Conventional-intensity was more effective than low-intensity warfarin therapy for preventing recurrent venous thromboembolism


**Question**
In patients with unprovoked venous thromboembolism (VTE), is low-intensity warfarin therapy as effective as conventional-intensity warfarin therapy for the long-term prevention of recurrent VTE?

**Design**
Randomized [allocation concealed]*†, blinded [clinicians, patients, outcome assessors, data collectors, monitoring committee, and data analysts]*†,‡ controlled trial with mean follow-up of 2.4 years (Extended Low-Intensity Anticoagulation for Thromboembolism [ELATE] study).

**Setting**
16 academic clinical centers in Canada and the United States.

**Patients**
738 patients (mean age 57 y, 55% men) with ≥ 1 episode of unprovoked VTE (defined as objectively confirmed, symptomatic, proximal deep venous thrombosis or pulmonary embolism that occurred in the absence of a major risk factor for thrombosis) who had completed ≥ 3 months of oral anticoagulant therapy at the conventional intensity. Exclusion criteria were other indications for warfarin therapy, contraindication to long-term warfarin therapy, known antiphospholipid antibodies, allergy to contrast medium, or life expectancy < 2 years. Follow-up was 99.9%.

**Intervention**
After stratifying for clinical center and whether the patient had completed 3 to 4 or > 4 months of initial anticoagulant therapy, patients were allocated to warfarin therapy with a target international normalized ratio (INR) of 1.5 to 1.9 (low-intensity warfarin group, n = 369) or warfarin therapy with a target INR of 2.0 to 3.0 (conventional-intensity warfarin group, n = 369).

**Main outcome measures**
Recurrent VTE, major bleeding episodes, any bleeding episodes, and death.

**Main results**
Analysis was by intention to treat. The mean INR was 1.8 in the low-intensity warfarin group and 2.4 in the conventional-intensity warfarin group. Patients in the low-intensity warfarin group had a greater risk for recurrent VTE than did those in the conventional-intensity warfarin group. Groups did not differ for major or any bleeding episodes, or death (Table).

**Conclusions**
In patients with unprovoked venous thromboembolism (VTE), conventional-intensity warfarin therapy was more effective than low-intensity warfarin therapy for long-term prevention of recurrent VTE. Low-intensity warfarin therapy did not reduce the risk for bleeding.

Source of funding: Canadian Institutes of Health Research.

For correspondence: Dr. C. Kearon, McMaster University, Hamilton, Ontario, Canada. E-mail kearone@mcmaster.ca.

*See Glossary.
†Information provided by author.

**Low-intensity vs conventional-intensity warfarin therapy in unprovoked venous thromboembolism at mean 2.4 years‡**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Low-intensity warfarin</th>
<th>Conventional-intensity warfarin</th>
<th>RRI (95% CI)</th>
<th>NNH (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent venous thromboembolism</td>
<td>4.3%</td>
<td>1.6%</td>
<td>176% (10 to 567)</td>
<td>35 (11 to 620)</td>
</tr>
<tr>
<td>Major bleeding episode</td>
<td>2.4%</td>
<td>2.2%</td>
<td>20% (~60 to 194)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Any bleeding episode</td>
<td>10.6%</td>
<td>8.4%</td>
<td>28% (~19 to 100)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Death</td>
<td>4.3%</td>
<td>2.2%</td>
<td>107% (~10 to 361)</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

‡Abbreviations defined in Glossary; RRI, NNH, and CI calculated from data in article using Cox proportional hazards model.

**Commentary**
In patients with unprovoked (or idiopathic) VTE who have received 3 months of vitamin K antagonists (VKAs) with a target INR of 2.0 to 3.0, uncertainty exists about the intensity and duration of anticoagulation. The study by Kearon and colleagues has strengthened the evidence that lowering INR below 2.0 for extended secondary prophylaxis with conventional-intensity warfarin therapy for preventing recurrent disease, but increases the risk for bleeding (1). This results in more recurrences without diminishing the risk for bleeding. Clinical decision making for secondary prophylaxis of unprovoked VTE will need a shift in thinking about VTE as an acute event to a chronic disease and consideration of the risk for bleeding and patient preference.

Rebecca Beyth, MD, MS
Baylor College of Medicine
Houston, Texas, USA

References