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Risk of Bleeding with Dabigatran in 2010–2011 Medicare Data

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In reply

We appreciate the chance to respond to comments on our recent paper comparing the risk of bleeding with dabigatran and warfarin among Medicare patients newly diagnosed with atrial fibrillation (AF).[1] We found that, compared with warfarin users, the risks of major bleeding and gastrointestinal bleeding were higher, and the risk of intracranial bleeding was lower among dabigatran users. Our results on intracranial and gastrointestinal bleeding are consistent with the RE-LY trial and a recent study by Graham et al. that also uses Medicare data.[2] However, these two studies found no difference in the risk of major bleeding between dabigatran 150mg and warfarin, after combining existing and new patients.[2] We agree with both Miyares and Liu et al. that it is important to separately examine two doses.[3,4] We have now rerun our analysis for 150mg dose only and found that the hazard ratio of major bleeding is 1.56 (95% CI, 1.34–1.81) for dabigatran 150mg compared to warfarin. In our sample, only 9.6% (n=125) of dabigatran users initiated the 75mg regimen so we did not compare dabigatran 75mg and warfarin.

Henriksen et al. point out that our patients differ from those in the RE-LY study and the Danish population-based study and ask about the external validity of our study.[5] Most Medicare patients are older than 65 years old, so our study cohort is slightly older and has more comorbidities. The relatively-low rate of using antiplatelet agents in our sample is because aspirin, a commonly-used antiplatelet agent, is an over-the-counter drug in the US and therefore may not be completely captured in the claims data. Nevertheless, we expect that our results can be generalized to patients older than 65 who are newly diagnosed with AF and who start warfarin or dabigatran within 60 days of the first diagnosis. We are also grateful to Henriksen et al. for noting several discrepancies between Figures 2 and 3 and the text—the confidence intervals in these figures are not correctly aligned but the text associated with these figures is accurate.[5]

Below we discuss several differences that may explain why Graham et al. and our study, both using Medicare data, reached different conclusions.[2,6] First, Graham et al. analyzed 2012 data in addition to the 2010–2011 data that we used. It is possible that prescribing

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patterns have changed over time. We recently obtained 2012 data, and found, compared to 2010, patients with higher risks of bleeding were more likely to initiate dabigatran 75mg in 2012. For instance, 18.5% of dabigatran initiators with chronic kidney disease, a risk factor for bleeding, initiated dabigatran 75mg in December 2010, compared to 46.9% in December 2012. In addition, 11.9% of dabigatran initiators older than 75 years initiated the 75 mg dose in December 2010, compared to 38.5% in December 2012. Consequently, because high-risk patients were more likely to initiate the low dose in 2012, it is plausible that the overall bleeding rate with dabigatran decreased between 2010 and 2012, as Miyares notes.[3]

Second, the two studies used different sample-selection methods. Our study examined patients newly diagnosed with AF, defined as having one inpatient or two outpatient claims with primary or secondary ICD-9 code 427.31,a standard practice to identify a chronic condition.[7] However, Graham et al. defined their study cohort on the basis of one inpatient or outpatient diagnosis of AF, and included both existing patients and new patients.[2] Klil-Drori and Azoulay suggest that, if new warfarin users were more likely to have a fatal bleeding after the first outpatient diagnosis than dabigatran users, our requirement of two outpatient diagnoses may disproportionately exclude warfarin users with a high risk of bleeding.[8] We have now investigated this possibility. Our data included 114 warfarin users and 22 dabigatran users who had only one outpatient claim during our study period. After including them in the sample, the hazard ratio of major bleeding for dabigatran compared to warfarin changed from the original 1.58 (95% CI, 1.36–1.83) to 1.56 (95% CI, 1.35–1.81). That is, results do not change much whether we use one or two outpatient claims.

Third, we used propensity score weighting to mitigate potential selection biases, whereas Graham et al. used propensity score matching.[2] We believe that propensity score weighting is the better approach because it does not exclude individuals from the analysis; instead, it balances treatment groups by assigning higher weights to individuals with similar characteristics in two treatment groups. We agree with Zint and Kreuzer that the weighting method could be sensitive to extreme weights.[6] We have run a sensitivity analysis, however, which suggests that our results are not affected regardless of whether individuals with relatively large weights are included or excluded.

Given the potential clinical implications of our work, we plan to pursue many of the issues raised by the commentators in future studies. We thank them all for their detailed comments.

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