

Letters to the Editor

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This letter is written in response to the article titled “New Oral Anticoagulants for Stroke Prevention in Atrial Fibrillation” by Daniel Hilleman, PharmD, which was published in the November/December 2012 issue of *The American Journal of Pharmacy Benefits*. A response letter from Dr Hilleman can be found on the next page.

TO THE EDITOR

It is our intent to clarify some factual inaccuracies about Pradaxa (dabigatran etexilate mesylate) and the clinical evidence supporting its use. When Pradaxa was first approved in 2010, the US Food and Drug Administration (FDA)-approved prescribing information did not recommend dose adjustments for patients taking P-glycoprotein (P-gp) inhibitors (ketoconazole, dronedarone) with moderate renal function. The author states that changes to these recommendations were based on postmarketing experience.¹ To clarify, the November 2011 changes to the Pradaxa prescribing information were not made in response to a safety signal or post-marketing experience. This update was meant to refine the dosing recommendations to emphasize appropriate dosing decisions in patients with renal impairment.

In a discussion about the mortality results from the Randomized Evaluation of Long-Term Anticoagulation (RE-LY) trial, the author incorrectly states that the 12% reduction in all-cause mortality had a *P* value of 0.51. The correct *P* value for all-cause mortality was 0.051.^{1,2} Following the initial publication of the RE-LY trial results, the events in the study were readjudicated and published in 2010. This was done to check the consistency of the primary and secondary efficacy and safety data.³ We take issue with Dr Hilleman’s statement that these findings altered the relative risk of myocardial infarction in the Pradaxa 150 mg arm and reduced confidence in the results from RE-LY.¹

RE-LY was a complex study of 18,113 patients accruing approximately 36,000 patient years in 951 clinical centers across 44 countries.² This systematic review of all outcomes data reinforces confidence in the reliability of the study findings. Moreover, the statistical significance of the primary efficacy outcome of stroke/systemic embolic event was not impacted by this

readjudication (*P* <.0001).^{2,3} Dr Hilleman also reviewed adverse event reports from the Institute of Safe Medication Practices (ISMP) and referenced an ablation study to corroborate the ISMP findings. The patients in an ablation study were not representative of all patients on Pradaxa or warfarin, and provided no insight regarding results of adverse event reporting over an entire patient population. Other ablation studies that followed the dosing instructions found on the label had no increase in thrombotic or bleeding events between Pradaxa and warfarin.^{4,5} In addition, a study conducted by the FDA (Mini-Sentinel pilot program) found no increase in bleeding events in patients new to Pradaxa versus patients new to warfarin.⁶

Given the inaccuracies described above, we are concerned about the article’s objectivity in light of both editorial support and author funding from Janssen Pharmaceuticals Inc, the marketer of Xarelto in the United States. As a company, Boehringer Ingelheim encourages all clinicians to continue to publish literature in an unbiased manner to help healthcare professionals understand Pradaxa and educate them on its proper use.

REFERENCES

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RESPONSE

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I would like to thank Dr Smith from Boehringer Ingelheim, Inc, for his timely response to my review article on the new oral anticoagulants published in the November/December 2012 issue of *The American Journal of Pharmacy Benefits*.¹ There were 2 oversights made in the original manuscript, which were pointed out by Dr Smith. The *P* value for the difference in all-cause mortality between warfarin and dabigatran in the RE-LY trial was in fact 0.051 and not 0.51, as was stated in the review.² In addition, it was my mistake in assuming that the change in FDA prescribing information for dabigatran and the interactions with P-glycoprotein (P-gp) inhibitors was due to postmarketing experience. Rather, the changes to the prescribing information were “meant to refine the dosing recommendations to emphasize appropriate dosing decisions in patients with renal impairment.” Regardless of those errors, neither oversight actually impacts conclusions about the use of dabigatran. The drug does not statistically reduce all-cause mortality compared to warfarin and the concomitant use of P-gp inhibitors with dabigatran is discouraged.

My statement of concern about the significantly higher rate of myocardial infarction with dabigatran 150 mg twice-daily compared with warfarin was based on the original RE-LY publication, and was corroborated at that time by a meta-analysis published by Uchino and Hernandez, suggesting a higher rate of acute coronary events with dabigatran.³ I never stated that I believed that dabigatran was in fact associated with a higher rate of myocardial infarction, but rather that a reanalysis of results already published in the *New England Journal of Medicine* raises concerns about the reliability of the study’s findings. Dr Smith’s assertion that the RE-LY study results were readjudicated to “check the consistency of the primary and secondary efficacy and safety data” in and of itself raises the issue of reliability.⁴ Would the original study results in over 18,000 patients—which were already published in the *New England Journal of Medicine*—have to be reanalyzed if the increase in the prevalence of myocardial infarction with dabigatran was not observed?

Dr Smith also suggests that I selectively decided to identify a study where dabigatran was used during atrial fibrillation ablation, demonstrating a higher risk of bleeding compared to warfarin.⁵ Dr Smith cites 3 other studies where dabigatran was used during atrial fibrillation ablation.⁶⁻⁸ No relative increase in bleeding was observed with dabigatran in these studies. I thank Dr Smith for pointing out these studies. However, my review was written, peer-reviewed, edited, and finalized in early to mid-2012. I do not believe that the 3 studies cited by Dr Smith had been published at the time my review was completed. My intent was certainly not to present selectively negative data for dabigatran in the setting of atrial fibrillation ablation or in any other setting.

Finally, Dr Smith questions the objectivity of the review “in light of both editorial support and author funding from Janssen Pharmaceuticals, Inc.” Unfortunately, Dr Smith, from Boehringer Ingelheim, has misstated what was clearly disclosed, as required by *The American Journal of Pharmacy Benefits*, regarding financial conflicts of interest. I did not receive any funding to author the paper. As stated in the disclosure, I received lecture fees from Janssen Pharmaceuticals not related to the authorship of this review. My role as the author of this review is clearly stated in the Authorship Information section. I will leave it to the readers to decide who has a greater potential conflict of interest regarding the topic of this review. I stand by my conclusion at the end of this review which essentially states that the relative efficacy and safety of these new oral anticoagulant drugs will be decided by use in real-world settings.

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