

THE SCYLLA AND CHARYBDIS OF ORAL ANTICOAGULANT TREATMENT

TREATMENT with oral anticoagulant drugs (i.e., coumarin derivatives such as warfarin) is effective in the prevention of venous and arterial thromboembolism. In patients with atrial fibrillation, anticoagulation reduces the risk of stroke by 70 percent.¹ The principal problem with anticoagulation is the variability of the effect of coumarin derivatives on the hemostatic system; patients may require very different doses (up to 10-fold differences) to reach the same level of anticoagulation, and the required dose may also vary over time in an individual patient. Since underanticoagulation is ineffective and overanticoagulation may lead to hemorrhage, anticoagulant treatment needs to be monitored and adjusted to steer safely between the Scylla of thrombosis and the Charybdis of bleeding. The realization that such monitoring requires experience and specialization led to the emergence of anticoagulation clinics as early as the 1950s in the Netherlands, and more recently in Italy, Canada, and the United States. There is no doubt that monitoring by specialized anticoagulation clinics improves the quality of care and reduces the rate of complications; when adequately controlled, oral anticoagulant therapy is effective and safe.²

Two major issues remain to be resolved. First, what intensity of anticoagulation should be the goal for each of the indications for this therapy? The introduction of the international normalized ratio (INR),³ an international standard for measuring the anticoagulant effect of therapy that allows prothrombin-time ratios measured with different thromboplastins to be compared, has made it possible to perform and interpret studies of the optimal intensity of anticoagulant therapy. The second question is whether it is advantageous to use other antithrombotic drugs, notably aspirin, either alone or in combination with oral anticoagulants, in the treatment of arterial disease. Both questions arise from the desire to obtain the best benefit–risk profile: to prevent thrombosis as effectively as possible while causing as little bleeding as possible.

In this issue of the *Journal*, Hylek and colleagues⁴ report on their investigation of the optimal intensity of oral anticoagulation to prevent ischemic stroke in patients with nonrheumatic atrial fibrillation. They studied 74 patients with atrial fibrillation who had had a stroke even though they were receiving anticoagulant therapy, and compared the intensity of anticoagulation (as indicated by the INR) with that in a random sample of patients who were receiving anticoagulant therapy for atrial fibrillation but who did not have strokes. The risk of stroke was minimal at INRs of 2.0 or higher. This risk increased sharply

when the INR fell below 2.0, whereas there was no further protection with more intense anticoagulation.

Hylek and coworkers used a case-control approach, which has the advantage that the inclusion of even a relatively small number of case patients can yield the person-time equivalent of a very large follow-up study. It is important to note that with this approach a cross section of patients without stroke should be sampled as controls (as Hylek et al. did), rather than a cross section of their INR values, since under- and overanticoagulated patients are usually seen more frequently in the clinic than are patients with a stable degree of anticoagulation. Sampling patients and examining their previous INR values has been called the "cross section of the files" method,⁵ which takes into account the different intervals for monitoring different patients. Despite its advantages, the case-control approach has two disadvantages. First, the results apply only to one side of the spectrum — in this case, to ischemic strokes and not to hemorrhagic complications. And second, only relative risks can be estimated and not absolute rates of disease. So it cannot be directly inferred from the study by Hylek and colleagues which intensity of anticoagulant treatment is associated with the lowest risk of all untoward events. Several other reports make such estimates possible, however.

In two previous studies, INR-specific rates of complications were calculated according to a person-time method within a cohort.⁶ The first study was conducted among patients with mechanical heart valves who were routinely treated in four Dutch anticoagulation clinics.⁷ The second was the European Atrial Fibrillation Trial, a study of secondary prevention in patients with atrial fibrillation who had previously had a minor stroke.⁸ The latter study, although it included far fewer patients with strokes than the study by Hylek et al., reported very similar results with respect to the risk of stroke, which increased at INR values below 2.0. The risk of hemorrhage increased at INRs above 4.5. For patients with mechanical heart valves, the optimal level of anticoagulation was slightly more intense; the incidence of thromboembolism increased at INR values below 2.5, and bleeding increased at values of 4.5 or higher.⁷

In patients with atrial fibrillation, therefore, the INR should be maintained at all times between 2.0 and 4.5, and in patients with mechanical heart valves it should be held between 2.5 and 4.5. With some margin of safety built in at both ends, reasonable target ranges for the INR are 2.5 to 3.5 (target, 3.0) for patients with atrial fibrillation, and 3.0 to 4.0 (target, 3.5) for those with mechanical heart valves. Interestingly, researchers have pinpointed these optimal levels through observational studies (both follow-up and case-control) and not by means of randomized trials. Because of the variability of the effect

of anticoagulant therapy, the optimal intensity of anticoagulation cannot be easily studied in a randomized fashion.⁶ Moreover, even if the variability of effect were overcome by including very large numbers of patients, an endless series of randomized trials, each with a slightly different target INR, would be required.

As Hylek and coauthors point out, these accumulating data put an end to the push for ever lower intensities of anticoagulation, and indeed a study with a lower target (the Stroke Prevention in Atrial Fibrillation III trial, with a target INR range of 1.2 to 1.5) was recently terminated prematurely because there was too little clinical effect of treatment.⁹

Aspirin is an antithrombotic agent that inhibits platelet aggregation. It prevents thrombosis but appears to be less effective than oral anticoagulation for virtually all indications, including the prevention of thromboembolism in patients with atrial fibrillation. Its great advantages are that no monitoring is needed and that it is associated with a lower risk of hemorrhage than are oral anticoagulants. Several studies have compared aspirin with warfarin, and together with other studies of these agents, they point to a higher overall reduction in the risk of cardiovascular events (including both thromboembolism and hemorrhage) with oral anticoagulants.¹⁰⁻¹²

It is still unclear whether the risk of hemorrhage increases with age,^{7,13} but elderly patients with atrial fibrillation are certainly at the highest risk for ischemic stroke and will benefit most from oral anticoagulant therapy. The first choice for antithrombotic therapy in all patients with atrial fibrillation is therefore an oral anticoagulant agent. Treatment should be monitored by specialized anticoagulation clinics to minimize risks. Only if good control of the intensity of anticoagulation is not possible, or for the exceptional patient who has a high risk of bleeding or whose compliance is expected to be poor, may aspirin be the drug of choice.

Several studies are under way, both in patients with atrial fibrillation and in patients with mechanical heart valves, to investigate the efficacy of the combination of oral anticoagulants and aspirin. The hypothesis that anticoagulation at a moderate intensity combined with inhibition of platelet aggregation may have beneficial clinical effects is worthy of testing. So far, however, combination therapy has not been found to be superior to well-controlled anticoagulant treatment.^{9,14-16} Therefore, the time has not yet arrived for this combination therapy to be used in routine clinical practice.

The optimal intensity of oral anticoagulation that can now be recommended for various indications takes the form of ranges around target levels. We still need to increase the proportion of INR values that are actually within these optimal ranges. The next step will be to define individualized levels of antico-

agulation for patients with different risk profiles, a step that may eventually lead to individually customized anticoagulant treatment.

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