Review Article

Systematic review of the management of atrial fibrillation in patients with heart failure

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Aims To systematically review the management of atrial fibrillation (AF) in patients with heart failure.

Methods Studies investigating the management of AF in patients with heart failure published between 1967 to 1998 were identified using MEDLINE, the Cochrane register and Embase databases. Reference lists from relevant papers and reviews were hand searched for further papers.

Results Eight studies pertaining to acute and twenty-four pertaining to chronic AF were identified. For patients with acute AF ventricular rate control, anticoagulation and treatment of heart failure should be pursued simultaneously before cardioversion is attempted. Digoxin is relatively ineffective at controlling ventricular response and for cardioversion. Intravenous diltiazem is rapidly effective in controlling ventricular rate and limited evidence suggests it is safe. Amiodarone controls ventricular rate rapidly and increases the rate of cardioversion. There are insufficient data to conclude that immediate anti-coagulation, transoesophageal echocardiography to exclude atrial thrombi followed by immediate cardioversion is an appropriate strategy. Patients with chronic AF should be anti-coagulated unless contra-indications exist. It is not clear whether the preferred strategy should be cardioversion and maintenance of sinus rhythm with amiodarone or ventricular rate control of AF combined with anticoagulation to improve outcome including symptoms, morbidity and survival. Electrical cardioversion has a high initial success rate but there is also a high risk of early relapse. Amiodarone currently appears the most effective and safest therapy for maintaining sinus rhythm post-cardioversion. Digoxin is fairly ineffective at controlling ventricular rate during exercise. Addition of a β-blocker reduces ventricular rate and improves symptoms. Whether digoxin is required in addition to β-blockade for the control of AF in this setting is currently under investigation. If pharmacological therapy is ineffective or not tolerated then atrio-ventricular node ablation and permanent pacemaker implantation should be considered.

Conclusion There is a paucity of controlled clinical trial data for the management of AF among patients with heart failure. The interaction between AF and heart failure means that neither can be treated optimally without treating both. Presently treatment should be on a case by case basis.

Introduction

Chronic heart failure and atrial fibrillation each affect 1–2% of the population, and the prevalence of both rises steeply with age[1–4]. They share common risk factors and consequently frequently coexist. Chronic heart failure may affect more than 50% of patients with atrial fibrillation[5] while the prevalence of atrial fibrillation increases in proportion to the severity of chronic heart failure[6–8] (Fig. 1). There is also evidence of a causal, reciprocal relationship between the two[9–11]. Recent data from the Framingham study indicated that chronic heart failure was associated with a 4:5 and 5:9-fold risk of atrial fibrillation for men and women, respectively[12]. The occurrence of atrial fibrillation often causes acute
heart failure or an acute exacerbation of chronic heart failure\cite{13,14}. There is also evidence of a subtle cardiomyopathy associated with atrial fibrillation\cite{11} and a number of case reports detailing reversible chronic heart failure linked to fast uncontrolled atrial fibrillation\cite{15–19}. Advances in the treatment of heart failure have improved mortality\cite{6} and have perhaps led to a reduction in the incidence of associated atrial fibrillation\cite{20,21}, while effective management of atrial fibrillation will improve symptoms and may retard the progression of chronic heart failure.

This systematic review describes the published evidence for the management of both acute and chronic atrial fibrillation in patients with heart failure. The management of heart failure has been extensively reviewed elsewhere\cite{22}, our intention is to focus on the practical management of atrial fibrillation in the setting of heart failure rather than its role in the progression of heart failure. Key deficiencies in our knowledge are identified and future areas of research suggested.

**Methods**

A literature search from 1967 to 1998 was performed using MEDLINE, the Cochrane register and Embase databases. Papers containing the terms atrial fibrillation and heart failure, and their synonyms, were identified and scrutinized to determine whether they met the inclusion criteria for the review which are as follows:

- Acute atrial fibrillation was defined as atrial fibrillation of <48 h duration or when it was apparent that recent-onset, uncontrolled atrial fibrillation had precipitated worsening heart failure necessitating urgent heart rate control or cardioversion. Chronic atrial fibrillation was defined as atrial fibrillation lasting ≥48 h. The mean duration of atrial fibrillation of the patient population determined how the trial was categorized if there were both acute and chronic atrial fibrillation patients, as defined above. Where there was a mixture of atrial fibrillation and other supraventricular tachyarrhythmias the trials were included for analysis only if atrial fibrillation represented >70% of the study population. Studies confined to atrial fibrillation among patients with accessory pathways or documented paroxysmal atrial fibrillation were excluded.

- The definition of chronic heart failure was broad and included any definition used by the study investigators or a mean ejection fraction of ≤45%. Where there was a mixture of patients with and without chronic heart failure the trial was included for analysis if either >50% of patients were in NYHA classes II–IV or >50% had a history of chronic heart failure. Subgroup data on patients with atrial fibrillation and heart failure in large trials were included when relevant data were given.

The reference lists of papers that satisfied the inclusion criteria and of reviews were scrutinized to identify further papers not identified by the original search procedure.

**Results**

**Acute atrial fibrillation**

Five complete trials and three trials with subsets of patients with heart failure met the inclusion criteria. Some trials investigated twin outcomes of ventricular rate control and cardioversion (Tables 1 and 2) whereas others were confined to the assessment of rate control alone (Table 2). Six trials investigated amiodarone and/or digoxin and two were devoted to diltiazem. Studies frequently took place in a coronary care or intensive care setting where intravenous agents could be
<table>
<thead>
<tr>
<th>Study author, year, reference</th>
<th>Type of study</th>
<th>n</th>
<th>Ventricular function</th>
<th>Duration of AF</th>
<th>Initial heart rate (beats. min (^{-1})) mean ± SD</th>
<th>Drug administered/dose</th>
<th>Conversion to sinus rhythm/ time to conversion</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DAAF trial group 1997</strong>([23])</td>
<td>Double-blind randomized, placebo controlled(^1)</td>
<td>28</td>
<td>Not given</td>
<td>21±7 ± 30.4 h(^2)</td>
<td>122 ± 23 bpm(^3)</td>
<td>Dig. IV, 0.88 ± 0.35 mg (mean ± SD)</td>
<td>6/15 — dig. group, 5/13 — placebo group time to conversion not given</td>
<td>None</td>
</tr>
<tr>
<td><strong>Hou et al. 1995</strong>([25])</td>
<td>Single blind, randomized digoxin controlled</td>
<td>50</td>
<td>Mean FS: Dig: 27%, Am: 26%</td>
<td>Dig: 4 h</td>
<td>Am: 14 h (median)</td>
<td>Dig: 0.013 mg/kg × 3 at 2 h intervals</td>
<td>Am: IV 300 mg in 1 h, 960 mg over next 23 h</td>
<td>Dig: 17/24 (71%) 6.5 h (median) Am: 24/26 (92%) 2.5 h (median)</td>
</tr>
<tr>
<td><strong>Clemo et al. 1998</strong>([29])</td>
<td>Retrospective</td>
<td>38</td>
<td>EF: 40 ± 16%</td>
<td>23/38 patients (61%) had an AF/SVT of &lt;24 h</td>
<td>149 ± 13</td>
<td>Am. IV: 242 ± 137 mg at 1 h (range 60 to 1000) and at 24 h 1137 ± 280 mg (range 99–2500)</td>
<td>11/38 (30%) in 24 h/time not given</td>
<td>0 (non-CVS side effect)</td>
</tr>
<tr>
<td><strong>Kumar 1996</strong>([28])</td>
<td>Retrospective</td>
<td>8</td>
<td>&lt;15% (EF)</td>
<td>&gt;30 min</td>
<td>152 ± 9</td>
<td>Am. IV: 300 mg in 1 h</td>
<td>7/8 (87.5%) reversion 27 ± 13 min (mean) 7/16 (44%) using either oral or IV route/ time not given</td>
<td>None</td>
</tr>
<tr>
<td><strong>Andrivet et al. 1994</strong>([27])</td>
<td>Prospective, randomized(^4)</td>
<td>16</td>
<td>Not given</td>
<td>Not given(^5)</td>
<td>140 for both groups (mean)</td>
<td>Am. Oral group — 2026 ± 79 mg in 24 h, IV group — 1038 ± 62.0 mg in 24 h</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)Subgroup of atrial fibrillation patients with coronary heart failure in a trial of 239 patients.

\(^2\)Mean ± standard deviation for all patients.

\(^3\)Mean ± standard deviation for both groups, no significant difference between groups.

\(^4\)Open label trial comparing oral vs intravenous amiodarone, subgroup of chronic heart failure patients (16 of 72 patients in trial).

\(^5\)56% of all patients in trial had atrial fibrillation duration of <48 h.

Dig. = digoxin, Am. = amiodarone, Dilt. = diltiazem, bpm = beats per minute, SD = standard deviation, IV = intravenous, CHF = chronic heart failure, SVT = supraventricular tachycardia, DAAF = digoxin in acute atrial fibrillation trial group, AF = atrial fibrillation, Afl = atrial flutter, NYHA = New York Heart Association Class, EF = ejection fraction, FS = fractional shortening, Exc. = excluded, PMVT = polymorphic ventricular tachycardia, T. de P. = torsades de pointes, ECV = electrical cardioversion.

<table>
<thead>
<tr>
<th>Study author, year, reference</th>
<th>Type of study</th>
<th>n</th>
<th>Ventricular function</th>
<th>Duration of AF</th>
<th>Initial heart rate (bpm)</th>
<th>Drug administered/dose</th>
<th>Heart rate slowing effect of drug</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hou et al. 1995[23]</td>
<td>Single-blind, randomised, digoxin controlled</td>
<td>50</td>
<td>Mean FS: Dig — 27% Am. — 26%</td>
<td>Median: Dig — 4 h Am. — 14 h</td>
<td>Dig: 163 ± 26 Am: 157 ± 20 (mean ± SD)</td>
<td>Dig: 0·013 mg/kg × 3 at 2 h intervals Am: IV 300 mg in 1st hour 1960 mg over next 23 h</td>
<td>Dig: — 150 bpm Am: — 122 bpm (at 1 h)</td>
<td>Dig: — 0, Am: — 2 (1 worsening heart failure and 1 death)</td>
</tr>
<tr>
<td>Goldenberg et al. 1994[26]</td>
<td>Randomised, double-blind, placebo controlled</td>
<td>37</td>
<td>36% (EF)</td>
<td>—</td>
<td>&gt;120</td>
<td>Dilt. IV/ (First dose 0·25 mg/kg over 2 min, if not effective then 0·35 mg/kg)</td>
<td>Dilt. — 36/37 response rate* placebo — 0/15 median response time — 5 min</td>
<td>3 (8%) — symptomatic hypotension. No worsening of chronic heart failure</td>
</tr>
<tr>
<td>Clemo et al. 1998[29]</td>
<td>Retrospective</td>
<td>38</td>
<td>40 ± 16% (EF)</td>
<td>23/38 patients (61%) had AF for &lt;24 h</td>
<td>149 ± 13 (mean ± SD)</td>
<td>AM IV/ 1 h — 242 ± 137 mg (range 60 to 1000) 24 h — 1137 ± 280 mg (range 99–2500)</td>
<td>15 min — 134 ± 14 1 h — 109 ± 18 24 h — 99 ± 15 (bpm, mean ± SD)</td>
<td></td>
</tr>
<tr>
<td>Heywood et al. 1991[30]</td>
<td>Uncontrolled study</td>
<td>9</td>
<td>34 ± 18 (mean EF ± SD)</td>
<td>—</td>
<td>142 (mean)</td>
<td>Dilt. IV/ initial dose 0·25 mg/kg (0·30 mg/kg) given if heart rate reduction &lt;10%</td>
<td>114 bpm median response time 5 min</td>
<td>None</td>
</tr>
</tbody>
</table>

*Response rate defined as 20% reduction in baseline heart rate or heart rate less than 100 achieved. Figures for diltiazem incorporate all placebo non-responders who were given diltiazem. For abbreviations, see Table 1.
given and close, sometimes invasive, monitoring could be carried out.

**Randomized controlled studies (Tables 1 and 2)**

In the DAAF (Digitalis in Acute Atrial Fibrillation) trial[23] of the 28 patients who had heart failure no difference was seen in cardioversion rates at 16 h between placebo and intravenous digoxin. Galve et al.[24] compared intravenous amiodarone and placebo in a randomized controlled trial. Eleven of the 100 patients suffered from mild chronic heart failure; severe chronic heart failure was excluded. Digoxin was administered at a dose of 1-5 mg over 24 h to both groups of patients. Only two out of the 11 heart failure patients converted to sinus rhythm and even if both were in the amiodarone group this represents a low rate of cardioversion. The presence of heart failure predicted a lower likelihood of cardioversion. Hou et al.[25] compared intravenous amiodarone to intravenous digoxin in an open-label randomized study of uncontrolled atrial fibrillation. Forty-six percent of patients in the digoxin group and 54% of patients in the amiodarone were in NYHA (New York Heart Association) class IV. Eleven patients had ischaemic heart disease of whom seven had been admitted with a myocardial infarction. Seventeen patients (34%) were receiving inotropic therapy but only 10 (20%) were receiving ACE inhibitors. Groups were well matched, apart from the mean duration of atrial fibrillation, which was 4 and 14 h in the digoxin and amiodarone groups respectively (P<0.05 for the difference). Amiodarone was infused via a central line or large peripheral vein at 5 mg.min⁻¹ for the first hour and reduced subsequently. The mean (± SD) dose of amiodarone administered over 24 h was 1383 ± 250 mg. Digoxin was administered intravenously at a relatively low dose of 0.013 mg·kg⁻¹·h⁻¹ in three divided doses each 2 h apart. The mean serum concentration of digoxin at 24 h was only 1.02 ± 0.36 ng·ml⁻¹. At 24 h 71% of patients in the digoxin group and 92% in the amiodarone group had reverted to sinus rhythm (P<0.005). Amiodarone achieved ventricular rate control more rapidly with a significant reduction in heart rate within 20 min compared to >1 h with digoxin.

Goldenberg et al.[26] compared intravenous diltiazem with placebo in a double-blind study followed by administration of open-label diltiazem to non-responders. Severe chronic heart failure, defined as an ejection fraction <25%, was present in 24% of patients. Heart rate was greater than 120 in all patients (uncontrolled atrial fibrillation). Digoxin was prescribed for 59% of patients. There was a rapid reduction in heart rate with diltiazem (21/22 ‘responded’ in a mean time of approximately 5 min)(Table 2). All 15 patients initially randomized to placebo, showed no response, but responded to diltiazem in the unblinded phase. There were no cardioversions. Hypotension occurred in 8% but there was no worsening of heart failure.

**Other types of data**

Andriev et al.[27] studied the effectiveness and safety of oral amiodarone compared to intravenous amiodarone in the management of patients with recent onset supraventricular tachycardia (16 of the 72 patients had a history of documented chronic heart failure or pulmonary oedema) in a prospective, uncontrolled study. Seven of 16 patients converted to sinus rhythm using oral or intravenous amiodarone. There was no evidence of exacerbation of chronic heart failure. No significant difference was seen in rates of conversion between the two groups. Kumar et al.[28], in a retrospective review of patients with severe left ventricular dysfunction (ejection fraction <15%), described reversion to sinus rhythm in seven of eight patients in 1 h using 300 mg of intravenous amiodarone. However, Cleme et al.[29] retrospectively investigated intravenous amiodarone in haemodynamically unstable ICU patients in whom ‘conventional’ measures to control acute atrial fibrillation, including attempts at electrical cardioversion, intravenous digoxin and esmolol, had failed. Mean ejection fraction was 40 ± 16% (mean ± SD) and mean heart rate was 149 ± 13 beats.min⁻¹. The mean dose of amiodarone at 1 and 24 h was less than in the study by Hou et al.[25] (Table 1). There was a rapid and sustained reduction in heart rate but a low (30%) rate of cardioversion rate at 24 h. In the above studies investigating amiodarone only one out of 99 patients experienced an exacerbation of heart failure with amiodarone and one terminally ill patient died, both adverse events occurring in the study by Hou et al.[25]. There were no adverse events with digoxin.

Heywood et al.[30] demonstrated similar results to Goldenberg et al.[26] in an uncontrolled study of intravenous diltiazem in nine patients with chronic heart failure [ejection fraction 32 ± 18% (mean ± SD)] with a mean ventricular rate of 142 beats.min⁻¹. There was a rapid, sustained reduction in heart rate. Again no exacerbation of heart failure was observed.

**Chronic atrial fibrillation**

Twenty-four trials were identified that fulfilled inclusion criteria for chronic atrial fibrillation; seven involved cardioversion, nine described maintenance of sinus rhythm post cardioversion, 11 described ventricular rate control (five pharmacological therapy, six catheter based studies). Three trials investigated two areas of management.

**Cardioversion (Table 3)**

Stambler et al.[31] investigating ibutilide, in a double-blind placebo-controlled randomized study, demonstrated a cardioversion rate of 31%. Arrhythmia duration predicted response (46% with atrial fibrillation...
Table 3  Studies of cardioversion from chronic atrial fibrillation in heart failure

<table>
<thead>
<tr>
<th>Author, year, reference</th>
<th>Study</th>
<th>n</th>
<th>Intervention</th>
<th>Ventricular function</th>
<th>NYHA class 1/2/3/4 (%)</th>
<th>Mean LA size (mm)/ arrhythmia duration/ previous cardioversions</th>
<th>Cardioversion</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stambler et al. 1996</td>
<td>Single blinded placebo controlled</td>
<td>121</td>
<td>I: 1·5 mg (n=40) I: 2·0 mg (n=41) vs placebo (n=41)</td>
<td>EF: ≤45% (mean) in all three groups 1</td>
<td>Not given</td>
<td>46 (mean)/14 days (mean duration) 2 not given</td>
<td>Ibutilide 3 = 31% placebo &lt;1%</td>
<td>6% of patients developed PMVT 4</td>
</tr>
<tr>
<td>Falk et al. 1997</td>
<td>Placebo controlled</td>
<td>91 (Afl 16)</td>
<td>D: 4·0 μg/kg n=32, D: 8·0 μg/kg n=29 placebo n=30</td>
<td>Not given</td>
<td>42/44/13/1</td>
<td>44-46/1.4-1.7 months (median between groups)/not given</td>
<td>low dose =10% high dose =19% placebo =0</td>
<td>3-2% (T.de P.)</td>
</tr>
<tr>
<td>Deedwani et al. 1999</td>
<td>Randomised, Placebo, controlled</td>
<td>103</td>
<td>Am. (n=51) 800 mg/day for 2 weeks, 400 mg/day for 50 weeks</td>
<td>Mean EF: Am. — 25% placebo — 26%</td>
<td>All 2-4</td>
<td>Not given</td>
<td>Am. — 16/51 (31% at 1 year), placebo — 4/52 (8%) (withdrawal rate)</td>
<td></td>
</tr>
<tr>
<td>Van Gelder 1991</td>
<td>Uncontrolled</td>
<td>246, (Afl55)</td>
<td>External ECV</td>
<td>FS 29</td>
<td>36/39/25/1</td>
<td>46 ± 8/28 ± 45 months (mean ± SD)/not given</td>
<td>70% for AF patients</td>
<td>0</td>
</tr>
<tr>
<td>Tieleman et al. 1996</td>
<td>Uncontrolled</td>
<td>129</td>
<td>Oral Am. 600 mg/day for 4 weeks</td>
<td>FS 29</td>
<td>23/52/25</td>
<td>47/53 months (median)/1-9 (mean)</td>
<td>18% after 1 month 6</td>
<td>0</td>
</tr>
<tr>
<td>Gosselink et al. 1992</td>
<td>Uncontrolled</td>
<td>89</td>
<td>Oral Am. 600 mg/day for 4 weeks</td>
<td>FS 30</td>
<td>18/50/29/3</td>
<td>48/30 months (median)/2 (mean)</td>
<td>16% at 1 month 6</td>
<td>1</td>
</tr>
<tr>
<td>Mostow et al. 1990</td>
<td>Uncontrolled</td>
<td>9</td>
<td>Oral Am. day 1: 2-4 g day 2: 1-6 g</td>
<td>Not assessed</td>
<td>Not given (5/9 had history of CHF)</td>
<td>42 (LA size not given for 2 patients)/33 months (mean)/not given</td>
<td>69 at mean of 24:5 h 7</td>
<td>2 patients</td>
</tr>
</tbody>
</table>

155% of patients had depressed left ventricular function.  
2The mean was taken from the mean of the three groups in the trial, there was no significant difference in this parameter between the groups.  
3Average of high and low dose ibutilide, no significant difference between doses.  
4Parameters of sex, race, heart failure and pulse rate were significantly associated with the development of polymorphic ventricular tachycardia (PMVT).  
525% refers to total percentage of patients in class 3 and 4.  
677% and 74% of remaining patients in the trials by Tieleman et al. and Gosselink et al. respectively cardioverted with electrical cardioversion.  
7Remaining three cardioverted with electrical cardioversion.  
For abbreviations, see Table 1.
Cardiac function was not a determinant of cardioversion success. There was no evidence of a negative inotropic effect but polymorphic ventricular tachycardia occurred in 6% of patients, all within 30 min of starting the infusion. There was no evidence of a raised threshold for electrical cardioversion in non-converters. Falk et al. using dofetilide[39] reported lower success rates. To what extent this reflects differences in relative dose or the population under study is not clear.

A post-hoc analysis was undertaken of the subset of patients with atrial fibrillation in the CHF-STAT study[33,34]. This was a controlled study investigating amiodarone in heart failure. Of the 103 patients with atrial fibrillation 31% cardioverted ‘spontaneously’ in the amiodarone group (n=51) compared to 8% in the placebo group (n=52) during a 4-year follow-up ($P=0.002$).

Only one study using electrical cardioversion alone[35] in a population of predominantly mild chronic heart failure fulfilled the criteria for inclusion. Successful cardioversion[35], defined as sinus rhythm lasting >24 h, was achieved in 70% of patients. Age and duration of atrial fibrillation were the only predictors of initial cardioversion success.

Two uncontrolled studies of amiodarone[36,37] demonstrated a pharmacological cardioversion rate of 16–18% after 4 weeks of oral amiodarone treatment (600 mg day$^{-1}$). Patients in these trials had had a number of previous failed attempts at electrical cardioversion. Higher des-ethyl amiodarone plasma levels, shorter arrhythmia duration, smaller left atrial dimensions and concomitant treatment with verapamil predicted a greater likelihood of success in the study by Tieleman et al.[38]. Mostow et al.[39] cardioverted six out of nine heart failure patients using a high oral loading dose of amiodarone within 48 h. In these three trials and the CHF-STAT substudy investigating amiodarone in chronic atrial fibrillation, 102/278 patients (4%) suffered adverse events.

### Maintenance of sinus rhythm after electrical cardioversion (Table 4)

The three placebo controlled trials of class 1 antiarrhythmic agents (flecainide[39], quinidine[40] and disopyramide[41]) indicate that the chances of remaining in sinus rhythm at 1 year are roughly doubled on treatment compared to placebo. However, there was a significant incidence (9–12%) of side effects. Porterfield et al.[42] investigating propafenone described sinus rhythm maintenance of only 46% at 15–6 months. Poor patient characterization, no control group and few patients weaken the findings of the study.

Three uncontrolled studies, in 109 patients, suggest that low dose amiodarone (~200 mg day$^{-1}$) may help maintain sinus rhythm post-cardioversion[37,38,43] (Fig. 2) with a low adverse event rate. Gosselink et al. demonstrated good long-term (3 years) tolerance at this dose[47]. Furthermore the reported results in severe heart failure in this study are impressive (13 out of 14 patients with severe chronic heart failure maintained sinus rhythm at 6 months).

Crijns et al.[44] investigated whether serial antiarrhythmic therapy improved arrhythmia outcome in patients with predominantly mild chronic heart failure. Patients were all initially treated with flecainide. In the event of drug failure patients were cardioverted if necessary and switched to sotalol or quinidine. Patients who failed stage 2 were then treated with amiodarone. Sixty-three percent of patients were in sinus rhythm at 2 years if repeat cardioversion (1±0.8 [mean ± SD] cardioversions per patient) was followed by a change in antiarrhythmic therapy. Only 31% would have been in sinus rhythm if repeat cardioversion had not been attempted.

The significance of various factors in predicting the arrhythmia free interval (from larger trials in Table 4) is described in Table 5. Conflicting results between trials probably reflect different size and follow-up periods.

### Rate control — drug therapy (Table 6)

Three trials investigating beta-blockers in patients with atrial fibrillation and chronic heart failure[45–47] described a reduction of resting and peak exercise heart rates with the majority of patients improving symptomatically. The agents studied were xamoterol[45] and pindolol[47], beta-blockers with intrinsic sympathomimetic activity, and practolol[46], a cardioselective beta-blocker with no intrinsic sympathomimetic activity. All three studies added beta-blockers to digoxin therapy, with higher doses of digoxin than are currently generally employed. Most studies were conducted without ACE inhibitors. Practolol[46] and pindolol[47] were evaluated after a short duration of treatment (<1 week of treatment) whereas xamoterol[45] was tested over 6 months and 24 h tapes, as opposed to ECGs, were used for heart rate analysis. The study of xamoterol showed a reduction in mean day-time heart rates, and an increase in nocturnal heart rate, reducing diurnal variation, and ejection fraction increased over 6 months[45] as assessed by radionuclide ventriculography. No trial investigated exercise tolerance. There was no evidence of exacerbation of chronic heart failure and beta-blockade was well tolerated among the 40 patients included.

The CHF-STAT sub-study on atrial fibrillation showed that amiodarone improved ventricular rate control when added to background therapy with digoxin[33] but there was no improvement in survival compared to placebo.

Marango et al.[48] investigated diltiazem for ventricular rate control, most patients had valvular heart disease as the cause of chronic heart failure. There was a greater decrease in 24-h mean heart rates with combination therapy compared to diltiazem alone. Diltiazem monotherapy or in combination with digoxin lowered exercise heart rates significantly compared to digoxin monotherapy.
<table>
<thead>
<tr>
<th>Author, year, reference</th>
<th>Type of study</th>
<th>Drug dose</th>
<th>n</th>
<th>Mean EF/FS</th>
<th>NYHA 1/2/3/4 (%)</th>
<th>Previous duration of AF</th>
<th>SR maintenance 6/12/24/36 months</th>
<th>Adverse events*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Gelder et al. 1989[39]</td>
<td>Randomised, placebo-controlled</td>
<td>Flecainide, 200 mg (dose for 86% of patients)</td>
<td>73 (AF 22%) flecainide 36 placebo 37</td>
<td>FS 30%</td>
<td>22/78/exc./exc.</td>
<td>12 ± 14 for flecainide, 21 ± 7 for placebo (mean ± SD)</td>
<td>58/49/4- (flec.) vs 49/36/- (placebo)</td>
<td>9%</td>
</tr>
<tr>
<td>Sodermark et al. 1975[40]</td>
<td>Randomised, placebo-controlled</td>
<td>Quinidine 0.8 g (mean)</td>
<td>176 (AF 7%), Quin. = 101, placebo = 75</td>
<td>—</td>
<td>32/62/8/-(Quin.) vs 26/59/12/- (control)</td>
<td>75% ≥ 1 month (in both groups)</td>
<td>60/51/4- (Quin.) vs 30/28/- (control)</td>
<td>12%</td>
</tr>
<tr>
<td>Karlson et al. 1988[41]</td>
<td>Randomised, placebo-controlled</td>
<td>Disopyramide 500 mg/day (standard dose)</td>
<td>90, disopyramide = 44, placebo = 46</td>
<td>—</td>
<td>28/67/6/0</td>
<td>Median duration: 4 months in both groups</td>
<td>55/50/-/- for disopyramide, 33/30/-/- for placebo</td>
<td>Disopyramide — 11% Placebo — 4.3%</td>
</tr>
<tr>
<td>Porterfield et al. 1989[42]</td>
<td>Uncontrolled</td>
<td>Propafenone, 775 mg (mean effective dose)</td>
<td>26</td>
<td>—</td>
<td>—</td>
<td>&gt;24 h</td>
<td>60/51/-/- (Quin.) vs 30/28/-/- (control)</td>
<td>19%</td>
</tr>
<tr>
<td>Gosselink et al. 1992[43]</td>
<td>Uncontrolled</td>
<td>Amiodarone, 204 mg (mean)</td>
<td>80</td>
<td>FS 30%</td>
<td>18/50/29/3</td>
<td>30 months (median)</td>
<td>-61/56/53</td>
<td>1% (1 patient)</td>
</tr>
<tr>
<td>Middelkauf et al. 1992[44]</td>
<td>Uncontrolled</td>
<td>Amiodarone 200 mg/day (standard dose)</td>
<td>20</td>
<td>EF 23%</td>
<td>—</td>
<td>&gt;60% patients with AF &gt; 1 year (median)</td>
<td>-85/-</td>
<td>0</td>
</tr>
<tr>
<td>Mostow et al. 1999[38]</td>
<td>Uncontrolled</td>
<td>Amiodarone 200-400 mg/day (standard dose)</td>
<td>9</td>
<td>—</td>
<td>Not given but 59 with CHF</td>
<td>33 months (mean)</td>
<td>44% at 12 months</td>
<td>0</td>
</tr>
<tr>
<td>Crijns et al. 1991[44]</td>
<td>Uncontrolled</td>
<td>Serial antiarrhythmic treatment</td>
<td>127 (AF 19%)</td>
<td>FS 30%</td>
<td>44/46/10/0</td>
<td>Median duration of 6 months</td>
<td>-65/63/- after a mean of 1-8 cardioversions</td>
<td>stage 1: 6% stage 2: 10% stage 3: 6%, 5%</td>
</tr>
<tr>
<td>Van Gelder et al. 1991[35]</td>
<td>Uncontrolled</td>
<td>Various drugs²</td>
<td>186 (AF 28.9%)</td>
<td>—</td>
<td>35/40/23/1</td>
<td>28 ± 45 months (mean and SD)</td>
<td>-42/36/-</td>
<td>5%</td>
</tr>
</tbody>
</table>

*Adverse event leading to withdrawal from trial (unless otherwise stated in controlled trials the figure is the withdrawals from active treatment group, placebo having no adverse events requiring withdrawal).

¹Stage 1 medication was flecainide 200–300 mg, day⁻¹. Stage 2 medication: sotalol 160 mg b.d. or quinidine 750 mg b.d if sotalol contraindicated, stage 3 medication: amiodarone 200-400 mg, day⁻¹.

²Trial assessing ‘natural’ arrhythmia free period rather than drug intervention, various antiarrhythmics used.

³NYHA class and absence of rheumatic valve disease predicted arrhythmia free period.

⁴10 deaths during follow up (five sudden), only one likely to be related to antiarrhythmic. For abbreviations, see Table 1.
Radiofrequency ablation of atrioventricular node and permanent pacemaker implantation

In four [49–52] of the five uncontrolled studies of atrioventricular node ablation followed by pacemaker implantation mean left ventricular function improved after the procedure. Assessment of left ventricular function was not confounded by rate, with the exception of the study by Twidale et al.[52], as baseline measurements were made after ablation. Three of these studies [50,52,53] described an improvement in symptoms and two found an improvement in exercise capacity [52,53]. Twidale et al.[52] in assessing predictors of outcome after radiofrequency ablation found a baseline ejection fraction ≤30%, the presence of significant mitral regurgitation before ablation and failure of cardiac performance to improve by 1 month to be independent predictors of death after the procedure. In the only reported randomized, controlled study investigating the two strategies, atrioventricular node ablation and pacemaker implantation appeared to be superior to pharmacological therapy in terms of some symptoms (palpitations and dyspnoea though symptoms improved in both groups) but no improvement in echocardiographic assessment of left ventricular function or exercise capacity was observed in either group [54].

Antithrombotic treatment

This was the subject of a previous extensive systematic review [55] to which the reader is referred.

In summary among patients with atrial fibrillation, chronic heart failure confers a substantial increase in cardioembolic risk and consequently a greater absolute benefit with warfarin therapy [56]. Aspirin is not an effective alternative in this patient group. Routine anticoagulation is recommended for 4 weeks before elective cardioversion [57]. Evidence regarding the use of transoesophageal echocardiography to exclude atrial thrombi prior to cardioversion without prior long-term anticoagulation has also been reviewed elsewhere [56,58,59].

Discussion

Effective treatment of atrial fibrillation in chronic heart failure patients is particularly important because it may...
Table 6  Ventricular rate control of chronic atrial fibrillation in patients with heart failure

<table>
<thead>
<tr>
<th>Author, year, reference</th>
<th>Type of study</th>
<th>n</th>
<th>Drug (dose)</th>
<th>Length of treatment</th>
<th>NHYA 1/2/3/4 (%)</th>
<th>Adverse events</th>
<th>% improvement symptoms</th>
<th>Heart rate (HR) reduction on study medication (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deedwania et al. 1998[33]</td>
<td>Randomised, placebo controlled</td>
<td>103</td>
<td>Am. 800 mg for 2 weeks, 400 mg for 50 weeks</td>
<td>1-3-5 years</td>
<td>All II-IV mean EF Am. — 25 Placebo — 26 0%</td>
<td>Am. — 7 (14%) Placebo — 1 (2%)</td>
<td>Not evaluated</td>
<td>24 hour mean ventricular rate reduced by 20% in 2 weeks, 18% at 6 months and 16% in 12 months Daytime HR: 100 to 70</td>
</tr>
<tr>
<td>Kudoh et al. 1993[45]</td>
<td>Uncontrolled</td>
<td>13</td>
<td>Xamoterol 100 mg b.d.</td>
<td>6 months</td>
<td>not reported 46 (6/13 patients)</td>
<td>36 (10 patients)</td>
<td>Resting HR: 98 to 77.5 Max. exercise HR: 148.9 to 105.4 (mean)</td>
<td></td>
</tr>
<tr>
<td>Yahalom et al. 1977[46]</td>
<td>Non-randomised, controlled[2]</td>
<td>28</td>
<td>Practolol³ 300 mg/day</td>
<td>1 week</td>
<td>46/29/25/0</td>
<td>0</td>
<td>36 (10 patients) Rest: 101 to 80, Exercise: 155.8 to 123.8 5 min recovery: 105.1 to 84.9 (means)[]</td>
<td></td>
</tr>
<tr>
<td>Cristodorescu et al. 1986[47]</td>
<td>Uncontrolled</td>
<td>12</td>
<td>Pindolol³ 14.7 mg ± 1.6 (mean ± SD)</td>
<td>5 days</td>
<td>0/0/67/33</td>
<td>0</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Maragno et al. 1988[48]</td>
<td>Uncontrolled dose response study</td>
<td>19</td>
<td>Dilt. 180 mg (10 patients) 240 mg (9 patients)</td>
<td>7 days</td>
<td>31/53/16/0</td>
<td>1[4]</td>
<td>42</td>
<td></td>
</tr>
</tbody>
</table>

1Leading to withdrawal from study.
2A group of patients in sinus rhythm being treated with digoxin for paroxysmal supraventricular rhythms were used as controls.
3Practolol and pindolol were added to betamethyldigoxin in the studies by Yahalom and Cristodorescu et al respectively.
4Statistically significant reduction in heart rates.
5Patients with minor side effects, two patients with worsening of Exercise tolerance after digoxin withdrawal phase.
6Reduction statistically significant. Effect correlated to diltiazem plasma levels. Combined therapy superior to diltiazem alone for reduction in mean 24 h rate. For abbreviations, see Table 1.
Table 7  Studies in radiofrequency ablation of atrioventricular node and permanent pacemaker implantation

<table>
<thead>
<tr>
<th>Author, year, reference</th>
<th>Type of study</th>
<th>n</th>
<th>Age (mean)</th>
<th>HR at rest</th>
<th>Baseline EF (mean) %</th>
<th>EF after ablation and PPI (mean)</th>
<th>Improvement in 1. symptoms 2. exercise tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brignole et al. 1998[54]</td>
<td>Randomised, controlled, double blind</td>
<td>32 (Abl+PM), 34 (drug)</td>
<td>&gt;90 in both groups</td>
<td>43 (Abl+PM), 44 (drug)</td>
<td>At 12 months, 44 (Abl+PM), 41 (drug)</td>
<td>1. Yes, both drug and Abl and Pm group‡ 2. No for both groups</td>
<td></td>
</tr>
<tr>
<td>Twidale 1993[49]</td>
<td>Uncontrolled</td>
<td>14</td>
<td>65</td>
<td>140 ± 25 (mean ± SD)</td>
<td>42</td>
<td>44 at 3 days and 47 at 6 weeks</td>
<td>1. Not evaluated 2. Yes</td>
</tr>
<tr>
<td>Brignole 1994[53]</td>
<td>Uncontrolled</td>
<td>23</td>
<td>67</td>
<td>&gt;100</td>
<td>47*</td>
<td>Dependent on baseline*</td>
<td>1. Yes 2. Yes</td>
</tr>
<tr>
<td>Edner 1995[50]</td>
<td>Uncontrolled</td>
<td>†+&lt; × 14†</td>
<td>68</td>
<td>—</td>
<td>32</td>
<td>39% at 65 days, 45% at 216 days</td>
<td>1. Not evaluated 2. Not evaluated</td>
</tr>
<tr>
<td>Heinz 1992[51]</td>
<td>Uncontrolled</td>
<td>10</td>
<td>64</td>
<td>&gt;120</td>
<td>28</td>
<td>EF 35% at 49 days</td>
<td>1. Not evaluated 2. Not evaluated</td>
</tr>
<tr>
<td>Twidale et al. 1998[52]</td>
<td>Uncontrolled</td>
<td>44</td>
<td>71</td>
<td>106 (mean)</td>
<td>34</td>
<td>43.8 at 1 month (20 increased EF by &gt;9%)</td>
<td>1. Yes 2. Yes</td>
</tr>
</tbody>
</table>

*Study qualified for inclusion as 64% of patients had NYHA ≥3 functional class. Nine patients had depressed LV systolic function with FS 23%. This improved to 31% at the end of the study period. In the remaining patients with normal systolic function, fractional shortening decreased by 10%.
†Three of the patients had paroxysmal AF (21%) but all 3 developed permanent AF during follow up.
‡Improvement in palpitations and effort dyspnoea were significantly greater in the Abl and Pm (ablation and pacemaker) group compared to the drug group. Scores for Minnesota Living With Heart Failure Questionnaire, NYHA class and Activity scale improved in both groups but there was no statistically significant difference between the two groups.
not only relieve the symptoms of the arrhythmia and reduce the risk of thrombo-embolic events but also improve the symptoms and possibly the prognosis of concomitant chronic heart failure. However although atrial fibrillation and chronic heart failure often coexist most studies of atrial fibrillation have excluded patients with chronic heart failure and therefore there is a lack of clinical trial evidence to guide treatment. The effectiveness and risks from drugs or other interventions for atrial fibrillation are likely to be influenced by the presence of chronic heart failure[60–62] and it is clear that the results of atrial fibrillation trials excluding patients with left ventricular dysfunction should not be extrapolated to a heart failure population. Also, the lack of appropriate control groups in many studies confounds the proper assessment of treatment effects. Fifty percent of patients may revert to sinus rhythm within 48 h of an episode of acute atrial fibrillation[63], although the rate is probably lower among patients with heart failure[64] rendering uncontrolled data difficult to interpret.

However, for both acute and chronic atrial fibrillation it is clear that effective treatment of the arrhythmia depends on optimum management of heart failure. A decrease in filling pressures and reduction of neuroendocrine activation[21] will enhance ‘spontaneous’ conversion to sinus rhythm in acute atrial fibrillation and help reduce ventricular rate in both acute and chronic atrial fibrillation. Similarly, the effective treatment of heart failure may not be possible until the ventricular rate is controlled or sinus rhythm restored.

**Rate control — drug therapy**

The optimum heart rate at rest and during exercise has not been defined in patients with atrial fibrillation and chronic heart failure. Most would agree a resting heart rate of <90 beats min\(^{-1}\) and on exercise <200 beats min\(^{-1}\) [32,33,54,56] are required but in light of the recent evidence of benefit of beta-blockers in chronic heart failure and other physiological studies it is probable that much lower rates are appropriate[65,66]

In acute atrial fibrillation digoxin is relatively slow and ineffective in controlling heart rate and does not increase the chance of a return to sinus rhythm[25]. Digoxin may also be ineffective in controlling the ventricular rate in chronic atrial fibrillation when sympathetic tone is increased[29,67–69], as occurs in worsening heart failure and during exercise[68,69]. However, in the context of chronic heart failure digoxin may improve symptoms and reduce heart failure hospitalization[70,71] at least in the absence of a beta-blocker. Used alone digoxin may be sufficient to control heart rate in atrial fibrillation in the immobile patient.

If rate control alone is the purpose of treatment then intravenous diltiazem appears a potentially more effective alternative to digoxin (Table 2), although experience is comparatively small[30,31]. The limited data that do exist suggest that diltiazem is safe[36,38,72,73]. The negative inotropic effects of diltiazem may be offset by a reduction in heart rate and peripheral vascular resistance[74,75]. For long-term control of chronic atrial fibrillation in patients with left ventricular dysfunction diltiazem is a controversial alternative due to concerns regarding safety in chronic heart failure[76], although some studies suggest benefit[77,78].

There are no data on the safety and efficacy of beta-blockers in acute atrial fibrillation and heart failure (as defined above) and concerns remain about their safety in severe, unstable heart failure. Only a few studies have investigated the role of beta-blockers in the management of chronic atrial fibrillation in the setting of chronic heart failure, presumably due to fears about their negative inotropic effects. However, these studies show that beta-blockers control ventricular rate effectively, improve symptoms and ventricular function and are well tolerated when added to digoxin (Table 5)[45–47]. However, two of the three studies of chronic atrial fibrillation patients were conducted with high intrinsic sympathomimetic activity beta blockers[45,46] that are generally felt to be contraindicated in chronic heart failure. Conventional beta-blockers may prove more effective but may also induce a greater number of pauses that could cause concern[79]. The landmark trials of beta-blockers in chronic heart failure[7,80–82] have not reported any interaction between the presence of atrial fibrillation and benefits on mortality[83] and beta-blockers should now be considered part of the routine management of chronic heart failure due to left ventricular systolic dysfunction in the absence of contra-indications. They should be cautiously uptitrated particularly in severe heart failure. Whether or not it is appropriate to use beta-blockers without digoxin for the management of atrial fibrillation in patients with chronic heart failure is currently the subject of a clinical trial[84].

In patients in whom both rapid rate control and cardioversion are considered appropriate amiodarone would appear to be the drug of choice. The ability of amiodarone to control tachycardia rapidly and improve haemodynamics[9,29] may explain why exacerbation of heart failure is observed infrequently despite the intrinsic negative inotropic effect of the drug[85]. In patients with chronic atrial fibrillation amiodarone controls ventricular rate[33,34,54], increases the chance of ‘spontaneous’ cardioversion[33,34] and will help maintain sinus rhythm in patients who undergo electrical cardioversion. As with beta-blockers it is uncertain whether the additional use of digoxin is necessary. However, the risk of long-term side effects of amiodarone render alternatives, such as beta-blockers, preferable for the long-term control of ventricular rate. Amiodarone should be reserved for those in whom a policy of cardioversion is being actively pursued or to increase the chance of maintaining sinus rhythm after cardioversion. Nonetheless in those with severe left ventricular dysfunction or in patients with previous drug-induced torsades de pointes there is some risk attached to the use of amiodarone[85–87] and it should be used with caution. It may be unwise to give amiodarone if the duration of

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atrial fibrillation is >48 h without prior chronic anticoagulant therapy[39] unless, possibly, the existence of pre-existing left atrial thrombus has been excluded by transoesophageal echocardiography[57,58,89].

**Cardioversion**

Electrical cardioversion is initially successful in 70% or more[35,89] of patients selected for this procedure. Structural[90] and electrophysiological changes[91] in the atria of patients with chronic atrial fibrillation, especially those with underlying disease and left ventricular dysfunction, reduce the chances of cardioversion and it is likely to have a lower rate of success in a less selected population of chronic atrial fibrillation (for instance those with atrial fibrillation for many years). Severe chronic heart failure reduces the likelihood of successful cardioversion in some studies probably reflecting the adverse effects of sympathetic activation and atrial distension[35,36,92]. Severe chronic heart failure also increases the risk of general anaesthesia. It seems wise, therefore, to optimize treatment of heart failure before attempting cardioversion whenever possible.

Pharmacological cardioversion does not require general anaesthesia and may not require admission to hospital but the rate of cardioversion is much lower[31,32,35]. The risk of embolic episodes subsequent to pharmacological cardioversion in inadequately anticoagulated patients is poorly quantified and is of concern. The studies of acute atrial fibrillation suggest a wide variation in cardioversion rates with amiodarone. This could be explained by a variation in dosing and loading protocols in trials[25,93], selection bias caused by previous failed attempts at cardioversion[28], differing duration of atrial fibrillation and the effects of concomitantly administered drugs, for instance digoxin[28]. However, even if amiodarone is found to be only modestly effective in cardioverting acute atrial fibrillation, pre-loading with amiodarone has been shown to improve subsequent electrical cardioversion rates[93] and maintenance of sinus rhythm thereafter. Cardioversion occurs with amiodarone alone in 15–20% of patients with chronic atrial fibrillation over a period of one month. Potential side effects such as pro-arrhythmia and exacerbation of heart failure appear uncommon and medium-term use is associated with a low frequency of serious adverse effects[37,43,61,94].

The study by Stambler[31] suggests that ibutilide may be an effective pharmacological agent for cardioversion of acute atrial fibrillation. Further evidence of its safety in heart failure is necessary.

In contrast, class I antiarrhythmic drugs should generally not be used in chronic heart failure because of the high risk of proarrhythmia[61,62] and the danger of exacerbating chronic heart failure[80].

The electrophysiological effects of digoxin therapy may reduce the chance of cardioversion[59] and reduce the anti-arrhythmic effects of concomitantly administered drugs[90]. However, digoxin may improve ventricular function and ventricular rate control, thus enhancing the chances of cardioversion. Currently there is no evidence to suggest that digoxin has any effect on cardioversion in atrial fibrillation in the presence or absence of heart failure[51,23,65,97]. Similarly, beta-blockers and diltiazem have not been shown to affect rates of cardioversion in chronic heart failure.

**Maintenance of sinus rhythm after cardioversion of chronic atrial fibrillation** (Table 4)

Studies of electrical cardioversion in patients with predominantly mild chronic heart failure and chronic atrial fibrillation suggest that about 70% will relapse into atrial fibrillation by 1 year without prophylactic antiarrhythmics (Fig. 2). Class I drugs whilst roughly doubling the chance of remaining in sinus rhythm[37,39,41] may increase mortality in chronic heart failure and should therefore be used with caution or avoided[19,25,61,98].

Amiodarone increases the chance of remaining in sinus rhythm to 42–85% at 1 year and appears to have a neutral or beneficial effect on survival in chronic heart failure[61,99,100]. However, despite Gosselink et al.[37] describing good long-term tolerance, doubts remain about the long-term toxicity and tolerance of amiodarone[94] and its safety in those with previous drug-induced torsades-de-points[86,87]. However, currently it is the safest and most effective prophylactic drug for the maintenance of sinus rhythm in patients with chronic heart failure. Novel class III antiarrhythmics[31,101,102] could replace amiodarone for conversion and maintenance of sinus rhythm if they are shown to be safe and effective inpatients with chronic heart failure, but they may not control the ventricular rate. So far only dofetilide has been shown not to increase mortality in chronic heart failure whilst being modestly effective in cardioverting and prolonging the arrhythmia free interval[80] in the subgroup of chronic heart failure patients with atrial fibrillation.

**Predictors of arrhythmia free interval** (Table 5)

Follow-up of unselected atrial fibrillation patients suggests that, after cardioversion, <30% remain in sinus rhythm after 5 years[103,104]. It is therefore important to identify subgroups of chronic atrial fibrillation and chronic heart failure patients in whom attempts at cardioversion and maintenance in sinus rhythm will be futile with current therapeutic strategies. Table 5 indicates that a long history of atrial fibrillation, rheumatic mitral valve disease or patients with severe chronic heart failure intolerant of amiodarone have a high rate of early relapse to atrial fibrillation after successful cardioversion. Repeated cardioversions appear inappropriate and rate control advisable in these patients.
Radiofrequency ablation of atrioventricular node and permanent pacemaker implantation

This is almost 100% successful in most tertiary care centres. The technique is relatively safe and can be performed without a general anaesthetic. Sudden death has been reported but may have been due to bradycardia-induced arrhythmia and may be prevented by pacing at higher rates\textsuperscript{105}. Improvements in ventricular function\textsuperscript{49–52} may reflect the decrease in heart rate and resolution of tachycardio-myopathy, the change from an irregular to a regular rhythm\textsuperscript{106} and/or the discontinuation of negative inotropic drugs. However, conventional right ventricular pacing may increase ventricular asynergy, exacerbate ventricular dysfunction and worsen chronic heart failure. Left ventricular or multi-site pacing may avoid such problems\textsuperscript{107}. Overall the trade-off between benefit and risk appears to be a positive one\textsuperscript{54,106,108} in patients with intractable symptoms and poor rate control despite pharmacological intervention. The only randomized controlled trial by Brignole et al. confirms the present practice of referring symptomatic patients for ablation only after pharmacological intervention has failed\textsuperscript{54}.

Innovative techniques

Radiofrequency ablation of the posterolateral atrioventricular node may control ventricular rate without the need of a pacemaker\textsuperscript{109}. Initial results have been encouraging but there are unresolved questions regarding the hazards of the procedure, particularly the risk of sudden death\textsuperscript{56}. The ‘maze’ procedure is the most promising surgical innovation for drug resistant atrial fibrillation patients but the attendant operative risk may preclude its use in patients with chronic heart failure\textsuperscript{110}. No data exist on the outcome of patients with chronic atrial fibrillation and chronic heart failure. These and other techniques, such as multisite pacing\textsuperscript{111}, atrial defibrillator\textsuperscript{112} and the radiofrequency equivalent of the maze procedure\textsuperscript{113}, have little evidence-base presently and should be considered experimental, to be used on an individual patient basis at tertiary care centres.

Conclusions

This review highlights the paucity of evidence on the management of atrial fibrillation in the context of heart failure, particularly acute atrial fibrillation. However, it appears appropriate to formulate some framework for the management of this problem. It is important to emphasize that effective management of atrial fibrillation can only be achieved with effective management of heart failure and conversely that effective treatment of atrial fibrillation is a necessary component of the effective treatment of heart failure\textsuperscript{114}.

### Table 8 Timing of cardioversion for acute atrial fibrillation in patients with heart failure

<table>
<thead>
<tr>
<th>Arguments for early cardioversion</th>
<th>Arguments for delayed cardioversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of electrophysiological remodelling</td>
<td>Cardioversion unlikely to be successful if heightened sympathetic tone and catecholamine excess</td>
</tr>
<tr>
<td>Improve haemodynamic status and heart failure with restoration of regular and lower heart rate</td>
<td>Increased risk of general anaesthetic for electrical cardioversion in patients with pulmonary oedema or severe heart failure</td>
</tr>
<tr>
<td>Ventricular rate control of AF in patients with heart failure difficult</td>
<td>High rate of spontaneous conversion to sinus rhythm in first 48 h</td>
</tr>
<tr>
<td>Avoidance/withdrawal of negative inotropic medication</td>
<td>Timing of onset of atrial fibrillation sometimes difficult to determine. Cardioversion poses embolic risk</td>
</tr>
</tbody>
</table>

**Figure 3** Heart rate reduction of acute atrial fibrillation in patients with heart failure. Results in diltiazem group are from subgroup of six patients in Goldberg et al.\textsuperscript{[26]} who were administered diltiazem infusion (10–15 mg. h\textsuperscript{–1}) following bolus dose. ● = amiodarone (Hou et al.\textsuperscript{[25]}); ■ = digoxin (Hou et al.\textsuperscript{[25]}); △ = diltiazem (Goldenberg et al.\textsuperscript{[26]}).
For acute ventricular rate control conventional treatment with intravenous digoxin appears less effective than intravenous diltiazem, but more experience with the use of diltiazem is required. Conservative physicians may wish to continue to use digoxin. High-dose intravenous amiodarone controls ventricular rate rapidly and increases the chance of cardioversion of acute atrial fibrillation (Fig. 3).

Cardioversion of chronic atrial fibrillation appears to improve exercise capacity and symptoms in younger patients, albeit not in double-blind controlled trials. However, there is no evidence that the risk of stroke or death is reduced by cardioversion compared to a strategy of rate control and anti-coagulation. Long-term mortality trials assessing these two strategies are being undertaken.

In some patients, cardioversion will be deemed inappropriate, for instance in frail elderly patients or patients who have a low probability of maintaining sinus rhythm. Rate control and anti-coagulation will be the preferred option. For patients who have left ventricular systolic dysfunction and who do not have contra-indications, beta-blockers must now be considered the agent of choice for long-term rate control. Whether digoxin is of value in addition to beta-blockers is uncertain but it will continue to have a role in patients who cannot be maintained on beta-blockers and in order to obtain rate control during up-titration of beta-blockers.
Whether digoxin should be withdrawn after beta-blockers have been established is currently subject to study. It is unclear whether digoxin, beta-blockers or calcium channel antagonists (diltiazem, verapamil) are preferable for rate control in chronic heart failure patients with preserved systolic function.

In the situation of acute atrial fibrillation and chronic heart failure electrical cardioversion should be attempted urgently if severe symptoms persist despite intensive medical therapy or if the patient is in impending shock. For those in whom elective cardioversion is deemed appropriate the optimum time for cardioversion is unclear; arguments for and against early cardioversion are listed in Table 8. If cardioversion of a patient with chronic atrial fibrillation and heart failure is considered appropriate and the patient is not already anticoagulated then in the absence of contraindications this should be undertaken for 4 weeks prior to attempted cardioversion. Amiodarone may be introduced after anticoagulation is established, as even if cardioversion does not occur with amiodarone alone, it will improve the success rate of electrical cardioversion and prolong the arrhythmia free period after conversion to sinus rhythm. It is not known whether the risk of embolism after pharmacological or electrical cardioversion differs. Care is required to avoid the risks of drug interactions between amiodarone and anti-coagulants and digoxin. In the event of successful cardioversion it would appear appropriate to withdraw digoxin but continue anticoagulation at least for several weeks until atrial function recovers. Beta-blockers, if initiated and tolerated, should be maintained if left ventricular systolic dysfunction is present. If sinus rhythm is maintained it is not clear when or indeed if amiodarone should be discontinued. Further studies to assess the optimal pharmacological strategy for maintenance of sinus rhythm after cardioversion are required. Patients who fail cardioversion and in whom symptoms are reasonably controlled should have their amiodarone withdrawn and their ventricular rate controlled by beta-blockers and/or digoxin. Patients with persistent troublesome symptoms or in whom ventricular rate control or pauses are problematic should be considered for repeated cardioversions or catheter ablation and pacing. How often cardioversion is attempted before accepting atrial fibrillation as permanent must be judged on an individual patient basis. Figure 4 describes a risk vs benefit approach to determine whether repeated cardioversions are appropriate in patients with chronic atrial fibrillation and chronic heart failure.

References


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