Challenges of defining a non–inferiority margin: a case study of non–inferiority randomized controlled trials of oral anticoagulants for prophylaxis of venous thromboembolic events after orthopedic surgery

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Background and aim

- Non-inferiority (NI) margin
- Draft FDA guideline 2010

Aim of study:
identify problems and difficulties in determining NI margin

case study on
RCTs of oral anticoagulants for prophylaxis of venous thromboembolic events (VTE) after orthopedic surgery.
Search strategy & publication selection (NI trials)

**Pubmed search term:**


326 articles

**Cochrane search term:**

"hirudin or bivalirudin or lepirudin or desirudin or argatroban or dabigatran or melagatran or ximelagatran or apixaban or edoxaban or otamixaban or rivaroxaban" in Title, Abstract or Keywords in Cochrane Central Register of Controlled Trials

592 articles

**Excluded 906 publications:**

Other indication : 332
Review and non – RCT articles : 68
Healthy volunteers: 105
Not in English : 6
Superiority trials : 8
Double publication : 387

12 articles /NI trials
<table>
<thead>
<tr>
<th>Name of Trial</th>
<th>Name of drug</th>
<th>Duration of therapy and fol. up (days)</th>
<th>Dosage of enoxaparin</th>
<th>NI margin</th>
<th>Method to determine NI margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colwell, et.al.</td>
<td>Ximelagatran</td>
<td>7-12</td>
<td>30 mg bid</td>
<td>RD = 5%</td>
<td>Used the same NI margin as published NI trial on Tinzarapin vs Enoxaparin</td>
</tr>
<tr>
<td>EXPRESS</td>
<td>Dabigatran</td>
<td>8-12</td>
<td>40 mg qd</td>
<td>RD = 2%</td>
<td>Not described</td>
</tr>
<tr>
<td>REMODEL</td>
<td>Dabigatran</td>
<td>6-10</td>
<td>40 mg qd</td>
<td>RD = 9.2%</td>
<td>- 67% preserved-effect of difference between enoxaparin and placebo</td>
</tr>
<tr>
<td>RE MOBILIZE</td>
<td>Dabigatran</td>
<td>12-15</td>
<td>30 mg bid</td>
<td>RD = 9.2%</td>
<td>- 67% preserved-effect of difference between enoxaparin and placebo - Based on one published placebo controlled trial</td>
</tr>
<tr>
<td>Re-Novate</td>
<td>Dabigatran</td>
<td>28-35</td>
<td>40 mg qd</td>
<td>RD = 7.7%</td>
<td>67% preserved-effect of difference between enoxaparin and placebo - Based on pooled analysis of 3 placebo controlled trials</td>
</tr>
<tr>
<td>EXTEND</td>
<td>Ximelagatran</td>
<td>32-38</td>
<td>40 mg qd</td>
<td>RD = 2%</td>
<td>Not described</td>
</tr>
<tr>
<td>RECORD 1</td>
<td>Rivaroxaban</td>
<td>35</td>
<td>40 mg qd</td>
<td>RD = 3.5%</td>
<td>Not described</td>
</tr>
<tr>
<td>RECORD 3</td>
<td>Rivaroxaban</td>
<td>10 - 14</td>
<td>40 mg qd</td>
<td>RD = 4%</td>
<td>Not described</td>
</tr>
<tr>
<td>RECORD 4</td>
<td>Rivaroxaban</td>
<td>11-15</td>
<td>30 mg bid</td>
<td>RD = 4%</td>
<td>Not described</td>
</tr>
<tr>
<td>ADVANCE 1</td>
<td>Apixaban</td>
<td>10 - 14</td>
<td>30 mg bid</td>
<td>RD = 5.6% RR = 1.25</td>
<td>Not described</td>
</tr>
<tr>
<td>ADVANCE 3</td>
<td>Apixaban</td>
<td>32-38</td>
<td>40 mg qd</td>
<td>RR = 1.25</td>
<td>Not described</td>
</tr>
<tr>
<td>ADVANCE 2</td>
<td>Apixaban</td>
<td>10 - 14</td>
<td>40 mg qd</td>
<td>RD = 5.6% RR = 1.25</td>
<td>Not described</td>
</tr>
</tbody>
</table>
Methods

Search of Placebo-controlled trials of active comparator → Pooled analysis of the point estimates

\[ M1 \]
Upper bound of 95% confidence interval (CI)

\[ RD \]

\[ RR \]
Statistical margin
Clinical margin

preserved effect
67% and 50%

\[ (1 - \text{preserved-effects})^* \rightarrow (M1) \]

\[ (1 - \text{preserved-effects}) \]

\[ (1/M1)^* \rightarrow \text{preserved-effects} \]

\[ I: \text{control effect vs. placebo} \]
\[ II: \text{increased risk of placebo vs. active comparator} \]
\[ III: \text{increased risk of placebo vs. active comparator after log transformation:} \]
\[ e^{\ln(1/M1) \cdot (1 - \text{preserved-effects})} \text{ or } (1/M1)^{1/2} \cdot \text{preserved-effects} \]
**Search strategy & publication selection**
*(placebo–controlled trials of enoxaparin)*

**Pubmed search term:**
("low-molecular weight heparin"[All Fields] OR "low molecular weight heparin"[All Fields] OR "enoxaparin"[All Fields]) AND ("placebos"[All Fields] OR "placebo"[All Fields]) AND "humans"[MeSH Terms]

409 articles

249 articles

**Cochrane search term:**
"("low-molecular weight heparin" OR "low molecular weight heparin" OR "enoxaparin") AND "placebo" in Title, Abstract or Keywords in Cochrane Central Register of Controlled Trials

Excluded 648 publications:
- Different drug (LMWH but not Enoxaparin) : 109
- Other indication : 13
- Review and non–RCT articles : 315
- Different treatment procedure and timing : 6
- Double publication : 205

10 articles/6 placebo-controlled trials

(2 trials were published in 2 different publications, 1 trial was published in 3 different publications)

4 placebo-controlled trials before year 2000
## Results – Placebo-controlled trials

<table>
<thead>
<tr>
<th>Name of author</th>
<th>Date of publication</th>
<th>Duration of therapy (days)</th>
<th>Dosage of enoxaparin</th>
<th>Mean age of subjects</th>
<th>Female subjects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turpie, et.al</td>
<td>Oct-86</td>
<td>14</td>
<td>30 mg bid</td>
<td>67</td>
<td>52</td>
</tr>
<tr>
<td>Leclerc, et.al</td>
<td>Jan-92</td>
<td>14</td>
<td>30 mg bid</td>
<td>69</td>
<td>60</td>
</tr>
<tr>
<td>Kalodiki, et.al</td>
<td>Jun-96</td>
<td>8 - 12</td>
<td>40 mg qd</td>
<td>67</td>
<td>65</td>
</tr>
<tr>
<td>Samama, et.al</td>
<td>Jan-97</td>
<td>10 ± 2</td>
<td>40 mg qd</td>
<td>69</td>
<td>42</td>
</tr>
<tr>
<td>Fuji, et.al (1)</td>
<td>Jun-08</td>
<td>14</td>
<td>20 mg qd, 20 mg bid, 40 mg qd</td>
<td>62</td>
<td>88</td>
</tr>
<tr>
<td>Fuji, et.al (2)</td>
<td>Jun-08</td>
<td>14</td>
<td>20 mg qd, 20 mg bid, 40 mg qd</td>
<td>70</td>
<td>84</td>
</tr>
</tbody>
</table>
Determining reference NI margin

<table>
<thead>
<tr>
<th>Study</th>
<th>Events Total</th>
<th>Control Events Total</th>
<th>RD</th>
<th>95% CI</th>
<th>W(fixed)</th>
<th>W(random)</th>
<th>RR</th>
<th>95% CI</th>
<th>W(fixed)</th>
<th>W(random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986-Turpie</td>
<td>6</td>
<td>50</td>
<td>-0.30</td>
<td>[-0.46; -0.14]</td>
<td>23.6%</td>
<td>25.1%</td>
<td>0.29</td>
<td>[0.13; 0.65]</td>
<td>12.9%</td>
<td>12.9%</td>
</tr>
<tr>
<td>1992-Leclerc</td>
<td>11</td>
<td>65</td>
<td>-0.41</td>
<td>[-0.56; -0.26]</td>
<td>27.6%</td>
<td>26.7%</td>
<td>0.29</td>
<td>[0.16; 0.52]</td>
<td>25.8%</td>
<td>25.8%</td>
</tr>
<tr>
<td>1996-Kalodiki</td>
<td>12</td>
<td>32</td>
<td>-0.55</td>
<td>[-0.77; -0.34]</td>
<td>13.6%</td>
<td>19.2%</td>
<td>0.40</td>
<td>[0.25; 0.65]</td>
<td>39.0%</td>
<td>39.0%</td>
</tr>
<tr>
<td>1997-Samama</td>
<td>11</td>
<td>78</td>
<td>-0.23</td>
<td>[-0.37; -0.10]</td>
<td>35.2%</td>
<td>29.1%</td>
<td>0.38</td>
<td>[0.20; 0.70]</td>
<td>22.3%</td>
<td>22.3%</td>
</tr>
</tbody>
</table>

Fixed effect model: 225 events, 203 control events
Random effects model: 30% events, 31% control events

Preserved-effects
Random-effects model

M1 = -0.23
Method 3

<table>
<thead>
<tr>
<th>Preserved-effects</th>
<th>RD</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>0.115</td>
<td>1.46</td>
</tr>
<tr>
<td>67%</td>
<td>0.076</td>
<td>1.28</td>
</tr>
</tbody>
</table>
Plot of NI trials results on reference NI margin (RD)

Note: 
- NI margin from publication, □: point estimate, 
  §: M2 based on 67% preserved effect, ^: M2 based on 50% preserved effect
Plot of NI trials results reference NI margin (RR)

<table>
<thead>
<tr>
<th>ADVANCE</th>
<th>RR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.02 (0.78 to 1.32)</td>
</tr>
<tr>
<td>2</td>
<td>0.62 (0.51 to 0.74)</td>
</tr>
<tr>
<td>3</td>
<td>0.36 (0.22 to 0.54)</td>
</tr>
</tbody>
</table>

**Note:** : NI margin from publication, •: point estimate.
$\$: M2 based on 67% preserved effect, $\wedge$: M2 based on 50% preserved effect
Challenges in determining a NI margin

Publication bias

Search of Placebo–controlled trials of active comparator

How similar should they be?

Pooled analysis of the point estimates

Fixed or Random Effect?

Which preserved effect to use?

Upper bound of 95\% confidence interval (CI)

Which effect measurement?

M1

RD

RR

M2

Clinical judgment

NI margin used in trials
Discussion and conclusion

• Determination of NI margin is still intricate

• Although a same comparator was used, a variation in NI margins among NI RCTs of oral anticoagulants for prophylaxis of VTE after orthopedic surgery exists

• Using different NI margins could lead to different conclusions.
Escher is project T6–202 of the Dutch Top Institute Pharma

Partners in Escher:
Formula for reference margin calculation

• for the RD
  \[(1 - \text{preserved-effects}) \times -(M1)\]

• for the RR:
  - preserved-effects of the control effect vs. placebo:
    \[\frac{1}{M1 + ((1-M1) \times \text{preserved-effects})}\]
  - preserved-effects of the increased risk of placebo vs. active comparator:
    \[1 + (((1 / M1) - 1) \times (1 - \text{preserved-effects}))\]
  - preserved-effects of the increased risk of placebo vs. active comparator after log transformation:
    \[e^{\ln(1/M1) \times (1 - \text{preserved-effects})}\] or
    \[(1/M1)^{(1 - \text{preserved-effects})}\]