To the Editor:

Dr. E. Loeliger is clearly upset with the ACCP recommendations for a less intense warfarin regimen. The ACCP members based their recommendations on the following considerations:

1. The risk of bleeding with oral anticoagulant therapy is strongly related to the intensity of the anticoagulant effect. Therefore, for each indication, the lowest intensity that has been shown to be effective should be recommended provided there is no evidence that a higher intensity is more effective.

2. The recommendations on the intensity of the anticoagulant effect were based on the results of randomized trials comparing different intensities of the anticoagulant effect. Randomized trials have been performed in the secondary prevention of venous thrombosis, in the prevention of systemic embolism in patients with tissue heart valves, and in the prevention of systemic embolism in patients with mechanical prosthetic heart valves. For all of these indications, the less intense anticoagulant effect was reported to be at least as effective as the more intense, but to be associated with significantly less bleeding. In one of the two studies in patients with mechanical prosthetic heart valves, aspirin and dipyridamole were also used.

3. When randomized studies comparing one level of intensity of anticoagulant effect with another were not available, the ACCP recommendations were based on studies comparing patients receiving oral anticoagulants with an untreated control group. In patients with nonvalvular atrial fibrillation, three studies have reported a risk reduction of approximately 70 percent using low-intensity therapy, with a minimal increase in bleeding. It is on this basis that we recommend less intense warfarin therapy in patients with nonvalvular atrial fibrillation. Furthermore, previous studies in patients with acute myocardial infarction have reported a significant reduction in stroke in patients treated with less intense anticoagulant therapy. It was for this reason that less intense warfarin therapy was recommended to prevent systemic embolism in patients with acute myocardial infarction.

To address Dr. Loeliger’s points:

We did not heed his warning against less intense warfarin regimens because his warning appears to be based on opinion rather than the application of rigorous criteria. He states that it is on good grounds that the Federation of Dutch Thrombosis Centres made certain recommendations, but he does not provide the grounds on which the recommendations were made.

The study demonstrating the addition of 100 mg of aspirin to warfarin in patients with mechanical prosthetic heart valves has not been published in full. The observed INR in both warfarin groups was approximately 3.1. Although there was not a significant increase in major bleeding, there was an increase in overall bleeding and a trend for increase in major bleeding. Therefore, we have initiated a study in patients with mechanical heart valves in which patients are randomized to receive low-intensity warfarin, 2.0 to 2.5 INR, plus 100 mg of aspirin or moderate-intensity warfarin, 3.0 to 3.5 INR, plus 100 mg of aspirin.

We do not think that the low incidence of major embolism that occurred in patients with tissue heart valves indicates that the treatment was ineffective. In addition, it is difficult to understand how Dr. Loeliger’s interpretation of our study in tissue heart valves (which he states indicates that an INR of 2.0 to 2.5 was as ineffective as an INR of 2.5 to 4.0) supports his arguments for the use of a higher INR in patients with tissue heart valves. Efficacy was similar in both groups, and there was a fourfold greater incidence of bleeding in the more intense group.

We based our statement on that there was increased bleeding in two large-scale studies in secondary prevention of acute myocardial infarction on the following figures: for the Sixty-Plus Study, the incidence of total hemorrhage was 17 percent in the oral anticoagulant group versus 1.4 percent in the placebo group, a statistically significant difference. The incidence of major bleeding was 4.1 percent in the oral anticoagulant group compared with 0.2 percent in the placebo group, and the incidence of fatal bleeding was 1.4 percent in the oral anticoagulant group compared with 0.2 percent in the placebo group. Although the incidence of major and fatal bleeding was not statistically significantly greater in the oral anticoagulant group, the relative increase was substantial.

Our statement that there appears to be an increased risk of bleeding in the second large-scale study was based on an incidence of bleeding in the warfarin group of 8.6 percent versus an incidence of 4.1 percent in the placebo group for total bleeding, an incidence of 2.1 percent versus 0 percent for major bleeding, and in incidence of 0.5 percent versus 0 percent for fatal bleeding. By contrast, the incidence of bleeding with a low-intensity warfarin regimen in the four atrial fibrillation studies was very low.

It is possible that an INR of 3.0 to 4.5 might be the most appropriate for the secondary prevention of acute myocardial infarction. However, if a less intense anticoagulant effect is equally effective and produces less bleeding, it would be preferable.

My main argument with Dr. Loeliger is that his statements are not based on the results of randomized trials comparing two intensities of warfarin therapy, but rather on his strong, entrenched opinions. It is possible that he is correct in some of his views, but they should be tested by performing appropriately designed randomized trials that have become the standard on which we base our clinical care in the 1990s.

Jack Hirsh, M.D.,
Hamilton Civic Hospitals Research Centre
Hamilton, Ontario, Canada

References


