Antiarrhythmic drug therapy: what is certain and what is to come

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KEYWORDS
Antiarythmic therapy; Atrial fibrillation

Despite recent advances in our understanding of the mechanisms and consequences of atrial fibrillation (AF), effective therapy for patients with AF remains difficult in many patients. Antiarrhythmic drug therapy includes control of ventricular rate as well as restoration and maintenance of sinus rhythm. The risks and benefits of each treatment modality must be assessed according to each patient’s circumstances. What is certain is that pharmacological treatment remains the mainstay of AF therapy. However, unlike other arrhythmias, there is still no highly effective therapy for treating AF. Class IC drugs, administered orally or intravenously, remain the first-choice therapy in patients with no organic heart disease. Ibutilide has recently been released for intravenous administration and results in a higher conversion rate, especially in patients with atrial flutter. A recently reported trial showed superiority of amiodarone over conventional antiarrhythmic drugs in maintaining sinus rhythm. Dofetilide is another new compound that was developed mainly for maintenance of sinus rhythm. Control of ventricular rate alone is a common strategy and is considered by many physicians to be the safest treatment option; also, it is a relatively simple approach, particularly in the elderly. Calcium channel blockers, beta-blockers and digitalis remain the more effective drugs in controlling heart rate. What is to come is a number of new antiarrhythmic drugs, mainly class III substances, with promising safety and effectiveness profiles, but they are still far from the marketing process. Recently reported studies showed how the rate control option could be a primary strategy in selected patients.

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Introduction

Antiarrhythmic drugs (AADs) are still the main therapeutic tools for treating patients with atrial fibrillation (AF). Their efficacy is particularly high in converting paroxysmal AF to sinus rhythm and in enhancing the positive results of non-pharmacological therapy. In fact, about 80% of patients treated for AF receive at least one type of AAD therapy. There are still questions about efficacy, tolerability and safety of these drugs, especially bearing in mind that AF is not a life-threatening arrhythmia. New drugs will soon be added to our clinical armamentarium that were developed in an attempt to combine better efficacy and lack of pro-arrhythmic effects. In the present review we clarify what we can retain as definite results from present experience with AADs in treating AF, what has less robust impact and what must be abandoned either relating to old or new AADs.
There are several characteristics of AF patients that may interfere with the evaluation of study results. These include duration of AF, underlying clinical conditions and correct use of the specific drug in the clinical setting.

The goals of AAD therapy are restoration of sinus rhythm, facilitation of electrical cardioversion (CV), prevention of AF recurrence and control of ventricular rate. There is no consensus on whether it is better to control heart rate or to maintain sinus rhythm in the general population of AF patients. The Pharmacological Intervention in Atrial Fibrillation (PIAF)\(^1\) and Strategy of Treatment of Atrial Fibrillation (STAF)\(^2\) studies, which were conducted in small populations of patients, and the larger Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM)\(^3\) and the Rate Control versus Electrical Cardioversion (RACE)\(^4\) studies consider this issue and provide interesting insights.

Restoration of sinus rhythm

AADs have a major role to play in restoring sinus rhythm. Several studies documented very high efficacy (>80%) for various AADs in restoring sinus rhythm, but often the ‘time’ within which CV occurs is not reported or, in general, an efficacy rate typically evaluated at 24 h is reported. According to those studies, different classes of AAD appear to yield similar results (Table 1). However, certain factors must be taken into account if one is to compare AADs and to evaluate the real differences between them, namely the route of administration, the ‘time’ to efficacy, the duration of AF, left ventricular function and the presence or absence of organic heart disease. There are also other important points to consider. First, the placebo effect is very consistent (>50% at 12—24 h) for durations of AF of 48 h or less. Second, the duration of AF has a critical impact on response to the AAD. Finally, in-hospital treatment is mandatory (ECG monitoring, proarrhythmic events) for precise evaluation.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of administration</th>
<th>Time to efficacy</th>
<th>Efficacy (%)</th>
<th>Adverse events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine(^5,6)</td>
<td>Oral</td>
<td>&lt;24 h</td>
<td>59—92</td>
<td>3—46</td>
</tr>
<tr>
<td>Procainamide(^7,8)</td>
<td>Intravenous</td>
<td>&lt;1.5 h</td>
<td>43—88</td>
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<td>Disopyramide</td>
<td>Intravenous</td>
<td>&lt;8 h</td>
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<td>7</td>
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<tr>
<td>Propafenone(^9—12)</td>
<td>Intravenous</td>
<td>&lt;4 h</td>
<td>43—89</td>
<td>0—17</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>&lt;5 h</td>
<td>72—86</td>
<td>10—14</td>
</tr>
<tr>
<td>Flecainide(^13,14)</td>
<td>Intravenous</td>
<td>&lt;2 h</td>
<td>65—96</td>
<td>7—31</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>&lt;5 h</td>
<td>78—95</td>
<td>21—23</td>
</tr>
<tr>
<td>Amiodarone(^15,16)</td>
<td>Intravenous</td>
<td>&lt;12 h</td>
<td>25—89</td>
<td>7—27</td>
</tr>
<tr>
<td>Sotalol(^17)</td>
<td>Intravenous</td>
<td>&lt;4 h</td>
<td>31—85</td>
<td>10—20</td>
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<td>Esmolol(^18)</td>
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<td>&lt;40 min</td>
<td>6—50</td>
<td>14—19</td>
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<tr>
<td>Ibutilide(^7,17,19—20)</td>
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<td>&lt;90 min</td>
<td>18—48</td>
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<tr>
<td>Dofetilide(^21—24)</td>
<td>Intravenous</td>
<td>&lt;2 h</td>
<td>30—35</td>
<td>3—8</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>&lt;36 h</td>
<td>6—18</td>
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<tr>
<td></td>
<td>&lt;12 h</td>
<td>35—45</td>
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<tr>
<td></td>
<td>&lt;24 h</td>
<td>55—85</td>
<td></td>
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<tr>
<td></td>
<td>&lt;48 h</td>
<td>76—92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Table 1** Antiarrhythmic drugs to restore sinus rhythm in paroxysmal atrial fibrillation

The intravenous dose of flecainide and propafenone is a bolus of 2 mg/kg (in 5—15 min), followed by a continuous infusion of 0.007 mg/kg per min. Propafenone at 600 mg and flecainide at 300 mg (in patients >70 kg) were tested as single oral loading doses and achieved significant good results in terms of CV rate (Fig. 1). After reviewing 21 controlled studies, Kahn\(^19\) concluded that, based on its efficacy and safety, a single oral dose of propafenone should be considered the first-line therapy for conversion of recent onset AF. The possible pro-arrhythmia during treatment with...
propafenone or flecainide is atrial flutter with 1:1 atrioventricular conduction, which has been found in fewer than 0.5% of patients if they are at rest when the peak plasma level occurs. To date, there are insufficient data to support the so-called ‘pill in the pocket’ approach of out-of-hospital treatment.

In addition, there are also several clinical conditions in which patients may not respond or have contraindications to treatment with class IC AADs (i.e. complete bundle branch block). In these cases, the new class III drug ibutilide (1 mg intravenously + 1 mg after 15 min) may be used, which has demonstrated a mean efficacy rate of 30–40% within 60–90 min. Its use must be strictly monitored with ECG because of the risk for torsade de pointes (1–5% of cases), which occurs more often in females, and in the presence of heart failure, hypokalaemia, long QT at baseline ECG and organic heart disease. Ibutilide has also been found to have a similar efficacy rate in patients with long-lasting AF (duration <90 days), in which it may be considered a preferred drug.

Intravenous amiodarone (bolus of 5 mg/kg in 15–20 min followed by 500–900 mg in a 12 h infusion) is also commonly used. Its efficacy rate is about 50–60% with a mean time to efficacy of 12 h. Adverse events are mainly hypotension (<0.5%). The presence of Wolff–Parkinson–White syndrome is a definite contraindication (possible 1:1 conduction). A central line infusion to avoid peripheral phlebitis must be considered. It has also been demonstrated that amiodarone as a single oral dose is effective and safe in patients with recent onset AF. In one study, 72 patients were randomly assigned to receive either oral amiodarone 30 mg/kg or placebo. The patients receiving amiodarone converted to sinus rhythm more effectively than did those receiving placebo (P < 0.0001). At 8 h, approximately 50% of the patients in the amiodarone group and 20% in the placebo group had converted to sinus rhythm, and after 24 h the proportions of patients who had converted were 87% and 35%, respectively. Amiodarone is the preferred drug in patients with heart failure, ischaemic heart disease and after coronary artery bypass grafting (CABG).

Dofetilide, a new class III AAD, offers an alternative to other common AADs and has been approved for the treatment of patients with AF and atrial flutter. Data from clinical published studies, which enrolled about 1000 patients, demonstrated that conversion to sinus rhythm occurs in 30% of the patients, but these data are mainly related to long-lasting AF episodes. In two studies, namely the European and Australian Multicenter Evaluation on Atrial Fibrillation Dofetilide (EMERALD) and the Symptomatic Atrial Fibrillation Investigators Evaluation of Dofetilide (SAFIRE-D), dofetilide 500 µg twice daily for 3 days achieved a conversion rate of about 30%. However, dofetilide has the single significant side effect of torsade de pointes. Therefore, dosage must carefully be adjusted according to the length of the QTc interval and creatinine clearance rate (Table 2).

Paroxysmal atrial fibrillation (duration <48 h) in patients with poor left ventricular function (or acute myocardial infarction or CABG)

There are few controlled studies in this clinical setting. However, poor left ventricular function (ejection fraction <35%) is certainly a reason not to use class I AADs, which have either specific negative inotropic effects (class IC) or have demonstrated higher mortality, at least in the long term, as is the case for quinidine. Intravenous amiodarone is thus the safest drug and it is effective. Intravenous ibutilide may be used but with caution because of the higher incidence of torsade de pointes.

Persistent atrial fibrillation (duration >48 h)

In this clinical setting the efficacy of AADs decreases to no more than 50% and patients should be anticoagulated before CV. Therefore, clinicians must consider the option of external CV (>90% efficacy rate with the biphasic waveform) preceded by transoesophageal echocardiography as first-line therapy. In patients with persistent AF we may consider two different scenarios. The first is related to the shorter time to conversion in patients who are already hypocoagulated or in
whom a transoesophageal echocardiography procedure has been performed to exclude auricular thrombi. In this context, intravenous ibutilide has an expected efficacy rate of 30—40% a short time after infusion. In this clinical context, intravenous amiodarone is probably less effective. The second scenario involves a longer time to electrical CV associated with warfarin therapy. There are few studies, particularly with oral amiodarone (600—800 mg/day) and oral propafenone (600—900 mg/day), of AAD pre-treatment during the period before electrical CV. The mean time to efficacy is 15 days. The rate of efficacy is around 35—50% with either drug, with propafenone acting slightly sooner.

While treating an active patient (not a bedresting patient) at home with propafenone, one must carefully consider that during propafenone administration the patient is exposed to a significant risk for atrial flutter with 1 : 1 atrioventricular conduction with possible side effects (syncope). In contrast, amiodarone is safe in this clinical setting. This is the main reason why we believe that treatment with amiodarone is preferable to that with propafenone or class IC AADs.

Recently, an interesting report was published in which the concomitant use of amiodarone and ibutilide was examined. The purpose of the study was to assess the efficacy and safety of CV with intravenous ibutilide in patients with AF or atrial flutter chronically treated with amiodarone. Patients were taking amiodarone (153 ± 259 days) and were administered ibutilide 2 mg intravenously. Ibutilide converted 54% of the patients with atrial flutter and 39% of the patients with AF. Despite a prolongation of the QT interval after ibutilide administration, only one episode of torsade de pointes occurred. These observations suggest that combination therapy may be a useful method for

<table>
<thead>
<tr>
<th>Drug</th>
<th>Most common adverse events</th>
<th>Contraindication</th>
<th>Special clinical indication</th>
<th>Efficacy (%) at:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone (700—2000 mg/week) 28—32</td>
<td>Pulmonary toxicity, photosensitivity, polyneuropathy, gastrointestinal disturbances, sinus bradycardia, torsade de pointes, hepatic toxicity, thyroid dysfunction</td>
<td>Clinical or subclinical hyperthyroidism</td>
<td>Congestive heart failure, ischaemic heart disease, CABG (not certain)</td>
<td>75—78.5 50—73</td>
</tr>
<tr>
<td>Dofetilide (250/1000 µg/day)*31,34</td>
<td>Torsade de pointes, heart failure, glaucoma, urinary retention, dry mouth</td>
<td>Heart failure</td>
<td>— 44—50 54</td>
<td></td>
</tr>
<tr>
<td>Flecaïnide (200—300 mg/day)*35—37</td>
<td>Negative dromotropic effects, congestive heart failure, AF, 2 : 1 AV conduction, ventricular tachycardia</td>
<td>Clearance creatinine &lt;20 ml/min</td>
<td>Atrial flutter 71 66</td>
<td></td>
</tr>
<tr>
<td>Quinidine (600—1500 mg/day)*28,38,39</td>
<td>Torsade de pointes, gastrointestinal disturbances, TAV nodal conduction</td>
<td>—</td>
<td>27—58 23—51</td>
<td></td>
</tr>
<tr>
<td>Procainamide (1000—4000 µg/day)*6</td>
<td>Torsade de pointes, lupus-like syndrome, gastrointestinal disturbances</td>
<td>Heart failure</td>
<td>— — 25</td>
<td></td>
</tr>
<tr>
<td>Propafenone (450—900 mg/day) 35,40—42</td>
<td>Negative dromotropic effects, congestive heart failure, AF, 2 : 1 AV conduction, ventricular tachycardia</td>
<td>Heart failure, ischaemic heart disease, left branch block</td>
<td>Lone AF</td>
<td>35—40</td>
</tr>
<tr>
<td>Sotalol (240—320 mg/day)*43,40</td>
<td>Torsade de pointes, bradycardia, congestive heart failure</td>
<td>Bronchospastic lung disease, sinus bradycardia</td>
<td>Hypertension 46—50 37—46</td>
<td></td>
</tr>
</tbody>
</table>

*Dosage must be adjusted for body size, age and creatinine clearance rate. In particular, the dosage adjustment for creatinine clearance is as follows: creatinine clearance >60 ml/min, dose 500 µg twice daily; 40—60 ml/min, 250 µg twice daily; 40—20 ml/min, 125 µg twice daily; <20 ml/min, contraindicated. CABG=coronary artery bypass grafting; AF=atrial fibrillation; AV=atrioventricular.

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achieving CV for patients with chronic AF or atrial flutter, particularly in those with previous negative response to monotherapy.

Atrial flutter conversion

When considering atrial flutter, we must take into account several differences as compared with AF. First, the duration of the arrhythmia is not a crucial issue for drug efficacy. Second, class I AADs play a minor role in stopping these arrhythmias (20–30% efficacy rate). Class III AADs, in contrast, have a very specific role to play.

Conversion to sinus rhythm can be achieved in up to 70% of patients with intravenous ibutilide, but this agent should be reserved for patients with either normal hearts or only mild left ventricular dysfunction. Fewer patients have been treated with dofetilide, but this agent is also highly efficacious. Amiodarone is effective but at a lower rate (≤60%) and needs a longer time for infusion. In patients with poor left ventricular function, because of the lower rate of pro-arrhythmia, amiodarone is preferable to ibutilide, which has a higher rate of efficacy but is associated with a high incidence of torsade de pointes (up to 8%). Direct current CV is nearly 100% effective and is ideal for patients with left ventricular dysfunction. Long-term maintenance of sinus rhythm may be achieved in 50–60% of patients with AADs, including sotalol, amiodarone, dofetilide, propafenone and flecainide, but this has the potential for causing significant pro-arrhythmia and side effects.

Use of antiarrhythmic drug treatment with external cardioversion

AADs have been used in patients with persistent AF to enhance their response to treatment with monophasic external CV. This strategy allows restoration of sinus rhythm in about 65–70% of patients.

Pre-treating patients with intravenous ibutilide resulted in restoration of sinus rhythm in 100% of patients, as compared 72% in the control group (no pre-treatment). In addition, class IC AADs have been used with success to enhance the efficacy of internal electrical CV, and amiodarone and sotalol may also influence the efficacy rate of CV. With the introduction of biphasic waves in external CV, the rate of success of the procedure has reached up to 94%. Therefore, the importance of pre-treatment with AADs to facilitate CV has decreased, but it may be useful in preventing early AF recurrence after successful CV. In many trials, about 50% of the patients are back in AF after 1–2 months. Pre-treating these patients with 400 mg/day oral amiodarone 1 month before CV and 1–2 months after resulted not only in ‘spontaneous’ reversion to sinus rhythm before CV in 15–20% but also in improved efficacy with monophasic CV and a greater proportion of patients with persistent sinus rhythm in the 2 months after CV. An Italian multicentre study is ongoing to confirm these findings.

Another issue regarding the use of AAD peri-CV is the case of immediate recurrence of AF or early recurrence of AF. When class IC drugs are promptly injected intravenously before a second CV, this may enhance the likelihood that a constant sinus rhythm will be achieved.

Maintenance of sinus rhythm

Maintaining sinus rhythm is one of the most difficult goals to achieve in patients with AF, even with all the clinical tools we have at our disposal. Many studies, with different AADs, have shown a similar high percentage of AF recurrence at 6–12 months (50–60%; Table 3). Of course, the final result may be influenced by the selected patient population, the types of AF and by the way in which AAD therapy is initiated. However, because of the difficulty in completely preventing episodes of AF, we should focus our attention on different goals when we begin AF prophylaxis. In particular, we should consider an increase in time to first recurrence or time in sinus rhythm as good primary results in order to enhance the quality of life of the patient and reduce the incidence of possible haemodynamic complications of AF, such as congestive heart failure, hypotension and angina. Although it has not yet been demonstrated that maintenance of sinus rhythm may improve survival, the clinical implications of frequent recurrence of AF or permanent AF (reduced global cardiac function and exercise tolerance, high risk for thromboembolic events) may justify, in many symptomatic patients, pharmacological treatment to maintain sinus rhythm. The AFFIRM and RACE studies dealt mainly with an elderly population with good left ventricular function.

The AADs recommended as first-choice therapies are amiodarone, sotalol, flecainide and propafenone. In many observational non-comparative and comparative studies and in the Canadian Trial of Atrial Fibrillation (CTAF), amiodarone was considered the most effective
drug in maintaining sinus rhythm (dosage 1400–
2800 mg/week). At 2-year follow-up 65% of
patients receiving amiodarone were free from AF
episodes, as compared with 37% of patients in the
propafenone and sotalol groups. However, the 15–
40% patient dropout rate is reportedly due to
intolerable adverse events. This is why we
recommend amiodarone as a second-line drug, to
be used when other antiarrhythmic treatments
have failed. However, the adverse events are
generally reversible after amiodarone dose
reduction (to the minimal effective dose) or
treatment interruption. Minor adverse events may
be managed while maintaining amiodarone
treatment (i.e. subclinical hypothyroidism may be
treated with low-dose active hormone). The only
certain contraindication is clinical or subclinical
hyperthyroidism. Periodic monitoring of thyroid
function is recommended. Fewer adverse events
have been observed with low-dose amiodarone
(500–1200 mg/week), which may be equally
effective in many patients. In the rhythm control
arm of the AFFIRM study, amiodarone was the most
commonly administered drug.

Sotalol, flecainide and propafenone are also
considered first-choice therapies. Although sotalol
is not effective in conversion of AF, it is as
effective as class IC drugs in maintaining sinus
rhythm after AF conversion at 1-year follow-up.40
The likelihood of remaining in sinus rhythm during
follow-up is higher in younger patients with a
smaller left atrial size and without concomitant
heart disease. Patients treated with sotalol must
initially be monitored by ECG (for at least 3 days)
in hospital because of the potential pro-
arrhythmic effect of this drug (it prolongs the QT
interval), especially in females and in those with
hypokalaemia.

Flecainide (200–300 mg/day) and propafenone
(450–900 mg/day) may be considered first-line
choices in patients with no organic heart disease
or hypertension. Compared with placebo,
propafenone and flecainide increased the overall
time free from AF and the interval to first
recurrence.35–38 Randomized and non-
randomized studies found good efficacy rates for
class IC drugs compared with quinidine and other
AADs.42 In an open-label randomized study
involving 100 patients with AF, propafenone and
sotalol were similar in preventing AF episodes (30% vs
37%, respectively). Class IC drugs may be
initiated out of hospital, with due consideration to
the general contraindications (Table 3). The
recent introduction of propafenone as a ‘slow-
release’ formulation will certainly improve patient
compliance and provide a more constant
therapeutic level over 24 h, and may improve
results (325 or 425 mg slow release twice daily) at
long-term follow-up. The duration of QRS and the
PR interval should be measured periodically during
long-term therapy.

Metoprolol can be used alone or in combination
with the class IC drugs amiodarone or sotalol. In
one study, 394 patients were randomly assigned
to receive placebo or metoprolol after successful
conversion of persistent AF. After 9 months of
follow-up, metoprolol demonstrated a good rate
of persistent sinus rhythm as compared with
placebo (51% vs 40%, \( P = 0.005 \)).

The combination of sotalol with amiodarone
should be proscribed (it excessively prolongs the
QT interval).

Dofetilide may be used with particular caution
in patients with reduced renal function. With
adequate dose adjustment, the incidence of
adverse effects may be reduced to 2.9% for
torsade de pointes, 0.4–1.6% for polymorphic and
monomorphic ventricular tachycardia, and 1.7% for
ventricular fibrillation.33 In the SAFIRE-D
study, a higher dose of dofetilide (125, 250 and
500 µg/day) prevented AF in 40%, 52% and 66% of
patients, respectively, at 6-month follow-up

<table>
<thead>
<tr>
<th>Drug</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
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<tr>
<td>Quinidine28,38,39</td>
<td>65</td>
<td>44–75</td>
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<tr>
<td>Disopyramide33</td>
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<td>Propafenone35–40–42</td>
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<tr>
<td>Flecainide35–37</td>
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<td>44</td>
<td>—</td>
<td>34–42</td>
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<tr>
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<td>—</td>
<td>75–78.5</td>
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<td>Metoprolol36</td>
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<td>Sotalol40,43</td>
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<tr>
<td>Dofetilide33,34</td>
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<td>—</td>
<td>71</td>
<td>66</td>
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<tr>
<td>Placebo</td>
<td>58</td>
<td>15–56</td>
<td>19–35</td>
<td>0–45</td>
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</table>
compared with placebo (24%). Furthermore, the combination of amiodarone with a beta-blocker may be useful in prolonging the time to first recurrence and postsurgery AF. In the randomized double-blind placebo-controlled trial Atrial Fibrillation Suppression Trial (AFIST), prophylaxis with oral amiodarone in combination with beta-blockers prevented AF and reduced the risk for cerebrovascular accidents in patients undergoing open-heart surgery (220 patients).

The role of disopyramide in the treatment of patients with AF has not been clearly demonstrated. Few randomized studies are available and many adverse events (heart failure and atrioventricular block) limit its use in clinical practice.59

Quinidine is effective in maintaining sinus rhythm (Table 1). However, its use is limited by the demonstrated high risk for torsade de pointes and the mortality rate (total mortality at 1 year with quinidine 2.9% vs 0.8% in patients with no quinidine).38

Control of heart rate

Control of heart rate is an important tool when sinus rhythm cannot be maintained or when adverse events caused by AADs are not tolerated or may be dangerous. The main goal while establishing a pharmacological therapy for heart rate control is to reduce heart rate to a normal physiological level at rest (<90 beats/min), to obtain physiological control during exercise and to improve exercise capacity. Although the concept of ‘adequate heart rate control’ in patients with AF is not universally defined, in clinical practice we may consider a good level of control during exercise as follows: for male patients: 227—age (in years) beats/min and for female patients 206—(0.6—age [in years]) beats/min. Exercise capacity should be monitored before and during therapy in order to adjust dosage and drug combinations to obtain a better result. A gradual treadmill test or 6-min walk test may be used to test the results.

When we consider heart rate control therapy, some advantages and disadvantages must be taken into account, in particular the following. First, the drugs used for heart rate control are simple and generally safer than drugs used for maintenance of sinus rhythm. Second, it often becomes difficult to maintain sinus rhythm in the long term, and recurrent AF episodes may worsen the patient’s quality of life. Finally, if pharmacological control of heart rate is difficult, then ablation and pacing therapy may be considered; their efficacy has been demonstrated, especially in symptomatic patients.

Verapamil and diltiazem are considered the drugs of choice for heart rate control in the context of AF. A gradual dose titration is necessary, especially in patients with initial signs of congestive heart failure (verapamil 240–360 mg, diltiazem 180–360 mg). Digitalis (0.250–0.320 mg/day) and beta-blockers (metoprolol 50–200 mg/day, propranolol 80–240 mg/day) may be considered of secondary importance. In particular, the combinations of calcium channel blockers and digitalis, beta-blockers and digitalis, and calcium channel blockers and beta-blockers may be useful in reducing the dosage of single drugs and, consequently, dosage-dependent side-effects.

A rational, step-by-step approach in heart rate control according to individual characteristics is presented in Table 4.

Amiodarone may have a role to play, particularly in patients with AF and congestive heart failure. The use of propafenone in heart rate control is seldom considered an option in this clinical setting. It is only used in patients with good left ventricular function, and only in resting conditions, possibly in combination with beta-blockers.

When high heart rate causes signs and symptoms of heart failure, electrical CV must be considered, possibly guided by transoesophageal echocardiography.

Maintaining sinus rhythm vs rate control

Restoration and maintenance of sinus rhythm is generally thought to be superior to rate control in patients with AF. However, there are data from prospective controlled trials comparing both therapeutic strategies. The PIAF1 study randomly assigned 252 patients with AF and compared rate control (125 patients treated with diltiazem) with rhythm control (127 patients treated with amiodarone). With respect to symptomatic improvement in patients with AF, the therapeutic strategies of rate control vs rhythm control yielded similar clinical results overall. However, exercise tolerance was better with rhythm control, although hospital admission was more frequent. These data may serve as a basis on which to select therapy in individual patients. The STAF2 study casts further doubt on the wisdom of CV as a routine strategy for the management of chronic AF. STAF is a randomized, prospective, multicentre study conducted in 2000 patients with AF. No significant differences have been found.
between rate and rhythm control in terms of death, cerebrovascular events, hospitalization and quality of life in the two groups.

The AFFIRM³ and RACE⁴ trials, conducted in different numbers of patients (4060 and 255, respectively), considered the important issue of rhythm control vs rate control. Although the primary end-points were different (AFFIRM, overall mortality; RACE, composite), the results from both trials revealed no survival advantage of the rhythm control vs rate control strategy, and a lower risk for adverse drug events with rate control together with a lower rate of hospitalisation. However, the main aim of the studies was to focus on the importance of anticoagulation with warfarin with an international normalized ratio greater than 2 in patients with at least one clinical risk factor for stroke, independently of the chosen strategy. The favourable characteristics of the patients who formed the rate control group (elderly, good left ventricular function, mainly hypertensive patients) must be considered when evaluating the patient population that was included in the studies. It is possible that younger patients highly symptomatic or a totally different population, such as heart failure patients, could benefit from a rhythm control strategy.

### What has to come

The new AADs being developed and under clinical investigation are pure class III drugs; they include azimilide, ambisilade, E4031, almokalan, sematilide, RP 58866 and tedisamil. These drugs are being investigated in relation to their antifibrillatory properties in prolonging the duration of the action potential and refractoriness.

Azimilide⁶¹ and ambisilade⁶² have similar electrophysiological characteristics (pure class III AADs that exert a non-selective blockade of the potassium channel) and may have better safety profiles with respect to pro-arrhythmic effects as compared with other class III drugs. Azimilide is a promising new compound being tested in healthy individuals, in whom it has shown a good safety profile when administered intravenously (4.5—9 mg/kg in a 15—60 min infusion) and orally (maintenance doses of 35, 100, 150 and 200 mg twice daily).⁶¹ Prichtett et al.⁶⁴ reported the results of a study assessing the effectiveness of azimilide in reducing the frequency of symptomatic arrhythmia recurrence in patients with AF, atrial flutter, or both. Efficacy analysis compared the time to first symptomatic

| Table 4 | Step-by-step approach in heart-rate control in patients with atrial fibrillation |
|---|---|---|
| Step 1 | Step 2 | Step 3 |
| Congestive heart failure patients | Digitalis (0.25—0.32 mg) **Recommendation:** IA **Contraindication:** WPW patients **Limitation:** not efficacious in active patients **Caution:** brady-tachy syndrome — in 20% worsens bradycardia, digitalis toxicity | Combination with calcium channel blocker or beta-blocker **Caution:** gradual dose titration | AV nodal modulation AV nodal ablation plus pacemaker |
| Active patients, COPD, ischaemic heart disease, left ventricular hypertrophy, no organic heart disease | Diltiazem (180—360 mg) or verapamil (240—360 mg) **Recommendation:** IB **Contraindication:** hypotension, heart block **Limitation:** heart failure **Caution:** patients with signs of heart failure | Amiodarone (rarely) **Recommendation:** IB, combination with digitalis | AV nodal modulation AV nodal ablation plus pacemaker |
| WPW syndrome, thyrotoxycosis | Beta-blockers (i.e. metoprolol 25—100 mg twice daily; propranolol 40—120 mg twice daily) **Recommendation:** IB **Contraindication:** asthma **Limitation:** heart failure, brady-tachy syndrome **Special indication:** in WPW syndrome, in combination with IA, IC, III | Association with sympatholytic drugs | AV nodal modulation AV nodal ablation plus pacemaker |

AV=atrioventricular; COPD=chronic obstructive pulmonary disease; WPW=Wolff—Parkinson—White. (Modified from Reiffel.⁶⁰)
recurrence in the combined dose groups (azimilide 100 mg and 125 mg) with that in the placebo group. Azimilide significantly lengthened the symptomatic arrhythmia-free interval compared with placebo. Ambasilde has shown similar effects to sotalol in experimental studies conducted in dogs. However, no conclusive clinical studies have evaluated ambasilde in humans.

Moricizine has been used in the treatment of 85 consecutive patients with AF (mean dose 609 ± 9 mg/day). Moricizine was well tolerated in a wide variety of patients, and therefore it may be a safe and effective agent for treating patients with AF. However, further studies are needed to draw definite clinical conclusions. Other classes of drugs such as selective serotonin reuptake inhibitors are also being developed for their possible supraventricular antiarrhythmic effect.

Conclusion

In conclusion, pharmacological therapy is still the mainstay of treatment for AF. However, there is much conflicting data on the management of AF patients, especially regarding rhythm or rate control. In paroxysmal AF, class IC drugs represent the first-choice therapy in patients with no organic heart disease or hypertension. When AF lasts longer than 3 days, electrical CV therapy plays a major role, particularly since the introduction of the biphasic waveform defibrillators. Amiodarone is the principal drug in the maintenance of sinus rhythm control to date, and is the most effective in long-term follow-up. The high incidence of side-effects often limits its use in patients with organic heart disease or with non-satisfactory results with previous AAD therapy. Clinical research is currently directed at the use of class III drugs that are new on the market, such as dofetilide and ibutilide, and pure class III drugs that are still being developed, have demonstrated good antifibrillatory effects both in AF and atrial flutter, and have a favourable side-effect profile.

The main points to consider when treating patients with AF may be summarized as follows.

• Know the drug properties and match them with the patient’s clinical condition.

• Adjust the dose to the specific patient and treat the adverse events, especially when the drug is effective.

• Consider when to expect the maximum effect and accurately control patient safety.

• Avoid pro-arrhythmic conditions by considering the clinically beneficial factors for the given drug.

• Do not expect complete AF prevention in the long-term but consider different efficacy criteria (interval free from arrhythmia and quality of life, among others).

• When using a combination of drugs, choose the most rational combination and preferentially reduce the dosage of single compounds.

• If there is reason, give a previously ineffective drug another chance to work by choosing a hybrid therapy.

• Never forget the role of warfarin therapy, especially when at least one risk factor for stroke is present.

• Do not give up too early with the conversion procedure, especially in symptomatic patients.

• Rate control may be a good choice in elderly patients with good left ventricular function.

References


