Response to Letter Regarding Article, “Management and Outcomes of Major Bleeding During Treatment With Dabigatran or Warfarin”

We thank Hifumi et al for their comments on our article.1 It is important to recognize that treatment of major bleeding on warfarin in the 5 phase III trials was according to local hospital guidelines and protocols, which are generally based on international recommendations.2 The low reversal rate of warfarin is surprising but reflects the way warfarin-associated bleeding was managed at the emergency departments where these patients were seen. We were able to capture information on treatment with blood products or any coagulation factor concentrates accurately because such information was available both from transfusion journals, case report forms, and adverse event narratives. It is however possible that treatment with vitamin K as well as repeated dosing were underreported, including for patients in the intensive care units (ICU), as details of vitamin K treatment were not captured in the case report forms. It is common practice in ICUs to order blood tests once or several times daily and to correct any residual or rebound coagulopathy with necessary measures, including repeated administration of vitamin K. It is therefore less likely that warfarin coagulopathy was not properly reversed in patients in the ICU.

Circulating hypo-carboxylated proteins might be a better indicator than actual vitamin K levels when it comes to biochemical assessment of vitamin K status.3 Nevertheless, neither such analyses nor of vitamin K are available on an emergent basis in the majority of hospitals.

In a cohort study with 107 warfarin-treated patients with asymptomatic international normalized ratio (INR) of 10.0 to 26.6 (acknowledging the inaccuracy of INR at these levels), a dose of 2.5 mg vitamin K provided substantial decrements of the INR after 1 day with only 1 patient demonstrating a rebound of the INR the following days.4 We therefore believe that absolute vitamin K deficiency, requiring repeated, high doses of vitamin K to control the bleeding, was rare in our studied population and would not explain the longer stay in ICU of the warfarin-treated patients. It is more likely that this difference is related to the higher number of intracranial bleeds with warfarin compared with dabigatran.1 Repeated high doses of vitamin K can also be problematic by making the patient refractory to vitamin K antagonists, resulting in difficulties to resume this treatment after the bleeding has been managed.5

Disclosures

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Ammar Majeed, MD
Coagulation Unit, Hematology Center
Karolinska University Hospital and Karolinska Institutet
Stockholm, Sweden

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Hun-Gyu Hwang, MD
Department of Medicine
Soonchunhyang University Gumi’s Hospital
North Kyungsang Province, South Korea

Stuart J. Connolly, MD
John W. Eikelboom, MD
McMaster University
Population Health Research Institute
Hamilton, ON, Canada

Michael D. Ezekowitz, MD
Lankenau Medical Center
Thomas Jefferson Medical College
Wynnewood, PA

Lars Wallentin, MD
Uppsala Clinical Research Center and Department of Medical Sciences
Uppsala, Sweden

Martina Brueckmann, MD
Boehringer Ingelheim Pharma GmbH & Co KG
Ingelheim, Germany

Faculty of Medicine Mannheim
University of Heidelberg
Mannheim, Germany

Mandy Fraessdorf, MD
Boehringer Ingelheim Pharma GmbH & Co KG
Ingelheim, Germany

Salim Yusuf, MD
McMaster University
Population Health Research Institute
Hamilton, ON, Canada

Sam Schulman, MD
Department of Medicine
McMaster University
Hamilton, ON, Canada

Karolinska Institutet
Stockholm, Sweden
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Ammar Majeed, Hun-Gyu Hwang, Stuart J. Connolly, John W. Eikelboom, Michael D. Ezekowitz, Lars Wallentin, Martina Brueckmann, Mandy Fraessdorf, Salim Yusuf and Sam Schulman

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