ATRIAL FIBRILLATION : A RISK FACTOR OR A RISK MARKER : DOES IT MATTER FOR THERAPY ?

ANTICOAGULANT / ANTITHROMBOTIC THERAPY
Disclosures

Consultancy / conferences / research grants:
Astra–Zeneca, Bayer, Boehringer Ingelheim,
Bristol-Myers Squibb / Pfizer, Correvio, Daiichi-Sankyo,
Meda, Sanofi, Servier
Does it matter for therapy?

J.Y. Le Heuzey

One sixth of all strokes attributable to AF (Wolf et al. Stroke 1991, 22 : 983-8)

Attributable: directly due or simply linked?
The detection of an atrial fibrillation in a patient referred for a stroke does not imply that atrial fibrillation is the cause of the stroke.

- Atrial fibrillation may be the consequence of stroke (1 to 2% ?)
- Imaging can detect a cerebral hemorrhage
- Another possible cause of cerebral ischemia is present in near 25% of cases:
  - Carotid stenosis 10%
  - Aortic atheroma 15%
  - Hypertension 50%
  - Lacunar infarction 10%

Adapted from MAS J.L.
Antiarrhythmic prophylaxis vs. warfarin anticoagulation to prevent thromboembolic events among patients with atrial fibrillation. A decision analysis.

Middlekauff HR, Stevenson WG, Gornbein JA. Arch Intern Med 1995;155:913–20

CONCLUSIONS: Based on data from randomised, controlled trials of quinidine and warfarin, warfarin therapy appears to be the safest strategy for thromboembolism prevention in the patient with atrial fibrillation.

Relative Risk Reduction of Stroke in Atrial Fibrillation
ASA Compared with Placebo and Warfarine compared with ASA

Adjusted-Dose Warfarin Compared with Placebo

<table>
<thead>
<tr>
<th>Trial</th>
<th>Relative Risk Reduction (95% CI)</th>
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<tbody>
<tr>
<td>AFASAK I (1)</td>
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<td>BAATAF (6)</td>
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<td>CAFA (7)</td>
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<td>SPINAF (8)</td>
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Adjusted-Dose Warfarin Compared with Placebo

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</table>

ACTIVE W: Stroke, Non-CNS Systemic Embolism, MI & Vascular Death

RR = 1.45
P = 0.0002

Lancet 2006; 367: 1903 - 12
RE-LY: Time to first intracranial bleed

First demonstration of a decrease in intracranial bleeding with a DOAC versus warfarin

This was confirmed in subsequent phase III trials with DOACs

Cumulative hazard rates

0.02

0.01

0.00

0.0

Years

0 0.5 1.0 1.5 2.0 2.5

Warfarin
Dabigatran etexilate 110 mg
Dabigatran etexilate 150 mg

RR, relative risk; RRR, relative risk reduction; CI, confidence interval; Sup, superior

Connolly et al., ESC meeting, Barcelona 2009
Stroke or systemic embolism (ITT)

**RE-LY** 2009

- Warfarin
- Dabigatran 110 mg
- Dabigatran 150 mg

No at risk:
- Warfarin: 6022
- Dab 110 mg: 6015
- Dab 150 mg: 6076

**ROCKET AF** 2011

- Warfarin
- Rivaroxaban

HR 0.88 (0.75, 1.03)

p<0.001 (non-inferiority)

p=0.12 (superiority)

**ARISTOTLE** 2011

- Warfarin
- Apixaban

21% RRR

A: 212 patients, 1.27% per year

W: 265 patients, 1.60% per year

p<0.001 (non-inferiority)

p=0.011 (superiority)

**ENGAGE AF-TIMI 48** 2013

- Warfarin
- Low-dose edoxaban
- High-dose edoxaban

No at risk:
- Warfarin: 7036
- High-dose edoxaban: 7035
- Low-dose edoxaban: 7034

All NOACs: Stroke or SEE

RE-LY
[Dabigatran 150 mg]

ROCKET AF

ARISTOTLE

ENGAGE AF-TIMI 48
[Edoxaban 60 mg]

Combined
[Random Effects Model]
N=58,541

Risk Ratio (95% CI)

Favours NOAC

Favours Warfarin

0.66 (0.53–0.82)

0.88 (0.75–1.03)

0.80 (0.67–0.95)

0.88 (0.75–1.02)

0.81 (0.73–0.91)

p<0.0001

Heterogeneity p=0.13

All NOACs: Major bleeding

Heterogeneity p=0.001

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>0.94 (0.82–1.07)</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>1.03 (0.90–1.18)</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>0.71 (0.61–0.81)</td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48</td>
<td>0.80 (0.71–0.90)</td>
</tr>
<tr>
<td>Combined</td>
<td>0.86 (0.73–1.00)</td>
</tr>
</tbody>
</table>

N=58,498

Atrial fibrillation

Valvular AF

Yes

No (i.e., non-valvular AF)

<65 years and lone AF (including females)

Assess risk of stroke (CHA₂DS₂-VASc score)

0

Oral anticoagulant therapy

Assess bleeding risk (HAS-BLED score)
Consider patient values and preferences

No antithrombotic therapy

≥2

NOAC
VKA

Oral anticoagulation over utilisation in low risk patients

Oral anticoagulation under utilisation in high risk patients
A minority of patients treated with VKAs in GARFIELD achieved adequate INR control over first 12 months

Preliminary data

Kakkar AK et al. Am Heart Assoc 2012;Abstr
LE HEUZERY J.Y. et al.
Thrombosis and Haemostasis 2014;
111 : 833 - 41
FEAR OF BLEEDING

Bruise

Epistaxis

Gingivorrhagia

... Hematuria
Menorrhagia
Rectorrhagia ...
Advantages of Direct Oral Anticoagulants

- No routine coagulation monitoring
- Less intracranial hemorrhages in the trials
- At least as effective as Warfarine
- Short half lifes
- Less inter and intraindividual variability of the effect
- Simplification or suppression of bridging
- No major interaction with food
- Fixed doses and more predictable response
Limitations of Direct Oral Anticoagulants

- No specific antidote at that time, difficulties in bleeding management
- Biological tests difficult to interpret
- Drug-drug interactions (PgP and CYP)
- Precaution +++ in patients with moderate renal failure (elderly), contraindication if more severe failure (creatinine clearance less than 30 ml/min with the Cockroft method)
- Therapeutics schemes to redefine in specific situations (for example coronary heart disease)
- Cost +++++++
Which is the best direct oral anticoagulant?

NO HEAD TO HEAD COMPARISON

- Slightly different populations in the trials: higher CHADS$_2$ score and more secondary prevention patients in ROCKET AF
- Ischaemic stroke reduction only with dabigatran 150 mg BID
- In the trials increase in gastrointestinal bleeding with dabigatran, rivaroxaban and high-dose edoxaban, not with apixaban and low-dose edoxaban
- Decrease in total mortality with apixaban and low-dose edoxaban
Which is the best direct oral anticoagulant?

- Discussion on dabigatran and myocardial infarction increased risk.
- Lower discontinuation rate with apixaban in ARISTOTLE and edoxaban in ENGAGE AF.
- Different rates of renal excretion (dabigatran > edoxaban > rivaroxaban > apixaban).
- Higher difficulty in switching QD vitamin K antagonist for a BID new oral anticoagulant than for a QD one.
Comparisons?
Pointers towards which DOAC to choose

1. **Previous stroke (secondary prevention)**
   - Consider best investigated agent or greatest reduction of 2\textsuperscript{nd} stroke
   - **Rivaroxaban**
   - **Apixaban**

2. **Previous GI bleeding or high risk**
   - Consider agent with the lowest reported incidence of GI bleed
   - **Apixaban**
   - [Edoxaban]

3. **High risk of ischaemic stroke, low bleeding risk**
   - Consider agent / dose with the best reduction of ischaemic stroke
   - **Dabigatran 150**

4. **High risk of bleeding, e.g. HAS-BLED $\geq$3**
   - Consider agent / dose with the lowest incidence of bleeding
   - **Dabigatran 110**
   - **Apixaban**
   - [Edoxaban]

5. **CAD, previous MI or high-risk for ACS/MI**
   - Consider agent with a positive effect in ACS
   - **Rivaroxaban**

6. **Renal impairment**
   - Consider agent least dependent on renal function
   - **Apixaban**
   - **Rivaroxaban**

7. **GI upset / disorders**
   - Consider agent / dose with no reported GI effects
   - **Apixaban**
   - **Rivaroxaban**
   - [Edoxaban]

8. **Patient preference**
   - Consider once-daily formulation
   - **Rivaroxaban**
   - [Edoxaban]

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*Adapted from Savelieva and Camm. Clin Cardiol 2014;37:32–47*
# Causes of Death and Influencing Factors in Patients With Atrial Fibrillation

A Competing-Risk Analysis From the Randomized Evaluation of Long-Term Anticoagulant Therapy Study

Eloi Marijon, MD, PhD; Jean-Yves Le Heuzey, MD; Stuart Connolly, MD; Sean Yang, MSc; Janice Pogue, PhD; Martina Brueckmann, MD; John Eikelboom, MD; Ellison Themeles, BA; Michael Ezekowitz, MB, ChB, DPhil; Lars Wallentin, MD, PhD; Salim Yusuf, FRCP, DPhil; for the RE-LY Investigators

## Causes of death in the RE-LY® trial – descriptive data

<table>
<thead>
<tr>
<th>Causes of death in RE-LY®</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>1371</td>
<td>100.00</td>
</tr>
<tr>
<td><strong>Cardiovascular death</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>512</td>
<td>37.35</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>305</td>
<td>22.25</td>
</tr>
<tr>
<td>Progressive heart failure</td>
<td>207</td>
<td>15.10</td>
</tr>
<tr>
<td><strong>Vascular</strong></td>
<td>139</td>
<td>10.14</td>
</tr>
<tr>
<td>Stroke/peripheral embolism</td>
<td>96</td>
<td>7.00</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>39</td>
<td>2.84</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>4</td>
<td>0.29</td>
</tr>
<tr>
<td>Others/unknown</td>
<td>191</td>
<td>13.93</td>
</tr>
<tr>
<td><strong>Noncardiovascular death</strong></td>
<td>491</td>
<td>35.81</td>
</tr>
<tr>
<td>Undetermined death</td>
<td>38</td>
<td>2.77</td>
</tr>
</tbody>
</table>

RE-LY, Randomized Evaluation of Long-term anticoagulant therapy
Effect of Nonfatal Stroke Event to Predict Overall Mortality and Specific Mode of Death

<table>
<thead>
<tr>
<th>Independent significant predictors for vascular mortalities</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke-related death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal major bleeding during follow-up</td>
<td>4.35</td>
<td>2.58–7.34</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>2.37</td>
<td>1.50–3.76</td>
<td>0.0002</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2.30</td>
<td>1.44–3.66</td>
<td>0.0005</td>
</tr>
<tr>
<td>Age &gt; 71 years</td>
<td>2.04</td>
<td>1.19–3.50</td>
<td>0.0097</td>
</tr>
<tr>
<td>No proton-pump inhibitor</td>
<td>2.77</td>
<td>1.11–7.14</td>
<td>0.0280</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>1.73</td>
<td>1.01–2.97</td>
<td>0.0470</td>
</tr>
<tr>
<td><strong>Hemorrhage-related death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal stroke during follow-up</td>
<td>3.80</td>
<td>1.07–13.5</td>
<td>0.0390</td>
</tr>
</tbody>
</table>

The strongest independent predictor of stroke-related deaths was nonfatal major hemorrhage, and of hemorrhage-related deaths was nonfatal stroke.

HR, hazard ratio; CI, confidence interval.

Marijon E., Le Heuzey J.Y. et al. 2013
1- Atrial fibrillation is one of the main causes of embolic strokes, due to a clot mainly coming from the left atrial appendage.

2- Nevertheless, in some cases the embolism is coming from other sources (aortic arch, carotid arteries ...) in patients with the same risk factors.

3- And finally in other patients stroke is not embolic and not directly related to atrial fibrillation but occurs in patients with the same profile in terms of thromboembolic risk factors.

4- Antithrombotic drugs have demonstrated, in randomised clinical trials, an efficacy for decreasing the number of strokes (all together) in atrial fibrillation patients.
CONCLUSIONS (II)

5- This efficacy is high for Warfarin (other VKAs ?) and DOACs, modest for antiplatelet drugs, probably by decreasing cardioembolic strokes (and the other ischemic strokes ?)

6- DOACs are at least non inferior to VKAs, they were superior in some trials and they dramatically decreased the number of intracranial hemorrhages in all

7- Concerning mortality, despite modest decreases observed with DOACs, as compared to Warfarin, the proportion of deaths due to stroke in atrial fibrillation patients remains low, as compared to sudden cardiac deaths and deaths due to heart failure
Atrial Fibrillation factor of cardioembolic stroke: interest +++ of antithrombotic drugs (anticoagulants, not antiplatelets)

Atrial fibrillation marker of stroke risk: interest of antithrombotics? needs more researches and evidence based demonstrations