Modern management of atrial fibrillation, from blood pressure control to anticoagulation

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December 6th, 2013
Prevalence of AF stratified by age and gender

European age-related prevalence

- Women (n=4053)
- Men (n=2590)

US age-related prevalence

- Women (n=7995)
- Men (n=10179)

Heeringa J et al. *Eur Heart J* 2006

Go AS et al, *JAMA* 2001
AF-related strokes are associated with greater disability and a higher mortality rate


<table>
<thead>
<tr>
<th>Patients with clinical parameter (%)</th>
<th>Strokes with AF (N=216)</th>
<th>Strokes without AF (N=845)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disability at clinical presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe limb weakness</td>
<td>40%</td>
<td>25%</td>
</tr>
<tr>
<td>Bedridden</td>
<td>60%</td>
<td>35%</td>
</tr>
<tr>
<td>P &lt; 0.005</td>
<td>P &lt; 0.0005</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>30-day post-stroke mortality (%)</th>
<th>Strokes with AF (N=103)</th>
<th>Strokes without AF (N=398)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strokes with AF</td>
<td>25%</td>
<td>15%</td>
</tr>
<tr>
<td>Strokes without AF</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>P &lt; 0.048</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Limitations of VKA therapy

- Unpredictable response
- Narrow therapeutic window (INR range 2.0–3.0)
- Slow onset/offset of action
- Routine coagulation monitoring
- Frequent dose adjustments
- Numerous drug–drug interactions
- Numerous food–drug interactions
- Warfarin resistance

INR control: Clinical trials VS. clinical practice (TTR)

Trials of new oral anticoagulants for SPAF

Direct thrombin inhibitor

RE-LY
- Dabigatran
- ~18 000 pts
- PROBE design
- Mean CHADS$_2$ 2.1
- Stroke or systemic embolism
- Major bleeding

Factor Xa inhibitors

ROCKET-AF
- Rivaroxaban
- ~14 000 pts
- Double blind
- Mean CHADS$_2$ 3.5
- Stroke or systemic embolism
- Major and non-major clinically relevant bleeding

ARISTOTLE
- Apixaban
- ~18 000 pts
- Double blind
- Mean CHADS$_2$ 2.1
- Stroke or systemic embolism
- Major bleeding
RE-LY® primary efficacy outcome: stroke or systemic embolism

Dabigatran 110 mg BID vs. warfarin

Dabigatran 150 mg BID vs. warfarin

Hazard ratio

Non-inferiority P value

Superiority P value

<0.001 0.30

<0.001 <0.001

ROCKET AF
primary efficacy endpoint ITT

**Stroke or systemic embolism**

HR=0.88 (0.75, 1.03)

- p<0.001 (non-inferiority)
- p=0.12 (superiority)

<table>
<thead>
<tr>
<th>Days since randomization</th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>7,081</td>
<td>7,090</td>
</tr>
<tr>
<td>120</td>
<td>6,879</td>
<td>6,871</td>
</tr>
<tr>
<td>240</td>
<td>6,683</td>
<td>6,656</td>
</tr>
<tr>
<td>360</td>
<td>6,470</td>
<td>6,440</td>
</tr>
<tr>
<td>480</td>
<td>5,264</td>
<td>5,225</td>
</tr>
<tr>
<td>600</td>
<td>4,105</td>
<td>4,087</td>
</tr>
<tr>
<td>720</td>
<td>2,951</td>
<td>2,944</td>
</tr>
<tr>
<td>840</td>
<td>1,785</td>
<td>1,783</td>
</tr>
</tbody>
</table>

**Number of subjects at risk**

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT population</td>
<td>7,081</td>
<td>7,090</td>
</tr>
</tbody>
</table>

ARISTOTLE
Primary Efficacy Outcome

Stroke or Systemic Embolism

HR 0.79 (95% CI, 0.66, 0.95)

Warfarin

Apixaban

p (non-inferiority) <0.001
p (superiority) = 0.011

21% RRR

Percent with event

Months

LAA Occlusion procedures

Surgical

Percutaneous

- PLAATO system
- WATCHMAN device
- Amplatzer cardiac plug
- LARIAT system
PROTECT AF: Intent-to-Treat
Primary Safety Results

Randomization allocation (2 device : 1 control)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Events (no.)</th>
<th>Total pt-yr</th>
<th>Rate (95% CI)</th>
<th>Events (no.)</th>
<th>Total pt-yr</th>
<th>Rate (95% CI)</th>
<th>Rel. Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>900 pt-yr</td>
<td>48</td>
<td>554.2</td>
<td>8.7 (6.4, 11.3)</td>
<td>13</td>
<td>312.0</td>
<td>4.2 (2.2, 6.7)</td>
<td>2.08 (1.18, 4.13)</td>
</tr>
</tbody>
</table>

**Event-free probability**

**Days**

0 365 730 1,095

**ITT Cohort:**
patients analyzed based on their randomly assigned group (regardless of treatment received)
### PROTECT AF: Intent-to-Treat Primary Efficacy Results

Randomization allocation (2 device : 1 control)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Device</th>
<th>Events (no.)</th>
<th>Total pt-yr</th>
<th>Rate (95% CI)</th>
<th>Control</th>
<th>Events (no.)</th>
<th>Total pt-yr</th>
<th>Rate (95% CI)</th>
<th>Rel. Risk (95% CI)</th>
<th>Non-inferiority</th>
<th>Superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>900 pt-yr</td>
<td></td>
<td>20</td>
<td>582.3</td>
<td>3.4 (2.1, 5.2)</td>
<td></td>
<td>16</td>
<td>318.0</td>
<td>5.0 (2.8, 7.6)</td>
<td>0.68 (0.37, 1.41)</td>
<td>0.998</td>
<td>0.837</td>
</tr>
</tbody>
</table>

**Device**

**Control**

**Posterior Probabilities**

**Device**

**Control**

**Posterior Probabilities**

**ITT Cohort:** patients analyzed based on their randomly assigned group (regardless of treatment received)
AFFIRM: Mortality with rate and rhythm control strategies

**Mortality (%)**

<table>
<thead>
<tr>
<th>Years</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
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<td></td>
</tr>
<tr>
<td>20</td>
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<tr>
<td>15</td>
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<tr>
<td>10</td>
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<tr>
<td>5</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
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</table>

**HR = 1.15**
95% CI: 0.99–1.34
P = 0.08

**AFFIRM** = Atrial Fibrillation Follow-up Investigation of Rhythm Management

AFFIRM: Stroke incidence with rate and rhythm control strategies

ATHENA study: Maintenance of sinus rhythm with dronedarone delays hospitalization for CV causes or death


Hospitalization due to CV events or death from any cause

Cumulative incidence, %

Years

Placebo

Dronedarone

P<0.001

n = 2327 1858 1625 1072 385 3
2301 1963 1776 1177 403 2

Technique of AF ablation

Ablation of triggering focus

Circumferential PV isolation
MANTRA-PAF
Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation

**MANTRA-PAF**
Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation

### Quality of Life Scores

<table>
<thead>
<tr>
<th>Summary Score</th>
<th>Baseline</th>
<th>12 Months</th>
<th>24 Months</th>
<th>P Value for Effect of Group</th>
<th>P Value for Effect of Time</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ablation</td>
<td>Drug Therapy</td>
<td>Ablation</td>
<td>Drug Therapy</td>
<td>Ablation</td>
<td>Drug Therapy</td>
</tr>
<tr>
<td>Physical component</td>
<td>44.3±8.9</td>
<td>45.2±8.9</td>
<td>50.2±8.5</td>
<td>47.5±9.7</td>
<td>50.0±8.8</td>
<td>47.9±8.9</td>
</tr>
<tr>
<td>Mental component</td>
<td>45.2±11.7</td>
<td>46.1±11.2</td>
<td>50.8±9.3</td>
<td>50.1±8.5</td>
<td>51.1±9.2</td>
<td>50.9±8.0</td>
</tr>
</tbody>
</table>