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Dabigatran's 'Real-World' Data About Risk of Myocardial Infarction and Gastrointestinal Bleeding Contradicts With Randomized Trials

We read with great interest the article by Larsen et al. (1) examining the safety of dabigatran, especially with regard to myocardial infarction (MI) and gastrointestinal bleeding using Danish national databases. They report a remarkable, highly significant 60% to 70% risk reduction in MIs with dabigatran as compared with warfarin ($p < 0.0001$). Similarly, they report a 40% reduction in incident gastrointestinal bleeding with 110 mg dabigatran twice daily compared with warfarin, which was again statistically significant.

While examination of observational administrative datasets may sometimes be helpful to answer certain questions, the gold standard for determining drug safety and efficacy is careful analysis of all available randomized controlled clinical trials. With regard to MI, several randomized trials have reported data with dabigatran. All of these studies (except the RE-SONATE [Twice-daily Oral Direct Thrombin Inhibitor Dabigatran Etexilate in the Long-term Prevention of Recurrent Symptomatic Proximal Venous Thromboembolism in Patients With Symptomatic Deep-vein Thrombosis or Pulmonary Embolism] trial with only single events in each arm) showed a numerical excess in MIs with dabigatran (2–6). Combined analysis of all these trials shows a 48% increase in MIs with dabigatran as compared to controls ($p = 0.005$) (Fig. 1). Removal of any single study, including the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial (3) that generated the hypothesis that dabigatran increases risk of MI, does not change the statistically significant excess in MIs. On the other hand, regarding the gastrointestinal bleeding risk, the RE-LY trial reported this event in 10% of patients receiving dabigatran 110 mg twice daily and in 7.5% of patients receiving warfarin ($p < 0.00001$ for dabigatran vs. warfarin) (2). In this trial the excess in gastrointestinal bleeding events was even more pronounced for dabigatran 150 mg twice daily compared with warfarin. The RE-COVER (Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism) trial also showed an excess in gastrointestinal bleeding with dabigatran as compared with warfarin (4.2% vs. 2.8%) (5). Therefore, the results of both the Larsen et al. (1) current observational study and the randomized controlled clinical trials show significant differences in MI and gastrointestinal bleeding rates with dabigatran versus warfarin, but in completely opposite directions. We think that the imperfect nature of observational studies mostly stemming from residual confounding despite propensity matching may explain the discrepancy between the current observational study and previous randomized trials. Can the authors provide their perspective on the risk of residual confounding in their analysis?

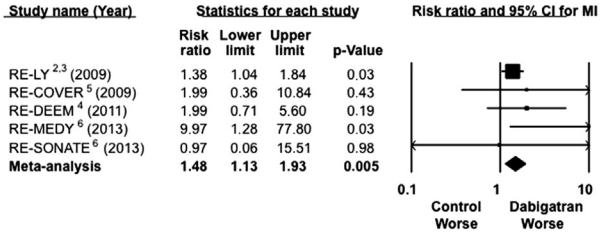

Figure 1 Forest Plot for the Effect of Dabigatran Versus Control on Incident MI

CI = confidence interval; MI = myocardial infarction; RE-COVER = Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism; RE-DEEM = RandomizEd Dabigatran Etexilate Dose Finding Study in Patients With Acute Coronary Syndromes Post Index Event With Additional Risk Factors for Cardiovascular Complications Also Receiving Aspirin and Clopidogrel: Multi-centre, Prospective, Placebo Controlled, Cohort Dose Escalation Study; RE-LY = Randomized Evaluation of Long-Term Anticoagulation Therapy; RE-MEDY = A Phase III, Randomised, Multicenter, Double-blind, Parallel-group, Active Controlled Study to Evaluate the Efficacy and Safety of Oral Dabigatran Etexilate (150 mg bid) Compared to Warfarin (INR 2.0-3.0) for the Secondary Prevention of Venous Thromboembolism; RE-SONATE = Twice-daily Oral Direct Thrombin Inhibitor Dabigatran Etexilate in the Long-term Prevention of Recurrent Symptomatic Proximal Venous Thromboembolism in Patients With Symptomatic Deep-vein Thrombosis or Pulmonary Embolism.

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Reply

Dabigatran's 'Real-World' Data About Risk of Myocardial Infarction and Gastrointestinal Bleeding Contradicts With Randomized Trials

Dr. Sipahi and colleagues express concern about the discrepancy of our observational study with randomized controlled studies, and point to residual confounding as a possible explanation. We have already discussed these issues in the paper (1), but will expand on our discussion in the following paragraph.

In observational studies of intended drug effects or safety, substantial confounding (by indication) is to be expected because the perceived risk is often closely related to the physician's choice of treatment (2). Where there is confounding, there is also the possibility of residual confounding. Taken to the extreme, heterogeneity in risk factors (measured or unmeasured) between treatment groups in key risk factors is a *possible* explanation for the observed associations. However, "possible" need not mean "plausible." Indeed, a careful choice of methods and principles can mitigate confounding concerns in observational studies (3).

In our study, we adopted a new-user design to ensure that meaningful comparisons were made (4). We explored both propensity score matching and regression-based confounder adjustment and found no appreciable differences between these approaches. Last, we found reassurance in the fact that estimates changed only modestly upon adjustment for key risk factors for the outcome. Any unmeasured confounders would have to be very strongly associated with treatment and outcome in order for estimates and conclusions to change qualitatively (5). While it is possible that such unmeasured confounders exist, we do not consider it very plausible.

There can be other explanations for the discrepancies between observational and randomized studies (6), which seem more plausible here. For example, differences in length of follow-up may result in different conclusions. Also, randomized controlled trials are externally valid only for the type of patients included in that trial. Our observational study represents a "real world" population, in which patients had a lower stroke risk cohort compared with the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial (7) participants (mean CHADS2 scores of 1.2 and 2.1, respectively), and correspondingly, a lower myocardial infarction risk as well. Also, our patients had a lower prevalence of prior myocardial infarction or fewer risk factors for the same (e.g., diabetes mellitus, hypertension), compared with the RE-LY trial.

In their letter, Sipahi et al. proclaim randomized trials as the gold standard for drug efficacy and safety assessments. While randomized controlled trials are indeed the gold standard in the sense of providing "fair" comparisons, they may not always provide the most relevant comparisons. Well-designed observational studies can address the question whether drug *treatment* works in daily clinical practice, not just whether the drug by itself works in ideal settings. Careful consideration of *all the available evidence* (randomized and observational) should be considered the gold standard for post-marketing drug evaluations (8).

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Please note: Dr. Lip has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, and Boehringer Ingelheim; and has been on the Speaker's Bureaus for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi. Drs. Larsen and Rasmussen have been on the Speaker's Bureaus for Bayer, BMS/Pfizer, and Boehringer Ingelheim. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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