DECLARATION OF CONFLICT OF INTEREST
New antithrombotic therapies: revisiting stroke prevention in atrial fibrillation

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# Disclosures for Lars Wallentin

<table>
<thead>
<tr>
<th>Company</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boehringer Ingelheim</td>
<td>Research grant</td>
</tr>
<tr>
<td>Bristol-Myers-Squibb-Pfizer</td>
<td>Research grant</td>
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<tr>
<td>Pfizer</td>
<td>Research grant</td>
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<tr>
<td>AstraZeneca</td>
<td>Research grant</td>
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<tr>
<td>GlaxoSmithKline</td>
<td>Research grant</td>
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<tr>
<td>Merck - Schering-Plough</td>
<td>Research grant</td>
</tr>
<tr>
<td>Eli Lilly &amp; Co.</td>
<td>Research grant</td>
</tr>
<tr>
<td>Regado Biosciences</td>
<td>Consultancy</td>
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<td>Athera Biotechnologies</td>
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<tr>
<td>Portola</td>
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<tr>
<td>Evolva</td>
<td>Consultancy</td>
</tr>
<tr>
<td>GE Health Care</td>
<td>Consultancy</td>
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</tbody>
</table>
Atrial fibrillation

- Most common arrhythmia
- 1.5% of the population
- Increases with age

Stroke risk

- Five fold increase at AF
- Risk related to risk factors
- Congestive heart failure
- Hypertension
- Age > 75
- Diabetes
- S2troke
- Reduced with antithrombotics
- Aspirin (− 19%)
- Warfarin (− 64%)
Targets for long-term antithrombotic treatment

Warfarin*

Tissue factor

Plasma clotting cascade *

Prothrombin *

Factor Xa *

Thrombin *

Fibrinogen

Fibrin

Thrombus

Collagen Thrombin

Aspirin

Tx A₂

PAR1

ADP

Conformational activation of GPIIb/IIIa

Platelet aggregation

PAR1-inhib

Clopidogrel
Prasugrel
Ticagrelor

GPIIb/IIIa inhibitors

Rivaroxaban
Apixaban
Edoxaban
Betrixaban

Fondaparinux
Idraparinux
LMWH

Dabigatran

AT

AT

Targets for long-term antithrombotic treatment
Alternatives to warfarin

• At least same anti-thrombotic effect
• Lower risk of bleeding – especially intracranial bleeding
• Few other side-effects
• Oral bioavailability – once or twice daily
• No food or drug interactions
• Broad therapeutic window at standard dosing
• Stable anticoagulation without frequent laboratory monitoring
• Good patient acceptability and long-term tolerance
# Pharmacology of novel anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Selective direct FIIa inhibitor</td>
<td>Selective direct FXa inhibitor</td>
<td>Selective direct FXa inhibitor</td>
<td>Competitive inhibitor of FXa</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>Oral prodrug with poor oral bioavailability</td>
<td>Good oral bioavailability</td>
<td>Good oral bioavailability</td>
<td>Good oral bioavailability</td>
</tr>
<tr>
<td>$T_{1/2}$</td>
<td>12 - 17 hours (80% renal excretion)</td>
<td>6 - 9 hours</td>
<td>12 hours</td>
<td>9 -11 hours</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Twice daily</td>
<td>Once daily</td>
<td>Twice daily</td>
<td>Once daily</td>
</tr>
<tr>
<td><strong>Time to max effect</strong></td>
<td>1 - 4 h</td>
<td>1 - 4 h</td>
<td>1 - 4 h</td>
<td>1 - 4 hr</td>
</tr>
</tbody>
</table>

Trial design comparing new agents in patients with AF

- Single, large trial (N = 14000 to 18000)
- Event driven – 450 primary events
- Randomized vs warfarin
- Double blind, double dummy or PROBE
- Non-inferiority (or superiority) - on and off treatment
- CHADS2 score ≥ 1 or ≥ 2
- Median TTR 2-3 for warfarin treated pts - aim = 65%
- Complete follow-up of all patients
# Trials with new agents vs warfarin (aim INR 2.0-3.0) in AF

<table>
<thead>
<tr>
<th></th>
<th>RELY</th>
<th>ROCKET</th>
<th>ARISTOTLE</th>
<th>ENGAGE-AF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample size</strong></td>
<td>18,113</td>
<td>14,266</td>
<td>18,201</td>
<td>20,500</td>
</tr>
<tr>
<td><strong>New treatment</strong></td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
<td>Edoxaban</td>
</tr>
<tr>
<td></td>
<td>110mg BID</td>
<td>20mg QD</td>
<td>5mg BID</td>
<td>30mg QD</td>
</tr>
<tr>
<td></td>
<td>&amp; 150mg BID</td>
<td></td>
<td></td>
<td>&amp; 60mg QD</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Non-inferiority</td>
<td>Non-inferiority</td>
<td>Non-inferiority</td>
<td>Non-inferiority</td>
</tr>
<tr>
<td></td>
<td>PROBE</td>
<td>Double-blind</td>
<td>Double-blind</td>
<td>Double-blind</td>
</tr>
<tr>
<td><strong>CHADS2</strong></td>
<td>≥ 1</td>
<td>≥ 2</td>
<td>≥ 1</td>
<td>≥ 2</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td>Stroke or systemic embolism</td>
<td>Stroke or systemic embolism</td>
<td>Stroke or systemic embolism</td>
<td>Stroke or systemic embolism</td>
</tr>
<tr>
<td><strong>Safety outcome</strong></td>
<td>Primary: Major Bleeding</td>
<td>Primary: Major Bleeding</td>
<td>Primary: Major Bleeding</td>
<td>Primary: Major Bleeding</td>
</tr>
</tbody>
</table>

Connolly S et al NEJM 2009; Patel M et al NEJM 2011; Granger C et al NEJM 2011; ENGAGE- AF Study Investigators. AHJ 2010
New antithrombotic therapies compared to warfarin
Stroke or systemic embolism

- Dabigatran 150 mg b.i.d.
- Dabigatran 110 mg b.i.d.
- Rivaroxaban 20 mg o.d.
- Abixaban 5 mg b.i.d.

References:
New antithrombotic therapies compared to warfarin
Hemorrhagic stroke

- Dabigatran 150 mg b.i.d.
- Dabigatran 110 mg b.i.d.
- Rivaroxaban 20 mg o.d.
- Abixaban 5 mg b.i.d.

Connolly S et al. NEJM 2009; Patel M et al. NEJM 2011; Granger C et al. NEJM 2011
New antithrombotic therapies compared to warfarin
Stroke of ischemic or unknown origin

- Dabigatran 150 mg b.i.d.
- Dabigatran 110 mg b.i.d.
- Rivaroxaban 20 mg o.d.
- Abixaban 5 mg b.i.d.

New antithrombotic therapies compared to warfarin
All-cause mortality

Dabigatran 150 mg b.i.d.
Dabigatran 110 mg b.i.d.
Rivaroxaban 20 mg o.d.
Abixaban 5 mg b.i.d.

New antithrombotic therapies compared to warfarin
Major bleeding

Abxixaban 5 mg b.i.d.
Rivaroxaban 20 mg o.d.
Dabigatran 110 mg b.i.d.
Dabigatran 150 mg b.i.d.

New antithrombotic therapies compared to warfarin
Major + clinically relevant bleeding

- Dabigatran 150 mg b.i.d.
- Dabigatran 110 mg b.i.d.
- Rivaroxaban 20 mg o.d.
- Abixaban 5 mg b.i.d.

References:
- Connolly S et al NEJM 2009
- Patel M et al NEJM 2011
- Granger C et al NEJM 2011
New antithrombotic therapies compared to warfarin
Gastrointestinal bleeding

- Dabigatran 150 mg b.i.d.
- Dabigatran 110 mg b.i.d.
- Rivaroxaban 20 mg o.d.
- Abixaban 5 mg b.i.d.

New antithrombotic therapies compared to warfarin
Intracranial hemorrhage

Dabigatran 150 mg b.i.d.
Dabigatran 110 mg b.i.d.
Rivaroxaban 20 mg o.d.
Abixaban 5 mg b.i.d.

New antithrombotic therapies compared to warfarin
Myocardial infarction

Dabigatran 150 mg b.i.d.
Dabigatran 110 mg b.i.d.
Rivaroxaban 20 mg o.d.
Abixaban 5 mg b.i.d.

New antithrombotic therapies compared to warfarin
Stroke or SE in relation to centre’s TTR

- Dabigatran 150 mg b.i.d.
- Dabigatran 110 mg b.i.d.
  - Abixaban 5 mg b.i.d.
- Dabigatran 150 mg b.i.d.
- Dabigatran 110 mg b.i.d.
  - Abixaban 5 mg b.i.d.
- Dabigatran 150 mg b.i.d.
- Dabigatran 110 mg b.i.d.
  - Abixaban 5 mg b.i.d.
- Dabigatran 150 mg b.i.d.
- Dabigatran 110 mg b.i.d.
  - Abixaban 5 mg b.i.d.

Wallentin Let al Lancet 2010; Wallentin L et al ESC 2011
# New anticoagulants compared to warfarin in AF 2011

<table>
<thead>
<tr>
<th>Effet on outcome event</th>
<th>D150</th>
<th>D110</th>
<th>Riva</th>
<th>Apix</th>
</tr>
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<tbody>
<tr>
<td>Noninferiority stroke</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Reduction hemorrhagic stroke</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
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New anticoagulants compared to warfarin in AF 2011

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<th>Apix</th>
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<tbody>
<tr>
<td>Noninferiority stroke</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Reduction hemorrhagic stroke</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Reduction ischemic stroke</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Reduction mortality</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Reduction major bleeding</td>
<td></td>
<td></td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Reduction hemorrhagic stroke</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Reduction ischemic stroke</td>
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<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Reduction mortality</td>
<td>(✓)</td>
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<td></td>
<td>✓</td>
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<tr>
<td>Reduction major bleeding</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Increase gastrointestinal bleeding</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Increase myocardial infarction</td>
<td></td>
<td>(✓)</td>
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<tr>
<td>Reduction mortality</td>
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<tr>
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<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
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<tr>
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<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase myocardial infarction</td>
<td>✓</td>
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<tr>
<td>Fewer treatment discontinuations</td>
<td></td>
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<tr>
<td>Validation in a second randomized trial</td>
<td></td>
<td></td>
<td></td>
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</table>

Three new anticoagulants superior to Warfarin for prevention of stroke and intracranial bleeding in AF available 2011

Warfarin: Risk for stroke and intracranial bleeding

Apixaban, Dabigatran, Rivaroxaban: side effects e.g. other bleedings, Survival, Patient preferences, Health economy