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Pharmacological Cardioversion of Atrial Fibrillation

Current Management and Treatment Options

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Abstract

Atrial fibrillation (AF) is the most common form of arrhythmia, carrying high social costs. It is usually first seen by general practitioners or in emergency departments. Despite the availability of consensus guidelines, considerable variations exist in treatment practice, especially outside specialised cardiological settings. Cardioversion to sinus rhythm aims to: (i) restore the atrial contribution to ventricular filling/output; (ii) regularise ventricular rate; and (iii) interrupt atrial remodelling. Cardioversion always requires careful assessment of potential proarrhythmic and thromboembolic risks, and this translates into the need to personalise treatment decisions. Among the many clinical variables that affect strategy selection, time from onset is crucial.

In selected patients, pharmacological cardioversion of recent-onset AF can be a safely used, feasible and effective approach, even in internal medicine and emergency departments. In most cases of recent-onset AF, pharmacological cardioversion provides an important – and probably more cost effective – alternative to electrical cardioversion, which can then be employed as a second-line therapy for nonresponders.

Class IC agents (flecainide or propafenone), which can be safely used in hospitalised patients with recent-onset AF without left ventricular dysfunction, can provide rapid conversion to sinus rhythm after either intravenous administration or oral loading. Although intravenous amiodarone requires longer conversion times, it is still the standard treatment for patients with heart failure. Ibutilide also provides good conversion rates and could be used for AF patients with left ventricular dysfunction (were it not for high costs).

For long-lasting AF most pharmacological treatments have only limited efficacy and electrical cardioversion remains the gold standard in this setting. However, a widely used strategy involves pretreatment with amiodarone in the weeks before planned electrical cardioversion: this provides optimal prophylaxis and can sometimes even restore sinus rhythm. Dofetilide may also be capable of restoring sinus rhythm in up to 25–30% of patients and can be used in patients with heart failure.

The potential risk of proarrhythmia increases the need for careful therapeutic decision making and management of pharmacological cardioversion. The results of recent trials (AFFIRM [Atrial Fibrillation Follow-up Investigation of Rhythm Management] and RACE [Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation]) on rate versus rhythm control strategies in the long term have led to a generalised shift in interest towards rate control. Although carefully designed studies are required to better define the role of pharmacological rhythm control in specific AF settings, this alternative option remains a recommendable strategy for many patients, especially those in acute care.

Atrial fibrillation (AF) is the most common form of sustained arrhythmia occurring in clinical practice,[1] and its prevalence is expected to rise in the coming years.[2] Management of AF carries high social costs related to hospitalisation. In the US, AF accounts for almost a million patient days per year spent in hospital.[1] Many different options are currently available to manage this arrhythmia.[3,4] For patients with AF of recent onset or with newly discovered/first-detected AF, restoration of sinus rhythm or control of ventricular rate are not the only reasons for hospitalisation. Other major reasons in-

clude exclusion of precipitating factors, establishment of anti-thromboembolic prophylaxis and (if necessary) restoration of cardiac compensation. Despite the trend towards a wider use of rate control instead of rhythm control for long-term management of patients with recurrent AF,[5-7] attempts to restore sinus rhythm with drugs remain a common practice. The latter approach is frequently preferred because clinical management becomes relatively straightforward once cardioversion has been achieved, and also because successful rhythm control stops atrial remodelling.[8] Not surprisingly, surveys[9,10] indicate that emergency and internal medicine departments usually opt for pharmacological cardioversion of AF (appropriate management of AF is not just the business of cardiologists). Thus, practical, evidence-based indications are required to help physicians decide when to select pharmacological rather than electrical cardioversion, and how to choose among the various drugs and regimens available.

The most recent set of American College of Cardiology (ACC)/American Heart Association (AHA) and the European Society of Cardiology (ESC) guidelines for the management of patients with AF[11] list general recommendations (types of recommendation, accompanied by levels of evidence) for administration of the main available drugs to patients with recent-onset and long-lasting AF. Physicians then have to try to select the most appropriate regimen to adopt for an individual patient in a specific setting.

By focusing on the risk-benefit and safety profiles of the various regimens in different clinical settings, this review aims to bring together practical information as a guide for clinical practice. We begin by stressing the crucial importance of time from onset of arrhythmia (recent-onset vs long-lasting AF) for the formulation of any rational treatment strategy; careful assessment of potential proarrhythmic and thromboembolic risks is also essential, and this translates into the need to personalise treatment decisions. We then provide a survey of the many drug regimens that can be, have been, or still are employed for pharmacological conversion of recent-onset AF. In long-lasting AF, the role of pharmacological conversion is more obscure: after underlining the central role played by electrical cardioversion in this setting, we focus on amiodarone (especially because of its role in maintaining sinus rhythm). We then address the issue of the proarrhythmic effects of antiarrhythmic agents, outlining possible risk factors for these potentially life-threatening adverse reactions. After a glance at some promising novel class III antiarrhythmic agents, we briefly consider the controversial question of where and how pharmacological conversion can usefully be attempted in routine clinical practice. To conclude, we comment the role of pharmacological cardioversion in the light of the results of recent trials (AFFIRM [Atrial Fibrillation Follow-up Investigation of Rhythm Management][5] and RACE [Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation][6]) on rate versus rhythm control strategies.

1. Preliminary Considerations: Importance of Time from Onset of Arrhythmia

Over the years, various classifications of AF have been reported in the literature,[12] in many cases without a precise definition of the temporal and clinical characteristics of each definition. According to the main current classification, as set out in the recent ACC/AHA/ESC guidelines,[11] AF is to be defined as 'paroxysmal' when it terminates spontaneously (usually within 24 hours, sometimes 1 week), 'persistent' when pharmacological or electrical cardioversion is effective, and 'permanent' when cardioversion fails or is not attempted. Furthermore, the 'first-detected' episode of AF should be distinguished. After two or more episodes, AF is considered 'recurrent' (irrespective of whether it is paroxysmal or persistent).

Management and treatment of AF is strongly influenced by the time that has elapsed from its onset, and most of the studies available in the literature regarding pharmacological cardioversion evaluated patients with so-called 'recent-onset' AF (lasting <48 hours from onset).[11] Therefore, in this

review, we must consider the therapeutic options reported for AF of 'recent onset' (a term that occasionally appears even in the ACC/AHA/ESC guidelines) and for 'long-lasting' AF.

2. Thromboembolic Risk in Atrial Fibrillation (AF): Implications for Clinical Management

The mechanical atrial dysfunction associated with the onset of AF is generally accompanied by hypercoagulability and endothelial dysfunction, determining a prothrombotic state and a substantial risk of thromboembolism.[13] Adequate prophylaxis is therefore essential for patients who have been in AF for >48 hours or who have AF of undetermined duration.

Traditionally, oral anticoagulants (with an international normalised ratio between 2.0 and 3.0) are administered for at least 3 weeks before any attempt at pharmacological/electrical cardioversion. An alternative approach is based on prompt anticoagulation with intravenous heparin, followed by transoesophageal echocardiography to rule out the presence of intra-atrial thrombi. In this case, cardioversion (pharmacological or electrical) can be safely performed[14] as long as oral anticoagulants are maintained for at least 1 month afterwards. In patients with AF lasting more than 48 hours, this latter approach allows an 'accelerated' cardioversion, which might – in theory – limit the extent of the AF-induced remodelling that develops over time. However, the ACUTE (Assessment of Cardioversion Using Transesophageal Echocardiography) trial[14] revealed no advantage in terms of medium-term (8 weeks) maintenance of sinus rhythm.

The risk of thromboembolism in AF lasting <48 hours[15] is considerably lower (probably <1%). According to current guidelines,[11] cardioversion may be performed without transoesophageal echocardiography or prolonged anticoagulation. Nevertheless, in high-risk patients with previous thromboembolism or severe left ventricular dysfunction, it is prudent either to delay cardioversion or use intravenous heparin and perform transoesophageal echocardiography.[15]

3. Front-Line Management of Recent-Onset AF

For AF of recent-onset (lasting <48 hours), appropriate front-line clinical management implies: (i) assessment of haemodynamic tolerance of AF (to rule out acute haemodynamic impairment); (ii) prophylaxis for AF-related thromboembolic complications; and (iii) acute treatment for conversion to sinus rhythm and/or rate control.

The first point is of most importance since the presence of acute haemodynamic impairment (as detected by the presence of hypotension or other signs of low cardiac output) dictates prompt conversion to sinus rhythm by electrical cardioversion. The second point, regarding the importance of thromboembolic prophylaxis is discussed in section 2. As regards the third point, the rationale for attempting rapid restoration of sinus rhythm is based on the need to: (i) prevent electrophysiological and structural remodelling;[8] (ii) avoid the need for oral anticoagulants (which, however, are a specific requirement in long-lasting AF);[15] (iii) reduce the length of hospital stay or in some cases avoid hospitalisation altogether by providing management in emergency departments or outpatient clinics;[16] and (iv) improve overall patient compliance and also tolerability to recurrent AF.

3.1 Spontaneous Conversion to Sinus Rhythm: Clinical and Methodological Implications

A series of controlled studies showed that in patients with recent-onset AF, restoration of sinus rhythm most often occurs spontaneously in 10–18% within 3 hours of hospitalisation, 55–66% within 24 hours, and 76–83% within 48 hours (see figure 1).[17-21] Clinical predictors of spontaneous conversion to sinus rhythm are absence of structural heart disease,[19,22] age <60 years[23] and AF of <24 hours duration.[21] These observations highlight the need for placebo-controlled trials to evaluate antiarrhythmic efficacy. They also suggest the clinical utility of adopting an observation period of some hours before active treatment in selected patients

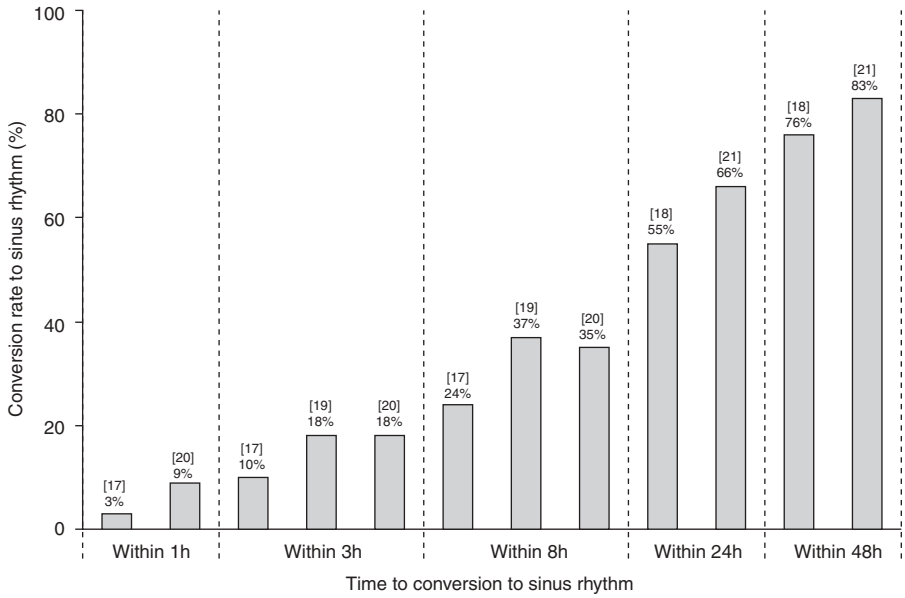

Fig. 1. Conversion rates to sinus rhythm at different time intervals, following the administration of placebo, according to a series of controlled studies.[17-21]

(those with the highest likelihood of spontaneous conversion).

3.2 Options for Pharmacological Cardioversion

A series of pharmacological options are available for converting AF of recent onset. However, the levels of evidence supporting the use of each option varies widely, depending on the designs of the available studies.[11,24] In the US, only intravenous ibutilide, oral quinidine and oral dofetilide currently have formal approval from the US FDA for conversion of AF.[25] Table I summarises efficacy, incidence of adverse effects and level of evidence (according to recent guidelines) of the different agents used in conversion of recent-onset AF.

3.2.1 Digoxin

For many years intravenous digoxin was widely used for all cardioversion purposes, including recent-onset AF. This approach has become irrevocably dated since a series of placebo-controlled trials using intravenous and oral digoxin conclusively demonstrated that this drug does not enhance conversion rates.[26-28] However, in practice, digoxin does continue to be used for rate control, particularly in patients with chronic heart failure or left ventricular dysfunction (in other settings it has been almost completely superseded by β-adrenoceptor antagonists and calcium channel antagonists).[7]

3.2.2 Quinidine

Treatment with oral quinidine was first proposed in 1918.[29] Quinidine has class IA properties and anticholinergic activity that can facilitate conduction through the atrioventricular node and accelerate ventricular response. Thus, concomitant pharmacological depression of the atrioventricular node is required. The quinidine preparation most commonly used for oral administration is quinidine sulphate. This preparation used to be administered orally by a titration including 200mg orally every 2 hours up to 1200mg, or 300–400mg three times daily. Nowadays, lower dosages of 300–600mg are commonly adopted with simple oral loading.[30] Heterogeneous studies (including some uncontrolled evaluations) suggest that the efficacy of quinidine in restoring sinus rhythm may vary between 30% and 90%.[18,31-33] An historical review[34] suggested 71% efficacy in sinus rhythm restoration. A meta-analy-

Table I. Effects of different agents in conversion of recent-onset (<48 hours) atrial fibrillation (reproduced from Boriani et al.,[22] with permission)

Drug	Type of recommendation[a]	Level of evidence[b]	Route of administration	Time of conversion	Efficacy (%)	Adverse effects (%)
Quinidine	IIb	B	PO	<24h	59–92	3–46
Procainamide	IIb	C	IV	<1.5h	43–88	2–12
Disopyramide	NA	NA	IV	<8h	55–86	7
Propafenone	I	A	IV	<4h	43–89	0–17
			PO	<5h	72–86	10–14
Flecainide	I	A	IV	<2h	65–96	7–31
			PO	<5h	78–95	21–23
Amiodarone	IIa	A	IV	<12h	25–89	7–27
Dofetilide	I	A	PO	<2h	43	15
Ibutilide	I	A	IV	<1.5h	31–60	25
Sotalol	III	A	IV	<4h	31–85	10–20
Esmolol	NA	NA	IV	<40min	6–50	14–19

a Types (classes) of recommendation for a treatment, summarising both the evidence and expert opinion: I, evidence for and/or general agreement that the treatment is useful and effective; II, conflicting evidence and/or a divergence of opinion about its usefulness/efficacy; IIa, weight of evidence/opinion is favourable; IIb, usefulness/efficacy is less well established by evidence/opinion; III, evidence and/or general agreement that it is not useful/effective and in some cases may be harmful.

b Levels of evidence: 'A' (highest), based on data from multiple randomised clinical trials; 'B' (intermediate), based on a limited number of randomised trials, non-randomised studies or observational registries; 'C' (lowest), primarily based on expert consensus.

IV = intravenous; **NA** = not available; **PO** = oral.

sis by Miller et al.[35] which included 200 patients revealed 'moderate' evidence of efficacy, with an odds ratio of 2.9 (95% CI 1.2, 7.0).

The safety and tolerability profile of quinidine presents some cause for concern. There is a high incidence of adverse effects, most often affecting the gastrointestinal tract. These may lead to dose reduction or withdrawal of treatment in up to 42–58% of patients.[35,36] Adverse events present a major obstacle to long-term prophylactic use of quinidine (against AF recurrences), and safety is a key issue also in the context of cardioversion. The most harmful adverse event following quinidine administration is torsade de pointes, which may cause syncope or cardiac arrest.[37] This arrhythmia has been reported during treatment with quinidine in 1–8% of treated patients.[37] QT prolongation may be either a toxic effect (related to drug doses and plasma concentrations) or an idiosyncratic reaction that can occur after the first dose, even in the context of low plasma concentrations. Although the latter form is unpredictable, some clinical risk factors (female sex, bradycardia, concurrent hypokalaemia) have been identified.[11] The risk is higher if the QT interval is prolonged for >0.55 seconds in the presence of hypokalaemia or bradycardia. However, the problem is not strictly related to quinidine dosage and can occur even at low or subtherapeutic plasma concentrations.[37] Moreover, torsade de pointes usually occurs after resumption of sinus rhythm in AF patients, its onset being favoured by the lower ventricular rate. Fatal complications due to the proarrhythmic effects of quinidine were reported by Tebbe et al.[38] in a large group of patients undergoing in-hospital treatment. In general, it seems advisable to suspend quinidine in the presence of QRS prolongation to >50% of the basal value, a QRS duration >140 msec or a QT/corrected QT (QTc) value >500 msec.[39]

A meta-analysis of the use of quinidine for long-term prophylaxis of AF recurrences,[40] which revealed an increase in all-cause mortality compared with controls, revived wider concerns about its use in clinical practice. However, no meta-analysis is available for the cardioversion setting.

3.2.3 Procainamide

Intravenous procainamide is not currently used for conversion of AF and the drug is not universally

available in Europe.[29] It remains the drug of choice in the US for wide complex tachycardia caused by anterograde conduction of AF over an accessory pathway.[30] At doses of 5–15 mg/kg (maximum dose 1000mg) delivered at 0.2–0.4 mg/kg/min over 10–15 minutes, procainamide has been reported to show limited efficacy compared with other currently available agents.[30] Fenster et al.[41] reported a conversion rate of 57%. In a blinded comparison with ibutilide, sinus rhythm restoration within 1.5 hours was observed in 15–20% of patients.[42] The most common adverse effect during intravenous administration is hypotension with depression of cardiac function. Torsade de pointes can occur as a consequence of excessive QT prolongation.[11]

3.2.4 Propafenone

The efficacy of propafenone in converting recent-onset AF has been evaluated in a series of trials dealing with both intravenous and oral administration. With intravenous administration (2 mg/kg bolus followed by 0.0078 mg/kg infusion), conversion rates ranging from 43% to 89% have been reported,[22] all significantly higher than with placebo. Propafenone undergoes hepatic metabolism and one of its metabolites (5-hydroxy-propafenone) contributes to drug effectiveness. These two factors explain the increasing conversion rates observed in the first hours, following production of metabolites in the liver.[17] Propafenone has also been administered as oral loading (450–600mg, depending on bodyweight), with conversion rates of 45–55% at 3 hours and 69–78% at 8 hours, always significantly higher than placebo (figure 2).[22] Conversion to sinus rhythm usually occurs within 3–4 hours of oral loading. This regimen has been tested in in-patient settings and is currently under evaluation for selected outpatients who have been previously tested in hospital.

Intravenous or oral administration of propafenone requires careful selection with systematic exclusion of patients with left ventricular dysfunction or congestive heart failure, sick sinus syndrome, intraventricular conduction defects (QRS duration ≥110 msec) and second- or third-degree atrioventricular block.[22] As with other class IC antiarrhythmic agents, there is a risk of transforming AF into a relatively slow atrial flutter with the possibility of 1 : 1 conduction in the ventricle, leading to an ECG pattern typical of so-called 'wide QRS complex tachycardia', which is not easy to distinguish from ventricular tachycardia. Such complications are strongly facilitated by adrenergic stimulation,[43] and they have been reported in 3.5–5% of patients treated with class IC antiarrhythmic drugs.[37,44-46] For this reason, it is advisable to keep patients at rest in the hours following intravenous or oral administration of propafenone or any other class IC agent. However, phases in which regularised atrial rhythm is accompanied by fast ventricular rate can also occur in AF patients not being treated with class IC agents.[47] To control the ventricular rate in cases of transformation of AF into atrial flutter, Marcus[44] proposed concurrent administration of calcium channel antagonists, β-adrenoceptor antagonists or digoxin, but the validity of this strategy has yet to be prospectively validated. Milder adverse effects include slight hypotension and gastrointestinal symptoms such as nausea.

3.2.5 Flecainide

The other class IC agent used to treat AF is flecainide. Here again, because of the negative ino-

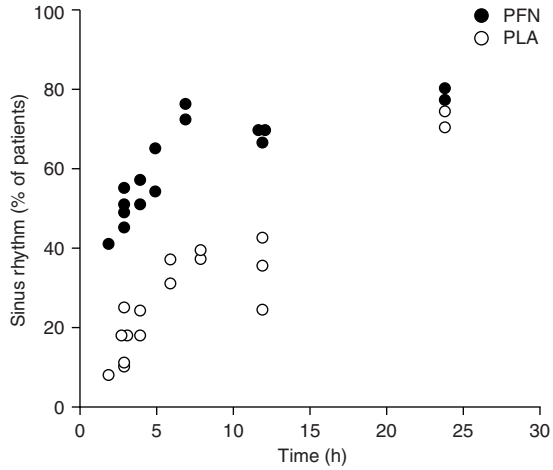

Fig. 2. Conversion rates to sinus rhythm at different time points following placebo (PLA) or propafenone (PFN) treatment in seven placebo-controlled trials (reproduced from Boriani et al.,[22] with permission).

tropic effects of the drug, it is essential to exclude patients with left ventricular dysfunction or heart failure. Flecainide was initially evaluated for intravenous treatment of patients with paroxysmal AF (1.5–2 mg/kg bolus in 10–20 minutes).[11] On the basis of three studies[48-50] and one comparative trial evaluating its efficacy versus oral quinidine,[51] intravenous flecainide seems to provide good conversion rates (67–86%) coupled with a relatively rapid effect, with the majority of conversions occurring within 2 hours of administration. Oral loading of flecainide (200–300mg as single dose) has also been tested in selected patients with little sign of underlying heart disease.[20,52,53] This approach most often restores sinus rhythm within 3–5 hours of administration, the overall efficacy being about 51% at 3 hours and 72% at 8 hours.[52] As with propafenone, it is important to bear in mind the risk of atrial flutter with 1 : 1 atrioventricular conduction common to all class IC agents and to keep patients at rest after either route of administration.

3.2.6 Cibenzoline

Introduced about 20 years ago, cibenzoline has class I antiarrhythmic activity, associated with some properties of class III and IV drugs.[54-58] Limited data are available regarding the efficacy of cibenzoline in cardioversion of AF. In a prospective, open-label study[59] involving 51 patients with atrial tachyarrhythmia (of whom 18 had AF) lasting at least 3 hours, intravenous cibenzoline (a slow bolus infusion of 1 mg/kg, followed by a 8 mg/kg/24h continuous infusion) achieved conversion in about 70% of patients, a result similar to that obtained in an analogous group treated with amiodarone. The brief duration of arrhythmia may have led to an overestimation of the efficacy of cibenzoline (5 of the 51 patients converted spontaneously to sinus rhythm). Thus, the available data provide little support for the use of cibenzoline in AF.

3.2.7 Amiodarone

In Europe, intravenous administration of amiodarone (5 mg/kg bolus followed by 1.5–1.8 g/24h) is widely used to treat AF, especially in the presence of contraindications to class IC agents. The reported efficacy of amiodarone ranges from 25% to 89% (table I).[22] However, in three controlled studies[20,52,60] amiodarone failed to show evident efficacy for acute treatment of recent-onset AF. The delayed effect can probably be ascribed to the pharmacokinetic profile of amiodarone and the absence of desethylamiodarone-related electrophysiological effects during acute administration.

Three relevant major meta-analyses have recently appeared.[61-63] In a meta-analysis of 13 studies involving 1174 patients, Chevalier et al.[62] found that intravenous amiodarone provided similar conversion rates to placebo at 1–2 hours, but was superior at 6–8 hours (56% vs 43% with placebo) and at 24 hours (82% vs 56%). Class IC agents (flecainide and propafenone) were shown to be more effective than amiodarone at 1–2, 3–5 and 6–8 hours. A meta-analysis[61] that did not focus on specific time intervals revealed 82% efficacy at 2–48 hours for intravenous amiodarone (vs 60% with placebo); no significant difference in efficacy was found between amiodarone and other antiarrhythmic agents, including class IC antiarrhythmic drugs. Finally, in a meta-analysis evaluating 91 studies and various antiarrhythmic agents administered for restoration and maintenance of sinus rhythm,[63] amiodarone did not differ from the pooled results of other antiarrhythmic agents; however, inclusion of other trials regarding cardioversion or long-term sinus rhythm maintenance prevented any definitive conclusions about the overall efficacy of amiodarone with respect to other agents.

Recently, Blanc et al.[64] compared oral loading of amiodarone 30 mg/kg and propafenone in recent-onset AF. At 24 hours, no difference was found in conversion efficacy (47% for amiodarone). However, the longer mean conversion time (6.9 vs 2.4 hours for propafenone) reinforced the concept that amiodarone is relatively slow acting. Despite this important limitation, amiodarone is a treatment of choice for AF in the setting of acute ischaemia, acute myocardial infarction or left ventricular dysfunction. Moreover, intravenous amiodarone may also be used in AF complicating cardiac surgery.

Clinical use of intravenous amiodarone requires some caution. In the presence of left ventricular

dysfunction and/or low cardiac output, haemodynamic impairment may occur, largely because of the effects of polysorbate 80, the solvent present in conventional amiodarone preparations for intravenous administration. An aqueous formulation of amiodarone is under clinical evaluation: initial experiences confirm its superior haemodynamic tolerability.[65] Intravenous amiodarone should not be used in AF associated with ventricular pre-excitation because of its predominant effect on the atrioventricular node, increasing conduction over the accessory pathway and the risk of ventricular fibrillation.[66] Finally, it should also be remembered that administration of amiodarone via a peripheral vein carries a risk of phlebitis.

3.2.8 Dofetilide

Dofetilide is a relatively new class III antiarrhythmic agent that prolongs action potential duration and refractoriness of both the atrial and the ventricular myocardium. Dofetilide can be administered either intravenously or orally, but only the oral formulation is currently approved for clinical use and only available in the US and Canada. Following oral administration there is a linear relationship between plasma dofetilide concentrations and the QTc interval.[67] Dofetilide is largely cleared by the kidneys, and the dosage needs to be adjusted in patients with impaired renal function.[68] Although oral dofetilide has a class I indication for both recent-onset and chronic AF,[11] the major prospective studies suggesting its clinical use were performed in patients with chronic persistent AF.

For recent-onset AF, studies on intravenous dofetilide have shown an overall efficacy ranging between 14% and 53%.[69-73] Its efficacy appears to be considerably higher in atrial flutter than in AF[69-74] (about 71% vs 30%). In the various studies, 3.6% of patients developed torsade de pointes, with 0.5% presenting sustained episodes.[69-74] As regards paroxysmal AF or paroxysmal atrial flutter, based on the results of four studies, use of oral dofetilide is not currently recommended by US FDA authorities.[68]

3.2.9 Ibutilide

Ibutilide is a class III antiarrhythmic drug that has been extensively evaluated in the US.[75-77] Although use of ibutilide is now authorised in many countries, the high cost of this agent has discouraged widespread adoption. Ibutilide was the first drug specifically designed, developed and approved in the US for AF conversion to sinus rhythm.[78] This agent has a short half-life, as a result of extensive tissue distribution, and is available only for intravenous administration, because of high first pass clearance by the liver.

Intravenous ibutilide (0.05–0.025 mg/kg in 10 minutes) has been used for conversion of both AF and atrial flutter. With AF its efficacy ranged between 27% and 40%, while higher conversion rates (30–71%) were obtained in patients with atrial flutter. When sinus rhythm restoration is achieved, it usually occurs after 60–90 minutes.[76,77,79,80] Otherwise, direct current (DC) cardioversion can be safely performed later[81] with high conversion rates.[82] The advantages of ibutilide are the rapidity of its action and the absence of negative inotropic effects[77,83] (even in patients with reduced left ventricular function[76]). Apart from hypotension and bradycardia, ibutilide infusion can also be associated with polymorphic ventricular tachycardia or torsade de pointes.[11,76,84]

Among 586 patients treated acutely with ibutilide, non-sustained polymorphic ventricular tachycardia was observed in 2.7%, while sustained polymorphic ventricular tachycardia occurred in 1.7%.[77] Other authors reported a slightly higher incidence of proarrhythmia.[35,79] Factors that increase the risk of proarrhythmia include female gender, non-White race, heart failure and bradycardia.[77] In view of the time dependency of QT prolongation and the time distribution of proarrhythmia, patients should be monitored by ECG for at least 4 hours after ibutilide administration to detect any proarrhythmic event.[11,30,75,76] Since ibutilide cannot be used orally, acute intravenous administration can be followed by administration of an appropriate antiarrhythmic drug for prophylaxis of recurrence.[30]

3.2.10 Sotalol

Sotalol is widely used for prophylaxis of AF. However, the available data do not support the use of sotalol for cardioversion, regardless of the route of administration. Whereas an early study[85] presented sotalol as a highly effective drug for conversion of acute AF, all but one[86] of the subsequent randomised trials have been highly unfavourable. In particular, it now appears that sotalol is inferior to quinidine[32] or flecainide,[87] and that it is only slightly superior to placebo.[88] The discrepancy between the efficacy of sotalol in preventing recurrence of AF and its limitations as a converting agent can be explained by its tendency to prolong atrial refractoriness more at low heart rates than at high rates – an effect known as 'reverse use dependence'.[89,90]

Adverse effects of sotalol are related to its β-adrenergic antagonistic activity (fatigue, dizziness, dyspnea, worsening of bronchospasm and, more seriously, bradycardia and hypotension) and to QT prolongation (risk of torsade de pointes).[91-93] However, the adverse effects of sotalol do not seem to be worse than those of class I drugs.

3.2.11 Comparisons Between Different Agents and Drug Regimens

Not many comparative studies exist regarding the efficacy of two or more drugs for pharmacological conversion of recent-onset AF. Demonstration of the superiority of any given agent within a specific setting appears problematic. For the purposes of this review, table II provides a summary of the results of the principal meta-analyses[35,61-63,94,95] available in the literature regarding the efficacy of the various drugs in terms of odds ratios and relative risk with respect to placebo. As shown in table II, the highest odds ratio values have been reported for flecainide and ibutilide.

Table II. Efficacy of different agents used for pharmacological cardioversion of recent-onset atrial fibrillation (AF) in terms of odds ratios and relative risks (95% CI) with respect to placebo, based on the main available meta-analyses/pooled analyses. Values in italics are extrapolated from the published data; all other values refer to data reported in the original articles

Treatment	Odds ratio (95% CI)	Relative risk (95% CI)
Class IA drugs[63]	*2.4 (1.9, 3.1)*	*1.6 (1.4, 2.0)*
disopyramide (IV)[94]	7.0 (0.3, 153.0)	NA
disopyramide (IV)[35]	7.0 (0.3, 153.0)	*5.6 (0.3, 109.7)*
quinidine[94]	2.9 (1.2, 6.9)	NA
quinidine[35]	2.9 (1.2, 7.0)	*2.4 (1.0, 5.5)*
Class IC drugs[63]	*4.0 (2.5, 6.6)*	*2.2 (1.5, 3.3)*
flecainide[94]	13.2 (6.4, 27.4)	NA
flecainide[35]	24.7 (9.0, 68.3)	*7.5 (3.1, 18.4)*
propafenone[94]	3.9 (2.3, 6.8)	NA
propafenone[35]	4.6 (2.6, 8.2)	*2.4 (1.4, 4.1)*
Class III drugs[63]	*2.1 (1.5, 3.0)*	*1.6 (1.2, 2.1)*
amiodarone (within 8h of administration)[62]	*1.3 (1.06, 1.8)*	1.2 (1.0, 1.5)
amiodarone (within 24h of administration)[62]	*3.7 (2.3, 5.9)*	1.4 (1.2, 1.7)
amiodarone (IV)[61]	*2.9 (1.8, 4.5)*	*1.4 (1.1, 1.7)*
amiodarone (IV infusion in AF lasting ≤48h)[95]	NA	1.40 (1.25, 1.57)
amiodarone (IV infusion in AF lasting >48h)[95]	NA	4.33 (2.76, 6.77)
amiodarone[94]	3.2 (2.5, 5.1)	NA
amiodarone (IV)[35]	5.7 (1.0, 33.4)	*1.7 (0.5, 6.0)*
dofetilide[94]	6.7 (4.5, 10)	NA
ibutilide (IV)[94]	30.7 (10.9, 86)	NA
ibutilide/dofetilide (IV)[35]	29.1 (9.8, 86.1)	*18.8 (6.1, 58.1)*
sotalol[94]	1.1 (0.1, 6.9)	NA
sotalol (oral)[35]	0.4 (0.0, 3.0)	*0.5 (0.1, 3.0)*

IV = intravenous; **NA** = not available.

3.2.12 Postoperative AF

Some mention should be made of postoperative AF, which can be considered a particular type of recent-onset AF. Occurring in about 20–50% of patients submitted to cardiac surgery,[11,96] especially in second and third postoperative days,[97] AF is the most common postoperative arrhythmia[96,98] and has high associated costs.[99] Alongside age, many other less well established pre-/intra-/postoperative factors have been proposed (valvular heart disease, previous episodes of AF, atrial enlargement, chronic lung disease and certain surgical techniques, etc.) for prediction of postoperative AF.[11,98,100] Pharmacological prevention of postoperative AF has been extensively evaluated; it is advisable to treat patients undergoing cardiac surgery with an oral β-adrenoceptor antagonist unless contraindicated.[11] Other reasonable options in high-risk patients are postoperative atrial pacing and (especially in patients with low ejection fraction) amiodarone.[11,100]

The high spontaneous conversion rate (up to 80%)[100,101] of postoperative AF supports the use of a rate control strategy (generally based on β-adrenoceptor antagonists because of the frequent presence of high adrenergic drive), except for haemodynamically unstable or highly symptomatic patients or when anticoagulation is contraindicated.[98,100,101] In the presence of haemodynamic instability, electrical cardioversion is advisable (a straightforward procedure in intensive care settings). In the remaining patients, it is preferable to use agents such as intravenous amiodarone or ibutilide,[11,96,98,100] avoiding class IC agents, especially after myocardial infarction[100] or in the presence of left ventricular dysfunction.

4. Long-Lasting AF

4.1 The Role of Pharmacological Cardioversion

While pharmacological cardioversion is a major option for haemodynamically stable patients with AF of recent onset, its use for persistent AF of long duration (i.e. >7 days according to ACC/AHA/ESC guidelines)[11] is largely confined to amiodarone and (to some extent) dofetilide. This situation is mainly because of the limited efficacy of most other drugs, and the widespread acceptance of electrical cardioversion as the gold standard in long-lasting AF. Although a study performed in an animal model of sustained AF (>7 days)[102] suggested that class I and III antiarrhythmic intravenous drugs could provide good efficacy for conversion to sinus rhythm, this concept has not been reflected in clinical practice, perhaps because of the influence of underlying heart disease, triggering factors and chronic remodelling. The design of the relatively few prospective studies regarding the clinical efficacy of antiarrhythmic agents in long-lasting AF usually involved a straight comparison between two antiarrhythmic agents (frequently without a placebo arm) among patients with heterogeneous durations of AF. While summarising the available evidence regarding the various agents, we concentrate on the role of amiodarone and dofetilide. Both of these drugs can be used in patients with structural heart alterations. Amiodarone has the advantage that it can be used in preparation for electrical cardioversion (as well as being more effective than class I agents in maintaining sinus rhythm).

Table III summarises efficacy, incidence of adverse effects, and level of evidence (according to recent guidelines) of the various agents within the setting of long-lasting AF.

4.1.1 Amiodarone

The drug that currently lays the strongest claim to play a major role in long-lasting AF is amiodarone. In addition to pharmacological cardioversion, amiodarone can also be used in preparation for electrical cardioversion; it can also help maintain sinus rhythm. It should be noted that oral administration of amiodarone leads to progressive accumulation (over a period of weeks) of desethyl-amiodarone, an important active metabolite that exerts antiarrhythmic effects in its own right.

As regards pharmacological cardioversion,[103] amiodarone achieved good conversion rates at 48 hours (44%) after intravenous administration. Although Zehender et al.[104] encountered a conversion

Table III. Effects of different agents in conversion of long-lasting (>7 days) atrial fibrillation

Drug	Type of recommendation[a]	Level of evidence[b]	Route of administration	Time of conversion	Efficacy (%)	Adverse effects (%)
Quinidine	IIb	B	PO	8.5h–3.5d	32–60	25–27
Propafenone	IIb	B	IV + PO	≤20d	6–41	3
Flecainide	IIb	B	IV + PO	1.5–7.5h	0–46	6–18
Amiodarone	IIa	A	IV + PO	7–20d	12–44	0–40
Dofetilide	I	A	PO	24–36h	6–30[c]	1–3[c]
Dofetilide	NA	NA	IV	20 min–6h	19–24	3–5
Ibutilide	IIa	A	IV	NA	16–50	NA
Sotalol	III	A	IV	NA	0–6	NA

a Types (classes) of recommendation for a treatment, summarising both the evidence and expert opinion: I, evidence for and/or general agreement that the treatment is useful and effective; II, conflicting evidence and/or a divergence of opinion about its usefulness/efficacy; IIa, weight of evidence/opinion is favourable; IIb, usefulness/efficacy is less well established by evidence/opinion; III, evidence and/or general agreement that it is not useful/effective and in some cases may be harmful.

b Levels of evidence: A (highest), based on data from multiple randomised clinical trials; B (intermediate), based on a limited number of randomised trials, non-randomised studies or observational registries; C (lowest), primarily based on expert consensus.

c Dose dependent.

IV = intravenous; **NA** = not available; **PO** = oral.

rate of only 10% at 72 hours from intravenous administration, subsequent oral administration led to a conversion rate of 40% by day 14. Subgroup analyses of prospective studies regarding patients with heterogeneous duration of AF indicate conversion rates of 27–34% within 4 weeks in patients with AF lasting at least 1 month.[105-107] Taken together, the available studies suggest that around 30–40% of patients with long-lasting AF are likely to convert within 2–4 weeks of oral amiodarone administration.

Data derived from studies where amiodarone was used in preparation for electrical cardioversion generally regard patients with more refractory AF. A series of studies on such patients provided homogeneous conversion rates of 12–25% before electrical cardioversion[108-112] (followed by eventual success rates of 67–100% after electrical shock). These findings are of especial clinical relevance in view of the generally long duration of the AF and the frequent failure of other treatments. Taken together, they strongly support the use of amiodarone for patients with long-lasting AF who are candidates for electrical cardioversion. However, it should be noted that the well known adverse effects can limit long-term treatment with this agent after cardioversion.

4.1.2 Dofetilide

Dofetilide is a relatively new class III antiarrhythmic agent that has been specifically tested for long-lasting AF/atrial flutter, and has gained US FDA approval for use in this setting.[113] Three randomised, controlled trials investigating the efficacy of intravenous dofetilide have all shown its superiority to placebo in long-lasting AF.[72,114,115] At a dose of 8 μg/kg, mean conversion rates in the long-lasting AF subgroup ranged from 19% to 24% (one trial also included a 4 μg/kg dosage arm, which provided a 10% conversion rate).[72] Much higher conversion rates were obtained in the long-lasting atrial flutter subgroups.

Oral dofetilide has been studied in two large-scale trials dedicated to chronic AF/atrial flutter. In the EMERALD (European and Australian Multicenter Evaluation on Atrial Fibrillation Dofetilide) trial,[116] patients with AF (the majority) or atrial flutter were randomised to receive either dofetilide 125, 250 or 500μg twice daily, sotalol 80mg orally twice daily or placebo. Dofetilide proved superior to sotalol in terms of conversion rates (up to 29% vs 6%) in AF patients, and it displayed a dose-dependent profile. The SAFIRE-D (Symptomatic Atrial Fibrillation Investigative Research on Dofetilide) trial[117] showed similar dose-dependent conversion rates (6–30%), while subgroup analysis confirmed

the superior efficacy of dofetilide in atrial flutter (67% vs 22% in AF). It should be noted that dofetilide did not seem to influence the reversion rates obtained at subsequent electrical cardioversion (about 70–80% in all arms). These two trials – along with a subgroup analysis[118] of the DIAMOND (Danish Investigations of Arrhythmia and Mortality ON Dofetilide) trials – showed that dofetilide is effective for sinus rhythm maintenance at 1 year.

Although dofetilide provides one of the two major pharmacological options for long-lasting AF, its availability (in the oral formulation only) is currently confined to the US and Canada. Initiation of treatment with dofetilide requires at least 4 days of in-hospital monitoring.

4.1.3 Quinidine

Although quinidine has been used in the management of long-lasting AF, few data exist to support its employment in this setting. Indeed, few studies have analysed the efficacy of quinidine for conversion of long-lasting AF to sinus rhythm. After the optimistic pioneering evaluations,[119,120] estimates of efficacy have ranged between 32% and 60%,[51,103,104,121] presenting similar efficacy in two comparative studies versus amiodarone[103,104] and superior efficacy with respect to flecainide.[51]

4.1.4 Flecainide

Despite the effectiveness of flecainide in recent-onset AF, prospective studies[48,87,122,123] suggest that this drug is much less effective for long-lasting AF and, therefore, cannot be considered an advisable therapeutic option in this setting. Borgeat et al.[51] found that while flecainide showed similar efficacy to quinidine in AF lasting <10 days, it had much lower efficacy in long-lasting AF. Prospective studies[48,87,122,123] have reported conversion rates with flecainide ranging from 0% to 46% in heterogeneous groups of patients with long-lasting AF.

4.1.5 Propafenone

Not surprisingly, propafenone shares with flecainide a similarly low efficacy profile for long-lasting AF. Initial optimism following the report from an uncontrolled study of a conversion rate of 65%[124] was tempered by subsequent studies showing conversion rates of 6–41%.[125-127] Two placebo-controlled trials[125,126] assessing the usefulness of propafenone before external electrical shock showed rates of conversion within 48 hours of 6–6.5%. Kochiadakis et al.[127] found that the efficacy of propafenone in patients with AF lasting >3 weeks was rather similar to that of amiodarone (41% vs 47% within 4 weeks).

4.1.6 Ibutilide

Very few data are available regarding the efficacy of intravenous ibutilide in conversion of long-lasting AF. Three small subgroup analyses reported efficacy levels of 16–50%;[79,80,84] however, confirmation from specifically targeted studies would be necessary to establish the role of ibutilide in this setting. Ibutilide has been successfully used for facilitating DC cardioversion of long-lasting AF,[128] although use of this agent in patients with very low ejection fraction may lead to severe proarrhythmia.

4.1.7 Sotalol

The few data present in the literature[87,129] suggest that sotalol is ineffective for conversion of chronic as well as acute AF (although it presents good efficacy for sinus rhythm maintenance).

5. Proarrhythmic Effects of Antiarrhythmic Drugs and Predisposing Factors

Many authors have reported associations between antiarrhythmic agents and potentially lethal proarrhythmic effects.[40,130,131] 'Proarrhythmia', that is, arrhythmia provoked or worsened by administration of antiarrhythmic drugs, by definition strictly refers to therapeutic doses or plasma concentrations.[37,132] Such reactions are generally considered relevant only if they significantly increase the incidence of symptomatic arrhythmias or result in an increase in mortality from arrhythmia with respect to placebo.[131] Otherwise, it is difficult to gauge whether a given drug has been proarrhythmic in a specific patient, both because of day-to-day variability in arrhythmia frequency (commonly seen even in the absence of drug therapy) and the characteristic progression of any underlying cardiopathy.

Table IV. Risk of proarrhythmic effects with antiarrhythmic drugs used in atrial fibrillation (AF) cardioversion

Effects	Drug	Incidence
Transformation of AF to atrial flutter with higher ventricular rate	Quinidine, class IA AA	Rare at current regimens
Transformation of AF to atrial flutter with 1 : 1 AV conduction and wide QRS	Flecainide, propafenone	3.5–5%
Torsade de pointes	Quinidine, class IA AA	1–8%
	Ibutilide, dofetilide, sotalol	Up to 8%
	Amiodarone	0.7%
VT or VF	Potentially all AA	Rare except when LV dysfunction or congestive heart failure are present
High-grade AV block	Class IA AA, class IC AA	Rare
Aggravation of sinus node dysfunction in sinus node disease	Potentially all AA	Variable according to drugs and underlying sinus node disease

AA = antiarrhythmic agents; **AV** = atrioventricular; **LV** = left ventricle; **VF** = ventricular fibrillation; **VT** = ventricular tachycardia.

Many different mechanisms underlie proarrhythmia, and each antiarrhythmic agent presents its own particular spectrum. Table IV shows the main proarrhythmic effects of the drugs used for treating AF or atrial flutter. Torsade de pointes – a polymorphic ventricular tachycardia that occurs in the setting of QT interval prolongation and can deteriorate to ventricular fibrillation – is associated with class IA and class III antiarrhythmic agents. This proarrhythmic event is mediated by early afterdepolarisation caused by substances that prolong the action potential duration. This phenomenon is often associated with quinidine administration, where it is not dose related.[37,133] Sotalol can also cause torsade de pointes, but here the risk is dose dependent, being estimated at around 1% for dosages of 160–240 mg/day, rising to 4–5% at >480 mg/day.[37,92] Although amiodarone can also cause torsade de pointes, the overall incidence is lower than that associated with class IA and other class III agents, even in patients with structural heart disease.[131,134,135] The reasons for this are almost certainly multifactorial,[135,136] and can largely be attributed to the β-antagonist properties of amiodarone and its calcium channel antagonising effect.[136,137]

Factors known to be associated with increased risk of developing torsade de pointes during treatment with the agents discussed in the previous sections include hypokalaemia, hypomagnesaemia, female gender, bradycardia (spontaneous or drug induced), renal/hepatic failure, some genetically determined conditions (e.g. latent forms of long-QT syndrome), left ventricular hypertrophy and association with drugs that prolong the QT interval.[132,136]

As a proarrhythmic effect of pharmacological conversion of AF, torsade more often (in about 69% of reported cases) occurs after restoration of sinus rhythm.[138] This is due to the facilitating effect of rate slowing during the transition to sinus rhythm. Clinically, on administration of class IA or class III agents for conversion of AF, a period of some hours of observation is, therefore, strongly recommended following conversion to sinus rhythm.[136]

Class IC antiarrhythmic drugs (propafenone, flecainide) have marked effects on conduction velocity and, like IA agents, can organise and slow the rate of AF, converting it to atrial flutter. In some patients the atrial rate is slow enough to allow 1 : 1 atrioventricular conduction, which can lead to rapid ventricular response with wide QRS complexes simulating ventricular tachycardia, followed by the risk of haemodynamic impairment.[37] The reported overall incidence of 1 : 1 atrioventricular conduction during treatment with class IC antiarrhythmic agents is 3.5–5%.[37] Conditions associated with adrenergic stimulation can favour this type of proarrhythmia by facilitating conduction through the atrioventricular node. β-Adrenoceptor antagonists, calcium channel antagonists and even digoxin have been proposed to overcome this problem. However, no controlled data are available regarding their efficacy in patients treated with class IC agents.

As shown in table IV, other types of arrhythmia related to depression of atrioventricular conduction and/or sinus node function can be caused by any antiarrhythmic agent, most often in the context of pre-existing sinus node dysfunction, atrioventricular block or bundle branch block.[37,139]

Induction of ventricular proarrhythmia (sustained ventricular tachycardia or ventricular fibrillation) are rare in the absence of marked impairment of left ventricular function or other predisposing factors (e.g. electrolyte disequilibrium). It should be noted that ventricular fibrillation can occur in the absence of torsade de pointes or QT prolongation,[140-142] especially in the first few days of administration of class IA drugs (or other agents with similar electrophysiological properties) to patients with left ventricular dysfunction.[141,142] Appearance of a sustained monomorphic ventricular tachycardia (or the shift from a non-sustained to a sustained form) is most commonly seen with class IC antiarrhythmic drugs, probably as a result of drug-induced slowing of conduction velocity. Such events are more frequent in patients with structural heart disease or previous ventricular tachyarrhythmias.[132] The tachycardia, which can be incessant and resistant to external cardioversion, is often precipitated by exercise.[143] An increase in resting sinus rhythm or QRS duration during exercise can provide an early warning.[144] If this arrhythmia develops during antiarrhythmic treatment and is unresponsive to external cardioversion, β-adrenoceptor antagonists or hypertonic sodium bicarbonate can be beneficial.[132]

6. Novel Drugs

Among the many agents currently under evaluation, the most promising are class III antiarrhythmic drugs.[145]

Although tedisamil was first evaluated as an antianginal agent,[146] its ability to inhibit many kinds of repolarising ion channels coupled with its relatively selective activity in atrial tissue directed attention to its potential for AF conversion. In a recent dose-finding multicentre, randomised trial,[147] intravenous tedisamil obtained good conversion rates in patients with AF and atrial flutter (46% and 57% in the 0.4 and 0.6 mg/kg groups, respectively, vs 9% in the placebo arm). The incidence of proarrhythmia was 1.8% (with isolated episodes of monomorphic self-terminating ventricular tachycardia and non-sustained torsade de pointes).

Another class III agent that has undergone phase II evaluation is RSD 1235. In a recent phase II Canadian multicentre, randomised trial,[148] this prototype atrial-specific compound[145] provided a conversion rate of 61% (vs 5.3% with placebo) in patients with AF lasting 3–72 hours, without any increase in proarrhythmic events.[148]

Dronedarone exerts similar electropharmacological effects to amiodarone, of which it is a derivate, while probably avoiding the adverse thyroid and pulmonary effects associated with the parent drug.[145] Dronedarone is being assessed for maintenance of sinus rhythm in ongoing multicentre, randomised trials (ADONIS [Australian-American-African Trial with Dronedarone in Atrial Fibrillation or Flutter for the Maintenance of Sinus Rhythm] and EURIDIS [European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm]). In the DAFNE (Dronedarone Atrial Fibrillation Study after Electrical Cardioversion) trial[149] dronedarone provided a higher incidence of cardioversion with respect to placebo (14.8% in the 1600mg arm vs 3.1%) during the 5–7 days between the first administration and the planned DC cardioversion – a result rather similar to that obtained with amiodarone pre-treatment in patients with long-lasting AF.[149]

Azimilide is a relatively pure class III agent which is expected to exert a similar therapeutic effect to dofetilide in AF patients, although specific data regarding conversion of AF and atrial flutter are still awaited.[145]

Further studies are required to further establish the roles of all these novel drugs.

7. Management of AF in Clinical Practice

As mentioned in the introductory section, the responsibility of managing AF often falls to emergency or internal medicine departments, in collaboration with general practitioners. Several studies have shown that AF can be appropriately treated in emergency departments,[10,82,150-153] and specific guidelines for the selection of patients requiring direct admission to a cardiology department are hard to define. Effective management and treatment of AF in non-cardiology hospital settings has been facilitated by the widespread availability of continuous telemetry in many wards (together with the option of cardiology consultations). Despite dissemination of clinical guidelines and evidence from clinical trials, in practice, therapeutic approaches vary considerably from one setting to another. In a questionnaire survey involving 214 UK physicians, Lip et al.[154] found that cardiologists were more likely to attempt pharmacological cardioversion first (39% vs 18% of non-cardiologists) and electrical cardioversion (86% vs 69%) later on. (Interestingly, the authors also found that most physicians were oriented to introduce antiarrhythmic drugs in patients with new-onset AF, but usually prescribed digoxin as a rate control agent.)

Management of AF weighs heavily on the health budget, accounting for about 45% of all hospital admissions for arrhythmia,[155] with an average length of stay of 4–5 days.[151,155,156] In an experience reported by Dell'Orfano et al.[151] the overall costs of pharmacological conversion were lower than those of electrical cardioversion, which, it should be noted, requires a longer hospital stay. Other authors analysed the possibility of performing electrical cardioversion as a front-line strategy for restoration of sinus rhythm, as a viable alternative to the conventional drugs-first approach. In an interesting multicentre, randomised trial comparing the effectiveness and costs of pharmacological and DC cardioversion,[157] 139 patients with AF lasting <6 months, left ventricular ejection fraction >40% and without recent myocardial infarction were randomly assigned to strategies based either on pharmacological cardioversion followed (if necessary) by electrical conversion or on electrical (prior to pharmacological) cardioversion. Although the efficacy of the first attempt was similar with pharmacological or electrical cardioversion (74% vs 73%), the drugs-first strategy obtained a significantly higher final conversion rate (96% vs 84%), probably due to the facilitating effect of the antiarrhythmic drug. (The low success rates of electrical cardioversion were somewhat unusual, as was the extensive use of oral quinidine for pharmacological conversion.) Another important finding of this trial was the significantly better cost effectiveness of the drugs-first strategy, especially in patients with lone AF. However, this treatment strategy was associated with a higher incidence of severe complications, mainly in patients with structural heart disease, while mild adverse events were preferentially associated with sedation (which was performed by a cardiologist, presumably to reduce expense). Finally, the hospital stay was 1 ± 2 days in the drugs-first arm and 2 ± 2 days in the other arm.

Key decisions for optimising in-hospital management of AF regard the duration of the observation period before active pharmacological/electrical intervention, and the choice of the most appropriate treatment. Both decisions have to be based on a series of clinical considerations related to clinical conditions:

- recent-onset versus long-lasting AF or AF of unknown onset
- haemodynamic stability
- chance of spontaneous conversion to sinus rhythm
- thromboembolic risk
- first AF episode versus recurrence
- previous antiarrhythmic drug treatments
- lone AF versus underlying heart disease
- triggering factors
- risk factors for proarrhythmia
- physician's propensity for pharmacological versus electrical cardioversion
- comorbidities
- healthcare setting.

Table V. Criteria of choice for atrial fibrillation (AF) treatment in different clinical settings

Clinical setting	Treatment of choice
AF of recent onset without signs or symptoms of heart failure or ventricular dysfunction	Flecainide IV or oral loading Propafenone IV or oral loading
AF with acute haemodynamic impairment, low cardiac output or shock	Electrical cardioversion
AF of recent onset in patients with ventricular dysfunction and/or heart failure	Amiodarone IV (with caution) Ibutilide IV (with caution)
AF of recent onset in patients with intraventricular conduction disturbances	Amiodarone IV
AF of recent onset in patients with Wolff-Parkinson-White syndrome	Procainamide IV Flecainide IV Propafenone IV
AF of recent onset in patients with acute myocardial infarction or acute myocardial ischaemia	Amiodarone IV
Postoperative AF (recent-onset)	Amiodarone IV Ibutilide IV
Long-lasting AF	Electrical cardioversion Amiodarone PO Dofetilide PO
Long-lasting AF with planned electrical cardioversion	Amiodarone PO

IV = intravenous; **PO** = oral.

Table V contains a series of suggestions based on the literature and our experience.

8. Conclusions

The results of the recent AFFIRM and RACE trials have tended to shift attention from rhythm control to (ventricular) rate control. Nevertheless, especially in acute settings, conversion of AF to sinus rhythm remains an important therapeutic option. The aims of this strategy are to: (i) restore the atrial contribution to ventricular filling and output; (ii) regularise ventricular rate; and (iii) interrupt atrial remodelling. In selected patients, pharmacological cardioversion of recent-onset AF can safely provide a feasible and effective option, even for internal medicine and emergency departments. In most patients with recent-onset AF, pharmacological cardioversion provides a more feasible – and probably more cost effective – alternative to electrical cardioversion, which can then be employed as a second-line option for nonresponders.

In the absence of specific recommendations and guidelines, the choice of drugs for use in different settings must largely rely on the judgement of individual physicians based on clinical skills and knowledge of the literature. Class IC agents can provide rapid conversion to sinus rhythm in hospitalised patients with recent-onset AF without left ventricular dysfunction. Although intravenous amiodarone requires longer conversion times, it is still the standard treatment for patients with heart failure. For long-lasting AF (>7 days), the efficacy of antiarrhythmic agents is limited and electrical cardioversion remains the gold standard. Nevertheless, amiodarone can provide a synergistic treatment: when it does not immediately interrupt AF, it can subsequently restore sinus rhythm in candidates for electrical cardioversion and, hence, help maintain sinus rhythm.

In view of the potential for proarrhythmic and adverse effects of the various drugs, choice of the most appropriate agent and route of administration should be based on evaluations of the risk-benefit ratio of each option in the context of the clinical picture of the individual patient.

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References

1. Waktare JE, Camm AJ. Acute treatment of atrial fibrillation: why and when to maintain sinus rhythm. Am J Cardiol 1998; 81 Suppl. 5A: 3C-15C
2. Go AS, Hylek EM, Chang Y, et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? JAMA 2003; 290 (20): 2685-92
3. Nattel S, Khairy P, Roy D, et al. New approaches to atrial fibrillation management: a critical review of a rapidly evolving field. Drugs 2002; 62 (16): 2377-97
4. Blaauw Y, Van Gelder IC, Crijns HJ. Treatment of atrial fibrillation. Heart 2002; 88 (4): 432-7
5. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002; 347 (23): 1825-33
6. Van Gelder IC, Hagens VE, Boscher HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med 2002; 347 (23): 1834-40
7. Boriani G, Biffi M, Diemberger I, et al. Rate control in atrial fibrillation: choice of treatment and assessment of efficacy. Drugs 2003; 63 (14): 1489-509
8. Nattel S. New ideas about atrial fibrillation 50 years on. Nature 2002; 415 (6868): 219-26
9. Innes GD, Vertesi L, Dillon EC, et al. Effectiveness of verapamil-quinidine versus digoxin-quinidine in the emergency department treatment of paroxysmal atrial fibrillation. Ann Emerg Med 1997; 29 (1): 126-34
10. Michael JA, Stiell IG, Agarwal S, et al. Cardioversion of paroxysmal atrial fibrillation in the emergency department. Ann Emerg Med 1999; 33 (4): 379-87
11. Fuster V, Ryden LE, Asinger RW, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the North American Society of Pacing and Electrophysiology. J Am Coll Cardiol 2001; 38 (4): 1231-66
12. Gallagher MM, Camm J. Classification of atrial fibrillation. Am J Cardiol 1998; 82 Suppl. 8A: 18N-28N
13. Peters NS, Schilling RJ, Kanagaratnam P, et al. Atrial fibrillation: strategies to control, combat, and cure. Lancet 2002; 359 (9306): 593-603
14. Klein AL, Grimm RA, Murray RD, et al. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation: Assessment of Cardioversion Using Transesophageal Echocardiography Investigators. N Engl J Med 2001; 344 (19): 1411-20
15. Albers GW, Dalen JE, Laupacis A, et al. Antithrombotic therapy in atrial fibrillation. Chest 2001; 119 (1 Suppl.): 194S-206S
16. Lesser MF. Safety and efficacy of in-office cardioversion for treatment of supraventricular arrhythmias. Am J Cardiol 1990; 66 (17): 1267-8
17. Boriani G, Capucci A, Lenzi T, et al. Propafenone for conversion of recent-onset atrial fibrillation: a controlled comparison between oral loading dose and intravenous administration. Chest 1995; 108 (2): 355-8
18. Capucci A, Boriani G, Rubino I, et al. A controlled study on oral propafenone versus digoxin plus quinidine in converting recent onset atrial fibrillation to sinus rhythm. Int J Cardiol 1994; 43 (3): 305-13
19. Boriani G, Biffi M, Capucci A, et al. Oral propafenone to convert recent-onset atrial fibrillation in patients with and without underlying heart disease: a randomized, controlled trial. Ann Intern Med 1997; 126 (8): 621-5
20. Boriani G, Biffi M, Capucci A, et al. Conversion of recent-onset atrial fibrillation to sinus rhythm: effects of different drug protocols. Pacing Clin Electrophysiol 1998; 21 (11 Pt 2): 2470-4
21. Danias PG, Caulfield TA, Weigner MJ, et al. Likelihood of spontaneous conversion of atrial fibrillation to sinus rhythm. J Am Coll Cardiol 1998; 31 (3): 588-92
22. Boriani G, Martignani C, Biffi M, et al. Oral loading with propafenone for conversion of recent-onset atrial fibrillation: a review on in-hospital treatment. Drugs 2002; 62 (3): 415-23
23. Boriani G, Biffi M, Capucci A, et al. Oral loading with propafenone: a placebo-controlled study in elderly and nonelderly patients with recent onset atrial fibrillation. Pacing Clin Electrophysiol 1998; 21 (11 Pt 2): 2465-9
24. Nattel S, Kneller J, Zou R, et al. Mechanisms of termination of atrial fibrillation by class I antiarrhythmic drugs: evidence from clinical, experimental, and mathematical modeling studies. J Cardiovasc Electrophysiol 2003; 14 (10 Suppl.): S133-9
25. Marinchak RA, Kowey PR, Rials SJ, et al. Atrial fibrillation. Curr Treat Options Cardiovasc Med 2000; 2 (4): 281-96
26. Falk RH, Knowlton AA, Bernard SA, et al. Digoxin for converting recent-onset atrial fibrillation to sinus rhythm: a randomized, double-blinded trial. Ann Intern Med 1987; 106 (4): 503-6
27. Jordaens L, Trouerbach J, Calle P, et al. Conversion of atrial fibrillation to sinus rhythm and rate control by digoxin in comparison to placebo. Eur Heart J 1997; 18 (4): 643-8
28. The Digitalis in Acute Atrial Fibrillation (DAAF) Trial Group. Intravenous digoxin in acute atrial fibrillation: results of a randomized, placebo-controlled multicentre trial in 239 patients. Eur Heart J 1997; 18 (4): 649-54
29. Levy S. Pharmacologic management of atrial fibrillation: current therapeutic strategies. Am Heart J 2001; 141 (2 Suppl.): S15-21
30. Kowey PR, Marinchak RA, Rials SJ, et al. Acute treatment of atrial fibrillation. Am J Cardiol 1998; 81 Suppl. 5A: 16C-22C
31. Antonelli D, Bloch L, Barzilay J. Combined administration of propranolol and quinidine in the conversion of paroxysmal atrial fibrillation. Clin Cardiol 1985; 8 (3): 152-3
32. Halinen MO, Huttunen M, Paakkinen S, et al. Comparison of sotalol with digoxin-quinidine for conversion of acute atrial fibrillation to sinus rhythm (the Sotalol-Digoxin-Quinidine Trial). Am J Cardiol 1995; 76 (7): 495-8
33. Capucci A, Villani GQ, Aschieri D, et al. Safety of oral propafenone in the conversion of recent onset atrial fibrillation to sinus rhythm: a prospective parallel placebo-controlled multicentre study. Int J Cardiol 1999; 68 (2): 187-96
34. Holzman D, Brown MG. The use of quinidine in established auricular fibrillation and flutter. Am J Med Sci 1951; 222 (6): 644-52
35. Miller MR, McNamara RL, Segal JB, et al. Efficacy of agents for pharmacologic conversion of atrial fibrillation and subsequent maintenance of sinus rhythm: a meta-analysis of clinical trials. J Fam Pract 2000; 49 (11): 1033-46

36. Kassotis J, Costeas C, Blitzer M, et al. Rhythm management in atrial fibrillation: with a primary emphasis on pharmacologic therapy: part 3. Pacing Clin Electrophysiol 1998; 21 (5): 1133-45
37. Falk RH. Proarrhythmia in patients treated for atrial fibrillation or flutter. Ann Intern Med 1992; 117 (2): 141-50
38. Tebbe U, Carlsson J, Seidl K, et al. Cardioversion in atrial fibrillation: results and complications in 1152 prospective patients. Study Group of the Working Society of Leading Cardiologic Hospital Physicians [in German]. Med Klin (Munich) 1995; 90 (12): 681-7
39. Marcus FI, Opie LH. Antiarrhythmic drugs. In: Opie LH, editor. Drugs for the heart. Philadelphia (PA): Saunders, 1995: 208-48
40. Coplen SE, Antman EM, Berlin JA, et al. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion: a meta-analysis of randomized control trials. Circulation 1990; 82 (4): 1106-16
41. Fenster PE, Comess KA, Marsh R, et al. Conversion of atrial fibrillation to sinus rhythm by acute intravenous procainamide infusion. Am Heart J 1983; 106 (3): 501-4
42. Volgman AS, Carberry PA, Stambler B, et al. Conversion efficacy and safety of intravenous ibutilide compared with intravenous procainamide in patients with atrial flutter or fibrillation. J Am Coll Cardiol 1998; 31 (6): 1414-9
43. Biffi M, Boriani G, Bronzetti G, et al. Electrophysiological effects of flecainide and propafenone on atrial fibrillation cycle and relation with arrhythmia termination. Heart 1999; 82 (2): 176-82
44. Marcus FI. The hazards of using type 1C antiarrhythmic drugs for the treatment of paroxysmal atrial fibrillation. Am J Cardiol 1990; 66 (3): 366-7
45. Murdock CJ, Kyles AE, Yeung-Lai-Wah JA, et al. Atrial flutter in patients treated for atrial fibrillation with propafenone. Am J Cardiol 1990; 66 (7): 755-7
46. Feld GK, Chen PS, Nicod P, et al. Possible atrial proarrhythmic effects of class 1C antiarrhythmic drugs. Am J Cardiol 1990; 66 (3): 378-83
47. Botto GL, Bonini W, Broffoni T, et al. Regular ventricular rhythms before conversion of recent onset atrial fibrillation to sinus rhythm. Pacing Clin Electrophysiol 1994; 17 (11 Pt 2): 2114-7
48. Goy JJ, Kaufmann U, Kappenberger L, et al. Restoration of sinus rhythm with flecainide in patients with atrial fibrillation. Am J Cardiol 1988; 62 (6 Suppl.): 38D-40D
49. Suttorp MJ, Kingma JH, Lie AHL, et al. Intravenous flecainide versus verapamil for acute conversion of paroxysmal atrial fibrillation or flutter to sinus rhythm. Am J Cardiol 1989; 63 (11): 693-6
50. Gavaghan TP, Koegh AM, Kelly RP, et al. Flecainide compared with a combination of digoxin and disopyramide for acute atrial arrhythmias after cardiopulmonary bypass. Br Heart J 1988; 60 (6): 497-501
51. Borgeat A, Goy JJ, Maendly R, et al. Flecainide versus quinidine for conversion of atrial fibrillation to sinus rhythm. Am J Cardiol 1986; 58 (6): 496-8
52. Capucci A, Lenzi T, Boriani G, et al. Effectiveness of loading oral flecainide for converting recent-onset atrial fibrillation to sinus rhythm in patients without organic heart disease or with only systemic hypertension. Am J Cardiol 1992; 70 (1): 69-72
53. Villani GQ, Rosi A, Piepoli M, et al. The efficacy of oral treatment with flecainide for paroxysmal atrial fibrillation: correlation with plasma concentration [in Italian]. G Ital Cardiol 1990; 20 (6): 564-8
54. Masse C, Cazes M, Sassine A. Effects of cibenzoline, a novel antiarrhythmic drug, on action potential and transmembrane currents in frog atrial muscle. Arch Int Pharmacodyn Ther 1984; 269 (2): 219-35
55. Millar JS, Vaughan Williams EM. Effects on rabbit nodal, atrial, ventricular and Purkinje cell potentials of a new antiarrhythmic drug, cibenzoline, which protects against action potential shortening in hypoxia. Br J Pharmacol 1982; 75 (3): 469-78
56. Holck M, Osterrieder W. Inhibition of the myocardial Ca2+ inward current by the class 1 antiarrhythmic agent, cibenzoline. Br J Pharmacol 1986; 87 (4): 705-11
57. Brugada J, Gursoy S, Brugada P, et al. Cibenzoline transforms random re-entry into ordered re-entry in the atria. Eur Heart J 1993; 14 (2): 267-72
58. Touboul P, Atallah G, Kirkorian G, et al. Electrophysiologic effects of cibenzoline in humans related to dose and plasma concentration. Am Heart J 1986; 112 (2): 333-9
59. Andrivet P, Mach V, Gnoc CV. A clinical study of intravenous cibenzoline in selected patients with recent-onset atrial tachyarrhythmia. Chest 1993; 103 (5): 1515-9
60. Galve E, Rius T, Ballester R, et al. Intravenous amiodarone in treatment of recent-onset atrial fibrillation: results of a randomized, controlled study. J Am Coll Cardiol 1996; 27 (5): 1079-82
61. Hilleman DE, Spinler SA. Conversion of recent-onset atrial fibrillation with intravenous amiodarone: a meta-analysis of randomized controlled trials. Pharmacotherapy 2002; 22 (1): 66-74
62. Chevalier P, Durand-Dubief A, Burri H, et al. Amiodarone versus placebo and classic drugs for cardioversion of recent-onset atrial fibrillation: a meta-analysis. J Am Coll Cardiol 2003; 41 (2): 255-62
63. Nichol G, McAlister F, Pham B, et al. Meta-analysis of randomised controlled trials of the effectiveness of antiarrhythmic agents at promoting sinus rhythm in patients with atrial fibrillation. Heart 2002; 87 (6): 535-43
64. Blanc JJ, Voinov C, Maarek M. Comparison of oral loading dose of propafenone and amiodarone for converting recent-onset atrial fibrillation: PARSIFAL Study Group. Am J Cardiol 1999; 84 (9): 1029-32
65. Gallik DM, Singer I, Meissner MD, et al. Hemodynamic and surface electrocardiographic effects of a new aqueous formulation of intravenous amiodarone. Am J Cardiol 2002; 90 (9): 964-8
66. Boriani G, Biffi M, Frabetti L, et al. Ventricular fibrillation after intravenous amiodarone in Wolff-Parkinson-White syndrome with atrial fibrillation. Am Heart J 1996; 131 (6): 1214-6
67. Le Coz F, Funck-Brentano C, Morell T, et al. Pharmacokinetic and pharmacodynamic modeling of the effects of oral and intravenous administrations of dofetilide on ventricular repolarization. Clin Pharmacol Ther 1995; 57 (5): 533-42
68. Elming H, Brendorp B, Pedersen OD, et al. Dofetilide: a new drug to control cardiac arrhythmia. Expert Opin Pharmacother 2003; 4 (6): 973-85
69. Suttorp MJ, Polak PE, van 't Hof A, et al. Efficacy and safety of a new selective class III antiarrhythmic agent dofetilide in paroxysmal atrial fibrillation or atrial flutter. Am J Cardiol 1992; 69 (4): 417-9
70. Sedgwick ML, Lip G, Rae AP, et al. Chemical cardioversion of atrial fibrillation with intravenous dofetilide. Int J Cardiol 1995; 49 (2): 159-66

71. Frost L, Mortensen PE, Tingleff J, et al. Efficacy and safety of dofetilide, a new class III antiarrhythmic agent, in acute termination of atrial fibrillation or flutter after coronary artery bypass surgery: Dofetilide Post-CABG Study Group. Int J Cardiol 1997; 58 (2): 135-40
72. Falk RH, Pollak A, Singh SN, et al. Intravenous dofetilide, a class III antiarrhythmic agent, for the termination of sustained atrial fibrillation or flutter: Intravenous Dofetilide Investigators. J Am Coll Cardiol 1997; 29 (2): 385-90
73. Bianconi L, Castro A, Dinelli M, et al. Comparison of intravenously administered dofetilide versus amiodarone in the acute termination of atrial fibrillation and flutter: a multicentre, randomized, double-blind, placebo-controlled study. Eur Heart J 2000; 21 (15): 1265-73
74. Crijns HJ, Van Gelder IC, Kingma JH, et al. Atrial flutter can be terminated by a class III antiarrhythmic drug but not by a class IC drug. Eur Heart J 1994; 15 (10): 1403-8
75. Kowey PR, VanderLugt JT, Luderer JR. Safety and risk/benefit analysis of ibutilide for acute conversion of atrial fibrillation/flutter. Am J Cardiol 1996; 78 Suppl. 8A: 46-52
76. Ellenbogen KA, Clemo HF, Stambler BS, et al. Efficacy of ibutilide for termination of atrial fibrillation and flutter. Am J Cardiol 1996; 78 Suppl. 8A: 42-5
77. Foster RH, Wilde MI, Markham A. Ibutilide: a review of its pharmacological properties and clinical potential in the acute management of atrial flutter and fibrillation. Drugs 1997; 54 (2): 312-30
78. VanderLugt JT, Mattioni T, Denker S, et al. Efficacy and safety of ibutilide fumarate for the conversion of atrial arrhythmias after cardiac surgery. Circulation 1999; 100 (4): 369-75
79. Abi-Mansour P, Carberry PA, McCowan RJ, et al. Conversion efficacy and safety of repeated doses of ibutilide in patients with atrial flutter and atrial fibrillation: Study Investigators. Am Heart J 1998; 136 (4 Pt 1): 632-42
80. Ellenbogen KA, Stambler BS, Wood MA, et al. Efficacy of intravenous ibutilide for rapid termination of atrial fibrillation and atrial flutter: a dose-response study. J Am Coll Cardiol 1996; 28 (1): 130-6
81. Sung RJ. Facilitating electrical cardioversion of persistant atrial fibrillation by antiarrhythmic drugs: update on clinical trial results. Card Electrophysiol Rev 2003; 7 (3): 300-3
82. Domanovits H, Schillinger M, Thoennissen J, et al. Termination of recent-onset atrial fibrillation/flutter in the emergency department: a sequential approach with intravenous ibutilide and external electrical cardioversion. Resuscitation 2000; 45 (3): 181-7
83. Stambler BS, Beckman KJ, Kadish AH, et al. Acute hemodynamic effects of intravenous ibutilide in patients with or without reduced left ventricular function. Am J Cardiol 1997; 80 (4): 458-63
84. Vos MA, Golitsyn SR, Stangl K, et al. Superiority of ibutilide (a new class III agent) over DL-sotalol in converting atrial flutter and atrial fibrillation: the Ibutilide/Sotalol Comparator Study Group. Heart 1998; 79 (6): 568-75
85. Campbell TJ, Gavaghan TP, Morgan JJ. Intravenous sotalol for the treatment of atrial fibrillation and flutter after cardiopulmonary bypass: comparison with disopyramide and digoxin in a randomised trial. Br Heart J 1985; 54 (1): 86-90
86. Joseph AP, Ward MR. A prospective, randomized controlled trial comparing the efficacy and safety of sotalol, amiodarone, and digoxin for the reversion of new-onset atrial fibrillation. Ann Emerg Med 2000; 36 (1): 1-9
87. Reisinger J, Gatterer E, Heinze G, et al. Prospective comparison of flecainide versus sotalol for immediate cardioversion of atrial fibrillation. Am J Cardiol 1998; 81 (12): 1450-4
88. Sung RJ, Tan HL, Karagounis L, et al. Intravenous sotalol for the termination of supraventricular tachycardia and atrial fibrillation and flutter: a multicenter, randomized, double-blind, placebo-controlled study. Sotalol Multicenter Study Group. Am Heart J 1995; 129 (4): 739-48
89. Hondeghem LM, Snyders DJ. Class III antiarrhythmic agents have a lot of potential but a long way to go: reduced effectiveness and dangers of reverse use dependence. Circulation 1990; 81 (2): 686-90
90. Schmitt C, Brachmann J, Karch M, et al. Reverse use-dependent effects of sotalol demonstrated by recording monophasic action potentials of the right ventricle. Am J Cardiol 1991; 68 (11): 1183-7
91. Hohnloser SH, Woosley RL. Sotalol. N Engl J Med 1994; 331 (1): 31-8
92. Hohnloser SH. Proarrhythmia with class III antiarrhythmic drugs: types, risks, and management. Am J Cardiol 1997; 80 Suppl. 8A: 82G-9G
93. Hohnloser SH. Indications and limitations of class II and III antiarrhythmic drugs in atrial fibrillation. Pacing Clin Electrophysiol 1994; 17 (5 Pt 2): 1019-25
94. McNamara RL, Tamariz LJ, Segal JB, et al. Management of atrial fibrillation: review of the evidence for the role of pharmacologic therapy, electrical cardioversion, and echocardiography. Ann Intern Med 2003; 139 (12): 1018-33
95. Letelier LM, Udol K, Ena J, et al. Effectiveness of amiodarone for conversion of atrial fibrillation to sinus rhythm: a meta-analysis. Arch Intern Med 2003; 163 (7): 777-85
96. Bharucha D, Kowey P. Management and prevention of atrial fibrillation after cardiac surgery. Am J Cardiol 2000; 85 Suppl.: 20D-4D
97. Klein M, Evans SJ, Blumberg S, et al. Use of P-wave-triggered, P-wave signal-averaged electrocardiogram to predict atrial fibrillation after coronary artery bypass surgery. Am Heart J 1995; 129 (5): 895-901
98. LeLorier P, Klein G. Prevention and management of postoperative atrial fibrillation. Curr Probl Cardiol 2002; 27 (9): 367-403
99. Hernandez J, Pelletier E, Clark M, et al. Post-operative treatment costs of atrial fibrillation under medicare [abstract]. Heart Rhythm 2004; 1: S123
100. Maisel WH, Rawn JD, Stevenson WG. Atrial fibrillation after cardiac surgery. Ann Intern Med 2001; 135 (12): 1061-73
101. Soucier R, Silverman D, Abordo M, et al. Propafenone versus ibutilide for post operative atrial fibrillation following cardiac surgery: neither strategy improves outcomes compared to rate control alone (the PIPAF study). Med Sci Monit 2003; 9 (3): PI19-23
102. Wijffels MC, Dorland R, Allessie MA. Pharmacologic cardioversion of chronic atrial fibrillation in the goat by class IA, IC, and III drugs: a comparison between hydroquinidine, cibenzoline, flecainide, and d-sotalol. J Cardiovasc Electrophysiol 1999; 10 (2): 178-93
103. Kerin NZ, Faitel K, Naini M. The efficacy of intravenous amiodarone for the conversion of chronic atrial fibrillation: amiodarone vs quinidine for conversion of atrial fibrillation. Arch Intern Med 1996; 156 (1): 49-53
104. Zehender M, Hohnloser S, Muller B, et al. Effects of amiodarone versus quinidine and verapamil in patients with chron-

ic atrial fibrillation: results of a comparative study and a 2-year follow-up. J Am Coll Cardiol 1992; 19 (5): 1054-9

105. Vardas PE, Kochiadakis GE, Igoumenidis NE, et al. Amiodarone as a first-choice drug for restoring sinus rhythm in patients with atrial fibrillation: a randomized, controlled study. Chest 2000; 117 (6): 1538-45
106. Horowitz LN, Spielman SR, Greenspan AM, et al. Use of amiodarone in the treatment of persistent and paroxysmal atrial fibrillation resistant to quinidine therapy. J Am Coll Cardiol 1985; 6 (6): 1402-7
107. Kochiadakis GE, Igoumenidis NE, Solomou MC, et al. Efficacy of amiodarone for the termination of persistent atrial fibrillation. Am J Cardiol 1999; 83 (1): 58-61
108. Gosselink AT, Crijns HJ, Van Gelder IC, et al. Low-dose amiodarone for maintenance of sinus rhythm after cardioversion of atrial fibrillation or flutter. JAMA 1992; 267 (24): 3289-93
109. Opolski G, Stanislawska J, Gorecki A, et al. Amiodarone in restoration and maintenance of sinus rhythm in patients with chronic atrial fibrillation after unsuccessful direct-current cardioversion. Clin Cardiol 1997; 20 (4): 337-40
110. Tieleman RG, Gosselink AT, Crijns HJ, et al. Efficacy, safety, and determinants of conversion of atrial fibrillation and flutter with oral amiodarone. Am J Cardiol 1997; 79 (1): 53-7
111. Manios EG, Mavrakis HE, Kanoupakis EM, et al. Effects of amiodarone and diltiazem on persistent atrial fibrillation conversion and recurrence rates: a randomized controlled study. Cardiovasc Drugs Ther 2003; 17 (1): 31-9
112. Capucci A, Villani GQ, Aschieri D, et al. Oral amiodarone increases the efficacy of direct-current cardioversion in restoration of sinus rhythm in patients with chronic atrial fibrillation. Eur Heart J 2000; 21 (1): 66-73
113. Brendorp B, Pedersen OD, Kober L, et al. Dofetilide: a new drug to control cardiac arrhythmia. Expert Opin Pharmacother 2003; 4 (6): 973-85
114. Lindeboom JE, Kingma JH, Crijns HJ, et al. Efficacy and safety of intravenous dofetilide for rapid termination of atrial fibrillation and atrial flutter. Am J Cardiol 2000; 85 (8): 1031-3
115. Norgaard BL, Wachtell K, Christensen PD, et al. Efficacy and safety of intravenously administered dofetilide in acute termination of atrial fibrillation and flutter: a multicenter, randomized, double-blind, placebo-controlled trial. Danish Dofetilide in Atrial Fibrillation and Flutter Study Group. Am Heart J 1999; 137 (6): 1062-9
116. Greenbaum R, Campbell TJ, Channer KS, et al. Conversion of atrial fibrillation and maintenance of sinus rhythm by dofetilide: the EMERALD study [abstract]. Circulation 1998; 98 (27 Suppl. I): 3326
117. Singh S, Zoble RG, Yellen L, et al. Efficacy and safety of oral dofetilide in converting to and maintaining sinus rhythm in patients with chronic atrial fibrillation or atrial flutter: the Symptomatic Atrial Fibrillation Investigative Research on Dofetilide (SAFIRE-D) study. Circulation 2000; 102 (19): 2385-90
118. Pedersen OD, Bagger H, Keller N, et al. Efficacy of dofetilide in the treatment of atrial fibrillation-flutter in patients with reduced left ventricular function: a Danish Investigations of Arrhythmia and Mortality ON Dofetilide (DIAMOND) substudy. Circulation 2001; 104 (3): 292-6
119. Stern S. Conversion of chronic atrial fibrillation to sinus rhythm with combined propranolol and quinidine treatment. Am Heart J 1967; 74 (2): 170-2
120. Hillestad L, Storstein O. Conversion of chronic atrial fibrillation to sinus rhythm with combined propranolol and quinidine treatment. Am Heart J 1969; 77 (1): 137-9
121. Rasmussen K, Wang H, Fausa D. Comparative efficiency of quinidine and verapamil in the maintenance of sinus rhythm after DC conversion of atrial fibrillation: a controlled clinical trial. Acta Med Scand Suppl 1981; 645: 23-8
122. Goy JJ, Grbic M, Hurni M, et al. Conversion of supraventricular arrhythmias to sinus rhythm using flecainide. Eur Heart J 1985; 6 (6): 518-24
123. Kuhlkamp V, Schmid F, Risler T, et al. Randomized comparison of flecainide and cibenzoline in the conversion of atrial fibrillation. Int J Cardiol 1991; 31 (1): 65-9
124. Porterfield JG, Porterfield LM. Therapeutic efficacy and safety of oral propafenone for atrial fibrillation. Am J Cardiol 1989; 63 (1): 114-6
125. De Simone A, Stabile G, Vitale DF, et al. Pretreatment with verapamil in patients with persistent or chronic atrial fibrillation who underwent electrical cardioversion. J Am Coll Cardiol 1999; 34 (3): 810-4
126. Bianconi L, Mennuni M, Lukic V, et al. Effects of oral propafenone administration before electrical cardioversion of chronic atrial fibrillation: a placebo-controlled study. J Am Coll Cardiol 1996; 28 (3): 700-6
127. Kochiadakis GE, Igoumenidis NE, Parthenakis FI, et al. Amiodarone versus propafenone for conversion of chronic atrial fibrillation: results of a randomized, controlled study. J Am Coll Cardiol 1999; 33 (4): 966-71
128. Oral H, Souza JJ, Michaud GF, et al. Facilitating transthoracic cardioversion of atrial fibrillation with ibutilide pretreatment. N Engl J Med 1999; 340 (24): 1849-54
129. Singh S, Saini RK, DiMarco J, et al. Efficacy and safety of sotalol in digitalized patients with chronic atrial fibrillation: the Sotalol Study Group. Am J Cardiol 1991; 68 (11): 1227-30
130. Boriani G, Biffi M, Branzi A, et al. Pharmacological treatment of atrial fibrillation: a review on prevention of recurrences and control of ventricular response. Arch Gerontol Geriatr 1998; 27: 127-39
131. Hohnloser SH, Singh BN. Proarrhythmia with class III antiarrhythmic drugs: definition, electrophysiologic mechanisms, incidence, predisposing factors, and clinical implications. J Cardiovasc Electrophysiol 1995; 6 (10 Pt 2): 920-36
132. Friedman PL, Stevenson WG. Proarrhythmia. Am J Cardiol 1998; 82 Suppl. 8A: 50N-8N
133. Roden DM, Woosley RL, Primm RK. Incidence and clinical features of the quinidine-associated long QT syndrome: implications for patient care. Am Heart J 1986; 111 (6): 1088-93
134. Middlekauff HR, Wiener I, Saxon LA, et al. Low-dose amiodarone for atrial fibrillation: time for a prospective study? Ann Intern Med 1992; 116 (12 Pt 1): 1017-20
135. Hohnloser SH, Klingenheben T, Singh BN. Amiodarone-associated proarrhythmic effects: a review with special reference to torsade de pointes tachycardia. Ann Intern Med 1994; 121 (7): 529-35
136. Hohnloser SH, Li YG. Drug treatment of atrial fibrillation: what have we learned? Curr Opin Cardiol 1997; 12 (1): 24-32
137. Brachmann J, Scherlag BJ, Rosenshtraukh LV, et al. Bradycardia-dependent triggered activity: relevance to drug-induced multiform ventricular tachycardia. Circulation 1983; 68 (4): 846-56
138. Prystowsky EN. Proarrhythmia during drug treatment of supraventricular tachycardia: paradoxical risk of sinus rhythm for sudden death. Am J Cardiol 1996; 78 Suppl. 8A: 35-41

139. Bigger Jr JT, Reiffel JA. Sick sinus syndrome. Annu Rev Med 1979; 30: 91-118
140. Ruskin JN, McGovern B, Garan H, et al. Antiarrhythmic drugs: a possible cause of out-of-hospital cardiac arrest. N Engl J Med 1983; 309 (21): 1302-6
141. Minardo JD, Heger JJ, Miles WM, et al. Clinical characteristics of patients with ventricular fibrillation during antiarrhythmic drug therapy. N Engl J Med 1988; 319 (5): 257-62
142. Stanton MS, Prystowsky EN, Fineberg NS, et al. Arrhythmogenic effects of antiarrhythmic drugs: a study of 506 patients treated for ventricular tachycardia or fibrillation. J Am Coll Cardiol 1989; 14 (1): 209-15
143. Anastasiou-Nana MI, Anderson JL, Stewart JR, et al. Occurrence of exercise-induced and spontaneous wide complex tachycardia during therapy with flecainide for complex ventricular arrhythmias: a probable proarrhythmic effect. Am Heart J 1987; 113 (5): 1071-7
144. Ranger S, Talajic M, Lemery R, et al. Amplification of flecainide-induced ventricular conduction slowing by exercise: a potentially significant clinical consequence of use-dependent sodium channel blockade. Circulation 1989; 79 (5): 1000-6
145. Singh BN. Atrial fibrillation: epidemiologic considerations and rationale for conversion and maintenance of sinus rhythm. J Cardiovasc Pharmacol Ther 2003; 8 Suppl. 1: S13-26
146. Dorian P. Antiarrhythmic drug therapy of atrial fibrillation: focus on new agents. J Cardiovasc Pharmacol Ther 2003; 8 Suppl. 1: S27-31
147. Hohnloser SH, Dorian P, Straub M, et al. Safety and efficacy of intravenously administered tedisamil for rapid conversion of recent-onset atrial fibrillation or atrial flutter. J Am Coll Cardiol 2004; 44 (1): 99-104
148. Roy D, Beatch G, Steill I, et al. RSD1235 rapidly and effectively terminates atrial fibrillation [abstract]. Eur Heart J 2003; 24: 720
149. Touboul P, Brugada J, Capucci A, et al. Dronedarone for prevention of atrial fibrillation: a dose-ranging study. Eur Heart J 2003; 24 (16): 1481-7
150. Crozier I, Melton I, Pearson S. Management of atrial fibrillation in the emergency department. Intern Med J 2003; 33 (4): 182-5
151. Dell'Orfano JT, Patel H, Wolbrette DL, et al. Acute treatment of atrial fibrillation: spontaneous conversion rates and cost of care. Am J Cardiol 1999; 83 (5): 788-90, A10
152. Kim MH, Conlon B, Ebinger M, et al. Clinical outcomes and costs associated with a first episode of uncomplicated atrial fibrillation presenting to the emergency room. Am J Cardiol 2001; 88 (1): A7, 74-6
153. Koenig BO, Ross MA, Jackson RE. An emergency department observation unit protocol for acute-onset atrial fibrillation is feasible. Ann Emerg Med 2002; 39 (4): 374-81
154. Lip GY, Zarifis J, Watson RD, et al. Physician variation in the management of patients with atrial fibrillation. Heart 1996; 75 (2): 200-5
155. Hall BW, Bialy D, Lehmann MH, et al. Hospitalization for arrhythmias in the United States, 1985 through 1999: importance of atrial fibrillation [abstract]. J Am Coll Cardiol 2002; 39 Suppl. 1: 89
156. Dell'Orfano JT, Kramer RK, Naccarelli GV. Cost-effective strategies in the acute management of atrial fibrillation. Curr Opin Cardiol 2000; 15 (1): 23-8
157. de Paola AA, Figueiredo E, Sesso R, et al. Effectiveness and costs of chemical versus electrical cardioversion of atrial fibrillation. Int J Cardiol 2003; 88 (2-3): 157-66

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