surgery [5]) and in critically ill patients [6]. In these patients, as with patients in the community, AF is associated with adverse outcomes [7]. Hence, regardless of the clinical setting, AF identifies patients at substantial risk for morbidity and mortality.

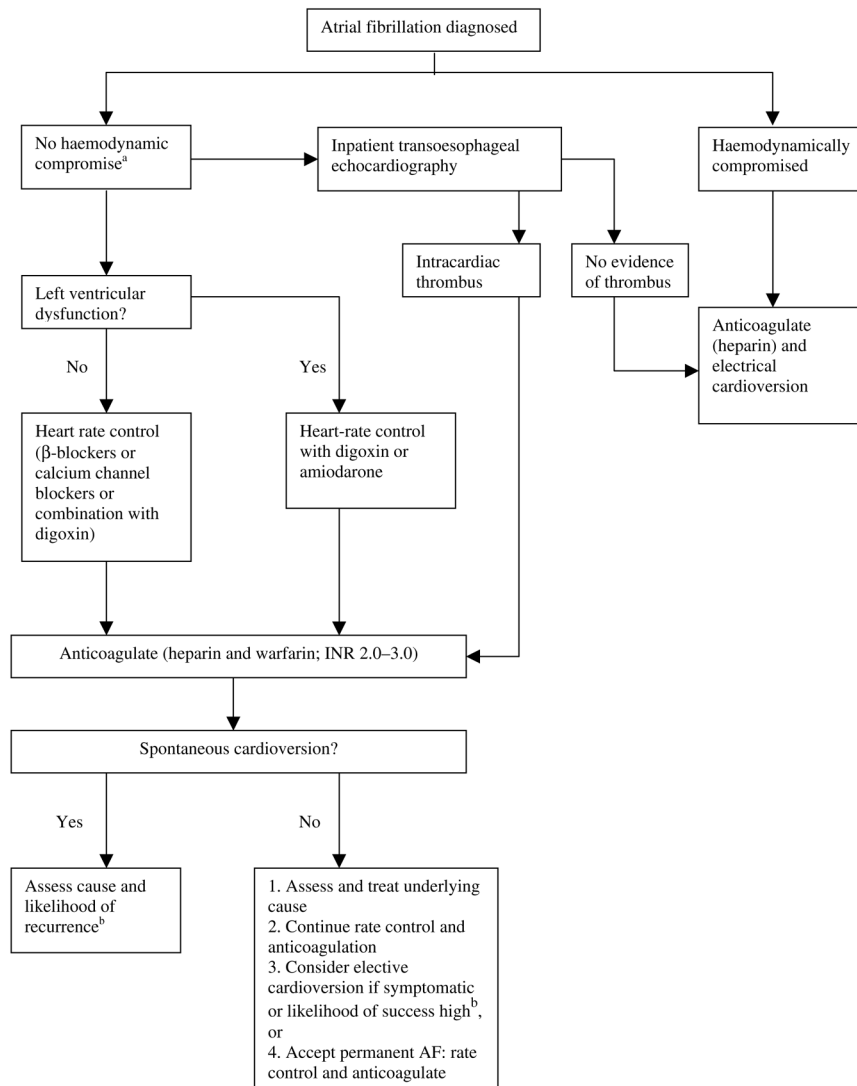
Classification of atrial fibrillation

Recent guidelines suggested that AF be classified on the basis of the temporal pattern of the arrhythmia [8]. AF is considered recurrent when a patient develops two or more episodes. These episodes may be paroxysmal if they terminate spontaneously (defined by consensus as 7 days) or persistent if electrical or pharmacological cardioversion is required to terminate the arrhythmia. Successful termination of AF does not alter the classification of persistent AF in these patients. Longstanding AF (defined as over 1 year) that is not successfully terminated by cardioversion, or when cardioversion is not pursued, is classified as permanent.

Regardless of the eventual classification, patients with AF should be assessed for symptomatic and haemodynamic compromise, which will guide subsequent management (Fig. 1), identification and correction of associated comorbidities and/or precipitants, and assessment of the patient's thromboembolic risk (Fig. 2) [9].

AF = atrial fibrillation.

Figure 1



Treatment algorithm for atrial fibrillation. ^aConsider anticoagulation and early cardioversion if symptomatic. ^bRefer to Table 5. INR, international normalized ratio; LV, left ventricular.

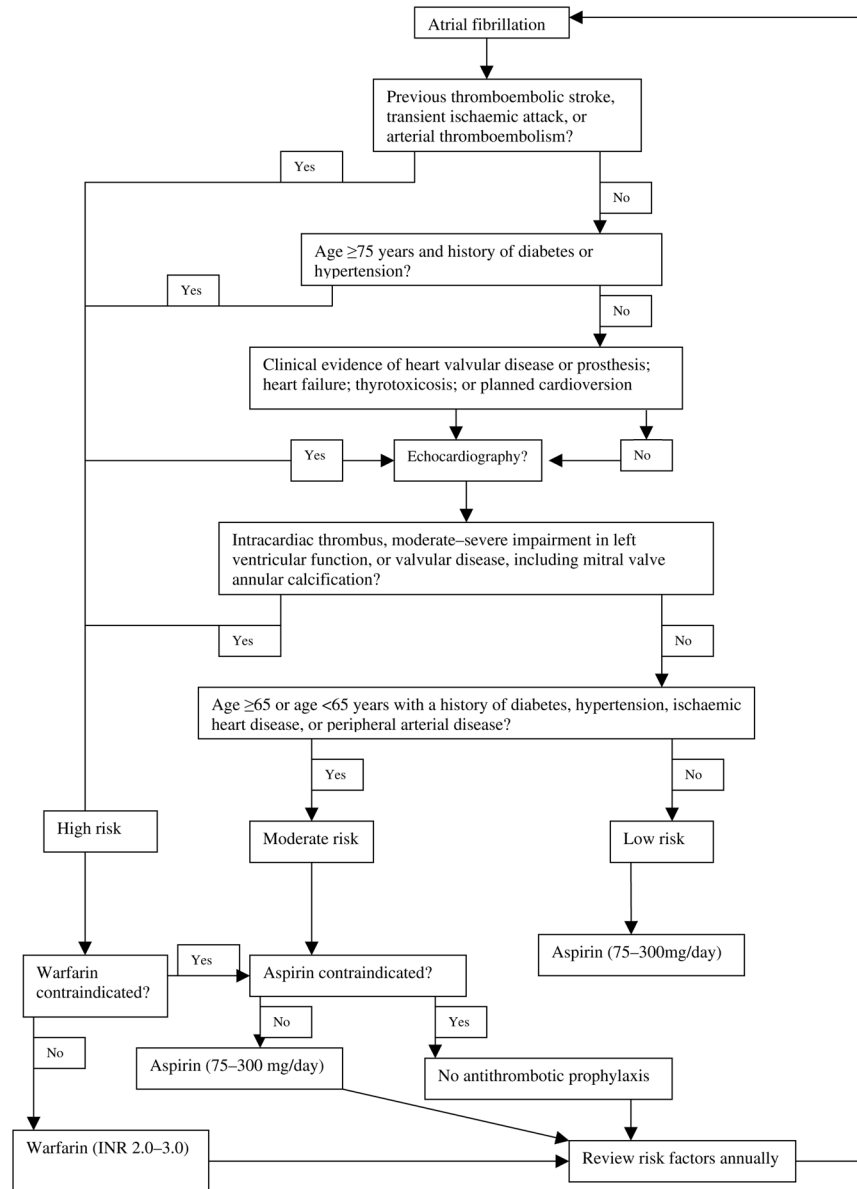
Atrial fibrillation with haemodynamic compromise

The haemodynamic compromise in AF may result from loss of atrial contribution to ventricular filling (and therefore preload and stroke volume) and/or from rate and irregularity of the ventricular response. Under normal circumstances, atrial contraction contributes 20–30% of ventricular stroke volume. This atrial contribution increases with age and in conditions associated with impaired ventricular relaxation, such as hypertensive heart disease and hypertrophic cardiomyopathy. Consequently, loss of this atrial contribution may result in more considerable haemodynamic insult in these patients. The irregularity of the ventricular response and rate-related

shortening of the diastolic filling interval results in further reduction in cardiac output [10,11].

Early cardioversion may be necessary in patients with evidence of haemodynamic compromise (acute pulmonary oedema, worsening angina, or hypotension) in relation to uncontrolled AF. Synchronized, direct current cardioversion is more effective and preferable to pharmacological cardioversion under these circumstances. Successful cardioversion depends on the energy used, the output waveform, paddle configuration, and the presence of underlying heart disease and co-morbidities. An initial energy of at least 200 J is recommended, although lower energies may be sufficient for

Figure 2



Risk stratification for anticoagulation treatment. INR, international normalized ratio.

devices that deliver biphasic waveforms. The anteroposterior paddle position is also associated with greater probability of success.

The underlying precipitant or contributory factors (Table 1) should also be addressed at the same time because attempts at cardioversion and maintenance of sinus rhythm without correcting the underlying precipitant are futile or even detrimental to the patient. There is evidence that atrial mechanical activity may not recover concurrently with electrical activity ('atrial stunning') after cardioversion. The lack of atrial contractility predisposes to the development of new thrombi

and risk for thromboembolic complications [12]. As such, anticoagulation (heparin in the acute setting) should be administered in the absence of contraindication and continued for at least 4 weeks following cardioversion. This, however, should not delay immediate cardioversion of haemodynamically compromised patients [8].

Atrial fibrillation without haemodynamic compromise: rate control or rhythm control

The necessity for cardioversion is less well established in haemodynamically stable patients with AF. Despite this, the management of these patients has traditionally been dominated

Table 1

Causes or precipitants of atrial fibrillation	
Type of disorder	Examples
Ischaemic heart disease	
Valvular heart disease	Mitral, aortic, or tricuspid valve disease
Cardiomyopathy	Systolic/diastolic dysfunction Hypertension: systemic or pulmonary Myocardial infiltration Myocarditis Idiopathic
Pericardial disease	Pericarditis Pericardial effusion Pericardial constriction
Intracardiac masses	Atrial myxoma Secondary neoplasms
Conduction disorders	Pre-excitation (e.g. Wolff–Parkinson–White, Lown–Ganong–Levine)
Congenital heart disease	Atrial septal defect Ventricular septal defect
Toxic/metabolic causes	Alcohol Thyrotoxicosis Corticosteroid excess (e.g. Cushing's) Pheochromocytoma
Pulmonary disease	Pneumonia Pulmonary embolism Interstitial lung disease Acute respiratory distress syndrome

by a drive to restore and maintain sinus rhythm – the so-called 'rhythm-control' strategy. Better exercise tolerance, quality of life, improved survival and lower risk for stroke with eventual discontinuation of anticoagulation have been cited

as the rationale for this approach [13]. However, limited efficacy and adverse effects associated with the use of antiarrhythmic therapy represent serious drawbacks to this approach. The 'rate-control' approach offers an alternative strategy by employing simpler and generally less toxic rate-lowering drugs, but this is intuitively less appealing and inconvenienced by the need for close attention to anticoagulation (Table 2).

The first of four studies (Table 3) [14–17] that compared the two management strategies, the Pharmacological Intervention in Atrial Fibrillation (PIAF) trial [14] recruited 252 patients and randomly assigned them to either the rate-control or rhythm-control arm. Diltiazem and the class III antiarrhythmic agent amiodarone were the main agents used in the former and latter groups, respectively. After 12 months of follow up, 10% in the rate-control group and 56% of the rhythm-control group were in sinus rhythm, and rhythm control was associated with better exercise tolerance (as assessed by 6-min walk test) but increased number of hospitalizations. There was no difference in quality of life between the groups.

In the Strategies of Treatment in Atrial Fibrillation (STAF) trial [15], 200 patients were randomly assigned to either rate control or rhythm control, and were followed up for a mean of about 20 months. Like the PIAF trial, patients in the rhythm-control arm were hospitalized significantly more often, usually for repeated cardioversion or antiarrhythmic therapy. However, that study was limited by lower than expected event rates, with nine primary end-points (a composite of death, cerebrovascular event, cardiopulmonary resuscitation and systemic emboli) in the rhythm-control arm, as compared with 10 in the rate-control arm (although this difference was not statistically

Table 2

Risks and benefits of rate control versus rhythm control			
Rhythm control		Rate control	
Benefits	Risks	Benefits	Risks
Relief of symptoms	Poor efficacy of antiarrhythmic drugs in maintaining sinus rhythm	Efficacious agents in maintaining rate control	Need for continuing anticoagulation with associated risks
Improved exercise tolerance		Relief of symptoms (quality of life scores) not significantly different compared with rhythm control	Rhythm control may not be an option for a first presentation of uncontrolled rate
Less need for anticoagulation therapy	Greater rates of adverse effects of antiarrhythmic drugs (including death)	Stroke risk no different to maintaining rhythm control	
Improved haemodynamic function	Major cardiovascular events may be more common in rhythm control (especially if other risk factors are present)	Overall mortality no different to rhythm control	
Prevention of tachycardia-induced cardiomyopathy	Greater rates of hospitalization compared with rate control	Greater cost-effectiveness of rate control compared with rhythm control	

Table 3**Studies of rate versus rhythm control**

Study	Number of patients	Primary end-point	Results	Comments
PIAF [14]	252	Proportion of patients with symptomatic improvement	Improved exercise tolerance with rhythm control	More frequent hospital admission with rhythm control
STAF [15]	200	Death, cardiopulmonary resuscitation, cerebrovascular event, systemic embolus	No difference in treatment strategies	Proportion of patients assigned to rhythm control low
RACE [16]	522	Cardiovascular death, heart failure, thromboembolism, bleeding, pacemaker implantation, severe adverse effects of drugs	No difference between treatment strategies	Lower risk of adverse drug effects with rate control
AFFIRM [17]	4060	Total mortality	No difference between treatment strategies	Lower risk for adverse drug effects with rate control

AFFIRM, Atrial Fibrillation Follow-up Investigation of Rhythm Management; PIAF, Pharmacological Intervention in Atrial Fibrillation; RACE, RAte Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation; STAF, Strategies of Treatment of Atrial Fibrillation.

significant). It was also limited by failure to maintain sinus rhythm in the rhythm-control group (only 23% of patients in the rhythm control group remained in sinus rhythm after 3 years).

The Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) study [16] tested the hypothesis that rate control was not inferior to rhythm control. In total, 522 patients were randomly assigned to either rate control with digitalis, nondihydropyridine calcium channel blocker and/or β -blocker, or to rhythm control. Regimens of sotalol, followed by flecainide or propafenone, and then amiodarone were used in a stepwise algorithm to maintain sinus rhythm. Anticoagulation could be discontinued if sinus rhythm was maintained for at least 1 month. After more than 2 years of follow up, sinus rhythm was maintained in 39% of the patients in the rhythm-control group as compared with 10% in the rate-control group, with no significant difference in the primary composite end-point of death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, need for pacemaker implantation and serious adverse events from antiarrhythmic therapy. This suggested that rate control is not inferior to rhythm control.

The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study [17] was the largest study to date comparing these two treatment strategies. In total, 4060 patients were enrolled in the study and followed up for a mean of 3.5 years. Digoxin, β -blockers and calcium channel blockers were used in the rate control arm, and amiodarone and sotalol were the most commonly used antiarrhythmic agents in the rhythm-control arm. At 5 years, about 35% of the rate-control group were in sinus rhythm, as compared with about 60% of those in the rhythm-control group. There was no significant difference in the primary outcome of overall mortality but patients in the rhythm-control group were

significantly more likely to be hospitalized and suffer adverse drug effects. The majority of strokes occurred when anticoagulation either was stopped or was subtherapeutic.

Taken together, these studies suggest that the rate-control strategy would be an acceptable primary approach to patients with recurrent, persistent AF. Although there are clear differences in the patient populations studied, there is no evidence to suggest that cardioversion of AF in critically ill patients in the absence of haemodynamic compromise is associated with a better outcome. Therefore, restoration of sinus rhythm should no longer be deemed imperative in asymptomatic and haemodynamically stable patients. The choice of rate-lowering drug, however, may vary between patient populations. An approach to the management of newly diagnosed AF is outlined in Fig. 1.

Pharmacological rate control

The aims of heart rate control are to minimize symptoms associated with excessive tachycardia and to prevent tachycardia-associated cardiomyopathy. Historically, digoxin has been the pharmacological agent of choice but it has limited efficacy in patients who are in a hyperadrenergic state such as thyrotoxicosis, fever, acute volume loss, post-operative state and during exertion [18]. Digoxin monotherapy may therefore be of little value in the critically ill, although it may be adequate for the older, sedentary patient.

Other agents include β -blockers and the nondihydropyridine calcium channel blockers such as diltiazem and verapamil (Table 4). β -Blockers are effective in reducing ventricular rate at rest and on exertion (hyperadrenergic state) [19] and may be of additional benefit in patients with concomitant coronary artery disease. Diltiazem and verapamil are also effective rate-lowering agents both at rest and during exercise [20]. These rate-lowering agents may therefore be more effective than

Table 4

Rate-lowering agents			
Drug	Dose	Contraindications	Comments
β-Blockers (e.g. metoprolol)	5 mg intravenous; can be repeated twice at 2-min intervals if necessary	Asthma, uncontrolled heart failure, bradycardia/heart block, Wolff–Parkinson–White	Useful in patients with concomitant coronary artery disease Use with caution in controlled heart failure
Calcium channel blockers (e.g. diltiazem, verapamil)	Diltiazem: up to 300 mg/day orally Verapamil: 5–10 mg intravenous over 2 min; can be repeated once 30 min later	Bradycardia/heart block, left ventricular failure, Wolff–Parkinson–White, concomitant use of β-blockers not recommended	Diltiazem less negatively inotropic compared to verapamil Verapamil may cause elevation of digoxin levels
Digoxin	62.5–250 µg/day (initial loading dose required)	Bradycardia/heart block, Wolff–Parkinson–White	Renally excreted Slow onset of action Poor efficacy in hyperadrenergic states Hypokalaemia increases risk of toxicity

digoxin in controlling ventricular rate during AF in the critically ill. Indeed, diltiazem has been shown to be superior to digoxin in controlling ventricular rate during acute AF [21].

Rate control, however, may not always be achieved with a single drug. In the study conducted by Farshi and coworkers [22], the combination of digoxin and atenolol was found to be more effective than the digoxin–diltiazem combination or monotherapy with digoxin, atenolol or diltiazem in controlling ventricular rate over 24 hours and during exertion. The combination of diltiazem and digoxin was also significantly more effective than digoxin monotherapy. Combination therapy should therefore be considered for AF that is uncontrolled with a single agent. The combination of diltiazem and digoxin is probably preferable to verapamil, in view of the latter's negative inotropic effect and potential interaction with digoxin.

β-Adrenergic receptor and calcium channel blocking classes of rate-lowering agents, however, are negatively inotropic and may precipitate or aggravate pulmonary oedema in patients with left ventricular dysfunction (Table 4). In addition, the associated blood pressure lowering effects may also limit their use in critically ill patients. Under these circumstances, amiodarone and digoxin are two pharmacological options, although β-blockers may be considered in stable heart failure. Studies suggest that amiodarone is haemodynamically well tolerated [23] and may be of at least equal efficacy in controlling ventricular rate as compared with diltiazem, with less hypotensive effect [24]. In addition, amiodarone is an effective agent for pharmacological cardioversion [25] (see below). Alternatively, a nonpharmacological approach (mainly atrioventricular node ablation coupled with pacing) can be considered. A detailed discussion on nonpharmacological interventions for AF is beyond the scope of this review.

Electrical and pharmacological cardioversion

With a number of the potential benefits (Table 2) apparently dispelled by the results of the studies described (Table 3),

cardioversion – electrical or pharmacological – now appears less crucial. Nonetheless, restoration and maintenance of sinus rhythm should still be considered in certain groups of patients. Patients with symptomatic AF, particularly if symptoms persist despite rate control, for example, may be candidates for 'rhythm control'. It is also reasonable to consider (elective) cardioversion, with initial rate control and adequate anticoagulation in patients presenting with AF for the first time, particularly in those who are at low risk for recurrence (Fig. 1 and Table 5).

Electrical or pharmacological cardioversion carries similar risks for thromboembolic complications. Therefore, a period (at least 3 weeks) of therapeutic anticoagulation is recommended before either form of cardioversion. Alternatively, transoesophageal echocardiography may be employed to guide cardioversion. The absence of thrombus in the left atrium (and appendage) suggests a low risk for thromboembolic complications [26]. Earlier cardioversion (with shorter term therapeutic anticoagulation) may be attempted in these cases.

Pharmacological cardioversion tends to be most effective for recent onset AF, which is generally defined as lasting for less than 1 week. Although a significant proportion of patients revert to sinus rhythm spontaneously within 48 hours, anti-arrhythmic therapy increases the likelihood of cardioversion to up to 90% if administered early enough and in adequate doses [27]. Vaughan-Williams class Ia, Ic and III anti-arrhythmic drugs are associated with increased conversion to sinus rhythm. One small study [28] suggested that intravenous amiodarone may be more effective than quinidine in restoring sinus rhythm, but a recent meta-analysis [29] failed to demonstrate superiority of one drug class over another. Class Ic and III may be preferable to class Ia antiarrhythmic drugs, however, in view of their better safety profile (Table 5). In a direct comparison study [30], amiodarone appeared superior to sotalol (another class III anti-arrhythmic agent) and propafenone (a class Ic agent) in maintaining sinus rhythm –

Table 5**Predictors of likelihood of cardioversion success and recurrence**

Predictor	Comment
Duration of arrhythmia	Shorter duration associated with higher rates of cardioversion
Structural heart disease	Valvular heart disease and cardiomyopathy associated with lower rates of cardioversion and higher recurrence rates
Left atrial dimension	Increased recurrence rates with large left atrial size

Table 6**Pharmacological cardioversion in atrial fibrillation**

Drug	Dose	Contraindications/adverse effects	Comments
Flecainide	300 mg orally or 2 mg/kg in over 10–30 min for cardioversion Maintenance dose of up to 150 mg twice daily	Hypotension, heart failure, coronary artery disease, proarrhythmia (atrial flutter)	Recommended (class I) for pharmacological cardioversion of recent-onset AF
Propafenone	2 mg/kg or 600 mg orally for cardioversion Maintenance dose up to 300 mg twice daily	Hypotension, heart failure, proarrhythmia (atrial flutter)	Recommended (class I) for pharmacological cardioversion of recent-onset AF
Quinidine	200mg orally, followed by 400 mg Maintenance dose of up to 400 mg four times daily	Gastrointestinal upset and proarrhythmia	Increased risk for death with long-term use
Sotalol	120–160 mg twice daily	Asthma, bradycardia/heart block, heart failure	Poor cardioversion efficacy Not recommended as first line
Amiodarone	1200 mg intravenous in 24 hours for cardioversion Maintenance dose of 200 mg (lower doses preferred) 30 mg/kg oral loading dose	Bradycardia/heart block, thyroid dysfunction, pulmonary and liver toxicity with long-term use	Effective for cardioversion and maintaining sinus rhythm Onset may be slow Toxic effects with long-term use
Dofetilide [33]	125–500 µg orally twice daily based on renal function and QT _c	QT interval prolongation, ventricular arrhythmias (in particular torsades de pointes), conduction disturbances also recognized	Class III agent for conversion and maintenance of sinus rhythm Risk for ventricular tachyarrhythmias Not licensed for use in UK
Ibutilide [34]	Dependent on patient weight: ≥60 kg, 1 mg intravenous; <60 kg, 0.01 mg/kg intravenous	As per dofetilide	Intravenous equivalent of dofetilide Not licensed for use in UK

AF, atrial fibrillation.

a finding that was supported by the more recent AFFIRM study [31].

All antiarrhythmic therapies carry with them potential toxicity and proarrhythmia, particularly in the presence of ischaemic and structural heart disease (Table 6). These risks should be considered in the individualization of antiarrhythmic therapy.

Regardless of the approach (rhythm or rate control), it is now clear that thromboembolic prophylaxis should be considered in all patients with AF that is not due to reversible causes, and particularly in the presence of risk factors for stroke. Adequate anticoagulation with warfarin is defined as an international normalized ratio in the range 2.0–3.0, in the

absence of prosthetic valves or rheumatic valvular heart disease (in which case the international normalized ratio should be maintained in the range 2.5–3.5) [7]. A risk stratification model to guide thromboembolic prophylaxis is outlined in Fig. 2 [32].

Conclusion

Recent prospective studies have shown that, in selected patients, rate control coupled with thromboembolic prophylaxis provides similar benefits to those with rhythm control. The choice of rate-control medication (digoxin, β-blockers, calcium channel blockers or amiodarone) should be based on clinical assessment, which includes assessing the presence of underlying heart disease and contraindications.

Although rate control is still often based on digoxin administration, calcium channel or β -adrenergic receptor blockers are generally more appropriate and effective for patients without left ventricular dysfunction, particularly in patients in a hyperadrenergic state. The preferred options for pharmacological rate control in patients with heart failure are digoxin or amiodarone, although β -blockers may be considered for patients with stable heart failure. Nonpharmacological options can also be considered in these patients, typically by multiple ablations to the left atria (around the pulmonary veins) to restore sinus rhythm or specific ablation of the bundle of His with pacemaker implantation for rate control. Pharmacological cardioversion and maintenance of sinus rhythm should still be considered for recurrent, symptomatic AF.

Competing interests

None declared.

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