Oral rivaroxaban for the treatment of symptomatic pulmonary embolism


Study Type: POEM

Purpose: Traditional treatment for PE has consisted of an injectable heparin or LMWH with bridging warfarin. This treatment has always had its issues with delays in hospital stay and monitoring. The Einstein trial evaluated using rivaroxaban alone to treat PE. This approach has been successful for treatment and prevention of acute DVT.

Duration: n = 4832, 4 years for randomization at 263 centers in 38 countries, most patients treated 9 mths

Trial Design: Randomized, open-label, noninferior trial, intention-to-treat. Rivaroxaban 15 mg twice daily for 3 weeks, then 20 mg daily vs. enoxaparin 1 mg/kg twice daily for at least 5 days and continued until INR was >2 on 2 consecutive days + warfarin or acenocumarol within 48 hours of start. NSAIDs discouraged. Clopidogrel (75 mg/day) and or aspirin (no more than 100 mg daily) was allowed.

Patients: 58 years old, 50% male, 85% weighed in the range of 50 to 100 kg, 85% had CrCl 50 to normal, 10% had CrCl < 50, 87% had PE documented by spiral CT, 12% by VQ scan, 55% were of the intermediate form and 25% extensive involving more than 25% of the lung with multi-lobes, 89% were hospitalized, 13% to ICU, 4 days from symptom to randomization, 65% cause unknown or unprovoked, 17% recent surgery, 16% immobilization, 9% estrogen, 4% cancer, ~20% had a previous VTE.

Inclusion: legal age, acute symptomatic PE with objective confirmation

Exclusion: any previous heparin or LMWH for 48 hours or more than a single dose of warfarin, thrombectomy, filter, fibrinolytic agent, CrCL < 30, liver disease, 3x normal ALT’s, endocarditis, active bleeding, SBP > 180/DBP > 110, use of strong CYP 3A4 inhibitors (protease inhibitors, ketoconazol fibrinolytic agent, CrCL < 30, liver disease, 3x normal ALT’s, endocarditis, active bleeding, SBP > 180/DBP > 110, use of strong CYP 3A4 inhibitors (protease inhibitors, ketoconazol, and or inducers (carbamazepine, phenytoin), pregnancy

Outcome Events: Primary outcome was symptomatic, recurrent VTE (DVT or fatal/nonfatal PE).

1. Are the results valid?
   * Randomized? Yes * Were patients accounted for? Yes
   * Double-blinded? No open-label * Were the groups similar? Yes
   * Placebo controlled? No, standard of care * Allocation concealment? Yes

2. What were the results?

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban</th>
<th>Enoxaparin + warfarin</th>
<th>p-value, ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>2.1%</td>
<td>1.8%</td>
<td>.003, 0.3%</td>
<td>333</td>
</tr>
<tr>
<td>VTE + major bleed</td>
<td>3.4%</td>
<td>4.0%</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Major bleed or clinically relevent nonmajor bleed</td>
<td>10.2%</td>
<td>11.1%</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Any major bleed</td>
<td>1.1%</td>
<td>2.2%</td>
<td>.003, 1.1%</td>
<td>NNH = 91</td>
</tr>
<tr>
<td>Fatal intracranial</td>
<td>&lt;0.1%</td>
<td>&lt;0.1%</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Nonfatal intracranial</td>
<td>&lt;0.1%</td>
<td>0.4%</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>2.4%</td>
<td>2.1%</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

Major bleeding = Hb reduction of 2 gm, need of 2 units of blood, intracranial, retroperitoneal, contributed to death
Clinically relevant nonmajor bleed = bleeding not meeting the major bleeding criteria, but needed intervention

Other analysis
- Most recurrences were nonfatal PE’s (~20 in each group, then DVT (~18 in each group), p = NS
- There were 2 fatal PE in rivaroxaban group and 1 in the LMWH/warfarin group, p = NS
- Adverse events were similar with either group, no difference in discontinuation of therapy, no difference in events causing prolong hospitalization rates

3. Will the results help me?
   * Most got at least 2 days of LMWH, or fondaparinux as a prerandomization treatment
   * 57% were treated with either regimen for 6 month, 38% for 12 months, 5% for 3 months
   * Mean days of treatment in either grp was 265 days, adherence was 94%
   * 11% of rivaroxaban and 12% of LMWH/warfarin group discontinued therapy
   * INR range was therapeutic in 63% of the warfarin group
   * Acute coronary events were low in both groups (<1% in either group)
   * Results were similar for rivaroxaban independent of obesity, renal function, age, extent of PE

Conclusion: Rivaroxaban alone is as effective as LMWH bridge to warfarin therapy in preventing recurrent VTE in patients with acute PE. The bleeding rates are similar with less major bleeding in the rivaroxaban group. Most patients were treated for 6 months. The disappointing fact was no difference in length of hospital stay no matter what regimen the patient was taking. Also, other than major bleeding, patients had similar adverse events between both groups. The major clinical benefit of this medication is a single-drug approach to treatment with no INR monitoring.

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