Low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism (letter)
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Low-Intensity Warfarin Therapy for the Prevention of Recurrent Venous Thromboembolism

TO THE EDITOR: We have two major concerns regarding the report by Ridker et al. on low-intensity warfarin therapy (April 10 issue). First, in this study, low-dose, long-term warfarin therapy resulted in a relative reduction in the risk of recurrent venous thromboembolism of 64 percent as compared with placebo. However, data from another trial show that full-dose warfarin is more effective than low-dose warfarin. Indeed, full-dose warfarin therapy has resulted in a relative reduction in risk of 90 percent. In addition, the risk of bleeding is similar with the two intensities of warfarin treatment (Table 1). Hence, the added efficacy of conventional, full-dose warfarin is not offset by an increase in the risk of major bleeding episodes, and the only possible evidence-based conclusion is that full-dose warfarin therapy is preferable to low-dose warfarin therapy.

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The standard of care for patients with a first episode of idiopathic venous thromboembolism is a minimum of 6 months of adequate, uninterrupted oral anticoagulant therapy, and for those with recurrent venous thromboembolism, a minimum of 12 months of such therapy. This minimal duration of adequate anticoagulant therapy has been shown to decrease the risk of recurrent

Table 1. Absolute Risks of Recurrent Venous Thromboembolism (VTE) and Major Bleeding Episodes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Intensity (INR)</th>
<th>Mean Follow-up</th>
<th>Absolute Risk</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Recurrent VTE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>yr</td>
<td>%/person-yr (95% CI)</td>
</tr>
<tr>
<td>Ridker et al.¹</td>
<td>1.5–2.0</td>
<td>2.0</td>
<td>7.2 (5.1–9.9)</td>
</tr>
<tr>
<td></td>
<td>2.1</td>
<td>2.6 (1.4–4.4)</td>
<td>0.9 (0.3–2.2)</td>
</tr>
<tr>
<td>Kearon et al.²</td>
<td>1.5–1.9</td>
<td>2.3</td>
<td>1.9 (1.1–3.1)</td>
</tr>
<tr>
<td></td>
<td>2.0–3.0</td>
<td>2.3</td>
<td>0.6 (0.2–1.4)</td>
</tr>
</tbody>
</table>

* INR denotes international normalized ratio, and CI confidence interval.

TO THE EDITOR: The standard of care for patients with a first episode of idiopathic venous thromboembolism is a minimum of 6 months of adequate, uninterrupted oral anticoagulant therapy, and for those with recurrent venous thromboembolism, a minimum of 12 months of such therapy. This minimal duration of adequate anticoagulant therapy has been shown to decrease the risk of recurrent
venous thromboembolism and possibly the risk of death. The high rate of recurrent venous thromboembolism in the inadequately treated patients in the placebo group of the study by Ridker et al. is certainly not surprising.

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TO THE EDITOR: Ridker et al. conclude that clinical practice should now consist of long-term, low-intensity warfarin therapy in patients with idiopathic venous thromboembolism who have completed at least three months of therapy with conventional-dose warfarin. In the absence of additional data, we believe that this conclusion is premature.

We are concerned about generalizing the results of this study to the treatment of all patients with idiopathic venous thromboembolism. About 38 percent of participants had a history of recurrent venous thromboembolism, and 29 percent had a family history of venous thromboembolism, so this study population clearly included a high proportion of patients who were likely to have thrombophilic conditions. Indeed, about 29 percent of participants had either factor V Leiden or prothrombin mutation G20210A, but the prevalence of other thrombophilic conditions (e.g., deficiencies in protein C, protein S, or antithrombin III or elevated factor VIII levels) is not reported. Although there was a protective effect in participants with factor V Leiden or a prothrombin mutation as well as in those without these conditions, it is conceivable that the benefit in the latter group was explained by protective effects of continued anticoagulant therapy in patients with other known thrombophilic conditions.

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TO THE EDITOR: In the Prevention of Recurrent Venous Thromboembolism (PREVENT) trial, as reported by Ridker et al., patients were randomly assigned to low-intensity warfarin or placebo after either a single or a recurrent episode of idiopathic venous thromboembolism. In the placebo group, the rate of recurrence was more than twice as high among patients who had had two or more previous episodes of venous thromboembolism as among those who had had a single episode (a cumulative risk of 23 percent [21 of 93] vs. 10 percent [16 of 160]). In our opinion, it is ethically questionable to randomly assign patients with recurrent venous thromboembolism to placebo. The recommended practice is to give such patients long-term, full-intensity oral anticoagulant therapy, especially in the case of an idiopathic recurrence,1,2 although there is no firm evidence supporting this recommendation. Low-intensity warfarin therapy also seems less efficacious after recurrent venous thromboembolism. In the low-intensity–warfarin group, the cumulative rate of recurrence among patients who had had two or more episodes of venous thromboembolism was 10 percent (10 of 102), whereas among patients who had had a single episode, it was 3 percent (4 of 153). In patients with recurrent venous thromboembolism, it would be more appropriate to compare long-term, low-intensity anticoagulant therapy with long-term, full-intensity anticoagulant therapy.

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TO THE EDITOR: Despite the significant results of the well-executed trial by Ridker et al. of low-dose warfarin therapy for the prevention of recurrent venous thromboembolism, I am left with one nagging question: What if low-dose warfarin simply converted symptomatic venous thromboembolism to asymptomatic venous thromboembolism? If this were so, the results of the trial would be much less impressive, given the lack of a significant difference between the groups in mortality or in the incidence of other relevant end points such as venous insufficiency or postphlebitic syndrome.1 I would have liked to see their results buttressed by screening of all patients for deep venous thrombosis at regular

intervals. Although the prevention of recurrent symptomatic venous thromboembolism alone may be a worthy goal, it must be balanced against the costs and nuisance associated with providing warfarin therapy to large numbers of patients. If a substantial number of patients in the treatment group did have clinically silent venous thromboembolism, long-term follow-up might not show differences in morbidity and mortality, and Ridker et al. did not prove that prophylactic treatment is better than a strategy that treats only symptomatic recurrences.

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THE AUTHORS REPLY: We concur with Dr. Seneviratne and colleagues that six months of full-dose anticoagulant therapy should be completed before the initiation of long-term, low-intensity warfarin for the prevention of recurrent venous thromboembolism. In our trial, the median duration of full-dose anticoagulant therapy before randomization was 6.5 months (interquartile range, 5.8 to 9.9), which is entirely consistent with the guidelines they cite.

Drs. Krishnan and Streiff raise the possibility that the benefit observed in the PREVENT trial might be restricted to high-risk subgroups. In designing our trial, we prespecified several subgroups and performed stratified analyses within these groups. As shown in the article, we found remarkable consistency among all patients enrolled and no evidence that any subgroup did not benefit from therapy.

Drs. Cosmi and Palareti question the inclusion in our trial of patients with more than one previous episode of venous thromboembolism. However, they also readily admit that there is little firm evidence to support this position. In our study, we found no significant evidence of a differential benefit of long-term, low-intensity warfarin among patients with multiple previous episodes of venous thromboembolism, as compared with patients with a single previous episode.

Dr. Aberegg wonders how our results might have differed if we had performed venous screening at regular intervals in order to identify asymptomatic recurrences. We purposely chose not to conduct screening at intervals because of the questionable relevance of such events and the minimal justification for the use of this expensive approach in the clinic.

On the basis of unpublished data from the Extended Low-Intensity Anticoagulation for Idiopathic Thromboembolism trial, van Dongen et al. argue that long-term use of full-intensity warfarin (international normalized ratio [INR], 2.0 to 3.0) is superior to low-intensity warfarin (INR, 1.5 to 2.0), since there appeared to be no excess risk of hemorrhage in that trial at the higher INR level. Although we await the final presentation of these data, we suspect that the surprisingly low rates of bleeding episodes achieved with full-intensity warfarin in the ELATE trial (0.9 percent per year) do not reflect general practice, a position we believe is supported by almost 50 years of experience with full-dose warfarin and abundant previous evidence that lower-intensity regimens result in lower rates of bleeding. Indeed, previous studies from the same investigative group reported an annual rate of major hemorrhage of 3.8 percent with long-term, full-intensity warfarin, data that are far more representative of actual clinical experience.

For purposes of clarification, we would like to add that the PREVENT protocol was approved by the ethics review boards at all centers, and all participants provided written informed consent before being enrolled in the study.

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