New anticoagulants
Basic concepts
Disclosures

- Received honoraria for work
  - In Steering Committees for VTE Rx studies on dabigatran – Boehringer Ingelheim
  - In Data Safety Monitoring Board for VTE Rx studies on rivaroxaban – Bayer Healthcare

- Drugs and indications discussed in this presentation may be non-approved and off-label in certain jurisdictions.
The Coagulation Cascade

- F XI → F Xla
- F IX → F IXa
- F VIII-VWF → F VIIIc
- TF
- F VII → F VIIa
- F V → F Va
- F X → F Xa
- VWF
- F II → F IIa
- Fibrinogen → Fibrin
Where do we slow it down?

- F XI → F XIa
- F IX → F IXa
- F VIII-VWF → F VIIIc
- F V → F Va
- F II → F IIA
- F X → F Xa
- F II → F IIA
- Fibrinogen → Fibrin
- TF → F VIIa
- TFPI → F VIIa
- TF → F VIIIa
- antiFIX
- antiFXI
- APC
- pentasaccharide
- Xa-inh + D T I
- ASIN
- NAPAs
Trying to eliminate current limitations

- Agents with more predictable pharmacokinetic characteristics
- Simplified administration
- Eliminated need for monitoring
- Reduced risk of bleeding
  - reversible agents

warfarin
Problems on the way

Often the development started with parenteral administration of the agent:
Thrombin inhibitors: hirudin derivatives → DTI
Factor Xa inhibitors: pentasaccharides → direct Xa-inhibitors
Species differences

- Animal models do not always reveal the correct dose (pentasaccharides)
- or the effect to be expected (ASIS=FVIIai)
- or the adverse effects (DTI from Merck – neuro-tox, ximelagatran – transaminases, razaxaban [Xa-inh] – bleeding)
Broad spectrum or selectivity?

- Warfarin and heparin interact with at least 4 coagulation factors each
- New agents are selective → easier to predict the dose-response relationship
- BUT at what shall we target our inhibition?
Targeting the initial phase

- ASIS – not better than UFH in PCI (phase II)
  Anti-angiogenic effect in cancer?
- TFPI (tifacogin) – no benefit in sepsis (phase III)
- NAPc2 – effective in TKR (phase II) and evaluated in ACS (phase II)*

F Xa inhibition

- Strategic – where intrinsic and extrinsic converge
- Rate-limiting step in thrombin generation
- Inhibition of 1 F Xa prevents formation of 138 F IIa
Types of Xa inhibitors and status

**Direct**
- Rivaroxaban [Bayer] – oral - marketed
- Apixaban [BMS & Pfizer] – oral - marketed
- Edoxaban [Daiichi-Sankyo] – oral, phase III THR, SPAF, ACS, VTE.
- Betrixaban [Portola] – oral, phase III medically ill, SPAF
- DPC-423 [BMS] – oral
- DX-9065a [Daiichi] – parenteral/oral. NSTEMI
- LY517717 [Lilly] – oral
- YM-150 [Astellas] – oral

**Indirect**
- Fondaparinux (Arixtra) [GSK] – parenteral – marketed ACS, Ortho proph, VTE
- Idraparinux [Sanofi] – parenteral VTE, SPAF (phase III finished) - withdrawn
- Biotinylated idraparinux [Sanofi] – stopped in phase III
Thrombin (IIa) inhibition

- Important – the last enzymatic step in coagulation
- Thrombin also involved in platelet activation, back-activation of F XI, F V and F VIII and other processes
- Actually an old concept
Fondaparinux

the first synthetic inhibitor of factor Xa

Total chemical synthesis

• single chemical entity
• designed for selectivity
• no risk of pathogen contamination
• batch-to-batch consistency
fondaparinux = Arixtra\(^{(R)}\)

a selective inhibitor of factor Xa

- Antithrombin (AT) is the main endogenous regulator of the coagulation cascade
- Fondaparinux binds to AT with very high affinity
- This reversible binding induces a critical conformational change in AT
- The conformational change in AT greatly potentiates its catalytic effect against factor Xa
Pentasaccharides
tailor made

Fondaparinux (Arixtra®)
MOST LIKE NATURAL
Once-a-day (1987)

Org31550
MORE POTENT
A new binding site discovered

Idraparinux, SanOrg34006
SIMPLIFIED (1992)
Once-a-week
### Idraparinux phase III

**Idraparinux 2.5 mg sc q 7 d vs. warfarin**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Duration</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>N=2,200</td>
<td>3 or 6 months</td>
<td>Non-inferior</td>
</tr>
<tr>
<td>2.</td>
<td>N=2,200</td>
<td>3 or 6 months</td>
<td>More deaths 7.6% vs 5.0 and VTE 3.7% vs 2.1%</td>
</tr>
<tr>
<td>3.</td>
<td>N=1,700</td>
<td>6 months</td>
<td>Superior effect versus placebo</td>
</tr>
<tr>
<td>4.</td>
<td>N=4,576</td>
<td>varying dur</td>
<td>Efficacy non-inferior</td>
</tr>
</tbody>
</table>

**Amadeus**

**SPAF**
A leech

Hirudo medicinalis
The original direct thrombin inhibitors

- Hirudin, 65 aa, 7 kDa – from the leech
- Desirudin lacks sulphate on Tyr-53, commercially produced in yeast
- Hirugen: Residues 53-64 of hirudin
- Bivalirudin: Phe-Pro-Arg-Pro linked to hirugen (Angiomax®)
- Lepirudin: (Leu1-Thr2)-63-desulfohirudin, produced in yeast (Refludan®)
The active site of thrombin

Thrombin

Ser 195
His 57
Asp 102
Arg
Inhibition of thrombin

Thrombin

Exosite I

Exosite II

Catalytic site

Antithrombin

Heparin

Heparin
Inhibition of thrombin

Thrombin

Exosite I

Exosite II

Antithrombin

Heparin
Inhibition of thrombin
- irreversible or reversible

Thrombin

+ Hirudin

+ Argatroban
  + Melagatran
  + Dabigatran
Thrombin-specific inhibitors

Active site of thrombin

P-pocket

D-pocket

D-Phe or analogous hydrophobic group

Arginine

Arginine aldehyde

Benzamidine

Proline or small hydrophobic residue

S-pocket
Hirulog 1 = bivalirudin = Angiomax
Factor Xa inhibitors
Which target is the best?

- Theory and reality is not the same
- Pharmacokinetic characteristics important
The thrombin molecule
Ximelagatran (oral DTI)

- Oral ximelagatran rapidly absorbed and biotransformed to the active form, melagatran
1st patient on ximelagatran

Courtesy Dr. Leif Lapidus, with permission from patient
Pattern in patients with ALT elevation
>3 x ULN

THrive III
February 16, 2006

AstraZeneca Decides to Withdraw Exanta™

Exanta withdrawn from market worldwide, further studies halted

Steve Stiles

Share price

- London: 28.11 GBP
- Stockholm: 325.30 SEK
December 22, 2005
and April 7, 2006
First patient included in RE-LY
and RE-COVER, respectively
## Important preclinical features of NOACs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anti-IIa</td>
<td>Anti-Xa</td>
<td>Anti-Xa</td>
<td>Anti-Xa</td>
<td></td>
</tr>
<tr>
<td>Time to maximum effect ($t_{max}$)</td>
<td>1.5-2 h</td>
<td>2 h</td>
<td>3-4 h</td>
<td>1-2</td>
<td>5 days</td>
</tr>
<tr>
<td>Half-life ($t_{1/2}$)</td>
<td>12-17 h</td>
<td>5-9 h</td>
<td>8-15 h</td>
<td>9-10</td>
<td>36-48 h</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>35%</td>
<td>92-95%</td>
<td>87%</td>
<td>40-59%</td>
<td>99%</td>
</tr>
<tr>
<td>Volume of distribution ($V_d$)</td>
<td>60-70 L</td>
<td>50 L</td>
<td>“low”</td>
<td>&gt;300 L</td>
<td>8 L</td>
</tr>
<tr>
<td>Renal elimination</td>
<td>80%</td>
<td>33%</td>
<td>25%</td>
<td>35-39%</td>
<td>0%</td>
</tr>
<tr>
<td>Interactions</td>
<td>P-gp</td>
<td>P-gp</td>
<td>P-gp, CYP3A4</td>
<td>P-gp, CYP3A4</td>
<td>CYP2C9 (S) CYP1A2 (R)*</td>
</tr>
<tr>
<td>Food effect</td>
<td>Absorption delayed, not reduced</td>
<td>Required for absorption of doses &gt;10 mg</td>
<td>Not reported</td>
<td>No</td>
<td>Green veggies, avocado, alcohol</td>
</tr>
</tbody>
</table>
Dabigatran etexilate is absorbed in the intestinal lumen. The absorbed drug then enters the blood. P-glycoprotein, an efflux transporter, is present in the gut wall. Ketokonazole and Quinidine block this transporter, doubling the bioavailability of Dabigatran etexilate. Rifampicin induces P-gp, leading to reduced levels of Dabigatran (bioavailability 5-7.5%).
Intracranial bleedings, SPAF studies

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Warfarin</th>
<th>No. of events (%/yr)</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabi 110</td>
<td>27 (0.23)</td>
<td>90 (0.76)</td>
<td>0.30</td>
<td>0.19-0.45</td>
</tr>
<tr>
<td>Dabi 150</td>
<td>38 (0.32)</td>
<td>90 (0.76)</td>
<td>0.41</td>
<td>0.28-0.60</td>
</tr>
<tr>
<td>Riva</td>
<td>55 (0.5)</td>
<td>84 (0.7)</td>
<td>0.67</td>
<td>0.47-0.93</td>
</tr>
<tr>
<td>Apixaban</td>
<td>52 (0.33)</td>
<td>122 (0.80)</td>
<td>0.42</td>
<td>0.30-0.58</td>
</tr>
</tbody>
</table>

Questions?