Antithrombotic Therapy
Current Status
and Future Directions

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## Disclosures

<table>
<thead>
<tr>
<th>Role</th>
<th>Disclosures</th>
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<tbody>
<tr>
<td>Research Support</td>
<td>Wyeth, CSL Behring, Baxter</td>
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<tr>
<td>Employee</td>
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<tr>
<td>Consultant</td>
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<td>Current studies</td>
<td>Bayer, Boehringer-Ingelheim, Sanofi-Synthelabo</td>
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<tr>
<td>Speakers Bureau</td>
<td>No conflicts of interest</td>
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<td>Scientific Advisory Board</td>
<td>CSL Behring</td>
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</table>
• Epidemiology of VTE

• Historical perspective on outcome assessment

• Current evidence based treatment recommendations for VTE

• Explosion of new compounds

• Challenges for the future
Clots and thrombosis

- autopsy studies that showed clots in legs and lungs of patients who died of pulmonary embolism (1846)
- theory on the pathogenesis of thrombosis ("Virchow’s triad", 1856)
  - stasis
  - blood components
  - vessel wall
The burden of the disease

- VTE is the 3rd most common type of cardiovascular disease\(^1\)
- VTE causes over 500,000 deaths in Europe and 300,000 deaths in the United States each year\(^2,3\)
- Annual deaths attributable to VTE are estimated to exceed the combined number of deaths from breast and prostate cancers, AIDS, and traffic accidents\(^4\)
- Total estimated cost for VTE-associated care = EUR 3.1 billion per year\(^5\)

5. Cohen AT, et al. Poster presented at the ISPOR 8th Annual European Congress; 2005; November 6-8; Florence, Italy.
Annual Incidence of Venous Thromboembolism

- Symptomatic, objectively confirmed and population based

- F. Anderson et al. VTE: 1.07 per 1000
  - 1991, Arch Intern Med
  - 66% first episode
  - DVT : PE = 2 : 1

- M. Nordstrom et al. DVT: 1.6 per 1000
  - 1992, J Intern Med

- M. Silverstein et al. First VTE: 1.17 per 1000
  - 1998, Arch Int Med

→ 2 per 1000 per year
Natural History

Untreated, symptomatic

- Isolated Calf DVT: ± 33% extend proximally
- Proximal DVT: ± 50% symptomatic PE in 3 months
- PE: – 26% fatal recurrent PE in 2 weeks
  – 26% non-fatal recurrence

C. Kearon et al. 2001, Haemostasis and Thrombosis
Three Phases in the Evaluation of Antithrombotic Therapies in VTE and Evolution of Outcome Assessment

- **First Phase** 1938 – late 1960’s
- **Second Phase** 1972 – early 1990’s
- **Third Phase** 1992 – 2010
First Phase

First use of heparin in 35 pts with VTE.
Murray and Best (1938)

Heparin i.v. in 209 VTE pts with only 3 deaths
Bauer (1946)

Heparin and dicoumarol in 329 PE pts with one death.
Allen et al (1947)

Heparin i.v. and nicoumalone vs no treatment randomized comparison in 35 PE pts.
Barritt and Jordan (1960)

Survival as major outcome
Second Phase

Studies about the appropriate monitoring of APTT and INR, as well as the duration of initial therapy (1972 to early 1990’s)

Symptomatic recurrent venous thromboembolism and major bleeding as major outcomes
Third Phase

Studies with LMWH, pentasaccharides, thrombin inhibitors and factor Xa inhibitors. (1992 – approx 2010)

Out of hospital treatment, no laboratory monitoring, ease of use, non-inferiority for efficacy and clinically relevant/non major bleeding as major outcomes. No distinction between initial and long term treatment
Treatment Spectrum

**Massive VTE** *(serious compromise of lung perfusion/impending gangrene)*
- thrombolysis (surgery)

**Minimal VTE** *(no tendency to extend or re-occur)*
- wait and see

**Other VTE**
- *(LMW)* Heparin and VKA
Heparin 1916–1937

- Discovered 1916
- Maclean
- Human use 1937
- Lancet 1960 – it works! (Barrit and Jordan)
- Animal derived
- Side-effects
- Intravenous, monitoring, adjustment
Current evidence-based treatment recommendations for venous thromboembolism

8th ACCP Chest 2008;133, 454-545
ACCP 2008 Treatment of venous thromboembolism

UFH (i.v., s.c., s.c. fixed doses)
LMWH
Fondaparinux
Thrombolysis

**Initial treatment**
- INR 2.0–3.0

**Long term-treatment**

**Extended* treatment**
- ≥ 5 days
- at least 3 months
- indefinite*

*With re-assessment of the individual risk-benefit at periodic intervals

INR = international normalized ration; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist.

Recommendations

- Initial therapy LMWH/UFH
- Alternatives for LMWH/UFH
- Thrombolytic therapy
- Caval filter
- Ambulation
- Start of VKA
- INR intensity
- VKA duration
- Long term treatment in cancer patients
- Compression stockings
Current problems in the treatment of venous thromboembolism

- Need for s.c. injections
- Monitoring and dose adjustment of vitamin K antagonists
- Efficacy excellent, but safety requires improvement (10% bleeding in 3 months)
- Optimal duration is unknown
- Best treatment in cancer patients
Coagulation cascade

**Initiation**
- TF/VIIa

**Propagation**
- II
  - X
    - IX
    - IXa
  - IIa
    - Va

**Thrombin activity**
- Xa

**Drug**
- Tissue factor Pathway inhibitor (TFPI) (Recombinant)
- Nematode Anticoagulant Peptide (NAPc2)
- Active Site Blocked Factor VIIa (FVIIai)
- TF Mo Ab
- Factor IXa Inhibitors (TTP 889: †)
- Direct Factor Xa Inhibitors
  - Apixaban
  - DU-176b
  - Rivaroxaban
  - YM-150
- Indirect Factor Xa Inhibitors
  - Fondaparinux
  - Idraparinux
  - Orally available heparins
  - Inhibitors of Factor VIIIa and Va
  - Protein C
  - Activated Protein C (drotrecogin alpha)
  - Soluble Thrombomodulin (ART-123)
- Hirudin
- Bivalirudin
- Argatroban
- Dabigatran
- Ximelagatran (†)
DE EERSTE ORALE ANTISTOLLING
ZONDER LABCONTROLE

Pradaxa
Transforming anticoagulation
Classical Pathway of the Evaluation of New Antithrombotics

- First: orthopaedic surgery
- Second: treatment of established venous thrombosis
- Third: atrial fibrillation acute coronary syndromes
Human Factor Xa/rivaroxaban complex

X-ray crystal structure
Roehrig et al., J Med Chem 2005

- Selective for Factor Xa ($K_i = 0.4 \pm 0.02$)
  - No effects on Factor VIIa, Factor IXa, Factor XIa, kallikrein, thrombin, activated protein C, plasmin, tPA, urokinase, trypsin, chymotrypsin ($IC_{50} > 20,000$-fold)
- Inhibits:
  - Free Factor Xa
  - Prothrombinase activity
  - Fibrin-bound Factor Xa
- Does not require a cofactor
- No direct effect on thrombin
- No direct effect on agonist-induced platelet aggregation
RECORD 1, 2 and 3 publications

**RECORD: phase III programme for VTE prevention**

- Rivaroxaban 10 mg once daily investigated
- Same study design and efficacy and safety outcomes
  - Randomized, active-comparator-controlled, parallel-group, double-blind, double-dummy
- Same independent, blinded adjudication committees

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RECORD1</strong></td>
<td>HIP replacement</td>
<td>Rivaroxaban 10 mg od for 5 weeks vs enoxaparin 40 mg od for 5 weeks</td>
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<tr>
<td><strong>RECORD2</strong></td>
<td>HIP replacement</td>
<td>Rivaroxaban 10 mg od for 5 weeks vs enoxaparin 40 mg od for 10–14 days then oral placebo</td>
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<tr>
<td><strong>RECORD3</strong></td>
<td>KNEE replacement</td>
<td>Rivaroxaban 10 mg od for 10–14 days vs enoxaparin 40 mg od for 10–14 days</td>
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<tr>
<td><strong>RECORD4</strong></td>
<td>KNEE replacement</td>
<td>Rivaroxaban 10 mg od for 10–14 days vs enoxaparin 30 mg bid for 10–14 days</td>
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</table>
Efficacy: Total VTE (primary endpoint)

- Rivaroxaban 10mg
- Enoxaparin 40mg

*Relative risk reduction based on raw incidences; p-values based on test on weighted absolute differences*
**Symptomatic VTE: summary**

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Incidence (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECORD1</td>
<td>Enoxaparin 40 mg od 11/2206</td>
<td>0.5%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban 10 mg od 6/2193</td>
<td>0.3%</td>
<td></td>
</tr>
<tr>
<td>RECORD2</td>
<td>Short-duration enoxaparin + placebo 15/1207</td>
<td>1.2%</td>
<td>p=0.004</td>
</tr>
<tr>
<td></td>
<td>Extended-duration rivaroxaban 3/1212</td>
<td>0.2%</td>
<td></td>
</tr>
<tr>
<td>RECORD3</td>
<td>Enoxaparin 40 mg od 24/1217</td>
<td>2.0%</td>
<td>p=0.005</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban 10 mg od 8/1201</td>
<td>0.7%</td>
<td></td>
</tr>
<tr>
<td>RECORD4</td>
<td>Enoxaparin 30 mg bid 18/1508</td>
<td>1.2%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban 10 mg od 11/1526</td>
<td>0.7%</td>
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</tbody>
</table>

Safety population who underwent surgery
RECORD1, n=4399; RECORD2, n=2419; RECORD3, n=2418; RECORD4, n=3034
Major bleeding: summary

**RECORD 1**
- **Rivaroxaban 101mg 1 od**
  - 0.3%
  - Incidence (%)
  - 6/2209

- **Enoxaparin 40 mg od**
  - 0.1%
  - Incidence (%)
  - 2/2224

**RECORD 2**
- **Short-duration enoxaparin + placebo**
  - <0.1%
  - Incidence (%)
  - 1/1229

- **Extended-duration rivaroxaban**
  - <0.1%
  - Incidence (%)
  - 1/1228

**RECORD 3**
- **Enoxaparin 40 mg od**
  - 0.5%
  - Incidence (%)
  - 6/1239

- **Rivaroxaban 10 mg od**
  - 0.6%
  - Incidence (%)
  - 7/1220

**RECORD 4**
- **Enoxaparin 30 mg bid**
  - 0.3%
  - Incidence (%)
  - 4/1508

- **Rivaroxaban 10 mg od**
  - 0.7%
  - Incidence (%)
  - 10/1526
Rivaroxaban ongoing

- Prevention VTE in elective knee and elective hip surgery (Record program) Phase III
- Treatment of VTE (Einstein program) Phase III
- Artrial fibrillation Phase III
- Acute conorary syndrome (ATLAS-TIMI) Phase II
New Anticoagulants

Coagulation cascade

Drug

- Tissue factor Pathway inhibitor (TFPI) (Recombinant)
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Idraparinux: once-weekly anticoagulant

Sulfate group on H block

Long half-life

Once weekly administration

Idraparinux for VTE treatment
Phase III programme – Van Gogh

Van Gogh PE
Idraparinux, 13 weeks
Idraparinux, 26 weeks
(LMW)H/VKA, 13 weeks
(LMW)H/VKA, 26 weeks

Van Gogh DVT
Idraparinux, 13 weeks
Idraparinux, 26 weeks
(LMW)H/VKA, 13 weeks
(LMW)H/VKA, 26 weeks

DVT/PE
(LMW)H/VKA, 26 weeks

Van Gogh Extension
Idraparinux 6 months
Double-blind
Placebo 6 months
Safety observational period
3/6 months
Final contact

3/6 months

(LMW)H = (low-molecular-weight) heparin; VKA = vitamin K antagonist.

Buller et al. NEJM 2007;357:1094-1104.
Buller et al. NEJM 2007;357:1105-1112.
Possible reasons for different results for efficacy for DVT vs PE

- Lower risk patients, or different burden of thromboembolism
- Failure to receive idraparinux and/or missed injections
- Diagnostic suspicion bias
- Pharmacokinetics and/or pharmacodynamics of idraparinux
- Chance
Biotinylated idraparinux: Structure and product profile

- Idraparinux active moiety responsible for pharmacological activity for both molecules
- Biotinylated part allows neutralization by avidin (extracted from white part of eggs)
- Bioequipotency of 3 mg biotinylated idraparinux with 2.5 mg idraparinux after a single injection
Biotinylated Idraparinux ongoing

• Prevention VTE no studies

• Treatment of VTE
  – Equinox (DVT) bioequipotency
  – Cassiopea (PE) Phase III

• Atrial fibrillation
  – Borealis Phase III
New Anticoagulants

Coagulation cascade

Initiation

TF/VIIa

TF/VIIa

IXa

IX

VIIa

X

Fibrinogen

Fibrin

Thrombin activity

II

IIa

Va

Xa

IXa

Factor IXa Inhibitors (TTP 889: †)
- Direct Factor Xa Inhibitors
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New Anticoagulants

- Tissue factor Pathway inhibitor (TFPI) (Recombinant)
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Dabigatran Etexilate

- An oral, small molecule, reversible, direct thrombin inhibitor
- Prodrug: dabigatran etexilate
- Absolute bioavailability $\sim 6.5 \%$
- Half life 14-17 hours
- Renal excretion 80%

### Dabigatran, a new oral direct thrombin inhibitor in development

#### Results of RE-MODEL, RE-MOBILIZE, and RE-NOVATE trials

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Dabigatran (150 mg)</th>
<th>Dabigatran (220 mg)</th>
<th>Enoxaparin (40 mg/30 mg bid)</th>
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</thead>
<tbody>
<tr>
<td>VTE+/−Mortality (%)</td>
<td>40.5</td>
<td>36.4</td>
<td>37.7</td>
</tr>
<tr>
<td>Major bleeding (%)</td>
<td>1.3</td>
<td>1.5</td>
<td>1.3</td>
</tr>
<tr>
<td>RE-MODEL TKR; 6-10 d; EU</td>
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<tr>
<td>RE-MOBILIZE TKR; 12-15 d; NA</td>
<td>33.7</td>
<td>31.1</td>
<td>25.3</td>
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<tr>
<td>RE-NOVATE THR; 28-35d; EU</td>
<td>8.7</td>
<td>6.0</td>
<td>6.7</td>
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</table>

Caprini, ISTH, 2007; Eriksson, ASH, 2006
Dabigatran etexilate ongoing

• Prevention VTE in elective hip/knee (Renovate; Remobilize) Phase III
• Treatment of VTE (Recover; Remedy) Phase III
• Atrial fibrillation (Rely) Phase III
Challenges for venous thromboembolism treatment - 2020 -

- Studying all new antithrombotic agents
- Improving facilities for out of hospital treatment/monitoring
- Better stratification for who should be treated long term
- Single drug treatment
- Heparin and vitamin K antagonists will play minor role. Challenges for compliance and monitoring
Conclusions

• Real explosion of compounds
• Some major failures
• Some will definitely survive
• There is life after warfarin and heparin