Anticoagulation Therapy in SELECTed Cancer Patients at Risk of Recurrence of Venous Thromboembolism

Annie Young PhD
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on behalf of the select-d Collaborative Group

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Disclosures

Honoraria from:
• Helsinn
• Bayer AG
• Leo Pharma

Educational grant from:
• Bayer AG
Study context

• Investigator-initiated academic trial
• Coordinated by the Warwick University Clinical Trials Unit
• Supported by an unrestricted grant from Bayer AG
• Rivaroxaban supplied by Bayer AG
• EudraCT number: 2012-005589-37
Background

- VTE in cancer is a major challenge
- Cancer patients are at increased risk of recurrent VTE and major bleeding on anticoagulant therapy\(^1\)
- LMWH is the recommended standard for treatment and prevention of recurrent VTE in cancer patients
- Direct oral anticoagulants (DOACs) are recommended for the management of patients with VTE *without* cancer
- Limited data for DOACs in patients with cancer-associated thrombosis

\(^1\)Hutten et al. *Journal of Clinical Oncology* 2000; 18, 3078-3083
Main research objectives

- To assess VTE recurrence in cancer patients with a first VTE, treated with rivaroxaban or dalteparin
- To assess rates of major and clinically relevant non-major bleeding
- To assess extended anticoagulation treatment beyond 6 months in selected patients
Study design (1)
Prospective, randomised, open-label, multicentre pilot phase III

Study population:
Active cancer with symptomatic DVT and/or any PE
ECOG PS ≤ 2

Stratification variables:
Stage of disease
Baseline platelet count
Type of VTE
Risk of clotting by tumour type

Rivaroxaban
15 mg bid for 21 days followed by 20 mg od

Dalteparin
200 IU/kg od for the first 30 days followed by 150 IU/kg od

n=530

6 months
Study design (2)

- Blinded

- Rivaroxaban

- Placebo

- Follow up

PE index event or CUS residual DVT at ~ 5 months

No residual CUS DVT at ~ 5 months

No treatment

6 months

12 months
Statistical considerations

• A sample size of 530 patients would provide:
  – estimates of VTE recurrence rates at 6 months to within +/- 4%
    assuming a VTE recurrence rate at 6 months of 10%
  – 300 patients for the second randomisation, assuming 70% eligible
    at 6 months and 80% agreed to participate
Trial progress

- First patient randomised in October 2013
- Changes to protocol based on DMC recommendations in June 2016
  - The second randomisation was closed to patients randomised into the trial after 31st August 2016 due to low recruitment (n=92)
  - Sample size reduced from 530 to 400 patients (increased the width of the 95% CI for VTE recurrence rate from 8% to 9%)
  - Patients with oesophageal and gastro-oesophageal cancer were excluded due to apparent imbalance in major bleeding rates compared to other tumour types
- Final bleeding adjudication committee, 24th November 2017
Recruitment between October 2013 and December 2016 from 58 sites across the UK

Screened 2060 patients

406 patients randomised

Allocated to dalteparin (n=203)

Allocated to rivaroxaban (n=203)

1105 ineligible
285 not approached due to clinical and other reasons
264 declined participation
## Baseline characteristics

<table>
<thead>
<tr>
<th>Factor</th>
<th>Dalteparin % (n=203)</th>
<th>Rivaroxaban % (n=203)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age: years, median (range)</strong></td>
<td>67 (34–87)</td>
<td>67 (22–87)</td>
</tr>
<tr>
<td><strong>Gender: male</strong></td>
<td>48</td>
<td>54</td>
</tr>
<tr>
<td><strong>Stage of Cancer:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- metastatic</td>
<td>59</td>
<td>59</td>
</tr>
<tr>
<td><strong>ECOG PS:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 0,1</td>
<td>76</td>
<td>72</td>
</tr>
<tr>
<td>- 2</td>
<td>21</td>
<td>26</td>
</tr>
<tr>
<td><strong>Qualifying VTE:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- symptomatic VTE</td>
<td>48</td>
<td>46</td>
</tr>
<tr>
<td>- incidental PE</td>
<td><strong>52</strong></td>
<td>54</td>
</tr>
<tr>
<td>Tumour Type</td>
<td>Dalteparin, % (n = 203)</td>
<td>Rivaroxaban, % (n = 203)</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>--------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Colorectal</td>
<td>23</td>
<td>27</td>
</tr>
<tr>
<td>Lung</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Breast</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Ovarian</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Oesophageal/gastro-oesophageal</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Prostate</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Bladder</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>21</td>
<td>18</td>
</tr>
</tbody>
</table>
VTE recurrence

### Table: VTE recurrences

<table>
<thead>
<tr>
<th></th>
<th>Dalteparin (n=203)</th>
<th>Rivaroxaban (n=203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE recurrences within 6 months, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT or PE</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>Other location</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>11% (7–16%)</td>
<td>4% (2–9%)</td>
<td></td>
</tr>
</tbody>
</table>

### Graph: Percentage of VTE recurrences over time

- **Dalteparin**
- **Rivaroxaban**

**Months from trial entry**

- **Numbers at Risk:**
  - Dalteparin: 203, 169, 129, 106
  - Rivaroxaban: 203, 170, 143, 123

**6-month lower limb DVT or PE recurrence rate**

- **Dalteparin:** 9% (6–15%)
- **Rivaroxaban:** 3% (1–7%)
**Bleeding - number of patients (%)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Dalteparin (n=203)</th>
<th>Rivaroxaban (n=203)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major</strong>*</td>
<td>6 (3%)</td>
<td>11 (5%)</td>
</tr>
<tr>
<td>Clinically relevant non-major</td>
<td>6 (3%)</td>
<td>25 (12%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>12 (6%)</td>
<td>36 (17%)</td>
</tr>
</tbody>
</table>

*1 fatal bleeding event in each arm

Most major bleeding events were gastrointestinal bleeding; no CNS bleeds
Most CRNMBs were gastrointestinal or urological
## Overall survival

<table>
<thead>
<tr>
<th></th>
<th>Dalteparin</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-months overall survival, % (95% CI)</td>
<td>70% (63–76%)</td>
<td>75% (69–81%)</td>
</tr>
</tbody>
</table>

- Overall 104 (26%) patients died
- 92 (88%) died from progressive cancer
- 2 (2%) fatal PEs
Summary

• Overall, 1 in 5 patients who were screened, participated in the study
• In this large randomised pilot study, estimates were established for recurrent VTE and major bleeding rates
• The total burden of recurrent VTE is reported:
  – 5% DVT/PE
  – 1% other venous sites
• The high mortality in the study population and clinician choice indicated that the second randomisation was not feasible
Main conclusion

• We conclude that in terms of therapeutic decision making, a careful discussion between the patient and the physician should take place concerning the risk of recurrence and the risk of bleeding
Thank you to all the patients who participated in select-d

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