Can rhythm control strategy reduce the risk of clinical and silent cerebral ischemia?

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Director of the School of Cardiology
University of Turin, Italy
No conflicts of interest related to this topic to declare
For 2 millions years in the evolution of the human species sinus rhythm has always been maintained. If we have been created in sinus rhythm there must be a reason.

Two reasons to pursue rhythm control strategy:

**Faith**

If we have been created in sinus rhythm there must be a reason.

**Rational**

For 2 millions years in the evolution of the human species sinus rhythm has always been maintained.
Atrial fibrillation therapy: Aims

- Symptoms relief and quality of life
- Reduction of related major comorbidities
  - e.g. clinical (stroke/TIA) and "silent" cerebral ischemia
- Reduction of mortality
CHADS2 score

- Congestive heart failure: 1
- Hypertension: 1
- Age > 75 years: 1
- Diabetes mellitus: 1
- Prior Stroke or TIA: 2

CHADS2 score

- Congestive heart failure: 1
- Hypertension: 1
- Age > 75 years: 2
- Diabetes mellitus: 1
- Prior Stroke or TIA: 2
- Vasculopathy: 1
- Age > 65: 1
- Sex: 1

Stroke rate/year (%)

- 0-0.78: 1.3-2
- 2.2-3.7: 3.2-5.9
- 3.2-5.9: 4-9.3
- 4-9.3: 6.7-15.2
- 6.7-15.2: 15.2-23.6

ESC Guidelines 2010; Olesen JB et al BMJ 2011

Gage JAMA 2001; Fang Circulation 2005
<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial name</strong></td>
<td>RELY</td>
<td>ROCKET AF</td>
<td>ARISTOTLE</td>
<td>ENGAGE AF-TIMI 48</td>
</tr>
<tr>
<td><strong>Brand Name</strong></td>
<td>Pradaxa</td>
<td>Xarelto</td>
<td>Eliquis</td>
<td>Lixiana</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>Warfarin (INR 2-3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>18.113</td>
<td>14.264</td>
<td>18.201</td>
<td>21.105</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>71.5 ± 8.7</td>
<td>73 (65-78)</td>
<td>70 (63-76)</td>
<td>72 (64-78)</td>
</tr>
<tr>
<td><strong>Age &gt; 75 yrs</strong></td>
<td>7258 (40.1%)</td>
<td>6229 (43.6%)</td>
<td>5678 (31.1%)</td>
<td>8474 (40.2%)</td>
</tr>
<tr>
<td><strong>CHADS2</strong></td>
<td>2.1</td>
<td>3.5</td>
<td>2.1</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>Study Design</strong></td>
<td>Open-label (warfarin)</td>
<td>Double-blind Non inferiority</td>
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<td>Double-blind</td>
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<td></td>
<td>Non inferiority</td>
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<td><strong>Dose of Study Drug</strong></td>
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<td>20 mg od 15 mg od</td>
<td>5 mg bid 2.5 mg bid</td>
<td>60 mg od 30 mg od</td>
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### Meta-Analysis of Efficacy and Safety of New Oral Anticoagulants Versus Warfarin in Patients with Atrial Fibrillation

**Stroke, Systemic Embolism**

<table>
<thead>
<tr>
<th>NOA</th>
<th>RR (CI)</th>
<th>W</th>
</tr>
</thead>
<tbody>
<tr>
<td>W</td>
<td>0.94 (0.82, 1.07)</td>
<td>399/6076</td>
</tr>
<tr>
<td>W</td>
<td>1.03 (0.89, 1.18)</td>
<td>395/7111</td>
</tr>
<tr>
<td>W</td>
<td>0.70 (0.61, 0.81)</td>
<td>327/9088</td>
</tr>
<tr>
<td>W</td>
<td>0.88 (0.71, 1.09)</td>
<td>1121/22275</td>
</tr>
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</table>

RRR 22%
ARR 0.7%

**Major Bleeding**

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<th>NOA</th>
<th>RR (CI)</th>
<th>W</th>
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<tbody>
<tr>
<td>W</td>
<td>0.41 (0.28, 0.60)</td>
<td>36/6076</td>
</tr>
<tr>
<td>W</td>
<td>0.66 (0.47, 0.92)</td>
<td>55/7111</td>
</tr>
<tr>
<td>W</td>
<td>0.42 (0.31, 0.59)</td>
<td>52/9088</td>
</tr>
<tr>
<td>W</td>
<td>0.49 (0.36, 0.66)</td>
<td>143/22275</td>
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RRR 12%
ARR 0.7%

**Intracranial Bleeding**

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<th>NOA</th>
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<tr>
<td>W</td>
<td>150 mg bid</td>
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RRR 51%
ARR 0.7%

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Miller C. et al. Am J Cardiol 2012
Annual Thromboembolic Risk per 100 pts year
Warfarin vs New Oral Anticoagulants

Dabigatran 150

Warfarin

NOAC

CHADS2 2.2

CHADS2 2.1

Dabigatran 110

Apixaban

CHADS2 2.1

Expected per 100 pts yrs

4% (C.I. 3.2-5.4)

Incidence per 100 pts yrs

0 3% 6%

1.69 1.11 1.69 1.53 1.60 1.27
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Total patients enrolled 71683 (38.6% ≥75 years)

Less than 2% treated with rhythm control strategy
Can a rhythm control strategy further reduce thromboembolic risk?
Management cascade for patients with AF

ESC 2010 AF guidelines

Atrial fibrillation

Record 12-lead ECG

Presentation
EHRA score
Associated disease
Initial assessment

Anticoagulation
issues

Assess
TE Risk

Oral anticoagulant
Aspirin
None

Rate and rhythm
control

AF type
Symptoms

Rate control
± Rhythm control
Antiarrhythmic drugs
Ablation

Treatment of underlying disease
'Upstream' therapy

Consider referral

ACEIs/ARBs
Statins/PUFAs
Others
ATHENA Substudy Stroke Reduction

4500 AF pts (Paroxysmal 75%) treated with Dronedarone 400 mg bid (OAT 1403, 61%) vs Placebo (OAT 1384, 59%)

Mean follow-up 21 ± 5 months

RRR: 34%
ARR: 0.6%

Placebo: 70/2327 (1.8%)
Dronedarone: 46/2301 (1.2%)

Pz a rischio
Placebo: 2327, 2275, 2220, 1598, 618, 6
Dronedarone: 2301, 2266, 2223, 1572, 608, 4

ATHENA. Circulation 2009;120:1174-1180
Rhythm Versus Rate Control Therapy and Subsequent Stroke or Transient Ischemic Attack in Patients With Atrial Fibrillation

Meytal Avgil Tsadok, Cynthia A. Jackevicius, Vidal Essebag, Mark J. Eisenberg, Elham Rahme, Karin H. Humphries, Jack V. Tu, Hassan Behlouli and Louise Pilote

57518 AF Quebec pts, aged > 65 y (1999-2007)

Equally treated with OAT (59% in both groups)

Incidence of Stroke/TIA per 100 pts/ys

CHADS$_2$ ≥ 2

RRR 25 %

Rate control tx
41193 pts

Rhythm control tx.
16325 pts Only AADs
What about rhythm control using TC ablation and long-term thromboembolic risk?
Incidence of cerebral thromboembolic events during long-term follow-up in patients treated with transcatheter ablation for atrial fibrillation

Fiorenzo Gaita¹*, Davide Sardi¹, Alberto Battaglia¹, Cristina Gallo¹, Elisabetta Toso¹, Arianna Michielon¹, Domenico Caponi², Lucia Garberoglio², Davide Castagno¹, and Marco Scaglione²

766 pts mean CHADS 2.0, undergoing AF ablation

CHADS ≤ 1
Off OAT

CHADS2 ≥ 2
On OAT

Mean follow up 60 months
Incidence of cerebral thromboembolic events during long-term follow-up in patients treated with transcatheter ablation for atrial fibrillation

Fiorenzo Gaita\textsuperscript{1*}, Davide Sardi\textsuperscript{1}, Alberto Battaglia\textsuperscript{1}, Cristina Gallo\textsuperscript{1}, Elisabetta Toso\textsuperscript{1}, Arianna Michielon\textsuperscript{1}, Domenico Caponi\textsuperscript{2}, Lucia Garberoglio\textsuperscript{2}, Davide Castagno\textsuperscript{1}, and Marco Scaglione\textsuperscript{2}

TE event rate observed per 100 pts/yr

Total event rate
5 years
\textbf{1.4\%}

766 pts
Incidence of cerebral thromboembolic events during long-term follow-up in patients treated with transcatheter ablation for atrial fibrillation

Fiorenzo Gaita, Elisabetta Toso, Davide Castagnoli

Maintenance of sinus rhythm with an ablation strategy in patients with atrial fibrillation is associated with a lower risk of stroke and death

Ross J Hunter, James McCready, Ihab Diab, Stephen P Page, Malcolm Finlay, Spornon, Michael Jones, Andrew Staniforth, Richard J Schilling

The Risk of Thromboembolism and Need for Oral Anticoagulation After Successful Atrial Fibrillation Ablation

Sakis Themistoclakis, MD, Andrea Corrado, MD, Francis E. Marchlinski, MD, Pierre Jais, MD

Risk of Stroke or Transient Ischemic Attack After Atrial Fibrillation Ablation with Oral Anticoagulant Use Guided by ECG Monitoring and Pulse Assessment

MICHAEL P. RILEY, M.D., PH.D., ERICA ZADO, PA-C, MATHEW D. HUTCHINSON, M.D., DAVID LIN, M.D., RUPA BALA, M.D., FERMIN C. GARCIA, M.D., DAVID J. CALLANS, M.D., JOSHUA M. COOPER, M.D., RALPH J. VERDINO, M.D., SANJAY DIXIT, M.D., and FRANCIS E. MARCHELINSKI, M.D.
TE event rate following AF ablation

Total patients evaluated 7384

Mean CHADS 2

TE event rate observed per 100 pts/yr

- Gaita: 0.28%
- Themistoclakis: 0.07%
- Hunter: 0.5%
- Riley: 0.2%
- Expected in CHADS 2 pts: 4.1(3.2-5.4)%
- NOAC (data from RELY and ARISTOTLE in CHADS 2 pts): 1.3%
What about silent cerebral ischemia and cognitive decline?
Atrial fibrillation and incident dementia

5.150 pts, mean age 73 yrs, Male 41%, Hypertension 57%
Not having atrial fibrillation or a history of stroke at baseline

Mean follow-up 7 yrs
Cognitive test performed annually

Conclusion:
Patients with AF have a cognitive performance comparable to that of those with at least five years older

Above 70 yrs of age cognitive performance physiologically declines
AF onset accelerates cognitive decline

Cognitive function (DSST score)
**Results**

suggest that AF is associated with a higher risk of cognitive impairment and dementia (RR, 1.40 [CI, 1.19 to 1.64]).

**Conclusion**

Further studies are required to elucidate:
- The association between AF and subtype of dementia
- The cause of cognitive impairment
Prevalence of Silent Cerebral Ischemia in Paroxysmal and Persistent Atrial Fibrillation and Correlation With Cognitive Function

Fiorenzo Gaita, MD,* Laura Corsinovi, MD, PhD,* Matteo Anselmino, MD, PhD,* Cristina Raimondo, MD,* Martina Pianelli, MD,* Elisabetta Toso, MD,* Laura Bergamasco, PROF,† Carlo Boffano, MD,‡ Maria Consuelo Valentini, MD,§ Federico Cesarani, MD,‖ Marco Scaglione, MD¶

Turin, Milan, and Asti, Italy
The number of SCI varies according to AF type

AF showed a higher risk for SCI compared with subjects in sinus rhythm (Odd ratio 11.2, p value < 0.001)

Correlation between AF type, SCI number and cognitive function

- 41 lesions/person
- 28 lesions/person
- 12 lesions/person

Immediate Memory

Controls (mean 12 SCI/person)

Paroxysmal AF (mean 28 SCI/person)

Persistent AF (mean 41 SCI/person)

An increased burden of SCI relates with worse cognitive performance

Rhythm control strategy associated with well-managed OAT can further reduce thromboembolic events in patients with AF.

Further clinical studies focusing on oral anticoagulation and rhythm control strategy are warranted to evaluate their impact on silent ischemia and cognitive decline.