Response by Piccini et al to Letters Regarding Article, “Polypharmacy and the Efficacy and Safety of Rivaroxaban Versus Warfarin in the Prevention of Stroke in Patients With Nonvalvular Atrial Fibrillation”

In Response:

We appreciate the opportunity to reply to comments made by Imprialos and colleagues. As they point out, concomitant antiplatelet therapy is associated with a significantly increased risk of bleeding in patients with atrial fibrillation who are receiving oral anticoagulation. Our analysis of polypharmacy and subsequent outcomes in ROCKET AF (Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) included an adjustment for antiplatelet therapy (previous aspirin). Despite adjustment for prior aspirin therapy, we found that increasing medication burden was associated with a higher risk of bleeding but not stroke.1 Of 9059 patients who did not report previous chronic aspirin use, only 6.2% (565) reported postrandomization aspirin use. Finally, patients taking persistent nonsteroidal anti-inflammatory agents and those on >100 mg aspirin daily were excluded from ROCKET AF.

Bouatou et al raise concerns that the outcomes data from ROCKET AF are not sufficiently reassuring to permit clinicians to use rivaroxaban with combined inhibitors. Those authors correctly point out, as highlighted in our Methods section, that patients taking a strong CYP3A4 inhibitor or inducer were excluded from ROCKET AF. Thus, the findings from our analysis clearly do not apply to strong CYP3A4 inhibitors, and this information is included in our report. The authors also correctly point out that we analyzed combined inhibitors only at baseline. From our analysis, we concluded that there was no evidence of heterogeneity of treatment outcomes according to the use of combined mild to moderate CYP3A4 and permeability glycoprotein inhibitors unless patients were taking ≥2 combined inhibitors. However, as we noted in our article,1 given the limitations of the sample size, larger studies in more heterogeneous populations are needed. We agree that the classification of mild to moderate CYP3A4 and permeability glycoprotein inhibitors is controversial; however, in our analysis and in the ROCKET AF trial, these medications were classified according to the official guidance from the US Food and Drug Administration.2 The authors propose that a cumulative dose-weighted model would be helpful. However, unlike the study they cite,3 which analyzes the glucocorticoid dose equivalents for anti-inflammatory activity, there are no well-accepted standards of dose equivalence for combined CYP3A4 and permeability glycoprotein inhibition across medication types (eg, amiodarone versus diltiazem). Although we appreciate the theoretical concerns about the impact of mild to moderate CYP3A4 and permeability glycoprotein inhibitors and concerns about our inability to accommodate genetic factors or dose, we believe that the strength of our analysis is the use of outcomes data in treated patients rather than pharmacokinetic data to guide prescribing decisions. The absence of any evidence of worse outcomes in 1314 patients receiving rivaroxaban and
≥1 combined inhibitors is reassuring but not definitive, hence our recommendation for further studies.

DISCLOSURES

Dr Piccini receives grants for clinical research from ARCA biopharma, Boston Scientific, Gilead, Janssen Pharmaceuticals, ResMed, and St. Jude Medical and serves as a consultant to GlaxoSmithKline, Johnson & Johnson, Laguna Pharmaceuticals, Medtronic, and Spectranetics. Dr Becker serves as a consultant/advisory board member for Janssen Research & Development, Portola, Cook, and Boehringer Ingelheim. Dr Breithardt has served as a consultant to Bayer HealthCare, Johnson & Johnson, Boehringer Ingelheim, Sanofi-Aventis, MSD, and 3M. Dr Berkowitz is an employee of Bayer HealthCare Pharmaceuticals. Dr Halperin has received consulting fees from Bayer AG HealthCare, Boehringer Ingelheim, Daiichi Sankyo, Johnson & Johnson, Ortho-McNeil-Janssen Pharmaceuticals, Pfizer, and Sanofi-Aventis. Dr Hankey has received consulting fees from Bayer and Sanofi. Dr Mahaffey’s full disclosures before August 1, 2013, are available at www.dcri.org. Disclosures after August 1, 2013, are available at https://med.stanford.edu/profiles/47970?tab=research-and-scholarship. Dr Nessel is an employee of Janssen Research and Development. Dr Singer has received research funding from Johnson & Johnson, Bristol-Myers Squibb, Boehringer Ingelheim, and Medtronic, as well as consulting fees from Boehringer Ingelheim, Bristol-Myers Squibb, CVS Health, Johnson & Johnson, Merck, Pfizer, and St. Jude Medical. Dr Fox has received research funding from Bayer, Janssen, and AstraZeneca; honoraria from Bayer, AstraZeneca, GlaxoSmithKline, Janssen, and Sanofi, and consulting fees from Bayer, Lilly, AstraZeneca, and Sanofi. Dr Patel has received research funding from Johnson & Johnson and AstraZeneca and has served on advisory boards for Bayer, Janssen, AstraZeneca, and Genzyme. The other authors report no conflicts.

AFFILIATIONS

From the Duke Clinical Research Institute (J.P.P., A.S.H., M.R.P.) and Duke Heart Center (J.P.P., J.B.W., M.R.P.), Duke University Medical Center, Durham, NC; University of Cincinnati College of Medicine, Cincinnati, OH (R.C.B.); Hospital of the University of Münster, Germany (G.B.); Bayer HealthCare Pharmaceuticals, Parsippany, NJ (S.D.B.); Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai Medical Center, New York, NY (J.L.H.); School of Medicine and Pharmacology, University of Western Australia, Crawley, Australia (G.J.H.); Ruprecht-Karls-University, Heidelberg, Germany (W.H.); Department of Medicine, Stanford University, CA (K.W.M.); Janssen Pharmaceutical Research and Development, Raritan, NJ (C.C.N.); Massachusetts General Hospital, and Harvard Medical School, Boston (D.E.S.); and University of Edinburgh and Royal Infirmary of Edinburgh, UK (K.A.A.F.).

REFERENCES

Response by Piccini et al to Letters Regarding Article, "Polypharmacy and the Efficacy and Safety of Rivaroxaban Versus Warfarin in the Prevention of Stroke in Patients With Nonvalvular Atrial Fibrillation"


_Circulation_. 2016;134:e7-e8
doi: 10.1161/CIRCULATIONAHA.116.022737

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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/134/2/e7

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/