Oral Anticoagulation in Patients After Cerebral Ischemia of Arterial Origin and Risk of Intracranial Hemorrhage

The European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) Study Group

Background and Purpose—In the recently published Warfarin Aspirin Recurrent Stroke Study (WARSS), a low-intensity anticoagulation regimen was used because of safety concerns. Such concerns are corroborated by the results of the Stroke Prevention in Reversible Ischemia Trial (SPIRIT), which was stopped early because of a high incidence of intracranial hemorrhage with a target international normalized ratio (INR) of 3.0 to 4.5. In the ongoing European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT), an intermediate anticoagulation regimen (INR 2.0 to 3.0) is used.

Methods—We performed an interim analysis of the incidence of intracranial hemorrhage in ESPRIT.

Results—Thus far the overall rate of intracranial hemorrhage is 0.31% (95% CI, 0.18% to 0.52%) per year and 1.21% if all of these were in the anticoagulation group.

Conclusions—We conclude that anticoagulation with achieved INR of 2.0 to 3.0 is reasonably safe in patients with cerebral ischemia of arterial origin. (Stroke. 2003;34:e45-e47.)

Key Words: anticoagulants ■ aspirin ■ cerebral ischemia ■ intracerebral hemorrhage

Recently the results of the Warfarin Aspirin Recurrent Stroke Study (WARSS) were published.1 This study investigated whether oral anticoagulation (international normalized ratio [INR] 1.4 to 2.8) is more effective than aspirin in the prevention of ischemic stroke or death after cerebral ischemia of arterial origin. In the early 1990s, at the design phase of the study, the investigators decided to use a low-intensity anticoagulation regimen because they were particularly concerned about the risk of intracranial hemorrhage. At a later stage these concerns were reiterated in correspondence about WARSS.2

The Stroke Prevention in Reversible Ischemia Trial (SPIRIT) was a trial similar to WARSS except that the intensity of the oral anticoagulation was much higher, with a target range of INR 3.0 to 4.5. SPIRIT was terminated after its first interim analysis because of a statistically and clinically significant excess of major hemorrhages in the anticoagulated patients (relative risk, 9.3; 95% CI, 4.0 to 22) in comparison with the patients who received aspirin. The annual incidence of intracranial hemorrhage was 3.7% in the group on anticoagulants. In 1997 we started a new study, the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT), with an intermediate intensity of anticoagulation. At the current stage of the trial we wished to study the incidence of intracranial hemorrhage after cerebral ischemia of arterial origin.

Subjects and Methods

ESPRIT is an open randomized clinical trial comparing (A) oral anticoagulation with a target INR between 2.0 and 3.0 or (B) the combination of aspirin (30 to 325 mg daily) and dipyridamole (400 mg daily) with (C) aspirin only (same dose).3,5 The trial seeks to recruit 4500 patients with a mean follow-up of 3 years. Primary outcome is the composite of vascular death, nonfatal stroke, nonfatal myocardial infarction, or major bleeding complication. All outcome events are recorded at the central trial office, and a committee that has no information about treatment assignment adjudicates classification. An extracranial hemorrhage is defined as major if it results in death or hospital admission. All INR values are collected for patients allocated to anticoagulant treatment. With Rosendaal’s method, we calculated the number of patient-years spent in each 0.5-U INR class.6

Results

As of November 19, 2002, 2191 patients had been enrolled in ESPRIT with a total follow-up time of approximately 4770 patient-years; 12 521 INR values had been recorded. The Figure shows the number of patient-years spent in each 0.5-U INR class for the patients allocated to anticoagulation. At the current stage of the trial we wished to study the incidence of intracranial hemorrhage after cerebral ischemia of arterial origin.

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which a total of 1235 patient-years had been accrued; the worst-case incidence would therefore be 1.21% per year (95% CI, 0.68% to 2.00%). By that time a total of 35 extracranial hemorrhages had been reported, resulting in an overall rate of 0.73% per year or 2.83% with the worst-case scenario. Five patients had 2 bleeding complications.

Discussion
On the basis of the ESPRIT data, the most likely incidence of intracranial hemorrhage is between 0.31% and 1.21% annually in patients after cerebral ischemia of arterial origin anticoagulated with a target INR between 2.0 and 3.0. This incidence compares favorably with that of SPIRIT and is compatible with that of any major hemorrhage in the WARSS trial (3.4% per year); WARSS did not report on intracranial hemorrhage separately. Rates for any major hemorrhage were 7.2% per year in SPIRIT and between 1.1% and 4.1% in ESPRIT. The worst-case scenario probably is an overestimation because the incidence of intracranial hemorrhage after aspirin treatment is in the order of 0.39% (95% CI, 0.22% to 0.50%) per year in similar patients. In a post hoc analysis in SPIRIT, the incidence of major hemorrhages in anticoagulated patients was approximately two thirds lower in those in whom the achieved INR ranged between 2.0 and 3.0 than in those in whom the target range of 3.0 to 4.5 was actually reached. In a direct comparison of data of anticoagulated patients from SPIRIT and the European Atrial Fibrillation Trial (which included patients with cerebral ischemia and atrial fibrillation), we found a 19-fold higher risk of intracranial hemorrhage among the patients with cerebral ischemia of presumed arterial origin if differences between the 2 patient groups were taken into account. In an observational study of INR-specific incidence of ischemic and hemorrhagic events in patients with cerebral ischemia of arterial origin followed by the Leiden anticoagulation clinic, the optimal INR was between 2.5 and 3.5. Thus, we conclude that oral anticoagulation with a target (and achieved) INR of 2.0 to 3.0 is reasonably safe in patients with cerebral ischemia of arterial origin. Of course, conclusions about efficacy cannot be drawn until the end of the ESPRIT study.

Acknowledgments
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References

Editorial Comment
Low-Dose or Moderate-Dose Anticoagulation: Dream or Hope for Stroke Prevention?

The preliminary contribution by the European/Australian Stroke Prevention in Reversible Ischemia Trial (ESPRIT) Study Group supports the idea that ESPRIT might settle the issue after Stroke Prevention in Reversible Ischemia Trial (SPIRIT) and Warfarin Aspirin Recurrent Stroke Study (WARSS) as to whether or not patients with noncardioem-
2.0 to 3.0) is more effective than lower values (INR, 1.5 to 2.8 as reported in WARSS) but less dangerous than higher ones (INR, 3.0 to 4.5 as reported in SPIRIT). The data presented in this article suggest that the latter is true, ie, that major hemorrhages such as observed in SPIRIT in excess—which caused premature discontinuation of this study—are unlikely to occur in ESPRIT. Even if this observation is finally confirmed once ESPRIT is finished, however, the chances are small that oral anticoagulation will turn out to be more effective if achieved with slightly higher values than those gained in WARSS. However, limitations of the data available from the ESPRIT study at this stage prevent any scientifically reasonable prediction because ESPRIT is an open-labeled rather than a double-blind, randomized trial (like WARSS), yet it has unknown variability of target INR ranges in individual subjects. WARSS was very effective in this view, achieving only minor variations of INR values during follow-up. Furthermore, WARSS has nicely shown that despite constantly higher INR values ranging close to the upper border zone fixed in the trial (INR, 2.8) in a subgroup of patients, both risks of secondary strokes and final outcome did not differ from those observed in another subgroup of patients with lower INR values. Thus, WARSS confirmed previous studies with different ranges of anticoagulation documented, eg, in patients with nonvalvular atrial fibrillation (Stroke Prevention in Atrial Fibrillation [SPAF] I through III). These studies showed that efficacy of anticoagulation, although achieved once levels of INR >1.5 were maintained, did not improve with higher INR values; in contrast, outcome tended to be worse because of increasing associated risks. Another study by the authors of the present article also demonstrated the same risk-to-benefit ratios for INR values >1.5. Considering these data altogether, it does not seem very likely that ESPRIT will be more successful than WARSS in providing evidence of what many of us might have suspected and hoped for, ie, that anticoagulation could be more powerful.

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