20th Cardiology Update 2013

Edoxaban in Venous Thromboembolism

The HOKUSAI VTE study

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Medizinische Klinik 2
Kardiologie – Angiologie – Intensivmedizin - stroke
## Risk factors for VTE (not exhaustive)

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Surgical therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Surgical therapy</td>
</tr>
<tr>
<td>Obesity</td>
<td>Malignancy</td>
</tr>
<tr>
<td>Varicose veins</td>
<td>Cardiac/respiratory failure</td>
</tr>
<tr>
<td>Immobility / Hospital stay</td>
<td>Myocardial infarction</td>
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<tr>
<td>Pregnancy</td>
<td>Paralysis of lower limb(s)</td>
</tr>
<tr>
<td>Biologic thrombophilia</td>
<td>Infection</td>
</tr>
<tr>
<td>Hormone therapy</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td><strong>Previous VTE</strong></td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Long-haul flights</td>
<td>Polycythæmia</td>
</tr>
</tbody>
</table>
## Attributable risk for DVT/PE

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>AR (%)</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalisation with surgery</td>
<td>23.8</td>
<td>(20.3–27.3)</td>
</tr>
<tr>
<td>Hospitalisation without surgery</td>
<td>21.5</td>
<td>(17.3–25.6)</td>
</tr>
<tr>
<td>Malignant neoplasm</td>
<td>18.0</td>
<td>(13.4–22.6)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>9.5</td>
<td>(3.3–15.8)</td>
</tr>
<tr>
<td>Neurological disease with extremity paresis</td>
<td>6.9</td>
<td>(3.5–10.2)</td>
</tr>
</tbody>
</table>

59% Medical

Sequelae of venous thromboembolism

**Immediate consequence of DVT**
- Pulmonary embolism

**Late consequences**
- Chronic pulmonary hypertension (PE)
- Postthrombotic syndrome (DVT)

10% of hospital deaths are due to PE
1% of all hospital admissions die from PE
Late sequelae

Pulmonary hypertension

- 20-50% with symptoms 1-2 years after proximal DVT
- 1-3% ulcers
- PTS rate halved by elastic compression

Postthrombotic syndrome

1.0% at 6 months
3.1% at 1 year
3.8% at 2 years

Pengo V et al.

Shbaklo H & Kahn SR.
Curr Opin Hematol 2008;15:494-8
Therapy of VTE

- Acute
- Intermediate
- Long term

- Initial
- Early maintenance
- Long term maintenance

- Anticoagulation

- Compression Therapy

- Thrombolysis
- Surgery
Anticoagulation in VTE

Initial therapy
LMH, Fondaparinux
exceptions: high-risk PE, renal impairment

Early maintenance therapy
VKA
exceptions: cancer, other comorbidities, planned procedures, very elderly, compliance issues...

Prolonged maintenance therapy
VKA
exceptions: rare cases
The ideal anticoagulant drug

• Rapidly inhibits thrombus progression
• Can be administered orally
• Exhibits a large therapeutic margin
• Has predictable pharmacokinetics and dose-response relationship
• Exhibits a low non-specific binding to plasma proteins
• Does not require laboratory monitoring
• Does not need frequent dose adjustments
• Produces few bleeding complications
• Produces few adverse events
• Exhibits few interactions with other drugs and with food
How ideal are heparins?

**Drawbacks of UFH/LMWH/fondaparinux**

- Need for antithrombin to inactivate thrombin
- Inability to inactivate fibrin-bound thrombin
- Laboratory monitoring
- Risk of heparin-induced thrombocytopenia (HIT)
- Parenteral application
- Animal origin (except fondaparinux)
- Suboptimal efficacy/safety ratio
How ideal are vitamin K antagonists?

**Drawbacks of VKA**

- Rapidly inhibits thrombus progression
- **Can be administered orally**
  - Exhibits a large therapeutic margin
  - Has predictable pharmacokinetics and dose-response relationship
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The HOKUSAII VTE study
Trial Hypotheses

1. A regimen of LMW(Heparin)/edoxaban is non-inferior (=not worse than) to the standard treatment regimen of LMW(Heparin)/warfarin in the treatment/prevention of VTE

2. The incidence of bleeding of LMW(Heparin)/edoxaban is equal or better to LMW(Heparin)/warfarin
Rationale and Background

The study is designed to reflect the current standard-of-care treatment of a VTE event

Double-blind study

Dose selection

- Phase 1 PK/PD
- Phase 2: prophylaxis and AF studies
- Population-PK modeling, logistic regression of PK exposure to bleeding events; and clinical trial simulations.
HOKUSAI Design
Randomized double blind study with clinical outcomes

Symptomatic confirmed VTE event

Heparin based initial treatment

- placebo warfarin
- placebo edoxaban

edoxaban 60mg

Day 1-5 Day 6-12

Sham INR

INR

warfarin

3 M 6 M 12 M

12 months of treatment or shorter ~ mitigating factors in subject’s clinical status
But efficacy and safety data will need to be collected during the entire 12-month study period
Inclusion criteria

1. Male or female subjects older than the adult legal lower age limitation (country specific)
2. Site confirmed acute symptomatic proximal deep vein thrombosis (DVT) of the leg and/or symptomatic pulmonary embolism (PE)
3. Able to provide written informed consent
1. Index event PE/DVT (≥40% PE patients)

2. Dose reduction
   a) Body weight ≤ 60 Kg
   b) Calculated CrCl 30 – 50 mL/min
   c) Concomitant use of strong PgP inhibitors

3. Transient (reversible) risk factors vs. idiopathic

A balanced randomization by region (local clinical practice) will be produced via the IXRS system
Flexible treatment duration

At least 3 months
Risk-benefit in individual patient
Possibility to prolong or shorten intended duration
Active approach to ensure VKA quality

- POC device
  - Standardisation of test and reagent
- DMC review: TTR per center
- Time between INR measurements and time since out of range INR
- Blinded feedback to centers, plus advice and education
- Feedback on improvement
- Goal TTR above 60%
Unique study features

- Flexible treatment duration (3-12 months)
- Simulate usual clinical practice
- Strict INR monitoring and feedback
- Follow-up of all patients for 12 months
- Primary efficacy analysis at 12 months, regardless duration of therapy
- Large study; strict non-inferiority margin
- Global distribution
Sample size consideration

- Event driven
- Non-inferiority margin 1.5
- $\alpha = 0.05$ (two-sided)
- 40% PE
- 80% power
- 7500 patients or more
Study conduct

- 437 active centers
- 37 countries (incl. Japan)
- Good distribution over Americas, Europe and Asia
- Recruitment finished in September 2012
- Follow-up almost finished
- Results to be awaited this year
Novel direct oral anticoagulants for treatment of VTE

- Rivaroxaban / Apixaban
- Dabigatran / Edoxaban

- Acute
- Intermediate term
- Long term

- Initial
- Early maintenance
- Prolonged / long term maintenance
Anticoagulation
Thank you for your attention