Lecture 2:

Diagnosis and pharmacological management

Prepared by: Dr Ronnie Jardine FCP(SA)
AF – diagnosis

- Feel the pulse
- Confirm with 12-lead ECG
- Occasionally – Holter ECG
  - Event-triggered ECG
  - Implanted devices
  - Loop recorders
Classification of Atrial Fibrillation

First diagnosed episode of atrial fibrillation

Paroxysmal (usually <48 h)

Persistent (>7 days or requires CV)

Long-standing Persistent (>1 year)

Permanent (accepted)
Time course and management of AF

- **Upstream** therapy of concomitant conditions
- **Anticoagulation**
- **Rate control**
  - Antiarrhythmic drugs
  - Ablation
  - Cardioversion

Types of AF:
- **Silent**
- **Paroxysmal**
- **Persistent**
- **Long-standing persistent**
- **Permanent**
Acute AF management

- Anti-coagulation
- Acute rate control
- ? Rhythm control
- Manage underlying conditions
Acute anti-coagulation

- SC enoxaparin 1mg/Kg BD

  or

- IV unfractionated heparin (bolus → infusion)
# Acute rate control

**Oral – beta-blocker / verapamil / diltiazem IV**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the acute setting, in the absence of pre-excitation, i.v. administration of β-blockers or non-dihydropyridine calcium channel antagonists is recommended to slow the ventricular response to AF, exercising caution in patients with hypotension or heart failure.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>In the acute setting, i.v. administration of digitalis or amiodarone is recommended to control the heart rate in patients with AF and concomitant heart failure, or in the presence of hypotension.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>In pre-excitation, preferred drugs are flecainide, propafenone or amiodarone.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>When pre-excited AF is present, β-blockers, non-dihydropyridine calcium channel antagonists, digoxin and adenosine are not recommended.</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation.  

Class: indicates the strength of recommendation.  

Level: indicates the quality of evidence.
Acute rhythm control

- Pharmacological cardioversion
  
or

- Electrical cardioversion
Figure 3: Indications for electrical and pharmacological cardioversion, and choice of antiarrhythmic drugs for pharmacological cardioversion in patients with recent-onset AF

Recent-onset AF

Yes

Haemodynamic instability

Emergency

Elective

No

Electrical

Patient/physician choice

Pharmacological

Structural heart disease

Severe

Intravenous amiodarone

Intravenous ibutilide<sup>a</sup> vernakalant<sup>b</sup>

Moderate

Intravenous flecainide ibutilide propafenone vernakalant

None

Intravenous amiodarone

Pill-in-the-pocket (high dose oral)<sup>c</sup> flecainide propafenone

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<sup>a</sup>Ibutilide should not be given when significant left ventricular hypertrophy (≥1.4 cm) is present.

<sup>b</sup>Vernakalant should not be given in moderate or severe heart failure, aortic stenosis, acute coronary syndrome or hypotension. Caution in mild heart failure.

<sup>c</sup>‘Pill-in-the-pocket’ technique – preliminary assessment in a medically safe environment and then used by the patient in the ambulatory setting.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Follow-up dose</th>
<th>Efficacy</th>
<th>Acute side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>5 mg/kg i.v. over 1 hour</td>
<td>50 mg/h</td>
<td>35-90% (effect is delayed by 8-24 h)</td>
<td>Hypotension, bradycardia, QT prolongation, (but low risk of proarrhythmia), phlebitis</td>
</tr>
<tr>
<td>Flecainide</td>
<td>2 mg/kg i.v. over 10 minutes, or 200-300 mg p.o. stat</td>
<td>N/A</td>
<td>55-85%</td>
<td>Hypotension, atrial flutter with rapid ventricular rates (1:1 – 2:1 AV conduction), QRS widening</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>1 mg i.v. over 10 minutes</td>
<td>Second infusion of 1 mg i.v. over 10 minutes after waiting for 10 minutes</td>
<td>31-44%</td>
<td>QT prolongation, torsade de pointes, bradycardia</td>
</tr>
<tr>
<td>Propafenone</td>
<td>2 mg/kg i.v. over 10 minutes, or 450–600 mg p.o. stat</td>
<td>N/A</td>
<td>52-85%</td>
<td>Hypotension, atrial flutter with rapid ventricular rates (1:1 – 2:1 AV conduction), QRS widening</td>
</tr>
<tr>
<td>Vernakalant</td>
<td>3 mg/kg i.v. over 10 minutes</td>
<td>Second infusion of 2 mg/kg i.v. over 10 minutes after waiting for 15 minutes</td>
<td>48-62%</td>
<td>Hypotension (particularly in the presence of heart failure), QT prolongation (but proarrhythmia uncommon), bradycardia</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; AV = atrioventricular; i.v. = intravenous; N/A = not applicable; p.o. = per os.
Vernakalant – IV for termination of AF

- 50% efficacy in 90 mins
- Median time 8–14 mins
- Ineffective against atrial flutter
- Only 27% cardioversion in heart failure
- Sneezing, dysgeusia, nausea, paraesthesia
- QT increase 25 sec but no torsades de pointes
- Hypotension and unsustained VT
- C/I with hypotension, ACS, NYHA class 3+4, severe AS, QT prolongation
Chronic AF management

- Anti-coagulation
- Chronic rate control
- ? Rhythm control
- Manage underlying conditions
Chronic rate control

Figure 8: Optimal level of heart rate control

AF resting heart rate < 110 b.p.m.

- No or tolerable symptoms: Accept
- Symptoms: More strict rate control
  - Exercise test if excessive heart rate during exercise
  - 24-hour ECG for safety

AF = atrial fibrillation.

ESC Guideline 2010.
Figure 9: Choice of rate control medication

- Atrial fibrillation
  - Inactive lifestyle: Digitalis
  - Active lifestyle
    - Associated disease
      - None or hypertension: β-blocker, Diltiazem, Verapamil, Digitalis
      - Heart failure: β-blocker, Digitalis
      - COPD: Diltiazem, Verapamil, Digitalis, β1-selective blockers

ESC Guideline 2010
<table>
<thead>
<tr>
<th>Table 6: Drugs for rate control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intravenous administration</strong></td>
</tr>
<tr>
<td><strong>Beta blockers</strong></td>
</tr>
<tr>
<td>Metoprolol CR/XL</td>
</tr>
<tr>
<td>N/A</td>
</tr>
<tr>
<td>Bisoprolol</td>
</tr>
<tr>
<td>2.5–10 mg o.d.</td>
</tr>
<tr>
<td>Atenolol</td>
</tr>
<tr>
<td>25–100 mg o.d.</td>
</tr>
<tr>
<td>Esmolol</td>
</tr>
<tr>
<td>N/A</td>
</tr>
<tr>
<td>Propranolol</td>
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<tr>
<td>10–40 mg t.i.d.</td>
</tr>
<tr>
<td>Carvedilol</td>
</tr>
<tr>
<td>3.125–25 mg b.i.d.</td>
</tr>
<tr>
<td><strong>Non-dihydropyridine calcium channel blockers</strong></td>
</tr>
<tr>
<td>Verapamil</td>
</tr>
<tr>
<td>40 mg b.i.d. to 360 mg o.d. (ER)</td>
</tr>
<tr>
<td>Diltiazem</td>
</tr>
<tr>
<td>60 mg t.d.s to 360 mg o.d. (ER)</td>
</tr>
<tr>
<td><strong>Digitalis glycosides</strong></td>
</tr>
<tr>
<td>Digoxin</td>
</tr>
<tr>
<td>0.125–0.25 mg o.d.</td>
</tr>
<tr>
<td>Digitoxin</td>
</tr>
<tr>
<td>0.05–0.1 mg o.d.</td>
</tr>
<tr>
<td><strong>Others</strong></td>
</tr>
<tr>
<td>Amiodarone</td>
</tr>
<tr>
<td>100–200 mg o.d.</td>
</tr>
</tbody>
</table>

ER = extended release formulations; N/A = not applicable. = available in SA
Principles of Antiarrhythmic Drug Therapy to Maintain Sinus Rhythm

1. Treatment is motivated by attempts to reduce AF-related symptoms

2. Efficacy of antiarrhythmic drugs to maintain sinus rhythm is modest

3. Clinically successful antiarrhythmic drug therapy may reduce rather than eliminate recurrence of AF
4. If one antiarrhythmic drug ‘fails’ a clinically acceptable response may be achieved with another agent.

5. Drug-induced proarrhythmia or extra-cardiac side-effects are frequent.

6. Safety rather than efficacy considerations should primarily guide the choice of antiarrhythmic.
ESC Guideline 2012.
## Recommendation for choice of an antiarrhythmic drug for AF control

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>The following antiarrhythmic drugs are recommended for rhythm control in patients with AF, depending on underlying heart disease:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Amiodarone</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>• Dronedarone</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>• Flecainide</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>• Propafenone</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>• d,l sotalol</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Amiodarone is more effective in maintaining sinus rhythm than sotalol, propafenone, flecainide (by analogy) or dronedarone (LoE A), but because of its toxicity profile should generally be used when other agents have failed or are contraindicated (LoE C).</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Dronedarone is recommended in patients with recurrent AF as a moderately effective antiarrhythmic agent for the maintenance of sinus rhythm.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>In patients without significant structural heart disease, initial antiarrhythmic therapy should be chosen from dronedarone, flecainide, propafenone, and sotalol.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>In patients with heart failure, amiodarone should be the drug of choice.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>β-blockers are recommended for prevention of adrenergic AF.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>If one antiarrhythmic drug fails to reduce the recurrence of AF to a clinically acceptable level, the use of another antiarrhythmic drug should be considered.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Dronedarone should be considered in order to reduce cardiovascular hospitalizations in patients with non-permanent AF and cardiovascular risk factors.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>β-blockers should be considered for rhythm (plus rate) control in patients with a first episode of AF.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Short-term (4 weeks) antiarrhythmic therapy after cardioversion may be considered in selected patients e.g., those at risk for therapy-associated complications.</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Dronedarone is not recommended for treatment of AF in patients with NYHA class III and IV, or with recently unstable (decompensation within the prior month) NYHA class II heart failure.</td>
<td>III</td>
<td>B</td>
</tr>
<tr>
<td>Dronedarone is not recommended in patients with permanent AF.</td>
<td>III</td>
<td>B</td>
</tr>
<tr>
<td>Antiarrhythmic drug therapy is not recommended for maintenance of sinus rhythm in patients with advanced sinus node disease or AV node dysfunction unless they have a functioning permanent pacemaker.</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; AV = atrioventricular; LoE = level of evidence; NYHA = New York Heart Association.

*Class of recommendation; Level of evidence.
AF is a progressive disease
Atrial tissue is a substrate that changes over time

PACs AT → Paroxysmal AF → Persistent AF → Permanent AF

Electrical remodelling of atria → Structural remodelling of atria

Atrial remodelling: 3 key components

- **Electrical remodelling**
  - Shortening of atrial refractory periods

- **Contractile remodelling**
  - Reduced atrial contractility
  - Sets the stage for thrombus formation

- **Structural remodelling**
  - Left atrium and left atrial appendage enlargement
  - Decrease in cardiac output

The *problems* of AF are...

- Symptoms
- Thrombo-embolism
- Tachycardia-induced cardiomyopathy
The **solutions** for AF are...

- **Symptoms**
  - RATE CONTROL
  - ? RHYTHM CONTROL
- **Thrombo-embolism**
  - ANTI-COAGULATION
  - ? LA APPENDAGE CLOSURE
- **Tachycardia-induced cardiomyopathy**
  - RATE CONTROL
- **ALL** AF patients need *rate control* and *anti-coagulation*

- **SOME** AF patients need *rhythm control* ie symptoms despite rate control or rhythm control is suspected to be a better strategy
When is rhythm control likely to be a better strategy?

- Younger patients
- Severe symptoms
- Diastolic dysfunction – hypertension – hypertrophic cardiomyopathy
- Mitral stenosis
AF strategy trials

Figure 7: Choice of rate and rhythm control strategies

Appropriate antithrombotic therapy

Clinical evaluation

Paroxysmal

Persistent

Long-standing persistent

Rhythm control

Remains symptomatic

Rate control

Failure of rhythm control

ESC Guideline 2010
Symptoms

- Light-Headedness
- Syncope
- Fatigue
- Palpitations
- Dyspnoea
- Chest Pain

## AF Symptom Score

<table>
<thead>
<tr>
<th>EHRA class</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>EHRA I</td>
<td>‘No symptoms’</td>
</tr>
<tr>
<td>EHRA II</td>
<td>‘Mild symptoms’; normal daily activity not affected</td>
</tr>
<tr>
<td>EHRA III</td>
<td>‘Severe symptoms’; normal daily activity affected</td>
</tr>
<tr>
<td>EHRA IV</td>
<td>‘Disabling symptoms’; normal daily activity discontinued</td>
</tr>
</tbody>
</table>

ESC guideline 2010. www.escardio.org/guidelines
Asymptomatic AF

- About 1 in 3 patients are asymptomatic
- Not necessarily a bonus – often present with cryptogenic stroke or tachy-cardiomyopathy
- Opportunistic screening valuable
- Even in symptomatic patients, 90% of episodes are asymptomatic*
- “Rhythm control” is not pursued in asymptomatic patients