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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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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, C*lostridium 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)

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. 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