

Correspondence

Duration of anticoagulation after first episode of unprovoked venous thromboembolism

To the Editor

In the July 2004 issue of this journal, Farraj¹ reported the results of long-term warfarin therapy for the prevention of recurrent venous thromboembolism in patients with unprovoked venous thromboembolism (VTE). We would like to congratulate the author for a job well done.

The duration of anticoagulation for unprovoked VTE continues to be a subject of heated debate. Several randomized studies have already shown that when it comes to duration of anticoagulation for such patients, the longer the better. But the key question is how long is long enough? Earlier studies have shown that 6 months is better than 6 weeks² and 12 months is better than 3 months.³ Meta-analysis of several randomized trials has already stated that 6 months is better than shorter ones.⁴

Several issues in Farraj¹ study need to be highlighted. Patients with known acquired or inherited thrombophilic states were correctly excluded from the study. However, the study patients were not subjected to any screening for thrombophilia following their first diagnosis of VTE. While routine testing for thrombophilia should probably be discouraged, it is our view that for a certain subset of patients testing is mandatory. This group would include young patients with unprovoked VTE and clinical features to suggest a hereditary hypercoagulable state, such as thrombosis prior to the age of 40 years or a history of VTE in a first degree relative. Our belief is based on the general consensus that antithrombin deficiency, antiphospholipid syndrome and probably homozygous Factor V Leiden are very thrombogenic states that warrant extended anticoagulation.⁵ Some patients with such conditions were excluded from the PREVENT trial⁶ that partly addressed a similar question. The study under discussion included patients as young as 26 years of age and if they were harboring such thrombogenic states, randomizing them to shorter duration of anticoagulation would probably expose them to higher risk of recurrence.⁷

On a slightly different note, several clinical trials are ongoing in an attempt to identify features that may constitute predictors of recurrence in patients with VTE. History of previous unprovoked VTE remains the most important predictor of recurrence. In a multicenter trial, 6 months of oral anticoagulant therapy was compared with life-long

anticoagulation in 227 patients who had had a second episode of VTE. After 4 years of follow-up, there were 23 recurrences of VTE in the group assigned to 6 months of therapy (20.7%), compared to only 3 in the group assigned to continuing therapy (2.6%). The relative risk of recurrence in the group assigned to 6 months of therapy, as compared with the group assigned to therapy of indefinite duration, was 8 (95% confidence interval, 2.5-25.9). However, there was a trend toward a higher risk of major hemorrhage when anticoagulation was continued indefinitely.⁸

New directions in identifying patients with higher risk of recurrence include the use of D-Dimer testing during warfarin therapy, which in one study was highly predictive of subsequent recurrence after stopping anticoagulation.⁹ Another predictor of recurrence is persistence of venous obstruction based on Doppler ultrasonography.¹⁰ Further studies utilizing both residual obstruction and D-Dimer testing are highly needed.

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Reply from the Author

I appreciate the comments of Dr. Abdel-Razeq and Dr. Radwi and agree with them on the need for further studies to delineate the time of anticoagulation needed and the predictors of recurrence. In our study, the patients were indeed tested upon diagnosis of venous thromboembolism for the presence of deficiencies of protein C, Protein S or antithrombin, the presence of Factor V Leiden, anticardiolipin antibodies or lupus anticoagulant. This actually led to 9 patients being excluded from the study. At the time of the study, we did not test however for prothrombin G20210A, increased fibrinogen level or hyperhomocysteinemia. Some thrombophilia tests are not carried out routinely as yet but as our knowledge of the causes of thrombophilia increase, the category of idiopathic venous thromboembolism will probably diminish significantly.

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