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ABSTRACT

Atrial fibrillation (AF) is the commonest atrial arrhythmia and represents a large burden on modern health services. Large multicentre randomised trials have demonstrated that a rhythm control strategy (using antiarrhythmic drugs and direct current (DC) cardioversion) has no morbidity or mortality advantage over rate control. Therefore, for most patients, attempts to cardiovert AF to sinus rhythm (SR) should be reserved for those patients who are symptomatic despite adequate rate control. For recent-onset AF (<24 h) the use of agents like flecainide can be highly successful to pharmacologically cardiovert AF, although caution should be exercised in patients who have the potential for structural or coronary artery disease because of the risk of proarrhythmia. If there any is doubt as to the suitability of a patient for pharmacological cardioversion then DC cardioversion is the safer option. Owing to the high recurrence rate of AF after cardioversion (71—84% at 1 year), the use of antiarrhythmic drugs to maintain SR is recommended. The irreversible side effects of amiodarone mean that it should be avoided whenever possible for long-term maintenance treatment, although it is useful in short courses (8 weeks—6 months), particularly for patients who had a successfully treated secondary cause for AF. Other agents like flecainide and sotalol are also useful but should not be used for patients with structural heart disease. Data supporting the use of newer agents like dronedarone are at present limited.

INTRODUCTION

Atrial fibrillation (AF) is the commonest cardiac arrhythmia and becoming increasingly common as the population of the developed world ages.[1] In this review I will examine the indications for cardioversion of AF and review the safety and efficacy of antiarrhythmic drugs that might be used to either perform cardioversion or prevent recurrence of AF after DC cardioversion (figure 1). Only evidence from randomised controlled trials is considered. The prevention of embolic stroke and anticoagulation will not be dealt with in this review and is covered by an excellent review by Lip and Boos.[2]

INDICATIONS FOR CARDIOVERSION OF AF

Trying to eliminate AF by the use antiarrhythmic drugs and/or direct current (DC) cardioversion (rhythm control) has no mortality or morbidity benefit over control of the ventricular rate.[3] Interventional treatments like catheter ablation are significantly more effective than drug treatment for the prevention of AF,[4] and these studies need to be repeated using catheter ablation for rhythm control. Based on current data, rhythm control should be reserved for those patients who are symptomatic. Determining which patients are symptomatic as a result of their AF can be difficult because symptoms can be insidious and vague (shortness of breath, lethargy, decreased exercise tolerance). As a result patients may delay presentation to their doctor and may adapt to the symptoms of AF and only be aware of the limitations that AF has caused them in retrospect after sinus rhythm (SR) has been restored. For patients in whom it is not clear whether their symptoms are related to AF, then cardioversion to SR can be used to identify what symptoms are caused by AF (as long as SR is maintained for more than a few days). For patients who are not aware when they return to AF after cardioversion then it is reasonable to conclude that they have truly asymptomatic AF. Cardioversion is also appropriate if the AF is the result of a successfully treated secondary cause—for example, thyrotoxicosis or pneumonia. Cardioversion may also be rarely used for those patients in whom rate control has been impossible. However, when rate-controlling drugs have been ineffective or not tolerated, catheter ablation of the AF or of the atrioventricular node combined with pacing is a suitable alternative (box 1).

ANTIARRHYTHMIC DRUGS USED FOR CARDIOVERSION OR PREVENTION OF AF RECURRENCE

The simplicity and wide availability of antiarrhythmic drugs to either augment or produce cardioversion means that this remains the treatment of first choice for rhythm control of AF. Antiarrhythmic drugs may be used either on their own in order to cardiovert AF (pharmacological cardioversion) or in association with a direct current (DC) shock in order to reduce the chances of AF recurrence.

Digoxin

Digoxin does not produce pharmacological cardioversion any more frequently than placebo.[5] Digoxin also has no advantage over placebo in the prevention of recurrence of AF after cardioversion.[6] Because of this digoxin has been used as the control for many studies examining the efficacy of a drug for cardioversion of AF. Digoxin can cause symptomatic bradycardia[5] but other proarrhythmia are rare, other than in overdose.

β Blockers

The efficacy of β blockers in cardioverting AF has not been compared with placebo in randomised studies. Only two randomised studies have compared the efficacy of β blockers with placebo in

maintaining SR after cardioversion.[7] Both of these demonstrated a small but significant reduction in AF recurrence in patients treated with metoprolol compared with placebo. Only one study has compared the efficacy of two different β blockers, carvedilol and bisoprolol and neither was better than the other in maintaining SR.[8] β Blockers are associated with the side effects of dyspnoea, dizziness and symptomatic bradycardia but other proarrhythmia has not been reported.[7]

Non-dihydropyridine calcium antagonists

Pretreatment with verapamil results in a modest but significant increase compared with digoxin in spontaneous cardioversion to SR before DC cardioversion (6–12% vs 0–1%, $p<0.05$).[9 10] However, the cardioversion rate with verapamil is modest so that it should not be considered a useful first-line agent for cardioversion of AF. As an agent for prevention of recurrence of AF after cardioversion, verapamil had no advantage over digoxin at 12 weeks' follow-up[9] and at 18 months' follow-up.[10] Pretreatment with diltiazem before DC cardioversion does not result in pharmacological cardioversion, does not increase the acute success rate for DC cardioversion and is not as effective in preventing AF recurrence at 1 month as amiodarone but is better than control (digoxin).[11] The addition of verapamil to other antiarrhythmic agents (flecainide, amiodarone or propafenone) does reduce AF recurrence rates, but again this effect is modest and did not reach statistical significance when used with amiodarone.[12 13] The rate-controlling properties of amiodarone mean that there is little value in combining this drug with verapamil but it is useful in combination with flecainide or propafenone. No serious adverse effects associated with calcium channel blockers have been reported in any of these studies.

Quinidine

Quinidine is a long-established antiarrhythmic drug which is now no longer being produced, although its unique efficacy in treating some inherited causes of arrhythmia may result in reversal of this decision. A meta-analysis of randomised trials demonstrated that it is associated with a doubling of the SR rates at 12 months after cardioversion (50% in SR) compared with controls (25% in SR) but it is associated with a mortality three times higher than controls.[14]

Disopyramide

Disopyramide is not a commonly used antiarrhythmic drug for AF but in a randomised controlled study did result in significantly more patients remaining in SR after cardioversion compared with placebo (54% vs 30% at 12 months).[15] Although side effects were more common for disopyramide patients than placebo patients, there was no excess mortality in this small study (n=90). When compared with propafenone, disopyramide had similar efficacy but was associated with more side effects.[16] Proarrhythmia was also not seen in this study. The efficacy of disopyramide for pharmacological cardioversion of AF has not been studied in controlled trials.

Propafenone

In two small studies propafenone was associated with a small but insignificant increase in cardioversion to SR.[17] In patients who have been in persistent AF for >2 weeks there appears to be little chance of propafenone achieving pharmacological cardioversion.[17] Using propafenone to prevent recurrence of AF after DC cardioversion approximately doubles the chances of maintaining SR at 6 months (40% vs 23%, $p<0.01$).[17] Propafenone treatment is associated with increased proarrhythmia (non-sustained VT) compared with placebo in patients without structural heart disease.[17] Propafenone is of equal efficacy to sotalol in preventing AF recurrence, although it is associated with an increased incidence of constipation.[18] The addition of propafenone to intravenous ibutilide results in a significant and remarkably high pharmacological cardioversion rate compared with ibutilide alone (71% vs 41%, p=0.004) even though the mean AF duration in this study was 100 days.[19] This regimen was associated with one episode of successfully cardioverted torsade de pointes, emphasising the need for monitoring of patients during administration.

Procainamide

Procainamide is associated with a small pharmacological cardioversion rate when compared with placebo in patients with persistent AF (mean duration 3.4 months) and has no effect on DC cardioversion rates.[20] There have been no randomised controlled studies examining the efficacy of procainamide in prevention of AF recurrence. Procainamide was better than propafenone.[21] Procainamide is associated with hypotension when used as an intravenous infusion but excess proarrhythmia has not been reported in randomised studies.[20]

Dofetilide

Dofetilide has been compared with placebo as an agent for pharmacological cardioversion of AF and maintenance of SR and was better than placebo for both purposes when given in the highest dose.[22] The study was not powered to examine mortality, which was similar in the placebo and dofetilide groups, but there was a greater incidence of QT prolongation and arrhythmia in the dofetilide group, with one sudden death presumed cardiac. Dofetilide has also been tested against placebo in patients with structural heart disease and heart failure.[23] It resulted in pharmacological cardioversion in 12% of patients compared with 2% of those receiving placebo at 1 month. After DC cardioversion, SR was maintained in a high proportion of patients in both the dofetilide and placebo groups (77% vs 44% $p<0.001$). Dofetilide was associated with torsade de pointes in 1.6% but no deaths.

The efficacy of dofetilide has also been compared with amiodarone and placebo for pharmacological cardioversion of new-onset AF. It was found to be better than both but associated with increased risk of proarrhythmia. However, the primary end point was at 3 h follow-up and the dose of amiodarone was a single 5 mg/kg infusion over 15 min which may have disadvantaged amiodarone which often needs longer infusions of higher doses to be effective. Torsade de pointes was only seen in the dofetilide group (8%).[24]

The association of dofetilide with relatively frequent proarrhythmic events has been one of the factors preventing it from being used widely as a first-line treatment for AF.

Amiodarone

Amiodarone is probably the antiarrhythmic drug that has been most closely studied for treatment of AF. It has been shown to be better than placebo in a general population[25] and better than digoxin,[26] and to be equivalent to sotalol for pharmacological cardioversion of AF if AF has been present for less than 24 h. If given for longer periods amiodarone and sotalol have equal efficacy for cardioverting AF of longer standing (mean 7 months).[27] Amiodarone is not as effective as flecainide for pharmacological cardioversion of recent-onset AF.[28]

Evidence for the effect of pretreatment with amiodarone on the success and energy required to DC cardiovert AF is varied, with some studies showing equivalence[25] and other non-blinded

studies showing superiority over placebo and diltiazem.[29] For maintenance of SR after cardioversion amiodarone is better than placebo,[26 30] β blocker,[30] sotalol,[26 31] propafenone[31] and other class I agents.[32] Because of the potential for irreversible side effects with long-term administration, duration and dosing regimen have also been investigated in randomised controlled trials. At 1 year after DC cardioversion there is a trend towards reduction in AF recurrence in those patients maintained on low-dose amiodarone (200 mg) for the entire 1 year follow-up period compared with those patients given a short course (8 weeks) but this was offset by a trend to increased side effects—notably, thyroid and liver problems.[25]

Another study compared the efficacy in preventing AF recurrence after DC cardioversion between 1-year continuous amiodarone and a short-course amiodarone (preloading followed by 1 month) followed by additional amiodarone dosing if AF recurred.[33] Continuing amiodarone for 1 year reduced AF recurrence but was associated with increased amiodarone-related adverse events. There was an increased incidence of all-cause mortality and hospitalisation in the episodic amiodarone group, which may in part have been the result of the difficulty of controlling anticoagulation.

In summary, amiodarone appears to be the most effective antiarrhythmic agent for prevention of AF but it has limited role for use in pharmacological cardioversion of AF. Use of amiodarone is limited by the side effects associated with it, with major side effects reported in up to 20% of patients in some studies.[33] However, amiodarone results in less proarrhythmia and fewer withdrawals than other antiarrhythmic drugs, particularly those of class I.[34]

Sotalol

The use of sotalol for pharmacological cardioversion of AF has been compared with digoxin as a surrogate for placebo. For recent-onset AF, solatol had similar cardioversion rates to those of digoxin and amiodarone (44%, 50%, 51%)[35] in one study, but in another had greater efficacy than digoxin and similar efficacy to amiodarone.[26] The differences in these results may be explained by the fact that patients had DC cardioversion after 12 h in the first study[35] but in the positive study pharmacological cardioversion took as long as 48 h.[26] Sotalol is not as effective as class I agents (quinidine) for pharmacological cardioversion of recent-onset AF (25% vs 60% cardioversion rates).[36] For use in pharmacological cardioversion of new-onset AF, sotalol does not appear to be associated with a high incidence of side effects. When compared with placebo for the prevention of AF recurrence after DC cardioversion, sotalol has similar efficacy to bisoprolol[37] and no greater efficacy than quinidine with[36] or without additional verapamil[38] but results in significantly less AF recurrence than placebo (65% vs 83%).[38] Although sotalol does not result in more adverse or serious adverse events than placebo or bisoprolol, death and torsade did not occur in patients treated with placebo or bisoprolol but was associated with sotalol (5%) and most events occurred at the start of drug treatment.[37 38]

Flecainide

Flecainide has been shown to be a highly effective agent for pharmacological cardioversion of recent-onset AF. It has similar efficacy to ibutilide[39] and greater efficacy than procainamide (92% SR vs 63%)[40] and sotalol (52% vs 23%).[41] In comparison with oral flecainide, intravenous flecainide is no more effective for pharmacological cardioversion of recent-onset AF, although intravenous flecainide has a more rapid onset of action (mean time to cardioversion 55 min vs

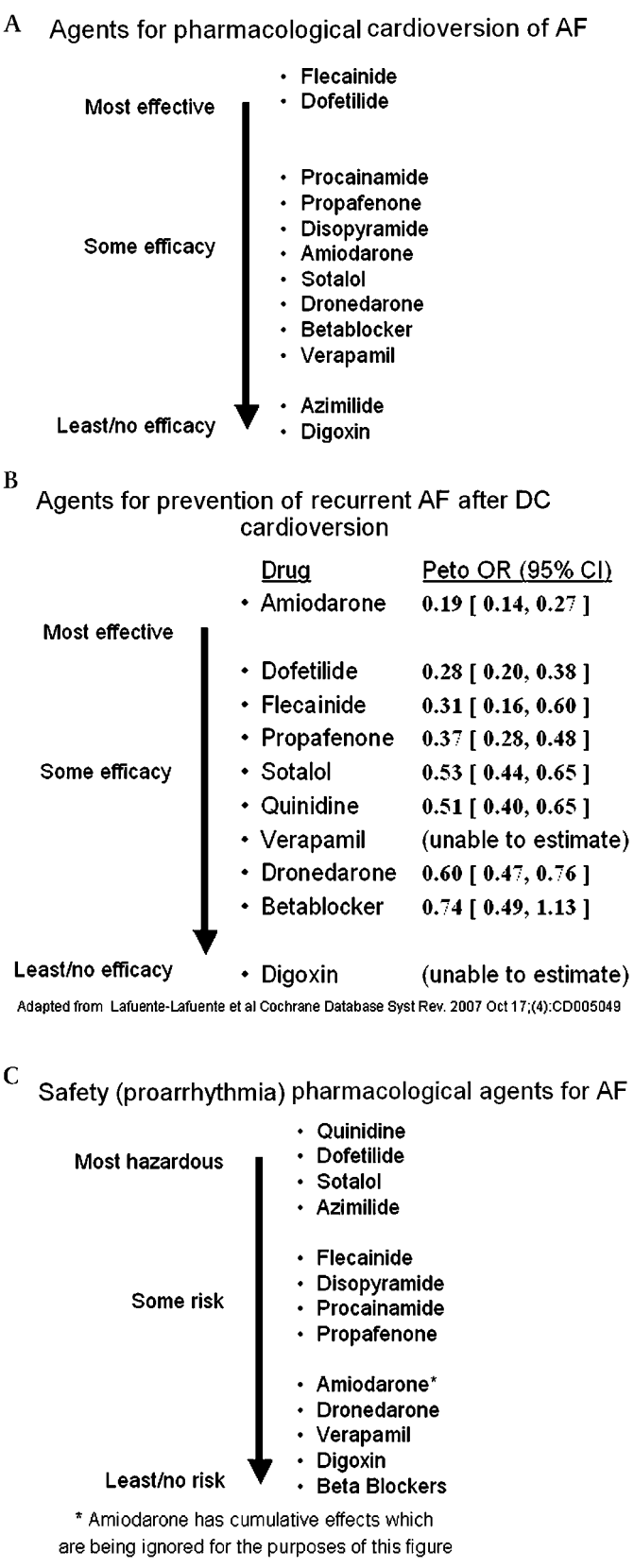

Figure 1 Three charts showing relative efficacy for (A) pharmacological cardioversion; (B) prevention or recurrence of atrial fibrillation (AF); (C) safety (cardiovascular mortality and proarrhythmia) of antiarrhythmic agents used for AF management. These figures are an approximation of the efficacy safety of these drugs as determined from published data and personal experience and may not be accurate because of lack of randomised controlled trials for some drugs.

110 min).[42] In this study, however, the oral preparation was a solution which is not widely and commercially available. The use of flecainide to prevent AF recurrence after DC cardioversion has not been tested against placebo in randomised trials but in comparison with no treatment it does increase arrhythmia-free survival[43] and has similar efficacy to amiodarone (38% AF recurrence vs 32%).[13] There are also insufficient data to comment on the safety of flecainide for prevention of recurrence of persistent AF, although when used in patients with no evidence of coronary artery disease it appears to have a low risk of serious adverse events.

Dronedarone

Dronedarone is a relatively new antiarrhythmic drug with similar properties to amiodarone. Because it does not contain iodine it does not appear to have the same side effects as amiodarone. Its use for pharmacological cardioversion of new-onset AF has not been tested but the incidence of pharmacological cardioversion in chronic AF increases with increasing dose (6–15% compared with placebo 3.1%).[44] For prevention of AF recurrence after DC cardioversion, a dose-ranging study demonstrated that dronedarone was better than placebo but still had a low rates of maintenance of SR at 6 months (35% vs 10%).[44] Dronedarone also appears to reduce hospitalisation for cardiovascular disease and death in high-risk patients with persistent AF and although AF suppression rates were around 50%, this effect does not seem to be explained by dronedarone's antiarrhythmic effect alone.[45] These data are yet to be published in full, as is a comparison of dronedarone with amiodarone (Dionysus study). Dronedarone does not appear to be associated with proarrhythmia or serious adverse events and the main side effects appear to be gastrointestinal.[44 45]

Non-antiarrhythmic agents

Although in observational studies statins have been associated with a lower incidence of AF, the only randomised controlled studies specifically examining AF recurrence after DC cardioversion have either had small patient numbers[46] or demonstrated no benefit of statin use.[47] Statins have therefore not yet been shown to be effective in preventing recurrence of AF after cardioversion and cannot be recommended for such use at this time.

In randomised trials of renin–angiotensin system antagonists (angiotensin receptor blockers (ARBs)) the addition of enalapril[48] or irbersartan[49] to amiodarone treatment was associated with a reduction in AF recurrence, which was significant in the irbersartan study. Meta-analysis of available studies suggests that the use of ARBs to reduce AF burden is most effective in patients with left ventricular dysfunction,[50] therefore pending more data, the use of ARBs for prevention of AF recurrence after DC cardioversion is only recommended for patients who already have a conventional indication (ie, left ventricular dysfunction).

OPTIMAL MANAGEMENT OF PATIENTS WITH AF REQUIRING RHYTHM CONTROL

For all haemodynamically stable patients with AF, the risk of embolic stroke should be dealt with before cardioversion. Patients who are shocked as a result of AF should be cardioverted as quickly as possible regardless of the risk of stroke (figure 2).

AF results in changes to atrial electrophysiology encouraging the maintenance of AF[51] such that antiarrhythmic drugs are most likely to be effective in cardioverting AF within 24 h of onset.[52] For patients presenting with a short history of symptomatic AF (<24 h), pharmacological cardioversion is a reasonable option. For those with no evidence of structural or ischaemic heart disease then intravenous flecainide is recommended. Flecainide has little effect on ventricular rate control and can rarely organise AF into atrial flutter with a 1 to 1 ventricular response necessitating urgent DC cardioversion. This can usually be avoided by giving additional diltiazem, verapamil or a β blocker. For those patients not suitable for flecainide then amiodarone is an option but an infusion should not be given through a peripheral line because of the risk of extravasation.[53] The inconvenience and risk associated with insertion of a central line may mean that DC cardioversion is preferred.

For patients presenting with AF of >24 h, pharmacological cardioversion is not recommended. The incidence of AF recurrence at 1 year after DC cardioversion is so high (71–84%[34]) that there is little value in performing DC cardioversion without the addition of an antiarrhythmic drug. The most effective drug for maintenance of SR after cardioversion is amiodarone but the irreversible side effects associated with long-term treatment mean that its use should be avoided if possible. Patients should also be informed of the side effects and give their consent before

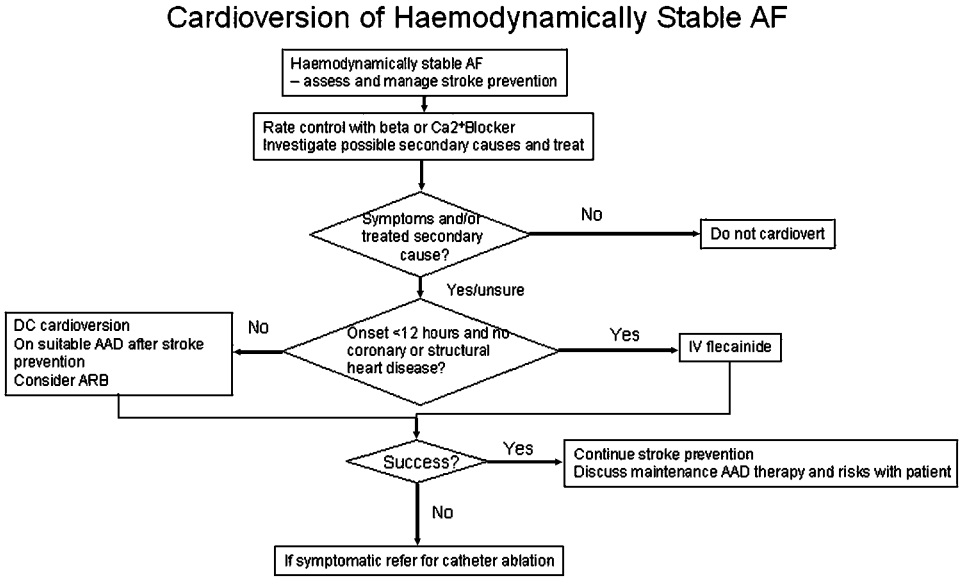

Figure 2 Flow chart for guiding cardioversion of atrial fibrillation (AF). Haemodynamically unstable patients should be given advanced life support and not treated using this flow chart. The choice of AAD used with DC cardioversion to prevent recurrence of AF depends on the patient (see text). Suitable choices might be amiodarone in the elderly or as a short course, or flecainide in combination with a β blocker or Ca^{2+} blockers. AAD, antiarrhythmic drug; ARB, angiotensin–renin blocker; DC, direct current.

Box 1 Indications for cardioversion

Symptomatic AF despite adequate rate control
Successfully treated secondary causes of AF
Unclear whether symptoms are related to AF
Rate control has failed or is not tolerated

starting amiodarone. Amiodarone is useful for maintenance of SR given for 2–6 months, particularly for those patients who have had a treated reversible cause for AF or for those patients in whom cardioversion is performed as a diagnostic procedure to assess whether symptoms are related to AF (although drug side effects can interfere with this). In patients for whom long-term drug treatment is required then flecainide (in combination with either a β blocker or calcium channel blocker for rate control) or sotalol are probably equally effective but should not be used in patients at high risk of proarrhythmia (inherited ion channelopathies, ischaemic heart disease or structural heart disease). Patients with structural heart disease should be offered an ARB.

SUMMARY

Cardioversion for AF is currently only indicated in those patients who have symptoms despite adequate heart rate control. For patients with new-onset AF then pharmacological cardioversion should be considered (<24 h). For patients with established persistent AF then DC cardioversion is more appropriate, although low long-term success rates mean that the addition of a pharmacological agent should be considered in all patients to improve their chances of remaining in SR.

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