Rationale and Treatment Challenges in Atrial Fibrillation

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AF is the most common cardiac arrhythmia\(^5\)

Europe: 4.5 to > 6 million people

US: 2.3 to 5.1 million people

- **Lifetime risk of developing AF is 25%** for men and women aged 40 years and older and remains stable across ages\(^1\) (Framingham Heart Study & Rotterdam study)\(^4,5\)

- **The prevalence** of AF increases from ~4% at ≥ 60 years to **9% at ≥ 80 years**\(^5\)

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AF is often associated with CV co-morbidities

- Baseline data from the Record AF survey including patients with paroxysmal or persistent AF

![Bar chart showing the percentage of patients with various conditions.](chart.png)

- Hypertension: 68%
- Dyslipidemia: 42%
- Congestive heart failure: 26%
- Coronary artery disease: 18%
- Diabetes mellitus: 16%

Atrial remodelling consists of 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

AF is a progressive disease

- Atrial tissue provides a substrate that may change over time

PACs: premature atrial contractions
AT: atrial tachycardia
AF progression is associated with cardiovascular hospitalizations

**Cardiovascular hospitalizations**

**RecordAF**

- **Progression**: 25%
- **No progression**: 15%

*P* < 0.0001

**Euro Heart Survey**

- **Progression**: 71%
- **No progression**: 50%

*P* < 0.001

Adapted from:
AF increases patients’ risk of death, HF and CV events

Fold risk increase with AF

- All-cause Mortality: 1.5–2.2
- Sudden cardiac death: 1.3
- Ischaemic Stroke: 4.8
- Debilitating stroke: 2.2
- HF: 3.4

CV= cardiovascular  HF= heart failure

Adapted from:
CV hospitalisation is predictive of long-term mortality in AF patients

Fold risk increase of all-cause mortality within 2.5 years\(^1\) (vs. patients not hospitalised)

- **2.43** within 3 months
- **2.02** within 6 months
- **1.43** within 12 months

Time to CV-related hospital re-admission

CV hospitalisations may be an appropriate surrogate end-point for mortality\(^2\)

Adapted from:
Patients with AF may present with a wide range of symptoms

- AF may also be asymptomatic

Impact of asymptomatic AF:
- Potential for underlying electrical and structural damage to atrial myocardium

- Palpitations
- Syncope
- Fatigue
- Thrombo-Embolism
- Dyspnoea
- Chest Pain
- Death

Real life data reveal the association of AF with negative CV outcomes

### The REACH registry

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with AF</th>
<th>Patients without AF</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>6814</td>
<td>56775</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>4.27 %</td>
<td>2.32 %</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CV death</td>
<td>3.16 %</td>
<td>1.42 %</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>1.36 %</td>
<td>1.11 %</td>
<td>0.1205</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>2.43 %</td>
<td>1.55 %</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, smoking, hypertension, diabetes, hypercholesterolemia

Stroke is the most common and devastating complication of AF

- The incidence of all-cause stroke in patients with AF is 5% per year\(^1\)
- AF is an independent risk factor for stroke\(^2\)
  - AF increases the risk of stroke ~5-fold\(^2\)
  - ~15% of all strokes in the U.S. are caused by AF\(^1\)
  - The risk for stroke increases with age\(^1\)
- Stroke risk persists even in asymptomatic AF\(^3\)

![Annual stroke rate (%)](chart)

Comprehensive management of AF should address the multiple impacts of the condition

In addition to stroke prevention and reduction of AF burden*, successful management of AF should aim to reduce hospitalisations and CV morbidity and mortality

Reduction in CV mortality
Prevention of stroke
Reduction in the risk of CV-events and hospitalisations
Reduction of AF burden*

Total percentage of time a patient has AF as determined by the number and duration of AF episodes
REDEFINE AF TREATMENT GOALS?
AF management is aimed at reducing symptoms and at preventing severe complications (ESC 2012 Guidelines)

- Reducing hospitalisation is a recognised therapeutic goal in AF

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

ESC 2010 AF Guidelines – clinical outcomes affected by AF

Longer time spent in AF predicts progression to permanent AF

**RecordAF**

Baseline factors predicting progression to permanent AF

- **Duration of AF ≥ 3 months (yes vs no)**
  (1.48; 1.24 to 1.79; \( P = 0.0001 \))

- **Persistent AF vs paroxysmal AF**
  (3.31; 2.65 to 4.13; \( P < 0.0001 \))

AF ≥ 3 months at baseline and persistent AF (vs paroxysmal) increased the risk of permanent AF, indicating AF duration as an important predictor of progression.

Several treatment strategies are available for AF

- Long-lasting AF usually renders maintenance of sinus rhythm more difficult
- It is likely that a window of opportunity to maintain sinus rhythm exists early in the course of management of a patient with AF

The remodelling-driven progression of untreated AF suggests the need for early sinus rhythm maintenance.

Hypothetical representation of the time course of atrial substrate remodelling in relation to the clinical appearance of AF.

ECV, electrical cardioversion.
**AFFIRM – follow-up Investigation on Rhythm Management**

- Time-dependent, On-Treatment, Multivariate Analysis of Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
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<tbody>
<tr>
<td>Age (per year)</td>
<td>1.06 (1.05 – 1.08)</td>
</tr>
<tr>
<td>CAD</td>
<td>1.56 (1.20 – 2.04)</td>
</tr>
<tr>
<td>CHF</td>
<td>1.57 (1.18 – 2.09)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.56 (1.17 – 2.07)</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.78 (1.25 – 2.53)</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>1.70 (1.24 – 2.33)</td>
</tr>
<tr>
<td>Normal LVEF</td>
<td>0.74 (0.55 – 0.98)</td>
</tr>
<tr>
<td>Mitral Regurg</td>
<td>1.36 (1.03 – 1.80)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>0.50 (0.37 – 0.69)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>1.42 (1.09 – 1.86)</td>
</tr>
<tr>
<td>Sinus Rhythm</td>
<td>0.53 (0.39 – 0.72)</td>
</tr>
<tr>
<td>AA Drug</td>
<td>1.49 (1.11 – 2.01)</td>
</tr>
</tbody>
</table>

Rhythm control and mortality in AF: long term benefit

- Population-based administrative databases, Quebec
- 26,130 patients
- 1999 to 2007

- > 65 years
- AF hospitalization
- No AF-related drug prescriptions < 1 year < admission (first documented AF)
- AAD < 7 days > discharge

Effect of rhythm vs rate control therapy on mortality. Point estimates and 95% CIs can be reported at selected time points during the follow-up. The adjusted hazard ratio (HR) at a corresponding point in time quantifies the relative risks of immediate death, for rhythm vs rate control drugs, among patients who were followed until that time (ie, had not died and were not censored until that time).

The longer the time spent in AF, the harder it is to restore and maintain sinus rhythm

Treatment goals of appropriate AF management?

Symptoms?  Rhythm?  Rate?

OR

Mortality & CV hospitalisation?

Conclusions

- Atrial fibrillation is the most common sustained arrhythmia and increases patients’ risk of:
  - hospitalisation
  - stroke
  - heart failure and death
  - sudden cardiac death
  - increased risk of CV morbidity and mortality

- AF can progress due to atrial remodelling

- AF can be a significant burden for the patient and society (increased risk of hospitalisations)

- Primary prevention and early effective treatment may slow down the remodelling process