Atrial fibrillation and stroke
- Current treatment -
Atrial fibrillation (AF)

- AF is the most common heart rhythm disturbance\(^1\)
- It is estimated 1 in 4 individuals aged 40 years will develop AF\(^1\)
- In 2007, 6.3 million people in the US, Japan, Germany, Italy, Spain, France and UK were living with diagnosed AF\(^2\)
- Due to the aging population, this number is expected to double within 30 years\(^3\)

AF prevalence increases with age

AF increases the risk of stroke

- AF is associated with a pro-thrombotic state
  - ~5 fold increase in stroke risk\(^1\)

- Risk of stroke is the same in AF patients regardless of whether they have paroxysmal or sustained AF\(^2,3\)

- Cardioembolic stroke has a 30-day mortality of 25\(\%\)\(^{4}\)

- AF-related stroke has a 1-year mortality of ~50\(\%\)\(^{5}\)

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Effect of first ischemic stroke in patients with AF (n=597)\textsuperscript{1}

Stroke

- Up to 3 million people worldwide suffer strokes related to AF each year\(^1\)\(^-\)\(^3\)

- AF-related strokes tend to be especially severe and disabling with half of patients dying within 1 year\(^3\)

Economic burden of AF

The American Heart Association estimates that the direct and indirect cost of stroke in the US is $65.5 billion\(^1\)

A German Registry has shown that the overall first-year cost of AF is €18,517\(^2\)

A 15% reduction in stroke-related hospital admissions in the UK would save an estimated £30 million/year\(^3\)

AF-related stroke is preventable

- 2/3 of strokes due to AF are preventable with appropriate anticoagulant therapy with a vitamin-K-antagonist (INR 2-3)\(^1\)

- Anticoagulation with a vitamin-K-antagonist (VKA) is recommended for patients with more than 1 moderate risk factor\(^2\)

- A meta-analysis of 29 trials in 28,044 patients showed that adjusted-dose warfarin results in a reduction in ischaemic stroke and in all-cause mortality\(^1\)

Effect of VKA compared to placebo

Stroke: 67%
Death: 26%

Narrow therapeutic range with VKA

The anticoagulant effect of vitamin K antagonists are optimized when therapeutic doses are maintained within a very narrow range.

INR control: clinical trials v. clinical practice

INR* control in clinical trial versus clinical practice (TTR**)


<table>
<thead>
<tr>
<th>INR</th>
<th>Clinical trial</th>
<th>Clinical practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.0</td>
<td>25%</td>
<td>66%</td>
</tr>
<tr>
<td>2.0-3.0</td>
<td>38%</td>
<td>44%</td>
</tr>
<tr>
<td>&gt;3.0</td>
<td>9%</td>
<td>18%</td>
</tr>
</tbody>
</table>

*INR = International normalized ratio

** TTR = Time in Therapeutic Range (INR2.0-3.0)
Limitations of VKA therapy

VKA therapy has several limitations that make it difficult to use in practice

- Unpredictable response
- Narrow therapeutic window (INR range 2-3)
- Routine coagulation monitoring
- Slow onset/offset of action
- Frequent dose adjustments
- Numerous food-drug interactions
- Numerous drug-drug interactions
- Warfarin resistance

Management of AF in clinical practice: prescription of vitamin K antagonists

- n = 23,657
  Medicare cohort, U.S.A.

- n = 5,333
  EuroHeart survey

- n = 11,379
  ATRIA cohort (managed care system, California, U.S.A.)
  Go AS, et al. JAMA 2003; 290: 2685
Dabigatran etexilate is a novel, small molecule, reversible, direct thrombin inhibitor.

For oral administration the prodrug dabigatran etexilate was developed.


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Dabigatran etexilate: a novel direct thrombin inhibitor

- Oral prodrug, converted to dabigatran, a potent reversible direct thrombin inhibitor (DTI)
- Half life of 12-17 h,
- ~ 80% renally excreted
- 6.5% bioavailability
- Rapid onset of action
- Predictable and consistent anticoagulant effects
- Low potential for drug-drug interactions, no drug-food interactions
- No requirement for routine coagulation monitoring
- Potent antithrombotic effects are achieved with direct thrombin inhibitors by specifically blocking the activity of thrombin (both free and clot-bound), the central enzyme in the process responsible for clot (thrombus) formation

The RE-LY® Study: Randomized Evaluation of Long-term anticoagulant therapy

Dabigatran Compared to Warfarin in 18,113 Patients with Atrial Fibrillation at Risk of Stroke


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RE-LY® – largest AF outcomes trial

**RE-LY®: Randomised Evaluation of Long term anticoagulant therapy**

- 18,113 patients randomised during 2 years\(^1,2\)
- 50% of enrolled patients are naïve to previous oral AC
- Median treatment duration: 2 years
- 951 centres in 44 countries
- Dec 2005 to March 2009
- Results first presented at ESC congress 2009 and published online in New England Journal of Medicine on Aug. 30th 2009


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Dabigatran etexilate is in clinical development and not licensed for clinical use in stroke prevention for patients with atrial fibrillation.

DOI 10.1056/NEJMoia0905561
Primary objective: To establish the non-inferiority of dabigatran etexilate to warfarin

Minimum 1 year follow-up, maximum of 3 years and mean of 2 years of follow-up

DOI 10.1056/NEJMoa0905561

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RE-LY® – inclusion criteria

1) Documented atrial fibrillation and

2) One additional risk factor for stroke:
   a) History of previous stroke, TIA, or systemic embolism
   b) LVEF less than 40%
   c) Symptomatic Heart Failure, NYHA Class II or greater
   d) Age of 75 years or more
   e) Age of 65 years or more and one of the following additional risk factors: Diabetes mellitus, CAD or Hypertension

DOI 10.1056/NEJMoa0905561

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RE-LY® – outcome measures

<table>
<thead>
<tr>
<th>Primary efficacy endpoint</th>
<th>Secondary efficacy endpoints</th>
<th>Safety criteria include</th>
</tr>
</thead>
<tbody>
<tr>
<td>All stroke (ischaemic + haemorrhagic) and systemic embolism</td>
<td>All stroke (ischaemic + haemorrhagic)</td>
<td>Bleeding events (major and minor)</td>
</tr>
<tr>
<td></td>
<td>Systemic embolism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All death</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All death</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All stroke (ischaemic + haemorrhagic)</td>
<td>Intracranial haemorrhage</td>
</tr>
<tr>
<td></td>
<td>Systemic embolism</td>
<td>Cerebral haemorrhage</td>
</tr>
<tr>
<td></td>
<td>Pulmonary embolism</td>
<td>Subdural haematoma</td>
</tr>
<tr>
<td></td>
<td>Acute MI</td>
<td>Subarachnoid haemorrhage</td>
</tr>
<tr>
<td></td>
<td>Vascular death (incl. deaths from bleeding)</td>
<td>Elevations in liver enzymes or hepatic dysfunction</td>
</tr>
</tbody>
</table>

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## 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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1 (%)</td>
<td>2.1</td>
<td>2.2</td>
<td>2.1</td>
</tr>
<tr>
<td>2 (%)</td>
<td>32.6</td>
<td>32.2</td>
<td>30.9</td>
</tr>
<tr>
<td>3+ (%)</td>
<td>34.7</td>
<td>35.2</td>
<td>37.0</td>
</tr>
<tr>
<td>CHF (%)</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>32.3</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>50.1</td>
<td>50.2</td>
<td>48.6</td>
</tr>
</tbody>
</table>


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99.9% complete follow-up
  - 20 patients of 18113 lost to follow-up

Percent Time in Therapeutic Range (TTR)
  - 67% warfarin-experienced
  - 61% warfarin-naïve
Stroke or systemic embolism (SSE)

Dabigatran 110 mg vs. warfarin

Dabigatran 150 mg vs. warfarin

Noninferiority p-value <0.001 Superiority p-value 0.34

Margin = 1.46

HR (95% CI)


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Total bleeding rates

RR 0.78 (95% CI: 0.74–0.83)  
p<0.001 (sup)

RR 0.91 (95% CI: 0.86–0.97)  
p=0.002 (sup)

D110 mg BID  
14.62  
1740 / 6,015  

D150 mg BID  
16.42  
1977 / 6,076  

Warfarin  
18.15  
2142 / 6,022

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Life threatening bleeding

RR 0.68 (95% CI: 0.55–0.83)  
RRR 32%

p<0.001 (sup)

RR 0.81 (95% CI: 0.66–0.99)  
RRR 19%

p=0.037 (sup)

1.22  
1.45  
1.80

% per year

D110 mg BID  
D150 mg BID  
Warfarin

145 / 6,015  
175 / 6,076  
212 / 6,022

RRR 32%  
RRR 19%

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Intra-cranial bleeding rates

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Cumulative hazard rates

Years

Warfarin
Dabigatran etexilate 110 mg
Dabigatran etexilate 150 mg

RR 0.40
(95% CI: 0.27–0.60)
p<0.001 (Sup)

RR 0.31
(95% CI: 0.20–0.47)
p<0.001 (Sup)

RRR 60%
RRR 69%

RR, Relative risk; CI, confidence interval; Sup, superior

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