Improving protection against venous thromboembolism with new oral anticoagulants?

VTE Prophylaxis in Orthopedic Surgery. The unfinished Business

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Orthopedic Department Klinikum Frankfurt-Höchst, Germany

2nd International SAVTE Symposium
Sheraton Hotel, Casablanca 1.-3. May 2012
Advances in Orthopedic surgery ...

- Shorter operation
- Minimal bone/soft tissue damage
- Reduced blood loss
- Full weight bearing
Increase in major orthopedic surgery

Statistisches Bundesamt, 2008
Increase in revision surgery

Revision surgery in total hip and total knee replacement between 2003 and 2009 in Germany.
Cost development in total hip replacement

Primary THR
209000
Costs for Health insurance
1.6 Mrd. €
Revision surgery
30000
resulting costs for Health insurance
330 Mio. €

Total hip replacement
In Germany 2009

Quelle: Barmer GEK Report Krankenhaus 2010

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The evolution of anticoagulants

Heparin

1930s

1940s

1980s

1990s

2002

2004

2008

Heparin

VKAs

LMWHs

Direct thrombin inhibitors

Indirect Factor Xa inhibitors

Oral direct thrombin inhibitors

Oral direct Factor Xa inhibitors

L.Boris. EFORT - Symposium 2011
Development to current anticoagulants

Improving VTE prophylaxis?

**NOT ALLOWED !!!**

<table>
<thead>
<tr>
<th>Incidence (%)</th>
<th>Total knee replacement</th>
<th>Total hip replacement</th>
<th>Hip fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>30.6</td>
<td>16.1</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>27.0</td>
<td>15.1</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>16.1</td>
<td>8.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.5</td>
<td>5.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.6</td>
<td>1.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31.1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Total DVT; †total VTE*

## Comparision between the NOACs

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Dabigatran</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>vs. Enoxaparin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EU-Regimen:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1x 40mg</td>
<td>RECORD 1</td>
<td>RE-NOVATE</td>
<td>Advance 3</td>
</tr>
<tr>
<td>preoperative start</td>
<td>THR, N=4.541</td>
<td>THR, N=3.494</td>
<td>THR, N=5.407</td>
</tr>
<tr>
<td></td>
<td>RECORD 2</td>
<td>RE-MODEL</td>
<td>Advance 2</td>
</tr>
<tr>
<td></td>
<td>THR, N=2.300</td>
<td>TKR, N=2.076</td>
<td>TKR, N=3.057</td>
</tr>
<tr>
<td></td>
<td>RECORD 3</td>
<td>RE-NOVATE II</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TKR, N=2.531</td>
<td>TKR, N=2.055</td>
<td></td>
</tr>
<tr>
<td><strong>vs. Enoxaparin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>US-Regimen:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2x 30mg</td>
<td>RECORD 4</td>
<td>RE-Mobilize</td>
<td>Advance 1</td>
</tr>
<tr>
<td>postoperative start (12-24h)</td>
<td>TKR, N=2.300</td>
<td>N=2.715</td>
<td>THR, N= 3.195</td>
</tr>
</tbody>
</table>

**Superiority:**

**Non-inferiority**

**Inferiority**

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What needs to be improved in VTE prophylaxis in THR and TKR today?

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Waiting for primary haemostasis before starting anticoagulation !!!

It takes about 8 hours for an initial platelet plug to solidify into a stable clot that will remain intact after administration of additional anticoagulant medications\(^1\)

The new oral anticoagulants

Rivaroxaban

Dabigatran

Apixaban

<table>
<thead>
<tr>
<th>Postoperative start</th>
<th>6-10 hours</th>
<th>1- 4 hours</th>
<th>12 - 24 hours</th>
</tr>
</thead>
</table>

“… start of prophylaxis decides about the balance between efficacy and safety after surgery…”

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Why new oral anticoagulants? 
oral administration with postoperative start

NOACs inhibit
- free Factor Xa/IIa
- fibrin-bound Factor Xa/IIa = Factor Xa/IIa in the clot
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The new oral anticoagulants

- **Rivaroxaban**
- **Dabigatran**
- **Apixaban**

<table>
<thead>
<tr>
<th>Elimination</th>
<th>1/3 Renal</th>
<th>80% Renal</th>
<th>¼ Renal</th>
</tr>
</thead>
</table>

“… high renal elimination needs dose adjustment in renal impairment”

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**LMWH & renal impairment**

- **Relevant renal impairment?**

  In relevant renal impairment (GFR < 30ml/min) cumulation risk in LMWH is depending from molecular weight.

<table>
<thead>
<tr>
<th>LMWH</th>
<th>Molec. Weight (D)</th>
<th>Xa/Fa ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certoparin</td>
<td>5200</td>
<td>2.2</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>6000</td>
<td>2.5</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>4500</td>
<td>4.3</td>
</tr>
<tr>
<td>Nadroparin</td>
<td>4500</td>
<td>4.0</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>6500</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Cumulation risk increases with decreasing molecular weight.

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### NOACs and renal impairment

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>&lt; 30</th>
<th>30 - 60</th>
<th>&gt; 60</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>&lt;15 not recommended; 15-30 use with care</td>
<td>OK carefull with other drugs</td>
<td>OK</td>
</tr>
<tr>
<td><strong>Dabigatran</strong></td>
<td>contraindication !</td>
<td>30 – 50: Dose adjustment 220 =&gt; 150mg use with care</td>
<td>OK</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td>&lt;15 not recommended; 15-30 use with care</td>
<td>OK Carefull wit other drugs</td>
<td>OK</td>
</tr>
</tbody>
</table>

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The new oral anticoagulants

<table>
<thead>
<tr>
<th>Drug</th>
<th>T ( \frac{1}{2} ) (Hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>~ 9</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>~ 16</td>
</tr>
<tr>
<td>Apixaban</td>
<td>~ 12</td>
</tr>
</tbody>
</table>

“… the shorter the \( \frac{1}{2} \) life, the easier the management of emergency situations when no antidote is available…”

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How should haemorrhagic complications associated with NOAC be managed?

- Treatment must be discontinued
- Source of bleeding must be investigated
- Initiation of appropriate treatment (e.g. surgical haemostasis, transfusion blood/PPSB)

Are there anticoagulant agents available for all NOACs?

- Antidote not available?
- Antidote: PCC => immediate and completely for Rivaroxaban
  => not for Dabigatran
The anticoagulant effect of FIIa/Xa inhibitors cannot be compared to the effect of VKA!

INR is only valid for VKA!
coagulation monitoring !

Appropriate tests* (FXa inhibitors)

- Prothrombin time (PT in seconds by Neoplastin-Plus Essay)
- Anti-Factor-Xa- Activity

Appropriate tests (FIIa inhibitors)

- aPTT
- Thrombin time
- Ecarin Clotting time

* Technoview Rivaroxaban for Technochrom Anti-Faktor-Xa-Assay (Fa. Technoclone)
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## VTE Risk in THR and TKR

<table>
<thead>
<tr>
<th></th>
<th>total DVT</th>
<th>Proximal DVT</th>
<th>total PE</th>
<th>fatal PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>THR</td>
<td>42–57 %</td>
<td>18–36 %</td>
<td>0,9–28 %</td>
<td>0,1–2,0 %</td>
</tr>
<tr>
<td>TKR</td>
<td>41–85 %</td>
<td>5–22 %</td>
<td>1,5–10 %</td>
<td>0,1–1,7 %</td>
</tr>
</tbody>
</table>

*Adapted from Geerts et al. Chest 2008;133:381S-453S*
cumulative VTE rate in THR & TKR


Extended prophylaxis in
THR 5 weeks
TKR at least 2 weeks
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Perioperative management with Rivaroxaban
( SPAF & treatment)

pre OP

♦ Xarelto® (20mg or 15mg in therapeutic dose) should be interrupted at least 24 hours before intervention

post OP

♦ Xarelto® 6 – 10 hours after intervention in same dose regimen as before as soon as adequate haemostasis has occurred

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Perioperative management with Dabigatran (SPAF)

**pre OP**

- Dabigatran should be interrupted between 1 and 4 days, depending on bleeding risk. Bridging with UFH or LMWH needed.

<table>
<thead>
<tr>
<th>Renal function (cr cl ml/min)</th>
<th>$T_{\frac{1}{2}}$ (hours)</th>
<th>Time to discontinue Dabigatran before an intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 80</td>
<td>~ 13</td>
<td>High bleeding risk 2 days 24 hours</td>
</tr>
<tr>
<td>50 - 80</td>
<td>~ 15</td>
<td>3 days 1-2 days</td>
</tr>
<tr>
<td>30 - 50</td>
<td>~ 18</td>
<td>4 days 2-3 days</td>
</tr>
</tbody>
</table>

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Thank you for your attention!