Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism


Study Type: POEM

Purpose: Does long-term, low-intensity warfarin therapy reduce the risk of recurrence of venous thromboembolism in patients who have had a previous idiopathic venous thrombosis? Also, would those with factor V Leiden or prothrombin polymorphism benefit from this therapy?

Study Duration: 3 years, 2.1 median follow-up

Trial Design: 28-day open-label run-in phase to ensure that all patients could achieve an INR of 1.5-2 without exceeding the dose of warfarin 10 mg, also patient were excluded if compliance was < 85%.

Randomized, double-blinded, multicenter, warfarin vs matching placebo with blinded evaluation of the INR by a central committee, sham dose adjustments of placebo were made to ensure blinding

Patients: 508 patients; 53 yrs; 47% female; 87% white; 10% black; BMI = 29.9, ~8% had history of diabetes, ~40% had > 2 previous thromboembolic events, median 6 month duration of full-dose warfarin therapy, ~2 month time between cessation of full-dose warfarin and enrollment. No statistical difference between patients in both groups.

Inclusion: men and women, 30 yrs and up, documented idiopathic (those not occurring within 90 days after surgery or trauma) venous thromboembolism, they had to have completed at least 3 months of full-dose warfarin

Exclusion: history of metastatic cancer, major GI bleed, hemorrhagic stroke, life expectancy of < 3 yrs, those being treated with antiplatelets including aspirin at dose > 325 mg, lupus anticoagulant antibodies, antiphospholipid antibodies

Outcome Events: See result section

1. Are the results valid?
   * randomized? yes
   * double-blinded? yes
   * were groups similar? yes
   * all patients accounted for? yes

2. What were the results

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Placebo</th>
<th>Warfarin</th>
<th>ARD*</th>
<th>P-value</th>
<th>NNT</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent venous thromboembolism</td>
<td>37 (14.6%)</td>
<td>14 (5.5%)</td>
<td>9.1%</td>
<td>&lt;.001</td>
<td>11</td>
<td>---</td>
</tr>
<tr>
<td>Bleeding Major</td>
<td>2 (0.8%)</td>
<td>5 (2%)</td>
<td>NS</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Bleeding Minor</td>
<td>34 (13.4)</td>
<td>60 (23.5)</td>
<td>10.1%</td>
<td>.002</td>
<td>---</td>
<td>10</td>
</tr>
<tr>
<td>Death</td>
<td>8 (3.2%)</td>
<td>4 (1.6%)</td>
<td>NS</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Cancer</td>
<td>9 (3.6%)</td>
<td>4 (1.6%)</td>
<td>NS</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>MI</td>
<td>2 (0.8%)</td>
<td>3 (1.2%)</td>
<td>NS</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Composite (RVT, major bleed, or death)</td>
<td>41 (16.2%)</td>
<td>22 (8.6%)</td>
<td>7.6%</td>
<td>.01</td>
<td>13</td>
<td>---</td>
</tr>
</tbody>
</table>

*ARD – Absolute Risk Difference

3. Will the results help me?
   * Median INR = 1.7 in the warfarin group, with a warfarin dose of 4 mg (range = 0.5 - 10 mg)
   * Of the total 51 events, 39 were DVT ‘s and 12 were PE’s
   * Of the 8 deaths, 2 were due to fatal pulmonary embolism, one death due to fatal hemorrhagic stroke, all these were in the placebo grp.
   * the absence or presence of factor V Leiden or prothrombin polymorphism had no effect on outcome
   * no real difference in males vs female
   * no differences between groups stratified on age, number of previous events, time since randomization, time since cessation of full-dose warfarin therapy
   * There were 15 recurrent events in those patients discontinuing therapy before the trial (n = 120) - 8 in the placebo grp, 7 in the warfarin grp

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