Response to Letters Regarding Article, “Periprocedural Bleeding and Thromboembolic Events With Dabigatran Compared With Warfarin: Results From the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Randomized Trial”

RE-LY is the largest randomized experience reporting outcomes after interruption of anticoagulant therapy. There was no excess of bleeding in patients taking dabigatran, including those having major or urgent surgery. David and colleagues correctly state that the majority of procedures performed during the RE-LY trial were minor. Nonetheless, our analysis included 1482 major procedures that had a 6% to 8% rate of major bleeding, which was numerically lower among dabigatran-treated patients.

Hjemdahl et al. opine that the high rate of major bleeding in RE-LY patients assigned to dabigatran 150 mg twice daily who had interruption for >72 hours before surgery suggests accumulation of dabigatran in patients with renal impairment. However, data from RE-LY do not support this interpretation, because the same pattern of bleeding based on the timing of study drug interruption was seen in the subgroup of patients with an estimated creatinine clearance of <60 mL/min. Instead, we believe that the results reflect the selection of longer treatment for >72 hours before surgery suggests accumulation of dabigatran in patients at higher risk of bleeding.

David et al. suggest that the rate of bleeding among warfarin-treated patients requiring emergency surgery in RE-LY is higher than observed in Europe; however, the Mayo Clinic study they cite reported a 1% to 3% bleeding rate in patients undergoing elective surgery, similar to the rate for comparable RE-LY patients. David et al. also refer to increased bleeding among patients undergoing catheter ablation for atrial fibrillation who were treated with dabigatran. However, this was an observational study in which dabigatran was held on the morning of the procedure, whereas warfarin was continued; thus, the relative hazards of interrupted compared with maintained anticoagulation could explain these findings. The assertion by David et al. that there is a “clear advantage” to vitamin K antagonists in the setting of emergency surgery is not supported by data and is clearly refuted by the evidence from the RE-LY trial.

Source of Funding
The RE-LY trial was funded by Boehringer-Ingelheim.

Disclosures
Dr. Healey has received consulting fees, lecture fees and grant support from Boehringer-Ingelheim, AstraZeneca, Bayer, St. Jude Medical and Boston Scientific. Dr. Connolly has received consulting fees, lecture fees, and grant support from Boehringer-Ingelheim. Dr. Ezekowtitz has received consulting fees, lecture fees, and grant support from Aryx Pharmaceuticals and Boehringer-Ingelheim and consulting fees from Sanofi-Aventis, as well as lecture fees and grant support from Portola Pharmaceuticals. Dr. Yusuf has received consulting fees, lecture fees, and grant support from Boehringer-Ingelheim and consulting fees from Astra-Zeneca, Bristol-Myers-Squibb, and Sanofi Aventis. Dr. Eikelboom has received consulting fees, lecture fees, and grant support from Boehringer-Ingelheim, Astra-Zeneca, Glaxo-SmithKline, and Sanofi-Aventis; consulting fees and lecture fees from Eisai Pharmaceuticals, Eli Lilly, and McNeil; and consulting fees from Coregenex Medical Corporation, Daiichi-Sankyo, and Bristol-Myers-Squibb. Dr. Oldgren has received consulting fees, lecture fees, and grant support from Boehringer-Ingelheim and lecture fees from Astra-Zeneca. Dr. Wallentin has received consulting fees, lecture fees, and grant support from Boehringer-Ingelheim; consulting fees from Regado and Athera; lecture fees from Eli Lilly and Astra-Zeneca; and grant support from Astra-Zeneca, Bristol-Myers-Squibb, Glaxo-SmithKline, and Schering-Plow. Dr. Douketis has received consulting fees from Boehringer-Ingelheim. The remaining authors have no relevant disclosures. Dr. Reilly is an employee of Boehringer-Ingelheim.

Jeff S. Healey, MD, MSc
John Eikelboom, MD
Sean Yang, MSc
Ellison Theemes, BA
Stuart J. Connolly, MD
Salim Yusuf, MD, DPhil
Population Health Research Institute
McMaster University
Hamilton, Ontario, Canada

James Douketis, MD
St. Joseph’s Healthcare Hamilton
McMaster University
Hamilton, Ontario, Canada

Lars Wallentin, MD, PhD
Jonas Oldgren, MD, PhD
Uppsala Clinical Research Centre
Uppsala, Sweden

Hein Heidbuchel, MD
University Hospitals Leuven
University of Leuven
Leuven, Belgium

Alvaro Avezum, MD
Instituto Dante Foczensi de Cardiologia
Sao Paulo, Brazil

Paul Reilly, MD
Boehringer-Ingelheim Pharmaceuticals
Ridgefield, CT

Michael Ezekowtitz, MB ChB, DPhil
Lankenau Institute for Medical Research
Wynnewood, PA

References
Response to Letters Regarding Article, "Periprocedural Bleeding and Thromboembolic Events With Dabigatran Compared With Warfarin: Results From the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Randomized Trial"
Jeff S. Healey, John Eikelboom, Sean Yang, Ellison Themeles, Stuart J. Connolly, Salim Yusuf, James Douketis, Lars Wallentin, Jonas Oldgren, Hein Heidbuchel, Alvaro Avezum, Paul Reilly and Michael Ezekowitz

Circulation. 2013;127:e506
doi: 10.1161/CIRCULATIONAHA.112.154732

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/127/11/e506

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/