To the Editor:

We read with interest the article by Hart et al1 on intracranial hemorrhage (IH) in patients with atrial fibrillation undergoing anticoagulation treatment with warfarin or dabigatran. They analyzed retrospectively the clinical spectrum of 154 IHs in 18,113 participants of the Randomized Evaluation of Long-term anticoagulant therapy (RE-LY) trial and found that the rates of IHs were lower in dabigatran-treated patients than in those treated with warfarin. However, several points need to be addressed by the authors before one can accept the conclusion that dabigatran is indeed safer than warfarin with respect to the most feared complication of anticoagulant therapy, cerebral bleeding. In particular, the following questions need to be answered: How was it ascertained in the RE-LY study that the patients randomly chosen for the dabigatran group actually took their medication? Whereas adherence to the warfarin regimen was controlled by the authors before one can accept the conclusion that dabigatran is indeed safer than warfarin with respect to the most feared complication of anticoagulant therapy, cerebral bleeding. In particular, the following questions need to be answered: How was it ascertained in the RE-LY study that the patients randomly chosen for the dabigatran group actually took their medication? Whereas adherence to the warfarin regimen was controlled by the international normalized ratio, no laboratory monitoring of the anticoagulant effect of dabigatran was reported. (2) Were measurements of dabigatran-plasma-concentrations carried out?

The history of stroke or transient ischemic attack in patients with IH was higher than in patients without IH. Was cerebral imaging performed before inclusion in the trial? If not, it could be speculated that more patients with cerebral pathologies predisposing to bleeding were included in the warfarin group and that this difference could explain the different prevalence of IH. This interpretation is supported by data in Appendix I showing that IH occurred in more warfarin-treated patients with prior stroke than in patients without, whereas in dabigatran-treated patients, there was no difference.1

Why were patients with hemorrhagic transformation of ischemic stroke excluded from the evaluation? Frequency of hemorrhagic transformation may depend on the blood coagulation state? Was the frequency of hemorrhagic transformation different between the 2 groups?

We miss data on the prevalence of international normalized ratio >3 in the warfarin group at the last control before IH occurred, at the onset of IH, or at hospital admission due to IH. Did patients with IH also show bleeding complications at other loci? Were microbleedings, which are regarded as risk factors for IH, included as bleeding complications?8

It is indicated in the “Methods” that details about reversal of anticoagulation were inconsistently available in the source documents, but we miss any information about this important topic in the results. Were the number of patients undergoing reversal of anticoagulation and their outcome the same in both treatment groups? Did patients with reversal of anticoagulation have better outcomes than those without? Was reversal of anticoagulation more frequently carried out in patients under dabigatran than under warfarin? This is of particular interest because reversal of anticoagulation in patients under dabigatran is reported to be challenging.5

It would be helpful for the interpretation to know how many of the patients included received a combination of dabigatran or warfarin and acetylsalicylic acid. It is also unclear whether patients under dabigatran had a more frequent history of falls than patients under warfarin.

In the “Methods,” it is indicated that outcomes were categorized as full recovery, survival with neurological deficit, or fatal, but we miss the data on recovery in the results. Were 30-day mortality rates available for all patients with IH?

There are also no data provided about the severity of bleeding. By which score was severity of IH assessed? Was there a difference in these scores between the 2 groups?

One cannot conclude that dabigatran causes IH less frequently than warfarin until these open questions have been sufficiently answered.

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Letter by Stöllberger and Finsterer Regarding Article, "Intracranial Hemorrhage in Patients With Atrial Fibrillation During Anticoagulation With Warfarin or Dabigatran: The Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) Trial"

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