Recent advances in oral anticoagulants

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Benha University
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Agenda

- Ideal anticoagulant.
- Drawbacks of warfarin.
- New anticoagulant targets.
- New OACs in clinical trials.
- Present status of old and new OACs
The Ideal anticoagulant

- Oral, fixed dosage, once daily.
- High efficacy, rapid onset and offset.
- Predictable dose response + Wide TW.
- Simple pharmacology.
- No need for monitoring.
- Available antidote.
- No or little interaction with food or drugs.
- Acceptable safety profiles.
Warfarin is not ideal?

- Narrow therapeutic window
- Unpredictable dose response
- Complex Pharmacology.
- Need frequent monitoring and dose adjustment
- Slow onset and offset of action.
- Frequent food and drugs interactions.
Need for Intense Monitoring With OAC

![Graph showing odds ratio vs. international normalized ratio (INR).]

**Narrow therapeutic index:**
- INR < 2.0 = higher risk for stroke
- INR > 3.0 = higher risk for bleeding

**Unpredictable INR (food/drug interactions, low specificity)**

New Anticoagulant Targets

**ORAL**

- TTP889
- Rivaroxaban
- Apixaban
- LY517717
- YM150
- DU-176b
- Betrixaban
- TAK 442

**PARENTERAL**

- TFPI (tifacogin)
- APC (drotrecogin alfa)
- sTM (ART-123)
- Fondaparinux
- Idraparinux
- DX-9065a

Adapted from Weitz & Bates, J Thromb Haemost 2007
### Anticoagulants in development

<table>
<thead>
<tr>
<th>Agent</th>
<th>Company</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Boehringer</td>
<td>3 DTI</td>
</tr>
<tr>
<td>AZD 0837</td>
<td>Astra-zinca</td>
<td>2 DTI</td>
</tr>
<tr>
<td>MCC 977</td>
<td>Mitsubishi</td>
<td>2 DTI</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Bayer</td>
<td>3 DFXaI</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Bristol, Sqb, Pfz</td>
<td>3 DFXaI</td>
</tr>
<tr>
<td>Betrixaban</td>
<td>Portola</td>
<td>2 DFXaI</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Daichi Sankyo</td>
<td>3 DFXaI</td>
</tr>
<tr>
<td>YM 150</td>
<td>Astellas</td>
<td>2 DFXaI</td>
</tr>
<tr>
<td>TAK-442</td>
<td>Takeda</td>
<td>2 DFXaI</td>
</tr>
</tbody>
</table>
Dabigatran Pharmacology

- **Inhibits both free and clot-bound thrombin.**
- **Predictable bioavailability.**
- **Peak at 1.5 hr after oral administration.**
- **Plasma half life is 14-17 hrs.**
- **Interactions: verapamil, quinidine.**
- **80% renal excretion.**
Dabigatran: phase III studies

- **RE-LY** (stroke prevention in patients with AF)
  - Planned enrolment 15,000 patients
  - Dabigatran 110 and 150 mg bid compared with warfarin
  - Treatment duration up to 3 years

- **RE-SOLVE, RE-COVER and RE-MEDY**
  - Ongoing studies in treatment and secondary prevention of VTE
Stroke Prevention in Atrial Fibrillation

**Status:** Ongoing; recruitment completed December 2007

- Largest atrial fibrillation outcomes trial to date
- 18,114 patients with atrial fibrillation were randomised to 1 of 3 treatment arms:
  - Oral dabigatran etexilate at two different blinded doses (single-blind)
  - Warfarin (INR 2.0–3.0) (open-label)
- Treatment will be continued for 20–24 months

**Primary outcomes:**

- **Efficacy** – Composite of stroke and systemic embolism
- **Safety** – Occurrence of bleeding events during treatment period
- Study results expected early 2009
RE-LY primary outcomes

- The 110mg dosage provided similar anti-thrombotic protection as warfarin with a lower annular rate of major bleeding.

- The 150mg dosage resulted in a lower rate of stroke/systemic embolization with similar risk of major bleeding.
Cumulative hazard rates of primary outcomes
Major Bleeding

- **Warfarin** .................. 3.36 %
- **Dabigatran 110** ...... 2.71 %,  
  \( p=0.003 \)
- **Dabigatran 150** ...... 3.11%  
  *ns*
- Life threatening, intracranial Minor bleeding higher with warfarin
- More major GI bleeding with 150 Dabigatran
Haemorrhagic Stroke

- **Warfarin** ........................................ 0.38%
- **Dabigatran 110mg** .............. 0.12%
- **Dabigatran 150mg** .............. 0.10%
GI bleeding & discomfort

Discontinuation

- Warfarin ........................................ 10.2%
- Dabigatran 110mg ................. 14.5%
- Dabigatran 150mg ............... 15.5%
Mortality

- Warfarin ............................4.13% pa
- Dabigatran 110mg .............3.75% pa .ns
- Dabigatran 150mg .............3.64% pa .ns
EDITORIAL

Published at www.nejm.org August 30, 2009 (10.1056/NEJMe0906886)

Can We Rely on RE-LY?

Brian F. Gage, M.D.
Can we Rely on RE-LY

“Because of Dabigatran’s twice daily dosing & greater risk of non haemorrhagic side effects, patients already taking warfarin with excellent INR control have little to gain by switching”

“in contrast, many other patients who have atrial fibrillation and at least one additional risk factor for stroke could benefit from Dabigatran”
Dabigatran for prevention of VTE after major orthopaedic surgery: ph3

- Dabigatran doses of 150 and 220 mg once daily (od) were investigated in all three studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of surgery</th>
<th>Comparator</th>
<th>Number of patients</th>
<th>Time to 1st administration of dabigatran</th>
<th>Treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-MODEL</td>
<td>TKR</td>
<td>Enoxaparin 40 mg od, starting evening before surgery</td>
<td>2010</td>
<td>1–4 hours post-surgery</td>
<td>6–10 days</td>
</tr>
<tr>
<td>RE-MOBILIZE</td>
<td>TKR</td>
<td>Enoxaparin 30 mg bid, starting 12–24 hours post-surgery</td>
<td>2615</td>
<td>6–12 hours post-surgery</td>
<td>12–15 days</td>
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<tr>
<td>RE-NOVATE</td>
<td>THR</td>
<td>Enoxaparin 40 mg od, starting evening before surgery</td>
<td>3494</td>
<td>1–4 hours post-surgery</td>
<td>28–35 days</td>
</tr>
</tbody>
</table>

TKR: total knee replacement; THR: total hip replacement
Results of VTE 1ry prevention trials

- **RE-NOVATE**: 1ry endpoints with doses 150mg & 220mg were non-inferior to enoxaparin with nearly similar rates of major bleedings.

- **RE-MODEL**: nearly the same results.

- **RE-MOBILIZE**: Dabigatran was inferior to enoxaparmin
## Dabigatran for prevention of VTE after major orthopaedic surgery

<table>
<thead>
<tr>
<th></th>
<th>Enoxaparin</th>
<th>Dabigatran (150 mg)</th>
<th>Dabigatran (220 mg)</th>
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<tbody>
<tr>
<td><strong>DVT, PE and all-cause mortality (%)</strong></td>
<td></td>
<td></td>
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<tr>
<td>RE-NOVATE</td>
<td>6.7</td>
<td>8.6 $p&lt;0.0001^*$</td>
<td>6.0 $p&lt;0.0001^*$</td>
</tr>
<tr>
<td>RE-MOBILIZE</td>
<td>25.3</td>
<td>33.7 $p=0.0009^{†}$</td>
<td>31.1 $p=0.02^{†}$</td>
</tr>
<tr>
<td>RE-MODEL</td>
<td>37.7</td>
<td>40.5 $p=0.0005^*$</td>
<td>36.4 $p=0.0345^*$</td>
</tr>
<tr>
<td><strong>Major bleeding (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-NOVATE</td>
<td>1.6</td>
<td>1.3</td>
<td>2.0</td>
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<tr>
<td>RE-MOBILIZE</td>
<td>1.4</td>
<td>0.6</td>
<td>0.6</td>
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<tr>
<td>RE-MODEL</td>
<td>1.3</td>
<td>1.3</td>
<td>1.5</td>
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</table>

*Non-inferior to enoxaparin; †inferior to enoxaparin
# Ongoing Dabigatran trials

<table>
<thead>
<tr>
<th>Acronym</th>
<th>RECOVER</th>
<th>RECOVER-2</th>
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<tr>
<td></td>
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<td>RE-MEDY</td>
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<tr>
<td>VTE</td>
<td></td>
<td></td>
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<td>acute treatment</td>
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<tr>
<td>Comparator</td>
<td>LMWH + VKA</td>
<td>Placebo</td>
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<tr>
<td>No. patients</td>
<td>2,600</td>
<td>4,500</td>
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<tr>
<td>Results expected</td>
<td>2011-2012</td>
<td>2011</td>
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Direct Factor Xa inhibition

- XIIa
- Xla
- IXa
- Vlla

Factor II (prothrombin)

Fibrinogen → Fibrin clot

Rivaroxaban
Apixaban
YM150
DU-176b
LY517717
Betrixaban
TAK 442

Tissue factor
Apixaban

- Oral, direct, selective factor Xa inhibitor
- Produces concentration-dependent anticoagulation
- Low incidence of drug interactions
- Good oral bioavailability
- Balanced elimination (~25% renal)
- Half-life ~12 hrs

He et al., ASH, 2006, Lassen, et al ASH, 2006
Apixaban phase 3 clinical trials

<table>
<thead>
<tr>
<th></th>
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<th>expect</th>
<th>Acronym</th>
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<tr>
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<td>Amplify</td>
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<td>Placebo</td>
<td>2,400</td>
<td>2012</td>
<td>Amplify ext</td>
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<tr>
<td>Post ACS</td>
<td>Placebo</td>
<td>11,000</td>
<td>2012</td>
<td>Appraise-2</td>
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</tbody>
</table>
Published results

- **Phase 2 data** suggested that apixaban may be safe and effective over a wide range of doses in prevention of VTE.

- **In Phase 3**, the rates of 1ry endpoints were similar for apixaban and enoxaparin with less clinically-relevant bleeding in apixaban arm (ADVANCE1,2)
These results strongly suggest that apixaban is an effective and safe anticoagulant.

- **APPRAISE-1**: a phase study in ACS was stopped prematurely due to excessive bleeding specially in high dose regimen in apixaban arm.

- **APPRAISE-2** (phase 3) is underway.
Apixaban for Prevention of VTE After Major Orthopaedic Surgery

Lassen et al. Blood 2006
Apixaban for the Treatment of DVT: The Botticelli-DVT Study

Composite of Symptomatic Recurrent VTE and Deterioration of Thrombotic Burden (%)

Major Bleeding (%)

Büller, Eur Heart J 2006
Rivaroxaban

- **Specific, competitive, direct FXa inhibitor**
- **Inhibits free and clot-associated FXa activity**
  - Prolongs time to thrombin generation
  - Inhibits peak thrombin generation
  - Reduces the total amount of thrombin generated

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Rivaroxaban: oral direct Factor Xa inhibitor

- Predictable pharmacology
- Low risk of drug interactions
- No requirement for monitoring
- Peak 3hrs after oral
- 4.9 hrs half life
- 80% bioavailability
- 66% renal excretion

Perzborn et al. 2005; Kubitza et al. 2005; 2006; 2007; Roehrig et al, 2005
<table>
<thead>
<tr>
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<th>Compar</th>
<th>No. pat</th>
<th>Expec</th>
<th>Acronym</th>
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<td>1,300</td>
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<td>Einstein ext</td>
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<td>16,000</td>
<td>Unkn.</td>
<td>Atlas/TIMI</td>
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</table>
Rivaroxaban 10 mg once daily is the optimum dose

Efficacy, n=618; safety, n=845
Eriksson et al. Circulation 2006
# Phase III RECORD programme in VTE prevention

<table>
<thead>
<tr>
<th>Study</th>
<th>Procedure</th>
<th>Duration of rivaroxaban therapy</th>
<th>Duration of enoxaparin therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECORD1</td>
<td>THR</td>
<td>5 weeks</td>
<td>5 weeks</td>
</tr>
<tr>
<td>RECORD2</td>
<td>THR</td>
<td>5 weeks</td>
<td>10–14 days, followed by placebo</td>
</tr>
<tr>
<td>RECORD3</td>
<td>TKR</td>
<td>10–14 days</td>
<td>10–14 days</td>
</tr>
<tr>
<td>RECORD4</td>
<td>TKR</td>
<td>10–14 days</td>
<td>10–14 days</td>
</tr>
</tbody>
</table>
Efficacy endpoints

Primary
- Total venous thromboembolism (VTE): any deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE), and all-cause mortality

Secondary
- Major VTE: proximal DVT, non-fatal PE, and VTE-related death
- DVT: any, proximal, distal
- Symptomatic VTE

All endpoints were adjudicated centrally by independent, blinded committees.
RECORD3: summary

**Total VTE**
- Enoxaparin 40 mg od: 18.9% RRR 49%
- Rivaroxaban 10 mg od: 9.6%

**Major VTE**
- RRR 62%
- Enoxaparin: 2.6%
- Rivaroxaban: 1.0%

**Symptomatic VTE**
- RRR 65%
- Enoxaparin: 2.0%
- Rivaroxaban: 0.7%

**Major bleeding**
- Enoxaparin: 0.5%
- Rivaroxaban: NS (0.6%)
**RECORD1: summary**

- **Total VTE**
  - RRR 70%
  - Enoxaparin: 3.7%
  - Rivaroxaban: 1.1%

- **Major VTE**
  - RRR 88%

- **Symptomatic VTE**
  - Enoxaparin: 0.5%
  - Rivaroxaban: 0.3%

- **Major bleeding**
  - Enoxaparin: 0.1%
  - Rivaroxaban: 0.3%
RECORD2: summary

- **Total VTE**: 9.3% for Rivaroxaban, 2.0% for Enoxaparin.
  - RRR: 78.9%

- **Major VTE**: 5.1% for Rivaroxaban, 0.6% for Enoxaparin.
  - RRR: 87.8%

- **Symptomatic VTE**: 1.2% for Rivaroxaban, 0.2% for Enoxaparin.
  - RRR: 80.1%

- **Major bleeding**: 0.1% for both Rivaroxaban and Enoxaparin.
Unresolved issues

- Long-term efficacy and safety?
- Cost and compliance?
- Available antidote?
- Specific drug monitoring test?
- Tendency for increased bleeding?
- Uses in renal failure and in patients with prosthetic valves?
Present status (2010)

- **Dabigatran, Apixaban and Rivaroxaban** are approved in 2009 for the prevention of VTE after major orthopaedic surgery.

- In AF, Warfarin will remain in use for certain subsets of patients; including those with mechanical heart valves.
Present status (cont.)

- The new OACs were inferior to enoxaparin in the treatment of VTE/PE, and phase 3 trials are ongoing.

- Phase 2 trials as regards ACS, recoded excessive bleeding and we are awaiting results of the ongoing phase 3 trials.