Intensity of Anticoagulant Treatment and Risk of Intracerebral Hematoma

To the Editor:

Franke et al. recently reported the results of a retrospective study examining the risks and severity of intracerebral hemorrhage (ICH) occurring during anticoagulant therapy. They conclude that the increased risk of ICH associated with anticoagulant therapy is not associated with the intensity of anticoagulation, suggesting an “all-or-nothing phenomenon with a low threshold.” This finding is contrary to a number of previous reports that have documented an increased risk of ICH with increasing intensity of anticoagulant therapy.

Kase et al. documented excessive anticoagulation in 75% of their anticoagulated patients who developed ICH. Also, they reviewed five additional reports in which 85% of the patients with ICH were anticoagulated beyond the therapeutic range at the time of the hemorrhage. In addition, Wintzen et al. reviewed 38 patients with ICH occurring during anticoagulation treatment and concluded that “the risk of bleeding rose with increasing intensity of anticoagulation.”

There are several possibilities for the apparent discrepancies between the conclusion of Franke et al. and these previous reports. In the study by Franke et al., there did not appear to be a significant relationship between over-anticoagulation and the risk of ICH in the subset of patients treated by the Thrombosis Center Heerlen. However, it is not clear that this was true for the remaining patients in the study. Among the remaining 41 ICH patients for whom anticoagulation intensity data were available, 29% were “over-anticoagulated” while only 7% were “under-anticoagulated.” (The percentage of non-Heerlen patients who were over-anticoagulated and did not suffer ICH is not reported.)

In addition, the “therapeutic range” (internationally normalized ratio [INR] 2.8–4.8) used by Franke et al. may be higher than optimal. Accumulating evidence suggests that lower levels of anticoagulation (INR 2.0–3.0) may be as effective as higher levels in preventing thromboembolic complications while providing substantially lower bleeding risk.

Finally, the data in Figure 2 of Franke et al. suggest that a relationship may exist between the intensity of anticoagulation and bleeding risk within the “therapeutic range” specified in their study (INR 2.8–4.8). It appears that the majority (75%) of patients within the defined therapeutic range who suffered ICH were in the upper half (INR 3.8–4.8) of that range. Therefore, this data appears to be compatible with a correlation between anticoagulant intensity and risk of ICH. If low intensity anticoagulant therapy becomes more universally accepted, we hope to observe significant reduction in anticoagulant associated ICH.

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References

The following is in response:

To the Editor:

Our conclusion that the use of anticoagulants increases the risk of intracerebral hemorrhage (ICH), but is not directly dependent on the degree of anticoagulation, is indeed based on the findings in patients who were under the care of the Thrombosis Center Heerlen. We found that the frequency of excessive anticoagulation (thrombotest values of <5%, INR of >4.8) did not differ between the groups of patients with ICH and those without ICH (see our Table 2). However, the 95% confidence interval in the patient group with ICH is rather wide and includes the possibility that there is a higher risk for more ICH to occur with more excessive anticoagulation.

On the other hand, the five additional reports reviewed by Kase et al. are based on very small numbers of patients (three to six) and do not justify the conclusion that excessive anticoagulation causes more ICHs than anticoagulation within the therapeutic range.

We agree with Albers that, within the defined therapeutic range, 75% of the patients with ICH in our study were in the upper half (INR 3.8–4.8) of the range (see our Figure 2). This suggests a higher risk of ICH with more intense anticoagulation, but one would also need to know the distribution of the INR values of patients without ICH in Heerlen as well as in the other centers. These are not available. We agree that it would be very interesting to study the occurrence of ICH during anticoagulant treatment of low-intensity therapy if these recommended lower levels are as effective as higher levels in preventing thromboembolic complications.

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