Long term anticoagulant therapy in patients with atrial fibrillation at high risk of stroke: a new scenario after RE-LY trial

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Disclosures: none
It has been estimated that 2.2 million people in America and 4.5 million in the European Union have paroxysmal or persistent AF.

The estimated prevalence of AF is 0.4% to 1% in the general population, increasing with age.

Accounts for approximately 1/3 of hospitalizations for cardiac rhythm disturbances.
AF Prevalence: Age and Gender

Prevalence of atrial fibrillation with age

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;55</td>
<td>Women 0.1%, Men 0.3%</td>
</tr>
<tr>
<td>55-59</td>
<td>Women 0.5%, Men 0.8%</td>
</tr>
<tr>
<td>60-64</td>
<td>Women 1.2%, Men 2.1%</td>
</tr>
<tr>
<td>65-69</td>
<td>Women 3.3%, Men 5.4%</td>
</tr>
<tr>
<td>70-74</td>
<td>Women 5.5%, Men 8.3%</td>
</tr>
<tr>
<td>75-79</td>
<td>Women 7.7%, Men 11.6%</td>
</tr>
<tr>
<td>80-84</td>
<td>Women 10.2%, Men 15.3%</td>
</tr>
<tr>
<td>&gt;85</td>
<td>Women 11.6%, Men 17.2%</td>
</tr>
</tbody>
</table>

JAMA 2001; 285: 2370
### Patient characteristics
Data from Euro Heart Survey on Atrial Fibrillation

<table>
<thead>
<tr>
<th></th>
<th>First detected</th>
<th>Paroxymal</th>
<th>Persistent</th>
<th>Permanent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>65</td>
<td>64</td>
<td>66</td>
<td>71</td>
</tr>
<tr>
<td><strong>Female gender (%)</strong></td>
<td>43</td>
<td>43</td>
<td>39</td>
<td>43</td>
</tr>
<tr>
<td><strong>Hypertension (%)</strong></td>
<td>67</td>
<td>62</td>
<td>66</td>
<td>64</td>
</tr>
<tr>
<td><strong>CAD (%)</strong></td>
<td>32</td>
<td>34</td>
<td>29</td>
<td>36</td>
</tr>
<tr>
<td><strong>Heart failure (%)</strong></td>
<td>26</td>
<td>23</td>
<td>35</td>
<td>49</td>
</tr>
<tr>
<td><strong>Valvular heart disease (%)</strong></td>
<td>21</td>
<td>19</td>
<td>24</td>
<td>40</td>
</tr>
<tr>
<td><strong>Diabetes (%)</strong></td>
<td>19</td>
<td>15</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td><strong>Previous tromboembolism (%)</strong></td>
<td>9</td>
<td>11</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td><strong>Stroke (%)</strong></td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>9</td>
</tr>
</tbody>
</table>
Consequences of atrial fibrillation

Thromboembolism
- Risk of stroke ↑ 5-fold

Mortality
- Risk ↑ 2 fold in CV disease

Reduction of quality of life

Impaired hemodynamics
- Heart failure

Hospitalization
- Risk ↑ 2-3-fold
Management of atrial fibrillation

Hemodynamic stabilization
  Rate – Rhythm control

Thromboembolism prevention
  Antithrombotic Therapy
Risk stratification
Stroke Risk in Atrial Fibrillation

Data from Framingham Heart Study

Stroke Rate (% per year)

Age (years)

50-59
60-69
70-79

Stroke 1991;22;983-988.
## Risk Stratification in AF

### Stroke Risk Factors

#### High-Risk Factors
- Mitral stenosis
- Prosthetic heart valve
- History of stroke or TIA

#### Moderate-Risk Factors
- Age >75 years
- Hypertension
- Diabetes mellitus
- Heart failure or ↓ LV function

#### Less Validated Risk Factors
- Age 65–75 years
- Coronary artery disease
- Female gender
- Thyrotoxicosis

#### Dubious Factors
- Duration of AF
- Pattern of AF
- Left atrial diameter

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AHA/ACC/ESC guidelines on atrial fibrillation 2006
Nonvalvular Atrial Fibrillation

Stroke Rates Without Anticoagulation According to Isolated Risk Factors

- Prior Stroke/TIA
- Age > 75 years
- Hypertension
- Diabetes
- Heart Failure ↓ LVEF

**The CHADS$_2$ Index**

*Stroke Risk Score for Atrial Fibrillation*

<table>
<thead>
<tr>
<th>Score (points)</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive Heart failure 1</td>
<td>32</td>
</tr>
<tr>
<td>Hypertension 1</td>
<td>65</td>
</tr>
<tr>
<td>Age &gt;75 years 1</td>
<td>28</td>
</tr>
<tr>
<td>Diabetes mellitus 1</td>
<td>18</td>
</tr>
<tr>
<td>Stroke or TIA 2</td>
<td>10</td>
</tr>
<tr>
<td>Moderate-High risk $\geq2$</td>
<td>50-60</td>
</tr>
<tr>
<td>Low risk 0-1</td>
<td>40-50</td>
</tr>
</tbody>
</table>

# The CHADS\textsubscript{2} Index

*Stroke Risk Score for Atrial Fibrillation*

<table>
<thead>
<tr>
<th>Score (points)</th>
<th>Risk of Stroke (%/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9</td>
</tr>
<tr>
<td>1</td>
<td>2.8</td>
</tr>
<tr>
<td>2</td>
<td>4.0</td>
</tr>
<tr>
<td>3</td>
<td>5.9</td>
</tr>
<tr>
<td>4</td>
<td>8.5</td>
</tr>
<tr>
<td>5</td>
<td>12.5</td>
</tr>
<tr>
<td>6</td>
<td>18.2</td>
</tr>
</tbody>
</table>

Approximate Risk threshold for Anticoagulation: 3% / year

Antithrombotic therapy in atrial fibrillation

ASA

Warfarin

ASA Clopidogrel

New antithrombotic drugs
Antiplatelet therapy vs placebo


Risk Reduction (%)

ASA

Relative RR vs. placebo 19%
Absolute risk reduction primary 0.8%/yr
Absolute risk reduction secondary 2.5%/yr
NNT primary prevention 125
NNT secondary prevention 40

Warfarin therapy vs placebo

Relative RR vs. placebo 64%
Absolute risk reduction primary 2.7%/yr
Absolute risk reduction secondary 8.4%/yr
NNT primary prevention 37
NNT secondary prevention 12

ASA + Clopidogrel

Documented AF + ≥1 risk factor for Stroke

ACTIVE W
ASA + Clopidogrel versus VKA
Failure of clopidogrel/ASA to prevent stroke, embolism, MI or vascular death compared to anticoagulant therapy

Lancet 2006; 367:1903-1912
## Antithrombotic Therapy for Atrial Fibrillation

**ACC/AHA/ESC Guidelines 2006**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Recommended Therapy</th>
</tr>
</thead>
</table>
| No risk factors  
CHADS$_2$ = 0 | Aspirin, 81-325 mg qd |
| One moderate risk factor  
CHADS$_2$ = 1 | Aspirin, 81-325 mg/d or Warfarin (INR 2.0-3.0, target 2.5) |
| Any high risk factor or  
>1 moderate risk factor  
CHADS$_2$ $>$ 2 or Mitral stenosis | Warfarin (INR 2.0-3.0, target 2.5) |
| Prosthetic valve | Warfarin (INR 2.5-3.5, target 3.0) |
# Limitations of Warfarin

<table>
<thead>
<tr>
<th>Limitation</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow onset of action</td>
<td>Overlap with a parenteral anticoagulant</td>
</tr>
<tr>
<td>Genetic variation in metabolism</td>
<td>Variable dose requirements</td>
</tr>
<tr>
<td>Multiple food and drug interactions</td>
<td>Frequent coagulation monitoring</td>
</tr>
<tr>
<td>Narrow therapeutic index</td>
<td>Frequent coagulation monitoring</td>
</tr>
</tbody>
</table>

- **Risk of fatal bleeding (1.5% per year)**
Adequacy of Anticoagulation in Patients with AF in Primary Care Practice

- **Warfarin**: 50%
- **Contraindication**: 25%
- **No compliance**: 25%
- **Therapeutic range**: 50%
  - **Higher**: 20%
  - **Lower**: 30%

New Oral Anticoagulants for Stroke Prevention in AF
PHASE III TRIALS IN PATIENTS WITH AF

Direct inhibitors of Xa

Rivaroxaban
→ ROCKET-AF (ongoing)
Apixaban
→ ARISTOTLE (ongoing)

Direct inhibitors of thrombin

Dabigatran
→ RE-LY
Ximelagatran
→ SPORTIF
Dabigatran etexilate (Boeringher Ingelheim) is not approved by the FDA.

Dabigatran etexilate is approved as Pradaxa® in over 28 countries for the primary prevention of venous thromboembolic events (blood clots) in adults who have undergone elective total hip or elective total knee replacement surgery.
Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*
## Comparison of Features of Dabigatran With Those of Warfarin

<table>
<thead>
<tr>
<th>Features</th>
<th>Warfarin</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Dosing</td>
<td>Variable</td>
<td>Fixed</td>
</tr>
<tr>
<td>Food effect</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Many</td>
<td>Few</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Half-life</td>
<td>Long</td>
<td>Short</td>
</tr>
<tr>
<td>Antidote</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
New treatment superior

SUPERIORITY

NON INFERIORITY

EQUIVALENCE

Standard treatment superior
Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Follow up (median): 2 years

18,113 patients with atrial fibrillation and a risk for stroke

- Dabigatran 110 mg
- Dabigatran 150 mg
- Warfarin sec INR

NEJM 2009; 12(361):139
## RE-LY: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dabigatran 110 mg</th>
<th>Dabigatran 150 mg</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>6015</td>
<td>6076</td>
<td>6022</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>71.4</td>
<td>71.5</td>
<td>71.6</td>
</tr>
<tr>
<td>Male (%)</td>
<td>64.3</td>
<td>63.2</td>
<td>63.3</td>
</tr>
<tr>
<td>CHADS2 score (mean)</td>
<td>2.1</td>
<td>2.2</td>
<td>2.1</td>
</tr>
<tr>
<td>0-1 (%)</td>
<td>32.6</td>
<td>32.2</td>
<td>30.9</td>
</tr>
<tr>
<td>2 (%)</td>
<td>34.7</td>
<td>35.2</td>
<td>37.0</td>
</tr>
<tr>
<td>3+ (%)</td>
<td>32.7</td>
<td>32.6</td>
<td>32.1</td>
</tr>
<tr>
<td>Prior stroke/TIA (%)</td>
<td>19.9</td>
<td>20.3</td>
<td>19.8</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>16.8</td>
<td>16.9</td>
<td>16.1</td>
</tr>
<tr>
<td>CHF (%)</td>
<td>32.2</td>
<td>31.8</td>
<td>31.9</td>
</tr>
<tr>
<td>Baseline ASA (%)</td>
<td>40.0</td>
<td>38.7</td>
<td>40.6</td>
</tr>
<tr>
<td>Warfarin Naïve (%)</td>
<td>49.9</td>
<td>49.8</td>
<td>51.4</td>
</tr>
</tbody>
</table>

Connolly et al., *NEJM*, 2009
Time in Therapeutic Range (TTR) with Warfarin in the RE-LY Trial

64%

As in other trials...
Dabigatran versus Warfarin in Patients with AF

**PRIMARY OUTCOME**

**Efficacy end-point**

<table>
<thead>
<tr>
<th></th>
<th>Systemic embolism or stroke</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin - adjusted dose</td>
<td>1.69</td>
<td>1.2</td>
</tr>
<tr>
<td>Dabigatran - 110 mg</td>
<td>1.53</td>
<td>1.34</td>
</tr>
<tr>
<td>Dabigatran - 150 mg</td>
<td>1.11</td>
<td>0.92</td>
</tr>
</tbody>
</table>
**RE-LY: Systemic embolism or stroke**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>HR</th>
<th>Non-inf p-value</th>
<th>Sup p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 110 vs. Warfarin</td>
<td>0.91</td>
<td>&lt;0.001</td>
<td>0.34</td>
</tr>
<tr>
<td>Dabigatran 150 vs. Warfarin</td>
<td>0.66</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Margin</strong></td>
<td><strong>1.46</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Connolly et al., NEJM, 2009
RELY: results by CHADS₂ Score

Dabigatran 110 vs. Warfarin

CHADS₂ 1

CHADS₂ 2

CHADS₂ 3+

Dabigatran 150 vs. Warfarin

p=0.41

p=0.81
### RE-LY: Secondary Efficacy Outcomes According to Treatment Group

<table>
<thead>
<tr>
<th>Event</th>
<th>Warfarin</th>
<th>Dabigatran 110 mg</th>
<th>Dabigatran 150 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>4.13</td>
<td>3.75</td>
<td>3.64</td>
</tr>
<tr>
<td>Vascular death</td>
<td>2.69</td>
<td>2.43</td>
<td>2.28</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.53</td>
<td>0.72</td>
<td>0.74</td>
</tr>
</tbody>
</table>

**Increased myocardial infarction:** Dabigatran harmful or Warfarin protective?

Dabigatran versus Warfarin in Patients with AF

BLEEDINGS

<table>
<thead>
<tr>
<th></th>
<th>Major bleeding</th>
<th>Hemorrhagic stroke</th>
<th>Gastrointestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin - adjusted dose</td>
<td>3.36</td>
<td>0.38</td>
<td>1.02</td>
</tr>
<tr>
<td>Dabigatran - 110 mg</td>
<td>2.71</td>
<td>0.1</td>
<td>1.12</td>
</tr>
<tr>
<td>Dabigatran - 150 mg</td>
<td>3.11</td>
<td>0.12</td>
<td>1.51</td>
</tr>
</tbody>
</table>

Dabigatran 150 mg increased G-I bleeding
RR = 1.50

Safety end-point
Net clinical benefit

- Major vascular events
- Major bleeding
- Death
Concerns with dabigatran

**Dyspepsia:**
12% in dabigatran group

**Drug interaction:**
P-glycoprotein inhibitors
Amiodarone
Verapamil
Quinidine

**Renal function**
Elderly
Low weight

**Hepatotoxicity:**
2% in dabigatran group
Differences in price

Warfarin (1 month): $35
(including cost of monitoring)

Dabigatran 110 mg (1 month): $339

Can we afford RE-LY?

Possible dabigatran scenarios in AF

**Lower-dose regimen**

- Elderly
- Renal insufficiency
- Lower stroke risk (CHADS$_2$ score of 1)

**Higher-dose regimen**

- Higher stroke risk (CHADS$_2$ score ≥ 2)
Conclusions

• The past twenty years have led to a considerable improvement in the antithrombotic prophylaxis of AF

• Warfarin has demonstrated his superiority compared with treatment with both ASA alone and ASA plus clopidogrel
Conclusions

- Dabigatran (as other new drugs) may represent a therapeutic revolution that will likely overcome conventional therapy offering both patients and clinicians a better tolerability and manageability.

- In this way, we hope this new drug(s) will bring effective anticoagulation to a wider segment of the population at risk and help to prevent strokes.