Oral Rivaroxaban Compared With Subcutaneous Enoxaparin for Extended Thromboprophylaxis After Total Hip Arthroplasty

Bengt I Eriksson, Lars C Borris, Richard J Friedman, Sylvia Haas, Menno V Huisman, Ajay K Kakkar, Tiemo J Bandel, Horst Beckmann, Eva Muehlhofer, Frank Misselwitz, William Geerts for the RECORD1 Investigators

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Landmark studies RECORD1, 2 and 3 all published in one week in June 2008

New Anticoagulants – The Path From Discovery to Clinical Practice

“... rivaroxaban was associated with significant reductions in symptomatic and asymptomatic venous thromboembolism and major venous thromboembolism, ... The frequency of major bleeding and other safety outcomes ... was low and did not differ between the study group”

“The path to safer and more effective anticoagulants is paved by scientific knowledge, discovery, due diligence on the part of sponsors working collaboratively with experienced clinicians, and evidence-based translation to patient care and widespread clinical practice”

Rivaroxaban: an oral, direct Factor Xa inhibitor

- 10 mg od was selected for investigation in the phase III RECORD programme based on an extensive phase II programme (N=2,857) that evaluated a wide dose range (total daily doses: 5–60 mg)

- Oral, one tablet, once daily
- Predictable pharmacokinetics and pharmacodynamics
- High bioavailability
- Rapid onset of action
- Fixed dose
- No requirement for coagulation monitoring

Kubitza et al., 2005; Turpie et al., 2005; Eriksson et al., 2006; 2006; 2007
RECORD1 study design

Inclusion criteria

- Patients aged ≥18 years, scheduled to undergo elective THR

Major exclusion criteria

- Active bleeding or high risk of bleeding
- Significant liver disease
- Anticoagulant therapy that could not be stopped
- Use of HIV-protease inhibitors

218 sites worldwide

- United States 3.6%
- Argentina, Colombia, Chile 3.3%
- Australia, South Africa 2.7%
- Germany 6.8%
- France 5.2%
- Finland 2.5%
- Denmark 3.3%
- Poland 15.4%
- Belgium 4.8%
- Brazil 2.6%
- Canada 2.9%
- Greece, Turkey 2.4%
- Israel 2.6%
- Hungary 5.9%
- Lithuania 2.8%
- Norway 1.9%
- Netherlands 4.4%
- Sweden 1.9%
- Spain 4.3%
- Slovakia, Czech Republic 7.3%
- United States 3.6%
- Argentina, Colombia, Chile 3.3%
- Australia, South Africa 2.7%
- Germany 6.8%
- France 5.2%
- Finland 2.5%
- Denmark 3.3%
- Poland 15.4%
- Belgium 4.8%
- Brazil 2.6%
- Canada 2.9%
- Greece, Turkey 2.4%
- Israel 2.6%
- Hungary 5.9%
- Lithuania 2.8%
- Norway 1.9%
- Netherlands 4.4%
- Sweden 1.9%
- Spain 4.3%
- Slovakia, Czech Republic 7.3%

Efficacy endpoints

Primary

- Total VTE: any DVT, non-fatal PE and all-cause mortality at 36 days (range, 30 to 42)

Secondary

- Major VTE: proximal DVT, non-fatal PE, and VTE-related death
- DVT: any, proximal, distal
- Symptomatic VTE

All endpoints were adjudicated centrally by independent, blinded committees

Safety endpoints

Main
- Major bleeding starting after the first blinded dose and up to 2 days after last dose (‘on-treatment’)
  - Bleeding that was fatal, into a critical organ or required re-operation
  - Extra-surgical-site bleeding associated with a drop in hemoglobin ≥2 g/dL or requiring transfusion of ≥2 units of blood

Other
- Any bleeding on treatment*
- Non-major bleeding*
- Hemorrhagic wound complications*#
- Cardiovascular adverse events
- Liver enzyme levels

All endpoints were adjudicated centrally by independent, blinded committees; *Up to 2 days after last dose of study medication; #Composite of excessive wound hematoma and surgical-site bleeding

Statistical analysis of the primary efficacy endpoint

Rivaroxaban better

Enoxaparin better

Test 1. Rivaroxaban non-inferior

Test 2. Rivaroxaban superior

Absolute risk difference ± 95% confidence interval between rivaroxaban and enoxaparin (delta)

Sample size determination:
Estimated incidence of primary efficacy endpoint with both drugs: 8%
Type 1 error rate: 2.5%
Estimated venographic invalidity rate: 25%

Study flow

Enoxaparin

2,275

2,224

2,206

1,678

1,558

1,492

Rivaroxaban

Enrolled (N=4,591)

Randomized (n=4,541)

Safety population

Safety population who underwent surgery

mITT population for major VTE

mITT population for primary efficacy (superiority)

PP population for primary efficacy (non-inferiority)

2,266

2,209

2,193

1,686

1,595

1,537

<table>
<thead>
<tr>
<th>Reason</th>
<th>Enoxaparin 40 mg od</th>
<th>Rivaroxaban 10 mg od</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>2,275</td>
<td>2,266</td>
</tr>
<tr>
<td>No intake of study medication</td>
<td>51</td>
<td>57</td>
</tr>
<tr>
<td>Valid for safety analysis</td>
<td>2,224 97.8%</td>
<td>2,209 97.5%</td>
</tr>
<tr>
<td>Inadequate assessment of thromboembolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Venography not performed</td>
<td>322</td>
<td>319</td>
</tr>
<tr>
<td>– Unilateral venography</td>
<td>105</td>
<td>105</td>
</tr>
<tr>
<td>– Indeterminate/non-evaluable venography</td>
<td>164</td>
<td>121</td>
</tr>
<tr>
<td>– Not in time window*</td>
<td>44</td>
<td>43</td>
</tr>
<tr>
<td>Planned surgery not performed</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>Wrong intake of study medication</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Inadequate evaluation of efficacy**</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Valid for mITT population</td>
<td>1,558 68.5%</td>
<td>1,595 70.4%</td>
</tr>
</tbody>
</table>

*The time window for valid venography was day 36±6; **Source data not verified

### Patient demographics

<table>
<thead>
<tr>
<th></th>
<th>Enoxaparin 40 mg od (n=2,224)</th>
<th>Rivaroxaban 10 mg od (n=2,209)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n %</td>
<td>1,242</td>
<td>1,220</td>
</tr>
<tr>
<td></td>
<td>55.8%</td>
<td>55.2%</td>
</tr>
<tr>
<td>Age, years (range)*</td>
<td>63.3 (18–93)</td>
<td>63.1 (18–91)</td>
</tr>
<tr>
<td>Weight, kg (range)*</td>
<td>78.3 (40–132)</td>
<td>78.1 (37–159)</td>
</tr>
<tr>
<td>Body mass index, kg/m² (range)*</td>
<td>27.9 (15.2–50.2)</td>
<td>27.8 (16.2–53.4)</td>
</tr>
<tr>
<td>Race, n %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Caucasian</td>
<td>2,049</td>
<td>2,041</td>
</tr>
<tr>
<td></td>
<td>92.1%</td>
<td>92.4%</td>
</tr>
<tr>
<td>– Hispanic</td>
<td>31</td>
<td>22</td>
</tr>
<tr>
<td>– Black</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>– Asian</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>– Other/missing</td>
<td>123</td>
<td>121</td>
</tr>
<tr>
<td>History of VTE, n %</td>
<td>55</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>2.5%</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

*Mean values

Primary efficacy endpoint

Total VTE

RRR=70%

ARD=−2.6% (−3.7, −1.5)

p<0.001

Incidence (%)

ARD (with 95% CI); mITT population, n=3,153

Primary efficacy endpoint: individual components

<table>
<thead>
<tr>
<th>n % (95% CI)</th>
<th>Enoxaparin 40 mg od (n=1,558)</th>
<th>Rivaroxaban 10 mg od (n=1,595)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy endpoint</td>
<td>58</td>
<td>3.7% (2.8, 4.8)</td>
<td>18</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>4</td>
<td>0.3% (0.1, 0.7)</td>
<td>4</td>
</tr>
<tr>
<td>Non-fatal PE</td>
<td>1</td>
<td>0.1% (&lt;0.1, 0.4)</td>
<td>4</td>
</tr>
<tr>
<td>DVT</td>
<td>53</td>
<td>3.4% (2.6, 4.4)</td>
<td>12</td>
</tr>
<tr>
<td>– Proximal only</td>
<td>31</td>
<td>2.0% (1.4, 2.8)</td>
<td>1</td>
</tr>
<tr>
<td>– Distal only</td>
<td>22</td>
<td>1.4% (0.9, 2.1)</td>
<td>11</td>
</tr>
</tbody>
</table>

mITT population, n=3,153
Secondary efficacy endpoints

**Major VTE**

- **Rivaroxaban 10 mg od**
  - 4/1,686
  - RRR=88%
  - RRD=−1.7% (−2.5, −1.0)
  - p<0.001

- **Enoxaparin 40 mg od**
  - 33/1,678

**Symptomatic VTE**

- **Rivaroxaban 10 mg od**
  - 6/2,193
  - ARD=−0.2% (−0.6, 0.1)
  - p=0.22

- **Enoxaparin 40 mg od**
  - 11/2,206

mITT population valid for major VTE, n=3,364, and symptomatic VTE in safety population who underwent surgery, n=4,399

Main safety endpoint

Major bleeding

- Enoxaparin 40 mg od 2/2,224
- Rivaroxaban 10 mg od 6/2,209

Incidence (%)

ARD=0.2% (–0.1, 0.5)

p=0.18

On-treatment major bleeding; unweighted ARD (with 95% CI); safety population, n=4,433

## Safety: components of bleeding

### On-treatment bleeding events; *major bleeding events could qualify for more than one subcategory; #event occurred before intake of first rivaroxaban dose; ‡extra-surgical-site bleeding; §composite of excessive wound hematoma and surgical-site bleeding; safety population, n=4,433

<table>
<thead>
<tr>
<th></th>
<th>Enoxaparin 40 mg od (n=2,224)</th>
<th>Rivaroxaban 10 mg od (n=2,209)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any bleeding</strong></td>
<td>131 5.9%</td>
<td>133 6.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Major bleeding</strong>*</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Into a critical organ</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Leading to re-operation</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Leading to fall in hemoglobin‡</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Leading to transfusion of ≥2 units of blood‡</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Non-major bleeding</strong>*</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically relevant non-major bleeding</td>
<td>54 2.4%</td>
<td>65 2.9%</td>
</tr>
<tr>
<td>– Hemorrhagic wound complications§</td>
<td>38 1.7%</td>
<td>34 1.5%</td>
</tr>
<tr>
<td>Other non-major bleeding</td>
<td>77 3.5%</td>
<td>71 3.2%</td>
</tr>
</tbody>
</table>

---

## Adverse events

<table>
<thead>
<tr>
<th></th>
<th>Enoxaparin 40 mg od (n=2,224)</th>
<th>Rivaroxaban 10 mg od (n=2,209)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any adverse event (all)</strong></td>
<td>1,471 66.1%</td>
<td>1,453 65.8%</td>
</tr>
<tr>
<td>On treatment</td>
<td>1,439 64.7%</td>
<td>1,413 64.0%</td>
</tr>
<tr>
<td>During follow-up</td>
<td>124 5.6%</td>
<td>147 6.7%</td>
</tr>
<tr>
<td><strong>Cardiovascular adverse events (all)</strong></td>
<td>10 0.4%</td>
<td>11 0.5%</td>
</tr>
<tr>
<td>On treatment</td>
<td>9 0.4%</td>
<td>5 0.2%</td>
</tr>
<tr>
<td>During follow-up*</td>
<td>1 &lt;0.1%</td>
<td>7 0.3%</td>
</tr>
<tr>
<td><strong>Wound-related infections (all)</strong></td>
<td>9 0.4%</td>
<td>9 0.4%</td>
</tr>
<tr>
<td>On treatment</td>
<td>8 0.4%</td>
<td>8 0.4%</td>
</tr>
<tr>
<td>During follow-up</td>
<td>1 &lt;0.1%</td>
<td>1 0.1%</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>5 0.2%</td>
<td>5 0.2%</td>
</tr>
</tbody>
</table>

*Events occurring more than 1 day after the last intake of study drug; †Patients may have had more than one event; safety population, n=4,433

# Liver function tests

<table>
<thead>
<tr>
<th>n/N %</th>
<th>Enoxaparin 40 mg od</th>
<th>Rivaroxaban 10 mg od</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT &gt;3×ULN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On treatment*</td>
<td>57/2,129 2.7%</td>
<td>43/2,128 2.0%</td>
</tr>
<tr>
<td>During follow-up</td>
<td>6/1,926 0.3%</td>
<td>3/1,931 0.2%</td>
</tr>
<tr>
<td>ALT &gt;3×ULN + bilirubin &gt;2×ULN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On treatment*</td>
<td>1/2,142 &lt;0.1%</td>
<td>1/2,143 &lt;0.1%</td>
</tr>
<tr>
<td>During follow-up</td>
<td>0/1,925 0.0%</td>
<td>0/1,943 0.0%</td>
</tr>
</tbody>
</table>

*From first intake of study drug up to 2 days after the last intake of study drug

RECORD1: summary

<table>
<thead>
<tr>
<th>Category</th>
<th>Incidence (%)</th>
<th>RR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total VTE</td>
<td>3.7</td>
<td>70</td>
</tr>
<tr>
<td>Major VTE</td>
<td>1.1</td>
<td>88</td>
</tr>
<tr>
<td>Symptomatic VTE</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.1</td>
<td></td>
</tr>
</tbody>
</table>

First study comparing a LMWH (enoxaparin) with an oral Factor Xa inhibitor (rivaroxaban) for extended prophylaxis (5 weeks) in patients undergoing elective, total hip arthroplasty

- Oral rivaroxaban 10 mg od was significantly more effective than subcutaneous, enoxaparin 40 mg od
- Rivaroxaban showed a similar safety profile to enoxaparin

Thank you to the patients, their relatives, the study nurses, and...