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Article in Press

Safety of Proton Pump Inhibitors Based on a Large, Multi-Year, Randomized Trial of Patients Receiving Rivaroxaban or Aspirin

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DOI: <https://doi.org/10.1053/j.gastro.2019.05.056>

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Background & Aims

Proton pump inhibitors (PPIs) are effective at treating acid-related disorders. These drugs are well tolerated in the short term, but long-term treatment was associated with adverse events in observational studies. We aimed to confirm these findings in an adequately powered randomized trial.

Methods

We performed a 3 × 2 partial factorial double-blind trial of 17,598 participants with stable cardiovascular disease and peripheral artery disease randomly assigned to groups given pantoprazole (40 mg daily, n = 8791) or placebo (n = 8807). Participants were also randomly assigned to groups that received rivaroxaban (2.5 mg twice daily) with aspirin (100 mg once daily), rivaroxaban (5 mg twice daily), or aspirin (100 mg) alone. We collected data on development of pneumonia, *Clostridium difficile* infection, other enteric infections, fractures, gastric atrophy, chronic kidney disease, diabetes, chronic obstructive lung disease, dementia, cardiovascular disease, cancer, hospitalizations, and all-cause mortality every 6 months. Patients were followed up for a median of 3.01 years, with 53,152 patient-years of follow-up.

Results

There was no statistically significant difference between the pantoprazole and placebo groups in safety events except for enteric infections (1.4% vs 1.0% in the placebo group; odds ratio, 1.33; 95% confidence interval, 1.01–1.75). For all other safety outcomes, proportions were similar between groups except for *C difficile* infection, which was approximately twice as common in the pantoprazole vs the placebo group, although there were only 13 events, so this difference was not statistically significant.

Conclusions

In a large placebo-controlled randomized trial, we found that pantoprazole is not associated with any adverse event when used for 3 years, with the possible exception of an increased risk of enteric infections.

[ClinicalTrials.gov](#) Number: [NCT01776424](#).

Keywords:

[Reflux](#), [Thrombosis](#), [CVD](#), [Bacteria](#)

Abbreviations used in this paper:

[CI](#) (confidence interval), [HR](#) (hazard ratio), [OR](#) (odds ratio), [PPI](#) (proton pump inhibitor)

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Conflicts of interest These authors disclose the following: Dr Moayyedi has received funding for research (related to inflammatory bowel disease and irritable bowel syndrome) from Allergan and Takeda. Dr Eikelboom reports receiving grant support and honoraria from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Daiichi Sankyo, Janssen, AstraZeneca, Eli Lilly, GlaxoSmithKline, and Sanofi-Aventis. Dr Connolly reports receiving lecture fees and consulting fees from Bristol-Myers Squibb, Pfizer, Portola Pharmaceuticals, Boehringer Ingelheim, Servier, Daiichi Sankyo, and Medtronic. Dr Hart reports receiving grant support, fees for serving as principal investigator of the Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients with Recent Embolic Stroke of Undetermined Source (NAVIGATE ESUS) trial, and advisory-board fees from Bayer. Dr Diaz reports receiving grant support from the Population Health Research Institute. Dr Alings reports receiving consulting fees from Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, and Sanofi-Aventis. Dr Lonn reports receiving consulting fees from Bayer, Amgen, Sanofi, Novartis, and Servier. Dr Anand reports receiving consulting fees and lecture fees from Bayer and Novartis. Dr Avezum reports receiving consulting fees from Boehringer Ingelheim. Dr Branch reports receiving grant support from Astellas and serving on an advisory board for Janssen. Dr Bhatt reports receiving grant support from Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic, Sanofi-Aventis, the Medicines Company, Roche, Pfizer, Forest Laboratories/AstraZeneca, Ischemix, Amgen, Eli Lilly, Chiesi, and Ironwood Pharmaceuticals, collaborating on research (uncompensated) with FlowCo, PLx Pharma, Takeda, and Merck, receiving fees for serving on data monitoring committees, an operations committee, a publications committee (USA co-national leader), and a steering committee from the Population Health Research Institute, serving as editor-in-chief of the *Harvard Heart Letter* for Belvoir Publications, serving as chief medical editor of *Cardiology Today's Intervention* for Slack Publications, receiving fees for serving on continuing medical education steering committees from WebMD, receiving advisory-board fees from Elsevier, serving on uncompensated advisory boards for Medscape Cardiology and Regado Biosciences, serving as editor-in-chief of the *Journal of Invasive Cardiology* for HMP Communications, serving as deputy editor for *Clinical Cardiology*, serving as guest editor and associate editor for the *Journal of the American College of Cardiology*, serving as chair of the research and publications committee of the Veterans Affairs Cardiovascular Assessment, Reporting, and Tracking system for the Department of Veterans Affairs, serving as site co-investigator for Biotronik and Boston Scientific, serving on an uncompensated advisory board for Cardax, and receiving fees for serving on data monitoring committees from the Cleveland Clinic, Duke University, and Mount Sinai School of Medicine. Dr Zhu reports receiving lecture fees from Bayer, Boehringer Ingelheim, and Sanofi. Dr Liang reports receiving lecture fees from Bayer, Boehringer Ingelheim, and Sanofi. Dr Maggioni reports receiving fees for serving as a study committee member from Novartis, Bayer, Fresenius Medical Care, and Cardiorentis. Dr Kakkor reports receiving grant support and fees for serving as steering committee chairman from Bayer, and consulting fees from Boehringer Ingelheim, Daiichi Sankyo Europe, Janssen, Sanofi, and Armetheon. Dr Fox reports receiving grant support and honoraria from AstraZeneca and honoraria from Sanofi/Regeneron Pharmaceuticals. Dr Parkhomenko reports receiving grant support and honoraria from Pfizer, Bayer, Janssen, AstraZeneca, Sanofi, and Merck Sharp & Dohme. Dr Störk reports receiving grant support from Servier and Boehringer Ingelheim, grant support and lecture fees from Novartis and Thermo Fisher Scientific, and lecture fees from Pfizer. Dr Dans reports receiving lecture fees from Pfizer and Boehringer Ingelheim. Dr Torp-Pedersen reports receiving grant support from Biotronik. Dr Verhamme reports receiving grant support, lecture fees, and consulting fees from Bayer HealthCare, Boehringer Ingelheim, Daiichi Sankyo, Pfizer, and Bristol-Myers Squibb, grant support from Sanofi and Leo Pharma, and consulting fees from Portola Pharmaceuticals. Dr Vinereanu reports receiving grant support, lecture fees, and consulting fees from Boehringer Ingelheim, Pfizer, and Novartis and grant support and lecture fees from Servier. Dr Lewis reports receiving lecture fees and honoraria from Pfizer/Bristol-Myers Squibb. Dr Steg reports receiving fees for serving on a steering committee from Amarin, Janssen, and CSL Behring, fees for serving on a steering committee and lecture fees from AstraZeneca, lecture fees and consulting fees from Bayer and Bristol-Myers Squibb, fees for preparation of educational material from Boehringer Ingelheim, consulting fees and fees for serving on a data and safety monitoring board from Eli Lilly and Merck Sharp & Dohme, consulting fees from Novartis and Regeneron Pharmaceuticals, fees for serving on a critical-event committee from Pfizer, fees for serving on a steering committee and consulting fees from Sanofi, and fees for serving on a steering committee, consulting fees, and fees for serving on a data and safety monitoring board from Servier. Dr Cook Bruns and Dr Muehlhofer are employed by Bayer. Dr Yusuf reports receiving grant support and honoraria from Bayer, Boehringer Ingelheim, Astra-Zeneca, Bristol-Myers Squibb, and Cadila Pharmaceuticals. The remaining authors disclose no conflicts.

Funding This work was supported by Bayer AG.

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