New therapeutic options in atrial fibrillation

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NO DISCLOSURES
Natural History of Atrial Fibrillation

<table>
<thead>
<tr>
<th>Outcome parameter</th>
<th>Relative change in AF patients</th>
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<tbody>
<tr>
<td>1. Death</td>
<td>Death rate doubled.</td>
</tr>
<tr>
<td>2. Stroke (includes haemorrhagic</td>
<td>Stroke risk increased; AF is associated with more severe stroke.</td>
</tr>
<tr>
<td>stroke and cerebral bleeds)</td>
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<tr>
<td>3. Hospitalizations</td>
<td>Hospitalizations are frequent in AF patients and may contribute to</td>
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<tr>
<td></td>
<td>reduced quality of life.</td>
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<tr>
<td>4. Quality of life and exercise</td>
<td>Wide variation, from no effect to major reduction. AF can cause</td>
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<td>capacity</td>
<td>marked distress through palpitations and other AF-related symptoms.</td>
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<tr>
<td>5. Left ventricular function</td>
<td>Wide variation, from no change to tachycardiomyopathy with acute</td>
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<tr>
<td></td>
<td>heart failure.</td>
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## Classification of AF-related symptoms (EHRA score)

<table>
<thead>
<tr>
<th>EHRA class</th>
<th>Explanation</th>
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<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>
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<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>
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</table>
Risk of Thrombus in AF

- Atria do not contract properly leading to stasis in the left atrium and appendage (LAA)
- LAA is a small muscular pouch attached to the main atrial chamber
- In non-valvular AF, ~90% of atrial thrombi occur in the LAA

Therapeutic range

International normalized ratio

Odds ratio

Stroke

Intracranial bleed
Time in Target Range INR

Real Life OAC Prescription

- Ineligible (n=517)
  - 50%

- Eligible (n=4736)
  - 35%

Nieuwlaat et al. EHJ 2005;26:2422–2434
## Requirements of new antithrombotic agents

<table>
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<tbody>
<tr>
<td>At least as effective as warfarin</td>
</tr>
<tr>
<td>Predictable response</td>
</tr>
<tr>
<td>Wide therapeutic window</td>
</tr>
<tr>
<td>Low incidence and severity of adverse effects</td>
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<tr>
<td>Oral fixed dose</td>
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<tr>
<td>No need for routine anticoagulation monitoring</td>
</tr>
<tr>
<td>Low potential for food or drug interactions</td>
</tr>
<tr>
<td>Fast onset and offset of action</td>
</tr>
<tr>
<td>Cost-effective</td>
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</table>

Adapted from Lip GY et al. EHJ Suppl 2005;7:E21–5
Novel Antithrombotic Therapies

Tissue factor/VIIa

Direct Thrombin Inhibitor(s)

Conclusions Re-Ly:

- Dabi 110 bid as effective and 150 bid more effective than Warfarin
- Dabi 110 bid safer and 150 bid as safe as Warfarin

Side Effects Dabigatran:

- Diarrhea
- Heartburn (dyspepsia)
- Indigestion
- Mild stomach pain or upset
- Nausea
LAA Occlusion

Holmes et al. Lancet 2009; 374: 534–42
Rate or Rhythm

**QOL**

Jenkins et al. Am Heart J 2005;149:112-20

**CVA**

De Denus et al. Arch Intern Med. 2005;165:258-262

**Heart Failure**

**Mortality**


De Denus et al. Arch Intern Med. 2005;165:258-262
Appropriate antithrombotic therapy

Clinical evaluation

- Paroxysmal
- Persistent
- Long-standing persistent
- Permanent

Rhythm control
- Remains symptomatic
- Failure of rhythm control

Rate control

- Younger age
- Troublesome symptoms despite rate control
- Problems with diastolic compliance requiring preservation of atrial contractility
Long-Term Rhythm Control

Relevant underlying heart disease

- CHF
  - NYHA III/IV or unstable NYHA II
  - Stable NYHA I/II
  - Dronedarone
  - Sotalol
  - Amiodarone

- CAD
  - Hypertension with LVH
    - Dronedarone

- No or minimal heart disease (including HT without LVH)

  - Paroxysmal AF
    - Dronedarone, Flecaïnine, Propafenone, Sotalol
    - Catheter ablation for AF
  - Persistent AF
    - Dronedarone, Sotalol
    - Amiodarone
Dronedarone

Maintenance of Sinus Rhythm vs. Placebo

<table>
<thead>
<tr>
<th>Study</th>
<th>Dronedarone</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>DAFNE</td>
<td>35/54</td>
<td>43/48</td>
</tr>
<tr>
<td>EURIDIS</td>
<td>150/411</td>
<td>95/201</td>
</tr>
<tr>
<td>ADONIS</td>
<td>154/417</td>
<td>89/208</td>
</tr>
<tr>
<td>ATHENA</td>
<td>779/1732</td>
<td>950/1741</td>
</tr>
<tr>
<td>Pooled (FE)</td>
<td>1118/2614 (43%)</td>
<td>1177/2198 (54%)</td>
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</table>

Cochran’s Q = 1.9, P=0.6
I² = 0%, 95% CI (0-85%)

Relative risk

Weight (%)

Liver enzymes (?)
Contra-indicated in NYHA III-IV
Decrease in incidence of CVA
Reduces cardiovascular mortality but not overall mortality

Singh et al. JACC 2010;55:1569–76
Hoy et al. Drugs 2009; 69: 1647-1663
Log-rank 𝑃 < 0.0001
Relative risk\(^1\) (95% CI) = 1.589 (1.275–1.98)

Patients at risk:

Dronedarone: 249, 99, 84, 40, 12, 0
Amiodarone: 255, 146, 126, 61, 13, 0
Rhythm Control

Medication
Long-Term Rhythm Control
Ablation – Longer-Term Results

![Graph showing arrhythmia-free survival over follow-up years with a table below indicating the number at risk at each year: 100, 78, 71, 67, 54, 18]
Rhythm Control

Medication

Ablation
Novelties in Ablation

Balloons

Multielectrode catheters
Atrial Remodelling

Hypertension, Heart Failure, Diabetes, OSAS, ...
• **Electrical remodelling**
  - Shortening of atrial refractory periods
  - Occurs rapidly (within several days) and contributes to the increased stability of AF

• **Contractile remodelling**
  - Reduced atrial contractility
  - Sets the stage for thrombus formation
  - May lead to atrial dilation further altering electrophysiologic properties
  - Occurs rapidly

• **Structural remodelling**
  - Histologic changes
  - Left atrium and left atrial appendage enlargement
  - Decrease in cardiac output
  - Occurs after a period of weeks to months

Van Gelder *et al.*, *Europace* 2006;8:943-949
Upstream Therapies

• RAAS Inhibition:
  – Heart Failure: Yes
  – Hypertension: Probably
  – Secondary prevention: ?

• Statins:
  – Post operative: Yes
  – Other: ?

• PUFA
  – ?
Future Challenges

- Earlier Detection
  - Associated disease
  - Initial assessment
- Easier and cheaper prevention TE events
- Better and safer AAD
  - Anticoagulant drugs
  - Ablation
- More effective PVI
- Prevent remodelling

- Atrial fibrillation
  - Record 12-lead ECG
    - Anticoagulation issues
      - Rate and rhythm control
        - Treatment of underlying disease ‘Upstream’ therapy