Antithrombotic Therapy After Cerebral Hemorrhages

To the Editor:

Oral anticoagulation (OAC) generally increases the likelihood of intracerebral hemorrhage (ICH). When there is an indication for OAC in a patient with a history of ICH, the clinician is in the difficult situation of assessing risks and benefits of OAC. In the absence of data from clinical trials, Eckman et al have used a decision-analysis model to compare the expected values of 3 treatment strategies—OAC, aspirin, and no antithrombotic therapy—in patients with ICH and atrial fibrillation (AF). They conclude that all survivors of lobar ICH and most survivors of deep hemispheric ICH with AF should not be offered OAC. Only patients with deep hemispheric ICH at high risk for stroke or embolism or low risk of ICH recurrence might benefit from OAC.

Before these recommendations are integrated into clinical practice, several assumptions in the decision-analysis model have to be clarified:

1. The origin of ICH is multifactorial. Some underlying pathologies such as vascular malformations or vasculitis are treatable. For others, no causal treatment is available. Cause and treatment influence the recurrence rate of ICH. Thus, in a patient with ICH and indication for OAC, the ICH origin has to be assessed, as does whether there was any kind of treatment. We miss this kind of evaluation in the model assumptions. Possibly, the assumption is that all “secondary” causes of ICH like vascular malformations, tumors, hemorrhagic infarcts, trauma, and vasculitis have been definitively excluded. If this is the case, it should be stated.

2. For patients with lobar ICH, a high annual recurrence rate of 15% is assumed on the basis of 1 study with 71 patients that also included patients with a previous ICH before the index ICH. This rate is much higher than the 0.9% to 5.7% reported by other studies. For patients with deep hemispheric ICH, an annual recurrence rate of 2.1% is assumed on the basis of a review of 4 studies. Why did the authors use data from a single study for calculation of the recurrence rate of lobar ICH and not aggregated data like they have used for deep hemispheric ICH? How would the outcome of the analysis change if the recurrence rate of lobar ICH were assumed to be 5.4%, as suggested by aggregated data?

3. The assumption that the site of the index ICH is predictive for the recurrence rate is further modified by a study of 243 patients that found no influences of the site of ICH on the recurrence rate, which was 2.1% per year.

4. The effect of OAC on recurrent ICH is assumed as a relative risk of 2. This is rather low in view of the findings of a study in which OAC was initiated in 25 patients after the index ICH and tripled the risk of recurrent ICH. How would the outcome change if a relative risk of 3 were assumed as the effect of OAC on recurrent ICH?

5. It is unclear why an annual risk of stroke of 4.5% is assumed. The risk for stroke/embolism depends on age and the risk factors of hypertension, diabetes, stroke, or transient ischemic attack. Depending on these factors, the annual rate of stroke/embolism varies between 1.0% and 8.9%. From these data, the 69-year-old man, on whom the base case focused, has an annual risk of stroke/embolism of 4.3% if he was without risk factors and of 5.7% if he had ≥1 risk factors.

6. Aspirin is recommended as an alternative to OAC. Aspirin dosages, however, shown to be effective in preventing stroke/embolism in AF are ≥300 mg/d. Because of gastrointestinal side effects, these dosages might frequently not be tolerated as a long-term therapy. Furthermore, the rate of aspirin-associated ICH in patients with ICH is unknown. Possibly, pathomechanisms such as amyloid angiopathy play a role in aspirin-associated and in OAC-induced ICH.

Facing these uncertainties, a decision-analysis model may be misleading. On the basis of controversially assessed and “soft” assumptions, the results of the model might pretend “objective” results. There is a need for clarification of risk factors for ICH during OAC. MR gradient-echo imaging or assessment of genetic factors may be helpful.

In the meantime, we recommend that, in patients with prior ICH and an indication for OAC, all available information should be collected. Additionally, an extensive evaluation concerning the cause of the ICH should be performed. Knowledge about the potential cause of the ICH and the patient’s present condition will enable us to estimate recurrent ICH risk. If the cause of the ICH cannot be assessed, the decision about OAC has to be individualized.

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Response

We appreciate the comments made by Drs Stollberger and Finsterer and wish to address their concerns and clarify some of the underlying assumptions in our analysis. We fully agree with the overall concern of their letter that decision analysis should be used as a tool for examining complex clinical decision making rather than as a substitute for clinical judgment with individual patients. Regarding some of the specific points raised, patients with secondary causes of intracerebral hemorrhage (ICH) were excluded from our model. Consistent with this, the data on which we based the risk of recurrent ICH1 and the outcomes of such bleeds2 excluded such patients with secondary causes of ICH.

For purposes of consistency with the outcomes of ICH, we used our own data for the annual recurrence rate of lobar ICH, thereby ensuring that the inclusion criteria for patients with lobar ICH were identical. We agree that our recurrence rate is higher than most published values, possibly because of our more conservative definition of lobar ICH, which excludes patients with even slight involvement of the basal ganglia. We explored the impact of changes in the rate of recurrent lobar ICH in extensive sensitivity analyses. The results of our analysis for patients with prior lobar ICH would continue to favor the avoidance of anticoagulant therapy unless the rate of recurrence were <1.4% per year, substantially lower than the 4.4% per year rate of recurrence noted in the review by Bailey et al.3

One of the major uncertain parameters in our analysis was the relative risk of recurrent ICH in patients receiving warfarin. In population studies of ICH, relative risks for ICH in the range of 7 to 10 are associated with the use of warfarin.4–7 In controlled trials of patients with nonvalvular atrial fibrillation, a 3-fold increase in risk
As Stollberger and Finsterer point out, in an observational study of 243 patients with primary ICH, in 25 patients in whom warfarin was initiated after the index bleed, the rate of recurrent ICH was increased 3-fold. In our analysis, we took the approach of using a conservatively low estimate of 2 for the relative risk of recurrent ICH. If anticoagulation was not favored, even with this very low relative risk, then the result was likely to be robust. This indeed proved to be the case. Furthermore, in sensitivity analyses, anticoagulant therapy would not have been favored in patients with a prior deep ICH unless the relative risk were <1.6.

As a large pooled analysis of patients with nonvalvular atrial fibrillation has noted, the risk of ischemic stroke varies substantially in response to a number of patient-specific risk factors such as diabetes mellitus, hypertension, prior myocardial infarction, and congestive heart failure. Because we did not further specify any risk factors for the hypothetical 69-year-old man used in our base-case analysis, we used the overall average rate of thromboembolism of 4.5% from the summary analysis. In sensitivity analyses, we explored the impact of either increasing or decreasing the annual rate of ischemic stroke resulting from atrial fibrillation. In patients with lobar ICH, withholding anticoagulation therapy remained the favored strategy even for ischemic stroke rates as high as 20% per year. In patients with deep ICH, anticoagulation therapy was preferred when the rate of ischemic stroke was >7% per year.

We examined the use of aspirin in a structural sensitivity analysis. We agree that there are many unknowns for aspirin (although it has been used successfully and at various doses in many studies), particularly the relative risk of recurrent ICH. Thus, we made no base-case assumptions for aspirin; rather, we explored only sensitivity analyses examining how patients receiving aspirin might do under varying assumptions for the relative risk of recurrent ICH and the annual rate of ischemic stroke. We felt that this analysis was important to perform, given the clinical use of aspirin in similar settings. Even if we do not know the true relative risk of recurrent ICH in patients receiving aspirin, the sensitivity analyses at least bound our uncertainty and allow a more informed decision to be made.

In summary, with regards to the use of decision analysis, we of course agree that these are only models. They contain many unknowns and need to be interpreted in light of the full and rich details of actual clinical scenarios. As with any decision support tool, they should not be blindly followed while good clinical sense is put aside. Rather, they help us to explore the impact of uncertainty in the value of major parameters or of patient-to-patient variability in the rate of events, the outcomes, consequences of those events, and even patient preferences for those health outcomes.
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