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 [H18546] aspirin [H18546] cerebral ischemia [H18546] intracerebral hemorrhage
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 intracranial 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\(^3\) 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.\(^1\) 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 0.80%) per year in similar patients.\(^3\) 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.\(^3\) 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.\(^7,8\) 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.\(^9\) 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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![ESPRIT INR distribution](image)


**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\(^1\) supports the idea that ESPRIT might settle the issue after Stroke Prevention in Reversible Ischemia Trial (SPIRIT)\(^2\) and Warfarin Aspirin Recurrent Stroke Study (WARSS)\(^3\) as to whether or not patients with noncardioembolic ischemic stroke benefit from oral anticoagulation versus platelet inhibition in secondary prevention of stroke. Ale Algra, on behalf of the ESPRIT Study Group, argues in favor of this hypothesis and claims that their study continues after WARSS so as not to miss the likelihood that moderate anticoagulation (international normalized ratio [INR]) values,
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.

M.G. Hennerici, MD, Guest Editor
Department of Neurology
University of Heidelberg
Mannheim, Germany

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M.G. Hennerici

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