Novel Anticoagulants in Stroke Prevention in Patients with Atrial Fibrillation
The Past, the Present and the Future

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Conflict of Interest Statement
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- MindFrame
- Fresenius
- CoAxia
- Abbott
- Novartis
- Schering
- Janssen-Cilag
- Sanofi
- MSD
- Astra-Zeneca
- GlaxoSmithKline
- Pfizer
- Paion
- Solvay
- Schering Plough
- Medtronic
- Lundbeck
- Syngis
- Tacrelis
- Boehringer Ingelheim
- D-Pharm
- BMS
- Bayer
- Wyeth
- Knoll
- Servier
- EV3
- J & J
Goals for anticoagulation therapy in AF

Prevent ischaemic stroke

Minimize haemorrhagic stroke (minimize risk of ICH)
Role of the Neurologist

- The neurologist will see the consequences of
  - Non-treatment
  - Undertreatment (aspirin)
  - Poor treatment (INR < 2.0)

  As ischemic stroke on his stroke unit

- The neurologist will see the consequences of
  - Overtreatment (INR > 4.5)

  As intracranial hemorrhage on the critical care unit
Novel Anticoagulants in Stroke Prevention in Patients with Atrial Fibrillation

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Most ischaemic strokes occur in patients who are suboptimally anticoagulated

Data from a prospective stroke registry of 597 patients with AF at high risk of stroke (*1 high-risk factor or ≥1 moderate-risk factor according to American College of Chest Physicians guidelines)
Limitations of traditional antithrombotics prevent effective stroke prevention

- **Aspirin**: insufficient protection in high-risk patients\(^1\)
  - Limited stroke risk reduction (relative risk reduction 19\%)\(^1\)

- **Vitamin-K-antagonists (e.g. warfarin)**:
  - Narrow therapeutic range,
  - Food/drug interactions,
  - Slow onset/offset of action,
  - Regular coagulation monitoring\(^2,3\)
  - High risk of bleeding\(^4\)

VKA = Vitamin K antagonist

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Not head-to-head comparison – no clinical conclusions can be drawn – adapted from references 1–5

*Edoxaban dose halved (from 60 mg to 30 mg OD in high dose group; from 30 mg to 15 mg OD in low dose group) if CrCl 30–50 mL/min, weight <60kg, or concomitant verapamil, quinidine or dronedarone

AT = as treated; BID = twice daily; CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat

Ischaemic stroke

<table>
<thead>
<tr>
<th>Treatment</th>
<th>NOAC</th>
<th>Warfarin</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 110 mg BID (ITT)^1-3</td>
<td>152 (1.28)</td>
<td>134 (1.14)</td>
<td>1.13</td>
<td>0.89–1.42</td>
</tr>
<tr>
<td>Dabigatran 150 mg BID (ITT)^1-3</td>
<td>103 (0.86)</td>
<td>134 (1.14)</td>
<td>0.75</td>
<td>0.58–0.97</td>
</tr>
<tr>
<td>Rivaroxaban (Safety AT)^4</td>
<td>149 (1.34)</td>
<td>161 (1.42)</td>
<td>0.94</td>
<td>0.75–1.17</td>
</tr>
<tr>
<td>Apixaban* (ITT)^5</td>
<td>140 (1.54)</td>
<td>136 (1.50)</td>
<td>1.02</td>
<td>0.81–1.29</td>
</tr>
<tr>
<td>Edoxaban 60 mg OD** (ITT)^6</td>
<td>236 (1.25)</td>
<td>235 (1.25)</td>
<td>1.00</td>
<td>0.83–1.19</td>
</tr>
<tr>
<td>Edoxaban 30 mg OD** (ITT)^6</td>
<td>333 (1.77)</td>
<td>235 (1.25)</td>
<td>1.41</td>
<td>1.19–1.67</td>
</tr>
</tbody>
</table>

Not head-to-head comparison – no clinical conclusions can be drawn – adapted from references 1–6

*Revised data; re-categorized following original publication

**Edoxaban dose halved (from 60 mg to 30 mg OD in high dose group; from 30 mg to 15 mg OD in low dose group) if CrCl 30–50 mL/min, weight <60kg, or concomitant verapamil, quinidine or dronedarone

AT = as treated; BID = twice daily; HR = hazard ratio; ITT = intention-to-treat; NOAC = novel oral anticoagulant

Haemorrhagic stroke

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of events (%/yr)</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran 110 mg BID (ITT)^1,2</strong></td>
<td>NOAC 14 (0.12)</td>
<td>0.31</td>
<td>0.17–0.56</td>
</tr>
<tr>
<td></td>
<td>Warfarin 45 (0.38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dabigatran 150 mg BID (ITT)^1,2</strong></td>
<td>NOAC 12 (0.10)</td>
<td>0.26</td>
<td>0.14–0.49</td>
</tr>
<tr>
<td></td>
<td>Warfarin 45 (0.38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rivaroxaban (Safety AT)^3</strong></td>
<td>NOAC 29 (0.26)</td>
<td>0.59</td>
<td>0.37–0.93</td>
</tr>
<tr>
<td></td>
<td>Warfarin 50 (0.44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Apixaban (ITT)^4</strong></td>
<td>NOAC 40 (0.24)</td>
<td>0.51</td>
<td>0.35–0.75</td>
</tr>
<tr>
<td></td>
<td>Warfarin 78 (0.47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em><em>Edoxaban 60 mg OD</em> (ITT)^5</em>*</td>
<td>NOAC 49 (0.26)</td>
<td>0.54</td>
<td>0.38–0.77</td>
</tr>
<tr>
<td></td>
<td>Warfarin 90 (0.47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em><em>Edoxaban 30 mg OD</em> (ITT)^5</em>*</td>
<td>NOAC 30 (0.16)</td>
<td>0.33</td>
<td>0.22–0.50</td>
</tr>
<tr>
<td></td>
<td>Warfarin 90 (0.47)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Not head-to-head comparison – no clinical conclusions can be drawn – adapted from references 1–5

*Edoxaban dose halved (from 60 mg to 30 mg OD in high dose group; from 30 mg to 15 mg OD in low dose group) if CrCl 30–50 mL/min, weight <60kg, or concomitant verapamil, quinidine or dronedarone

AT = as treated; BID = twice daily; HR = hazard ratio; ITT = intention-to-treat; NOAC = novel oral anticoagulant

### Intracranial bleeding

<table>
<thead>
<tr>
<th>Drug</th>
<th>NOAC</th>
<th>Warfarin</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran 110 mg BID</strong></td>
<td>27 (0.23)</td>
<td>90 (0.76)</td>
<td>0.30</td>
<td>0.19–0.45</td>
</tr>
<tr>
<td><strong>ITT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dabigatran 150 mg BID</strong></td>
<td>38 (0.32)</td>
<td>90 (0.76)</td>
<td>0.41</td>
<td>0.28–0.60</td>
</tr>
<tr>
<td><strong>ITT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>55 (0.5)</td>
<td>84 (0.7)</td>
<td>0.67</td>
<td>0.47–0.93</td>
</tr>
<tr>
<td><strong>Safety AT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td>52 (0.33)</td>
<td>122 (0.80)</td>
<td>0.42</td>
<td>0.30–0.58</td>
</tr>
<tr>
<td>(patients who received ≥1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dose of study drug)**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Edoxaban 60 mg OD</strong></td>
<td>61 (0.39)</td>
<td>132 (0.85)</td>
<td>0.47</td>
<td>0.34–0.63</td>
</tr>
<tr>
<td><strong>Safety on-treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Edoxaban 30 mg OD</strong></td>
<td>41 (0.26)</td>
<td>132 (0.85)</td>
<td>0.30</td>
<td>0.21–0.43</td>
</tr>
<tr>
<td><strong>Safety on-treatment)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Not head-to-head comparison – no clinical conclusions can be drawn – adapted from references 1–5

*Edoxaban dose halved (from 60 mg to 30 mg OD in high dose group; from 30 mg to 15 mg OD in low dose group) if CrCl 30–50 mL/min, weight <60kg, or concomitant verapamil, quinidine or dronedarone

AT = as treated; BID = twice daily; HR = hazard ratio; ITT = intention-to-treat; NOAC = novel oral anticoagulant

RE-LY® prior stroke subgroup analysis: time to stroke or systemic embolism in patients with/without previous stroke or TIA

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran 110 mg BID</th>
<th>Dabigatran 150 mg BID</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior stroke/TIA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number at risk (prior stroke)</td>
<td>1195</td>
<td>1159</td>
<td>1131</td>
</tr>
<tr>
<td></td>
<td>Dabigatran 150 mg BID</td>
<td>1233</td>
<td>1200</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1195</td>
<td>1159</td>
<td>1125</td>
</tr>
<tr>
<td>No prior stroke/TIA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number at risk (no prior stroke)</td>
<td>4819</td>
<td>4702</td>
<td>4578</td>
</tr>
<tr>
<td></td>
<td>Dabigatran 150 mg BID</td>
<td>4843</td>
<td>4739</td>
</tr>
<tr>
<td>Warfarin</td>
<td>4827</td>
<td>4703</td>
<td>4593</td>
</tr>
</tbody>
</table>

BID = twice daily; TIA = transient ischaemic attack
This study was not designed to compare NOACs against one another. Comparison between NOACs is not valid because of population differences among the studies. No head to head data are available.
Effects of novel oral anticoagulants vs warfarin on stroke or systemic embolism in patients with AF and previous stroke or TIA (1)

This study was not designed to compare NOACs against one another. Comparison between NOACs is not valid because of population differences among the studies. No head-to-head data are available.

AF = atrial fibrillation; TIA = transient ischemic attack; NOAC = novel oral anticoagulant.

Ntaios G et al. Stroke 2012 Nov 13 [Epub ahead of print]

<table>
<thead>
<tr>
<th>Stroke or Systemic Embolism</th>
<th>NOACs</th>
<th>Warfarin</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study or subgroup</td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>73</td>
<td>1694</td>
<td>98</td>
</tr>
<tr>
<td>RE-LY 110</td>
<td>55</td>
<td>1195</td>
<td>65</td>
</tr>
<tr>
<td>RE-LY 150</td>
<td>51</td>
<td>1233</td>
<td>65</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>179</td>
<td>3754</td>
<td>187</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>7876</td>
<td>7846</td>
<td>100%</td>
</tr>
<tr>
<td>Total events</td>
<td>358</td>
<td>415</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2=1.93$, df=3 (P=0.59); $I^2=0\%$
Test for overall effect: $Z=2.15$ (P=0.03)
Effects of novel oral anticoagulants vs warfarin on **haemorrhagic stroke** in patients with AF and previous stroke or TIA (2)

This study was not designed to compare NOACs against one another. Comparison between NOACs is not valid because of population differences among the studies. No head-to-head data are available.

AF = atrial fibrillation; TIA = transient ischemic attack; NOAC = novel oral anticoagulant.

Ntaios G et al. Stroke 2012 Nov 13 [Epub ahead of print]

### Haemorrhagic stroke

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>NOACs</th>
<th>Warfarin</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>12</td>
<td>1694</td>
<td>31</td>
</tr>
<tr>
<td>RE-LY 110</td>
<td>2</td>
<td>1195</td>
<td>18</td>
</tr>
<tr>
<td>RE-LY 150</td>
<td>5</td>
<td>1233</td>
<td>18</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>22</td>
<td>3754</td>
<td>30</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>7876</td>
<td>7846</td>
<td></td>
</tr>
</tbody>
</table>

**Total events**

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>41</td>
<td>97</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2=7.07$, df=3 (P=0.07); $I^2=58$

Test for overall effect: Z=4.79 (P<0.00001)
NOACs: Special Problems

- Patients > 80 years
- CrCl 30-50 l/min
- Prior GI bleed
- Prior intracerebral bleed
- Gait apraxia and falls
- Cognitive impairment
- Start after TIA or stroke
- Afib and carotid stenosis
- Afib and stable coronary heart disease
- Afib and DVT prevention
Outline

- Patients > 80 years
- CrCl 30-50 l/min
- Prior GI bleed
- Prior intracerebral bleed
- Gait apraxia and falls
- Cognitive impairment
- Start after TIA or stroke
- Afib and carotid stenosis
- Afib and stable coronary heart disease
- Afib and DVT prevention
Age and bleeding subgroup analysis in the RE-LY trial: major bleeding in key subgroups

- Both doses of dabigatran compared with warfarin were associated with an increasing relative risk of major bleeding with increasing age categories.
- No significant interactions between sex or body weight.

Conclusion 1

• In patients with age >75 years and increased risk of bleeding the 2 x 110 mg dose of dabigatran should be used

• In the ROCKET-AF and ARISTOTLE trials elderly patients had higher absolute rates of stroke and systemic embolism and higher absolute rates of major bleeding

• The overall relative effects of rivaroxaban or apixaban vs. warfarin were consistent among elderly (and younger) patients for both efficacy and safety
Outline

- Patients > 80 years
- **CrCl 30-50 l/min**
- Prior GI bleed
- Prior intracerebral bleed
- Gait apraxia and falls
- Cognitive impairment
- Start after TIA or stroke
- Afib and carotid stenosis
- Afib and stable coronary heart disease
- Afib and DVT prevention
Figure 5  Absorption and metabolism of the different new anticoagulant drugs. There are interaction possibilities at the level of absorption or first transformation, and at the level of metabolism and excretion. The brackets around (Cyp3A4) in the apixaban graph indicate a minor contribution of this pathway to hepatic clearance, the majority of the drug being excreted as unchanged parent. See also Table 4 for the size of the interactions based on these schemes.
Data from Phase III trials in patients with moderate renal impairment (CrCl 30–49 mL/min)

**Stroke and systemic embolism**

<table>
<thead>
<tr>
<th>Study drug (Study)</th>
<th>Warfarin (%/yr)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RE-LY®:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran 150 mg*¹,²</td>
<td>1.52</td>
<td>0.55</td>
</tr>
<tr>
<td>Dabigatran 110 mg*¹,²</td>
<td>2.15</td>
<td>0.77</td>
</tr>
<tr>
<td><strong>ROCKET AF:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban³</td>
<td>2.95</td>
<td>0.86</td>
</tr>
<tr>
<td><strong>ARISTOTLE:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban*⁴</td>
<td>2.11</td>
<td>0.79</td>
</tr>
</tbody>
</table>

*Includes patients with CrCl <50; HR = hazard ratio; Error bars = 95% confidence intervals

Data from Phase III trials in patients with moderate renal impairment (CrCl 30–49 mL/min)

**Major bleeding**

<table>
<thead>
<tr>
<th>Study drug</th>
<th>Warfarin (%)/yr</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY®: Dabigatran 150 mg*¹,²</td>
<td>5.44</td>
<td>1.01</td>
</tr>
<tr>
<td>RE-LY®: Dabigatran 110 mg*¹,²</td>
<td>5.29</td>
<td>0.98</td>
</tr>
<tr>
<td>ROCKET AF: Rivaroxaban³</td>
<td>4.49</td>
<td>0.95</td>
</tr>
<tr>
<td>ARISTOTLE: Apixaban⁴</td>
<td>3.21</td>
<td>0.50</td>
</tr>
</tbody>
</table>

*Includes patients with CrCl <50; HR = hazard ratio; Error bars = 95% confidence intervals

Conclusion 2

- Efficacy of new anticoagulants seems to be preserved in the CrCl range of 30-50 ml/min
- Bleeding risk might be increased (but less so compared to warfarin)
- Patients at old age, with low body weight and co-morbidity need to be monitored on a regular basis and dose of NOAC might be reduced
- Acute infections leading to fluid loss are a risk factor for bleeding with NOACs
Outline

- Patients > 80 years
- CrCl 30-50 l/min
- **Prior GI bleed**
  - Prior intracerebral bleed
  - Gait apraxia and falls
  - Cognitive impairment
- Start vafter TIA or stroke
- Afib and carotid stenosis
- Afib and stable coronary heart disease
- Afib and DVT prevention
Conclusion 3

• Detailed subgroup data not published for apixaban and rivaroxaban
• Prior GI bleed is not a contraindication for anticoagulation with NOACs when the source of bleeding has been identified
• In patients >75 years and a history of lower GI bleeding, the lower dose of dabigatran (2 x 110 mg) should be used
### Intracranial and Gastrointestinal Bleeding Events in New Users of Dabigatran and Warfarin from the Mini-Sentinel Distributed Database, October 2010 through December 2011.*

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Dabigatran</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of</td>
<td>Incidence</td>
</tr>
<tr>
<td></td>
<td>Patients</td>
<td>no. of events/100,000 days at risk</td>
</tr>
<tr>
<td><strong>Gastrointestinal hemorrhage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analysis with required diagnosis of atrial fibrillation</td>
<td>10,599</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Sensitivity analysis without required diagnosis of atrial fibrillation</td>
<td>12,195</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td><strong>Intracranial hemorrhage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analysis with required diagnosis of atrial fibrillation</td>
<td>10,587</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Sensitivity analysis without required diagnosis of atrial fibrillation</td>
<td>12,182</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>0.9</td>
<td></td>
</tr>
</tbody>
</table>

*Patients were included in the cohorts if, in the 183 days before the index dispensing of dabigatran or warfarin, they were enrolled in plans for drug and medical coverage and had been given a diagnosis of atrial fibrillation in any care setting. Patients were excluded from the cohorts if, in the 183 days before the index dispensing, they had a claim for an event of interest in an inpatient or emergency department setting or a claim for dispensing of dabigatran or warfarin. Events were assessed during drug exposure, from inpatient or emergency department settings only.
Outline

- Patients > 80 years
- CrCl 30-50 l/min
- Prior GI bleed
- **Prior intracerebral bleed**
- Gait apraxia and falls
- Cognitive impairment
- Start after TIA or stroke
- Afib and carotid stenosis
- Afib and stable coronary heart disease
- Afib and DVT prevention
Afib and Intracerebral Bleed

- Patients with prior intracerebral bleeds were excluded from the trials with NOACs
- Treatment with NOACs depends on the aetiology of the bleed
- Conditions that can be treated or controlled (e.g. hypertension) are no contraindication
- Sustained high bleeding risk (imaging information suggesting amyloid angiopopathy) is a clear contraindication
Types of Intracranial Haemorrhage

Intracranial Hemorrhages in RE-LY
n=154

- Intracerebral: 46%
- Subdural: 45%
- Subarachnoid: 8%

Mortality index after hemorrhagic stroke/ICH and ischaemic stroke: data from the RE-LY study

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>36% (32/90)</td>
</tr>
<tr>
<td>Dabigatran 150 mg BID</td>
<td>35% (13/37)</td>
</tr>
<tr>
<td>Dabigatran 110 mg BID</td>
<td>41% (12/27)</td>
</tr>
</tbody>
</table>

*RE-LY study. Boehringer Ingelheim, data on file
BID = twice daily; ICH = intracranial haemorrhage

In comparison: mortality after a major bleed* 6.8%
Cerebral microbleeds

FIGURE 3 | The distribution of sporadic small vessel disease in the brain and the topography of cerebral microbleeds (CMBs). (A) Cerebral amyloid angiopathy (CAA) preferentially affects the small arteries and arterioles of the cerebral cortex and gray-white matter junction by the deposition of amyloid-β in the vessel walls (purple); (B) hypertensive arteriopathy typically affects small deep arterial perforators (black). CMBs are a marker for the severity and type of small vessel disease; their anatomic distribution is meant to reflect the underlying pathological vessel damage. Hence, CMBs (dark, rounded lesions) located in cortical-subcortical regions are presumably caused by CAA (A), whereas CMBs located in deep brain regions mainly result from hypertensive arteriopathy (B). (A) is an axial susceptibility-weighted imaging (SWI) which is currently the most sensitive means to image CMBs. (B) is an axial T2*-weighted gradient-recalled echo (T2*-GRE) MRI.
Risk for recurrent ICH varies with location

HR = 3.8 (95% CI 1.3–11.0)  
\( p = 0.007 \)

Viswanathan et al, 2006
Conclusion 4

• In cases of high risk of ischemic stroke (CHADS2) and moderate risk of cerebral bleeding NOACs are clearly preferred over warfarin

• Re-initiation of oral anticoagulation after 4-8 weeks

• Safety data from prospective registries needed
Outline

- Patients > 80 years
- CrCl 30-50 l/min
- Prior GI bleed
- Prior intracerebral bleed
- Gait apraxia and falls
- Cognitive impairment
- Start after TIA or stroke
- Afib and carotid stenosis
- Afib and stable coronary heart disease
- Afib and DVT prevention
Afib Gait Apraxia and Falls

• Need to teach cardiologists to refer these patients for evaluation to a neurologist.
• Parkinson’s disease and normal pressure hydrocephalus are not per se contraindications to anticoagulation.
• Advanced small vessel disease with gait apraxia and cognitive impairment is a contraindication.

RISK OF FALLS?
Number needed to fall/J: 295
high risk of falls = high risk of ischemia
Outline

- Patients > 80 years
- CrCl 30-50 l/min
- Prior GI bleed
- Prior intracerebral bleed
- Gait apraxia and falls
- **Cognitive impairment**
- Start after TIA or stroke
- Afib and carotid stenosis
- Afib and stable coronary heart disease
- Afib and DVT prevention
Afib and Cognitive Impairment

• Cognitive impairment is not a contraindication for anticoagulation as long as compliance is controlled by a caregiver
• Severe small vessel disease is a contraindication
• New oral anticoagulants are easier to handle than vitamin-K antagonists (no INR control required)
Outline

• Patients > 80 years
• CrCl 30-50 l/min
• Prior GI bleed
• Prior intracerebral bleed
• Gait apraxia and falls
• Cognitive impairment
• **Start after TIA or stroke**
  • Afib and carotid stenosis
  • Afib and stable coronary heart disease
  • Afib and DVT prevention
When to Start a NOAC After an Acute Stroke?

‘As a rule of thumb the 1-3-6-12 day with re-institution of anticoagulation in patients with a transient ischaemic attack (TIA) after 1 day, with small, non-disabling infarct after 3 days, with a moderate stroke after 6 days, while large infarcts involving large parts of the arterial territory will be treated not before 2 (or even 3) weeks.’ EHRA PRACTICAL GUIDE

Patients with a very recent stroke were excluded from the AF trials as follows:

**RE-LY:** Stroke within 14 days or severe stroke within 6 months of screening

**ROCKET-AF:** Severe, disabling stroke (modified Rankin score of 4 to 5, inclusive within 3 months or any stroke within 30 days before the randomization visit

**ARISTOTLE:** Recent stroke (within 7 d)

**ENGAGE:** Stroke within 30 days

Heidbuchel European Heart Journal doi:10.1093/eurheartj/eh134
Patel N EJM 2011 Sep 8;365(10):883-91
Connolly et al. NEJM. 2009 Sep 17;361(12):1139-51
Granger et al. NEJM. 2011 Sep 15;365(11):981-92
Start after TIA or Stroke

- Patients who had a TIA or stroke could not be randomised in the first 7-14 days after the event

<table>
<thead>
<tr>
<th>Stroke Severity</th>
<th>Restart</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIA</td>
<td>as soon as imaging has excluded a cerebral haemorrhage</td>
</tr>
<tr>
<td>Mild Stroke</td>
<td>3-5 days after symptom onset</td>
</tr>
<tr>
<td>Moderate Stroke</td>
<td>5-7 days after stroke onset</td>
</tr>
<tr>
<td>Severe Stroke</td>
<td>2 weeks after stroke onset</td>
</tr>
</tbody>
</table>
Outline

• Patients > 80 years
• CrCl 30-50 l/min
• Prior GI bleed
• Prior intracerebral bleed
• Gait apraxia and falls
• Cognitive impairment
• Start after TIA or stroke
• **Afib and carotid stenosis**
• Afib and stable coronary heart disease
• Afib and DVT prevention
Afib and Carotid stenosis

• Patients with Afib and symptomatic carotid stenosis should be operated and not stented to avoid triple therapy (anticoagulation + aspirin + clopidogrel)
Concomitant Aspirin + clopidogrel subgroup analysis: major bleeding

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran 110 mg BID</th>
<th>Dabigatran 150 mg BID</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin + clopidogrel</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual rate (%)</td>
<td>4.72</td>
<td>4.66</td>
<td>5.21</td>
</tr>
<tr>
<td>RR (95% CI) vs. warfarin</td>
<td>0.77 (0.50–1.21)</td>
<td>0.81 (0.52–1.26)</td>
<td></td>
</tr>
<tr>
<td><strong>No Aspirin + clopidogrel</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual rate (%)</td>
<td>2.77</td>
<td>3.24</td>
<td>3.48</td>
</tr>
<tr>
<td>RR (95% CI) vs. warfarin</td>
<td>0.81 (0.61–0.94)</td>
<td>0.95 (0.82–1.10)</td>
<td></td>
</tr>
<tr>
<td>P value for interaction</td>
<td>0.8727</td>
<td>0.5167</td>
<td></td>
</tr>
</tbody>
</table>

A separate analysis found that concomitant use of antiplatelet therapy increases the risk of major bleeding, with similar effects seen for dabigatran 110 mg BID, 150 mg BID or warfarin.

BID = twice daily


Disclaimer: Dabigatran etexilate is now approved for clinical use in stroke prevention in atrial fibrillation in certain countries. Please check local prescribing information for further details.
Outline

- Patients > 80 years
- CrCl 30-50 l/min
- Prior GI bleed
- Prior intracerebral bleed
- Gait apraxia and falls
- Cognitive impairment
- Start after TIA or stroke
- Afib and carotid stenosis
- **Afib and stable coronary heart disease**
- Afib and DVT prevention
Afib and Stable Coronary Heart Disease

- Patients with stable coronary heart disease do not benefit from the combination of warfarin and aspirin.
- The bleeding risk is increased with the combination of aspirin and anticoagulation.
Outline

• Patients > 80 years
• CrCl 30-50 l/min
• Prior GI bleed
• Prior intracerebral bleed
• Gait apraxia and falls
• Cognitive impairment
• Start after TIA or stroke
• Afib and carotid stenosis
• Afib and stable coronary heart disease
• Afib and DVT prevention
Afib, Acute Stroke and DVT

- All new anticoagulants are effective in the prevention of deep vein thrombosis.
- In patients at risk of DVT after an acute stroke, DVT prevention with LMWH should be terminated 24 hours after the initiation of therapy with a new anticoagulant.
Summary

• Patients > 80 years
• CrCl 30-50 l/min
• Prior GI bleed
• Prior intracerebral bleed
• Gait apraxia and falls
• Cognitive impairment
• Start after TIA or stroke
• Afib and carotid stenosis
• Afib and stable coronary heart disease
• Afib and DVT prevention
• Thrombolysis
Novel Anticoagulants in Stroke Prevention in Patients with Atrial Fibrillation
The Past, the Present and the Future

Hans-Christoph Diener
Department of Neurology and Stroke Center
University Hospital Essen
Germany
Rationale for anti-dabigatran Fab approach

Safe restoration of coagulation:
- Binds dabigatran with high affinity
- No homology of dabigatran to endogenous receptors/ligands
  - Off-target binding is not expected
- No activated coagulation expected since Fab targets only dabigatran
- Shorter half life than full mAb (hrs vs days for a full mAb)

Easy and rapid administration:
- Administration route is intravenous, immediate onset of action

Low risk of adverse reactions:
- Humanized antibody fragment (Fab)
- No Fc receptor binding

Fc = fragment crystallizable; mAb = monoclonal antibody
A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa

Genmin Lu1, Francis R DeGuzman2, Stanley J Hollenbach2, Mark J Karbarz1, Keith Abe2, Gail Lee2, Peng Luan1, Athiwal Hutchaleelaha3, Mayuko Inagaki3, Pamela B Conley1, David R Phillips1 & Uma Sinha1

Figure 1  Design of r-Antidote and protein expression in CHO cells. (a) Schematic illustration of the domain structure of full-length human fX and r-Antidote (PRT064445) precursors. Using fX as a template, modifications were made in three regions to generate r-Antidote: deletion of a 34-residue fragment (residues 46–78) that contains the 11 GLA residues; replacement of the activation peptide (AP) with ArgLysArg (RKR) to form the RKRRKR linker that connects the light chain (LC) to the heavy chain (HC); and mutation of the active-site serine to alanine (S419A). Arrows indicate potential cleavage sites. (b) Reduced SDS-PAGE of purified r-Antidote showing bands of expected molecular weight (MW) for the light (~11 kDa) and heavy (~28 kDa) chains. The double bands of the heavy chain of plasma-derived fXa (pd-fXa) and r-Antidote correspond to the α- and β-isoforms. MK, molecular weight marker.
All strokes
The global incidence of stroke is approx. ~200 cases per 100,000 inhabitants

Ischemic stroke (85%)
- Stroke of other determined source, e.g. coagulopathy (~10%)
- Lacunar stroke (~25%)
  - e.g. Carotid stenosis, >70% stenosis ➔ intervention

Hemorrhagic stroke (15%)
- Cardioembolic stroke (20%)
  - e.g. atrial fibrillation, valve disease, ventricular thrombi

Cryptogenic (~25%)
- If clearly specified diagnostic criteria are fulfilled

ESUS (~20%)
Double blind randomized controlled clinical trial comparing safety and efficacy of dabigatran to ASA for secondary prevention of ESUS

Index ischemic stroke (ESUS)*
- mRS ≤ 3, age ≥ 60, or 50-59y + risk factors

“Diagnostic Pathway”:
- Assess with MRI/CT to rule out lacunae;
- carotid ultrasound, transcranial doppler;
- ≥ 24 hour rhythm monitoring to rule out AF

Primary endpoint:
Stroke + SEE

Pradaxa (150 or 110mg bid)*
Placebo (matching ASA)
ASA (100 mg)
Placebo (matching Pradaxa)

N=3000
N=3000

0 days - 3 months
0.5-3 years
30 day follow up

*All patients will receive Dabigatran 150mg bid, unless they are ≥ 75 years of age or have a CrCL < 50ml/min, who will receive 110mg bid

# Includes “TIA” with pathological imaging evidence according to the 2013 updated stroke definitions
Thank you for your attention