Atrial Fibrillation Rhythm Control: When and How?

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Introduction

- rhythm control therapy is indicated to improve symptoms in AF patients who remain symptomatic on adequate rate control therapy
Antiarrhythmic drugs for acute restoration of sinus rhythm (‘pharmacological cardioversion’)

- Pharmacological cardioversion restores sinus rhythm in approximately 50% of patients with recent-onset AF. Pharmacological cardioversion, conversely, does not require sedation or fasting

- Electrical cardioversion restores sinus rhythm quicker and more effectively than pharmacological cardioversion and is associated with shorter hospitalization.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>1st dose</th>
<th>Follow-up dose</th>
<th>Risks</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flecainide</td>
<td>Oral</td>
<td>200–300 mg</td>
<td>N/A</td>
<td>Hypotension, atrial flutter with 1:1 conduction, QT prolongation. Avoid in patients with IHD and/or significant structural heart disease.</td>
<td>595, 598</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>1.5–2 mg/kg over 10 min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>IVa</td>
<td>5–7 mg/kg over 1–2 hours</td>
<td>50 mg/hour to a maximum of 1.0 g over 24 hours</td>
<td>Phlebitis, hypotension, bradycardia/AV block. Will slow ventricular rate. Delayed conversion to sinus rhythm (8–12 hours).</td>
<td>596–601</td>
</tr>
<tr>
<td>Propafenone</td>
<td>IV</td>
<td>1.5–2 mg/kg over 10 min</td>
<td></td>
<td>Hypotension, atrial flutter with 1:1 conduction, QRS prolongation (mild). Avoid in patients with IHD and/or significant structural heart disease.</td>
<td>622, 625</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>450–600 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibutilideb</td>
<td>IV</td>
<td>1 mg over 10 min</td>
<td>1 mg over 10 min after waiting for 10 min</td>
<td>QT prolongation, polymorphic ventricular tachycardia/torsades de pointes (3–4% of patients). Will slow ventricular rate. Avoid in patients with QT prolongation, hypokalemia, severe LVH or low ejection fraction.</td>
<td>614, 615</td>
</tr>
<tr>
<td>Vernakalant</td>
<td>IV</td>
<td>3 mg/kg over 10 min</td>
<td>2 mg/kg over 10 min after waiting for 15 min</td>
<td>Hypotension, non-sustained ventricular arrhythmias, QT and QRS prolongation. Avoid in patients with SBP &lt;100 mmHg, recent (&lt;30 days) ACS, NYHA Class III and IV heart failure, QT interval prolongation (uncorrected QT &gt;440 ms) and severe aortic stenosis.</td>
<td>602–605, 618</td>
</tr>
</tbody>
</table>
Pill in the pocket’ cardioversion

• In selected patients with infrequent symptomatic episodes of paroxysmal AF, a single bolus of oral flecainide (200–300 mg) or propafenone (450–600 mg) can be self-administered by the patient at home to restore sinus rhythm, after safety has been established in the hospital setting.

• This approach seems marginally less effective than hospital-based cardioversion, but is practical and provides control and reassurance to selected patients

• Beta-blockers, verapamil, diltiazem, and digoxin do not reliably terminate AF or facilitate electrical cardioversion
Rhythm control management of recent onset atrial fibrillation.

AF = atrial fibrillation; HFrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVH = left ventricular hypertrophy.

*Ibutilide should not be used in patients with long QT interval.

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Electrical cardioversion

• Synchronized direct current electrical cardioversion quickly and effectively converts AF to sinus rhythm, and is the method of choice in severely haemodynamically compromised patients with new-onset AF.

• Intravenous midazolam and/or propofol. Continuous monitoring of blood pressure and oximetry during the procedure is important. Intravenous atropine or isoproterenol, or temporary transcutaneous pacing, should be available.

• Biphasic defibrillators are more effective than monophasic waveforms, Anterior–posterior electrode positions generate a stronger shock field in the left atrium than anterolaterally positioned electrodes, and restore sinus rhythm more effectively.

• Pre-treatment with amiodarone (requiring a few weeks of therapy), sotalol, ibutilide, or vernakalant can improve the efficacy of electrical cardioversion, and similar effects are likely for flecainide and propafenone.
Long-term antiarrhythmic drug therapy

• Treatment is aimed at reducing AF-related symptoms;
• Efficacy of antiarrhythmic drugs to maintain sinus rhythm is modest;
• Clinically successful antiarrhythmic drug therapy may reduce rather than eliminate the recurrence of AF;
• If one antiarrhythmic drug ‘fails’, a clinically acceptable response may be achieved with another agent;
• Drug-induced pro-arrhythmia or extracardiac side-effects are frequent;
• Safety rather than efficacy considerations should primarily guide the choice of antiarrhythmic drug.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Main contra-indications and precautions</th>
<th>Warning signs warranting discontinuation</th>
<th>AV nodal slowing</th>
<th>Suggested ECG monitoring during initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>600 mg in divided doses for 4 weeks, 400 mg for 4 weeks, then 200 mg once daily</td>
<td>Caution when using concomitant therapy with QT-prolonging drugs and in patients with SAN or AV node and conduction disease. The dose of VKAs and of digitalis should be reduced. Increased risk of myopathy with statins. Caution in patients with pre-existing liver disease.</td>
<td>QT prolongation &gt;500 ms</td>
<td>10–12 bpm in AF</td>
<td>Baseline, 1 week, 4 weeks</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>400 mg twice daily</td>
<td>Contra-indicated in NYHA Class III or IV or unstable heart failure, during concomitant therapy with QT-prolonging drugs, or powerful CYP3A4 inhibitors (e.g. verapamil, diltiazem, azole antifungal agents), and when CrCl &lt;30 ml/min. The dose of digitalis, beta-blockers, and of some statins should be reduced. Elevations in serum creatinine of 0.1–0.2 mg/dL are common and do not reflect a decline in renal function. Caution in patients with pre-existing liver disease.</td>
<td>QT prolongation &gt;500 ms</td>
<td>10–12 bpm in AF</td>
<td>Baseline, 1 week, 4 weeks</td>
</tr>
<tr>
<td>Flecainide</td>
<td>100–150 mg twice daily</td>
<td>Contra-indicated if CrCl &lt;50 mg/mL, liver disease, IHD or reduced LV ejection fraction. Caution in the presence of SAN or AV node or conduction disease. CYP2D6 inhibitors (e.g. fluoxetine or tricyclic antidepressants) increase plasma concentration.</td>
<td>QRS duration increases &gt;25% above baseline</td>
<td>None</td>
<td>Baseline, day 1, day 2–3</td>
</tr>
<tr>
<td>Flecainide slow release</td>
<td>200 mg once daily</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Propafenone</td>
<td>150–300 mg three times daily</td>
<td>Contra-indicated in IHD or reduced LV ejection fraction. Caution in the presence of SAN or AV node and conduction disease, renal or liver impairment, and asthma. Increases concentration of digitalis and warfarin.</td>
<td>QRS duration increase &gt;25% above baseline</td>
<td>Slight</td>
<td>Baseline, day 1, day 2–3</td>
</tr>
<tr>
<td>Propafenone SR</td>
<td>225–425 mg twice daily</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>d,l sotalol</td>
<td>80–160 mg twice daily</td>
<td>Contra-indicated in the presence of significant LV hypertrophy, systolic heart failure, asthma, pre-existing QT prolongation, hypokalaemia, CrCl&lt;50 mg/mL. Moderate renal dysfunction requires careful adaptation of dose. QT interval &gt;500 ms, QT prolongation by &gt;60 ms upon therapy initiation.</td>
<td>QT interval &gt;500 ms, QT prolongation by &gt;60 ms upon therapy initiation</td>
<td>Similar to high dose blockers</td>
<td>Baseline, day 1, day 2–3</td>
</tr>
</tbody>
</table>
Initiation of long-term rhythm control therapy in symptomatic patients with atrial fibrillation.

AF = atrial fibrillation; HF = heart failure; LVH = left ventricular hypertrophy;
Sotalol requires careful evaluation of proarrhythmic risk.
Catheter ablation should isolate pulmonary veins and can be performed using radiofrequency or cryoballoon catheters.
Catheter ablation as a first-line therapy is usually reserved for heart failure patients with tachycardiomyopathy.
Amiodarone is a second-choice therapy in many patients because of its extracardiac side-effects.

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Antiarrhythmic effects of non-antiarrhythmic drugs

• ACE inhibitors or ARBs are unlikely to have a relevant direct antiarrhythmic effect. However, it might be justified to consider adding ACE inhibitors or ARB therapy to antiarrhythmic drugs to reduce AF recurrences after cardioversion.

• Beta-blockers have also been reported to reduce symptomatic AF recurrences.

• Peri-operative statin therapy appeared to reduce the risk of post-operative AF in a number of small RCTs.
A F Ablation

• This is primarily achieved through isolation of the pulmonary veins
• AF ablation, when performed in experienced centers by adequately trained teams, is more effective than antiarrhythmic drug therapy in maintaining sinus rhythm, and the complication rate, though not negligible, is similar to the complication rate for antiarrhythmic drugs
• Catheter ablation of AF is effective in restoring and maintaining sinus rhythm in patients with symptomatic paroxysmal, persistent, and probably long-standing persistent AF, in general as second-line treatment after failure of or intolerance to antiarrhythmic drug therapy, or as first-line therapy in selected patients with paroxysmal AF
A F Ablation

• In patients who experience symptomatic recurrences of AF despite antiarrhythmic drug therapy, all RCTs showed better sinus rhythm maintenance with catheter ablation than on antiarrhythmic drugs.

• Fewer data are available reporting the effectiveness and safety of catheter ablation in patients with persistent or long-standing persistent AF, but all point to lower recurrence rates after catheter ablation compared to antiarrhythmic drug therapy with or without cardioversion
A F Ablation

• Most patients require more than one procedure to achieve symptom control.

• In general, better rhythm outcome and lower procedure-related complications can be expected in younger patients with a short history of AF and frequent, short AF episodes in the absence of significant structural heart disease.
A F Ablation

• Catheter ablation is more effective than antiarrhythmic drug therapy in maintaining sinus rhythm
• There is no current indication for catheter ablation to prevent cardiovascular outcomes (or desired withdrawal of anticoagulation), or to reduce hospitalization
• Sinus rhythm without severely symptomatic recurrences of AF is found in up to 70% of patients with paroxysmal AF, and around 50% in persistent AF.
• Very late recurrence of AF after years of sinus rhythm is not uncommon and may reflect disease progression, with important implications for continuation of AF therapies.
<table>
<thead>
<tr>
<th>Complication severity</th>
<th>Complication type</th>
<th>Rate 727, 748, 750, 754-759</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life-threatening complications</td>
<td>Periprocedural death</td>
<td>&lt;0.2%</td>
</tr>
<tr>
<td></td>
<td>Oesophageal injury (perforation/fistula)</td>
<td>&lt;0.5%</td>
</tr>
<tr>
<td></td>
<td>Periprocedural stroke (including TIA/air embolism)</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td>Cardiac tamponade</td>
<td>1–2%</td>
</tr>
<tr>
<td>Severe complications</td>
<td>Pulmonary vein stenosis</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td>Persistent phrenic nerve palsy</td>
<td>1–2%</td>
</tr>
<tr>
<td></td>
<td>Vascular complications</td>
<td>2–4%</td>
</tr>
<tr>
<td></td>
<td>Other severe complications</td>
<td>≈1%</td>
</tr>
<tr>
<td>Other moderate or minor complications</td>
<td>Asymptomatic cerebral embolism (silent stroke)</td>
<td>5–20%</td>
</tr>
<tr>
<td></td>
<td>Radiation exposure</td>
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</tbody>
</table>
Ablation of atrial fibrillation in heart failure patients

• Catheter ablation, compared with amiodarone therapy, significantly reduces recurrent AF in AF patients with HFrEF.

• Selected patients with HFrEF and AF can achieve recovery of LV systolic function after catheter ablation (probably reflecting tachycardiomyopathy).

• Several smaller trials suggest improved LV function after catheter ablation in HFrEF patients and reduced hospitalizations, especially in patients without a previous myocardial infarction.
Surgical rhythm control in patients with atrial fibrillation undergoing cardiac surgery.

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AF = atrial fibrillation; CABG = coronary artery bypass graft; LAA = left atrial appendage; PVI = pulmonary vein isolation.

AF surgery may be PVI in paroxysmal AF and bilateral maze in persistent or long-standing persistent AF.

Oral anticoagulation should be continued in patients at risk of stroke irrespective of AF surgery or LAA exclusion.
Choice of rhythm control therapy following treatment failure.

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Hybrid rhythm control therapy

• Combination or ‘hybrid’ rhythm control therapy seems reasonable, although there is little evidence from controlled trials supporting its use.

• Antiarrhythmic drug therapy is commonly given for 8–12 weeks after ablation to reduce early recurrences of AF after catheter ablation, supported by a recent controlled trial where amiodarone halved early AF recurrences compared with placebo.

• Prospective studies have not been done, but a meta-analysis of the available (weak) evidence suggests slightly better prevention of recurrent AF in patients treated with antiarrhythmic drugs after catheter ablation.

• Controlled trials to confirm this are desirable.
Conclusion

• Do not use rhythm control therapy in asymptomatic AF patients, nor in patients with permanent AF.
Future Trials

• Whether modern rhythm control management involving catheter ablation, combination therapy, and early therapy leads to a reduction in major cardiovascular events is currently under investigation, e.g. in the EAST – AFNET (Early treatment of Atrial fibrillation for Stroke prevention Trial) and CABANA (Catheter Ablation vs. Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial) trials