A 10 mg nomogram was more effective than a 5 mg nomogram for warfarin induction in outpatient venous thromboembolism


QUESTION: In outpatients with acute venous thromboembolism (VTE), is warfarin induction with a 10 mg nomogram more effective than with a 5 mg nomogram?

Design
Randomised (allocation concealed*), blinded (clinicians, patients, and outcome assessors),* controlled trial with 90 day follow up.

Setting
4 Canadian academic centres.

Patients
201 patients who were ≥ 18 years of age (mean age 55 y, 56% men) and had objectively confirmed acute VTE (deep venous thrombosis or pulmonary embolism). Exclusion criteria were a baseline international normalised ratio (INR) > 1.4, platelet count < 50 × 10⁹ cells/ml, need for hospital admission, use of oral anticoagulant therapy in the previous 2 weeks, or high risk of major bleeding. 90 day follow up was complete.

Intervention
Patients were allocated to warfarin induction with either a 10 mg (n=104) or a 5 mg warfarin nomogram (n=97). Treatment began with full dose subcutaneous low molecular weight heparin (LMWH) (dalteparin or tinzaparin) and continued daily for 5 days until the INR reached therapeutic levels (> 1.9).

Main outcome measures
Time to a therapeutic INR. Secondary outcomes included proportion of patients with INRs of 2.0 to 3.0 on the fifth day, recurrent VTE, major bleeding, and mortality.

Main results
Analysis was by intention to treat. Patients in the 10 mg nomogram group had a shorter mean time to a therapeutic INR and were more likely to have a therapeutic INR at day 5 than were patients in the 5 mg nomogram group (table). The groups did not differ for rates of VTE, major bleeding, or death (table).

Conclusion
In outpatients with venous thromboembolism, a warfarin nomogram using 10 mg loading doses was more effective than a warfarin nomogram using 5 mg loading doses.

*See glossary.

COMMENTARY
VTE is a common and potentially fatal disease that annually affects 2 persons per 1000.1,2 Although advances in diagnostics and treatment have been made, much more work is needed to lessen the burden of this chronic disease. Recent work has focused on determining the optimal duration3 and intensity of therapy4 to prevent recurrent disease. Efforts to improve the ease and efficiency of management and patient convenience without sacrificing safety would be further advances. Newer therapies, such as LMWH, have shifted treatment of acute VTE to the outpatient setting where maximising the efficiency and safety of warfarin loading could reduce the time needed to achieve a therapeutic INR. This could potentially be translated into cost savings if the overlap of heparin and warfarin therapies and the frequency of INR testing were minimised.

The study by Kovacs et al attempted to maximise the efficiency of warfarin loading. As the authors rightly conclude, patients who require inpatient treatment are clinically different, and this nomogram may not be appropriate for them or other patients who require a lower loading dose. The trial’s main strength was the 90 day follow up, although the study was not powered to detect significant differences in the outcomes of recurrent VTE, major bleeding, or death. Thus, firm conclusions about the safety of the 10 mg nomogram cannot be made.

The 10 mg nomogram resulted in a therapeutic INR in less time and with fewer INR measurements. A formal cost analysis would have added significantly to the authors’ findings. None the less, Kovacs et al should be applauded for conducting high quality work to define “best practices” in the treatment and management of acute VTE.


Outcomes 10 mg loading dose 5 mg loading dose Mean difference (95% CI)

<table>
<thead>
<tr>
<th>Time to therapeutic INR &gt;1.9</th>
<th>4.2 days</th>
<th>5.6 days</th>
<th>1.4 days (1.1 to 1.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBI (CI)</td>
<td>RNT (CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with therapeutic INR at 5 days</td>
<td>83%</td>
<td>46%</td>
<td>78% (43 to 128)</td>
</tr>
<tr>
<td>RBI (CI)</td>
<td>RNT (CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous thromboembolism at 90 days</td>
<td>2.9%</td>
<td>0%</td>
<td>–</td>
</tr>
<tr>
<td>RBI (CI)</td>
<td>RNT (CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding at 28 days</td>
<td>0.96%</td>
<td>1.0%</td>
<td>6.7% (~786 to 90)</td>
</tr>
<tr>
<td>Death at 90 days</td>
<td>0%</td>
<td>1.0%</td>
<td>100% (~256 to 100)</td>
</tr>
</tbody>
</table>

RNT = relative risk. Other abbreviations defined in glossary; mean difference, RBI, RRR, RNT, RII, RNT, and CI calculated from data in article.
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