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CLINICAL AT

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

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See Covering the Cover synopsis on 587; see editorial on page 604.

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.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Observational studies have raised concerns that proton pump inhibitors may be associated with increased risk of pneumonia, fracture, clostridium difficile associated diarrhea, other enteric infections, cardiovascular disease, chronic renal disease, dementia and all-cause mortality

NEW FINDINGS

Long term adverse events were similar in the pantoprazole compared to the placebo arms of a randomized trial with 53,000 patient years of follow up; with the possible exception of enteric infections, which were slightly higher in the pantoprazole group.

LIMITATIONS

Some of the outcomes did not have enough events to exclude a modest increased risk

IMPACT

Proton pump inhibitors are not associated with any longterm harm, except possibly other enteric infections, however this needs further confirmation. Therefore the benefits are likely to outweigh the risks of these medications provided they are used for clinically appropriate indications.

Proton pump inhibitors (PPIs) are one of the most widely used classes of drugs in the United States.[1] PPIs are the most effective drugs for treating gastroesophageal reflux disease.[2] Given their profound impact in reducing acid secretion,[3] PPIs are recommended in many other acid-related conditions, such as the management of dyspepsia,[4] as part of *Helicobacter pylori* eradication therapy,[5] and for prevention of peptic ulcer bleeding in high-risk patients on aspirin and/or non-steroidal anti-inflammatory drugs. Recent randomized controlled trial data also suggest that high-dose PPI therapy may reduce high-grade dysplasia and esophageal adenocarcinoma in patients with Barrett's esophagus.[6] Acid secretion returns to normal within 12–24 hours of discontinuation of therapy, so PPIs are often used long term, particularly in patients with gastroesophageal reflux disease symptoms.[2] Acid-related conditions such as dyspepsia and gastroesophageal reflux disease occur in >25% of the population[7,8] and, given that most patients take PPI therapy long term, it is not surprising that the United States spends >$5 billion annually on these drugs.[9] Omeprazole was the first PPI to be developed and is on the World Health Organization list of essential medications.[10]

Given how commonly acid suppressive medications are used, it is important to ensure that this class of drugs is safe. However, concerns have been raised regarding potential harms of long-term PPI therapy. Observational studies have suggested an association between PPI therapy and risk of pneumonia,[11] fracture,[12] enteric infection,[13] *Clostridium difficile*–associated diarrhea,[14] cerebrovascular events,[15] chronic renal failure,[16] dementia,[17] and all-cause mortality.[18] These articles are often reported in the media with sensational headlines that can alarm patients taking PPI therapy. There are balancing articles that more carefully discuss the risks and benefits of taking PPI therapy,[19] but these receive less media attention. These associations may relate to confounding, as patients receiving PPI may be inherently sicker and statistical adjustments in observational analyses cannot rectify differences in known and unknown confounders.[20] There is equipoise between concerns regarding the long-term safety of PPI therapy vs their efficacy in treating acid-related diseases. We have previously reported that rivaroxaban 2.5 mg twice daily with aspirin daily reduced cardiovascular outcomes in patients with stable cardiovascular disease.[21] In this trial, we also evaluated whether the PPI pantoprazole is more effective than placebo in preventing upper gastrointestinal events in patients receiving aspirin and/or rivaroxaban, and we also prospectively evaluated the safety of PPIs in this setting.

Methods

Trial Design

The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial is a 3 × 2 partial factorial, multicenter, double-blind, randomized placebo-controlled trial evaluating patients with stable atherosclerotic vascular disease. The detailed study design has been published previously.[22] Participants were randomized to rivaroxaban 2.5 mg twice daily with aspirin 100 mg once daily, rivaroxaban 5 mg twice daily alone, or aspirin 100 mg once daily alone to compare the primary outcomes of cardiovascular death, stroke or myocardial infarction in these 3 arms. All participants who were not already taking a PPI at baseline (64%) were randomized to receive either pantoprazole 40 mg or matching placebo once daily. We use the term *participants*, rather than *patients*, as not all of those taking part in this research would have been patients throughout the trial but all participated in the randomized controlled trial. The rivaroxaban part of the trial was stopped early for evidence of reduction in major vascular events from the combination of rivaroxaban and aspirin compared with aspirin alone.[21] The pantoprazole part of the trial was continued as planned for 3 years[22] and the protocol is available in the Supplementary Material. Participants in the PPI arm were recruited from 580 centers in 33 countries and the trial was conducted according to Good Clinical Practice. All relevant authorities and research ethics boards approved the trial. Written informed consent was obtained from all participants. All authors had access to the study data and reviewed and approved the final manuscript. Bayer AG sponsored the trial; all data were analyzed independently at the Population Health Research Institute and the first author acts as a guarantor for the veracity of the data and analyses.

Abbreviations used in this paper: **CI, confidence interval; HR, hazard ratio; OR, odds ratio; PPI, proton pump inhibitor.**

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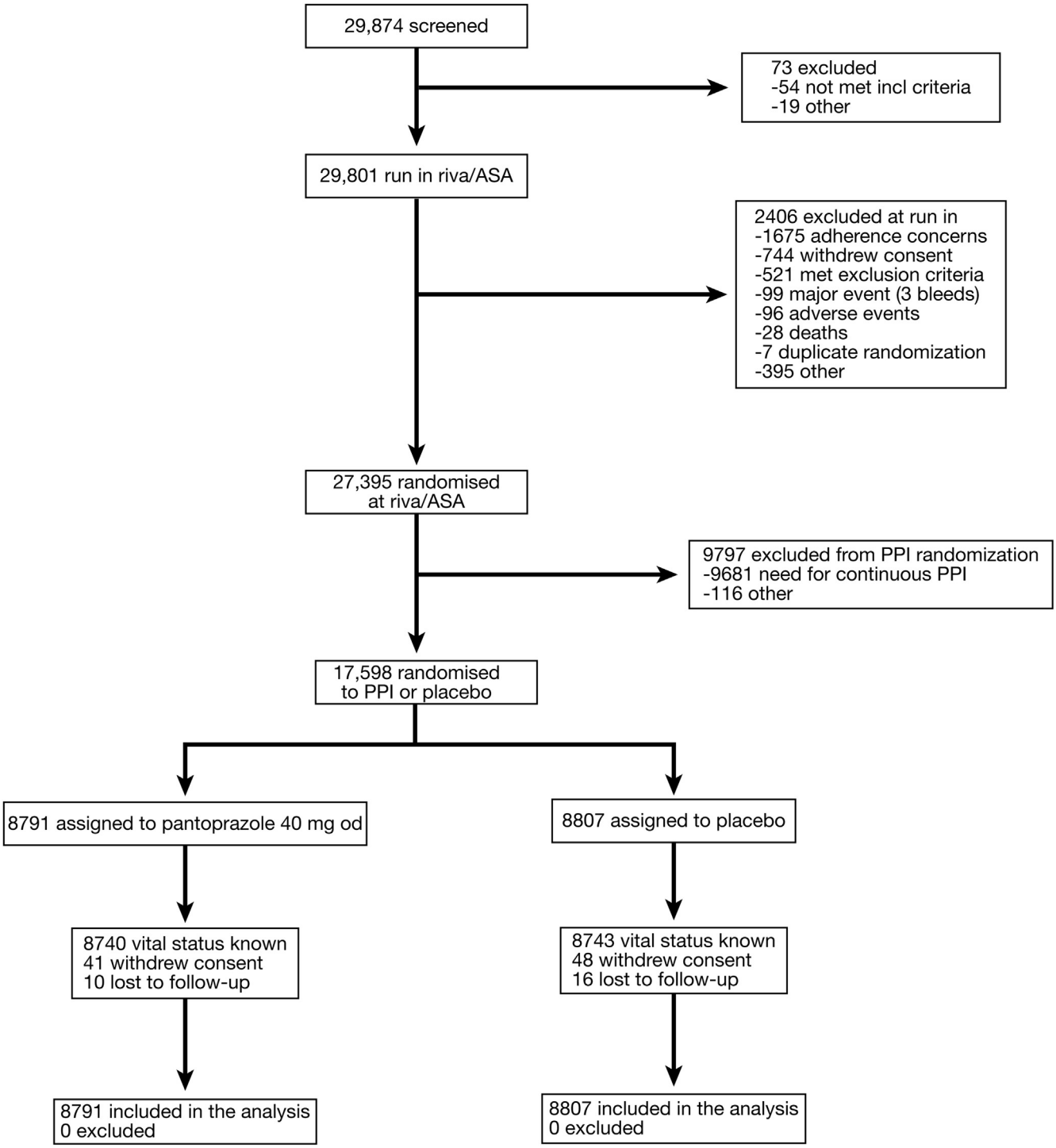

Figure 1. Consort diagram.

Randomization, Concealment of Allocation and Blinding

All participants were randomly assigned to receive low-dose rivaroxaban with aspirin, rivaroxaban alone, or aspirin alone stratified by center and use of PPIs. Eligible participants were further randomized 1:1 to receive pantoprazole (40 mg once daily) or matched placebo stratified by center. The randomization schedules were computer-generated and delivered through an interactive web response system. All active interventions and placebo were identical in appearance and taste. Participants, health care staff, and researchers were blinded to treatment allocation.

Trial Population, Intervention, and Follow-Up

Participants were eligible if they had stable coronary or peripheral arterial disease and were aged 65 years or older.

Younger atherosclerotic participants were eligible if they had arterial disease involving 2 cardiovascular beds and/or had 2 additional risk factors (see Supplementary Material). Patients were randomized to receive pantoprazole 40 mg once daily or placebo, except if they had a clinical need for long-term PPI therapy or were unwilling to discontinue their H_2 receptor antagonist or PPI therapy. If participants were otherwise eligible for the cardiovascular component of the trial,[21,22] they continued in the study and all outcomes were measured. Participants were excluded if they had a high risk of bleeding from any site, had severe heart failure, significant renal impairment, need for dual antiplatelet therapy, or known hypersensitivity to any of the study drugs. Further details of exclusion criteria are given in the Supplementary Material. Following randomization participants were seen at 1 month, 6 months, and then at 6-month intervals for 3 years. Adherence to study medication was assessed by return tablet count at each visit with >80% of medication taken being defined as compliant. We defined discontinuation as any patient that permanently discontinued pantoprazole or placebo at any point in the trial and for the remainder of the trial.

Outcomes

The rates of cardiovascular disease events (eg, myocardial infarction, stroke, cardiovascular death, coronary heart disease, and acute limb ischemia) as defined by the primary and secondary efficacy outcomes for the rivaroxaban and/or aspirin arms of the trial[22] were compared between the pantoprazole and placebo arms. We defined safety outcomes of special interest based on previous reports of possible harms of PPI therapy, [11–18] including pneumonia, *C difficile* infection, other enteric infections, fracture, gastric atrophy, chronic kidney disease, and dementia. We also evaluated diabetes mellitus and chronic obstructive lung disease, as previous observational data had suggested increased rates of these diseases in patients taking PPI therapy, although this was not the primary focus of the analyses.[23] In addition, hospitalization rates for both cardiovascular and non-cardiovascular events were evaluated in the pantoprazole and placebo groups. Participants were interviewed every 6 months and questioned whether they had a new onset of any of these events with questions on the case record form so that each participant was asked about each adverse event and medical records were reviewed as appropriate. Cardiovascular events were independently adjudicated, but all of the other events were taken from the interview without adjudication.

Sample Size Calculations and Statistical Analyses

Sample size calculations for the trial were not calculated based on safety outcome assumptions. Retrospective calculations based on observed proportions of the safety outcomes in the trial varied, depending on the frequency of adverse events seen in the study. Excluding *C difficile*, where the event rate was very small, the smallest effect size that could be detected related to pneumonia with an odds ratio (OR) of 1.27 and the largest related to dementia with an OR of 2.06. Power calculation results are provided in more detail in Supplementary Table 1. All of these calculations assumed the proportions seen in the placebo group with 80% power and 5% type I error.

All events occurring in the randomized participants are included in the intention-to-treat analysis utilizing the time to the first occurrence of the cardiovascular events, mortality, cancer, and hospitalizations for pantoprazole vs placebo from the time of randomization until the date of formal trial termination. Differences in rates between pantoprazole 40 mg once daily vs pantoprazole placebo were evaluated using a log-rank test stratified by antithrombotic study treatment (3 strata levels: rivaroxaban 2.5 mg twice daily + aspirin 100 mg once daily; rivaroxaban 5 mg twice daily + aspirin placebo; rivaroxaban placebo + aspirin 100 mg once daily), conducted at a 2-sided 5% type I error level. Kaplan-Meier estimates of cumulative risk were used to evaluate the timing of event occurrence in the pantoprazole and placebo study groups. Hazard ratios (HRs) and 95% confidence intervals

Table 1. Baseline Characteristics of Participants

Characteristic	Pantoprazole (n = 8791)	Placebo (n = 8807)
Age, *y*, mean ± SD	67.6 ± 8.1	67.7 ± 8.1
Female sex, n (%)	1937 (22)	1869 (21)
Race, n (%)		
White European	5265 (60)	5267 (60)
Asian	1363 (15.5)	1384 (16)
Black/African American	97 (1)	108 (1)
Latin American	2066 (23.5)	2048 (23)
Geographic region, n (%)		
North America	1241 (14)	1243 (14)
South America	2209 (25)	2194 (25)
Western Europe	2187 (25)	2207 (25)
Eastern Europe	1890 (21.5)	1895 (21.5)
Asia Pacific and other	1264 (14)	1268 (14)
Body mass index, mean ± SD	28.3 ± 4.7	28.4 ± 4.7
Smoking status, n (%)		
Current	2064 (23.5)	2010 (23)
Former	3764 (43)	3808 (43)
Never	2693 (34)	2989 (34)
Previous MI, n (%)	5403 (61.5)	5404 (61)
Previous stroke, n (%)	350 (4)	366 (4)
Previous cancer, n (%)	450 (5)	491 (6)
Previous peptic ulcer, n (%)	228 (3)	222 (2.5)
Inflammatory bowel disease, n (%)	37 (0.4)	56 (0.6)
Diverticulitis, n (%)	131 (1.5)	120 (1.4)
Liver disease, n (%)	85 (1)	83 (1)
Diabetes, n (%)	3363 (38)	3369 (38)
Heart failure, n (%)	2181 (25)	2138 (24)
Estimated GFR, n (%)		
<30 mL/min	75 (0.9)	77 (0.9)
30 to <60 mL/min	1878 (21)	1917 (22)
≥60 mL/min	6838 (78)	6810 (77)
Medication, n (%)		
Taking PPI at start of trial	56 (0.6)	78 (0.9)
NSAIDs	425 (5)	447 (5)
SSRIs	257 (3)	258 (3)
Hypoglycemic agents	2785 (32)	2784 (32)
ACE inhibitor/ARBs	6269 (71)	6286 (71)
β-blockers	6137 (70)	6122 (70)
Calcium channel blockers	2237 (25)	2265 (26)
Lipid-lowering agents	7775 (88)	7823 (89)
Diuretics	2572 (29)	2522 (29)

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; GFR, glomerular filtration rate; NSAID, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin re-uptake inhibitor.

Table 2. Cardiovascular Events, Cancers and Hospitalizations

Outcome	Pantoprazole, 40 mg od (n = 8791)		Placebo (n = 8807)		Pantoprazole vs placebo	
	First events, n (%)	Annual rate, %/y	First events, n (%)	Annual rate, %/y	HR (95% CI)	*P* value
Primary efficacy outcome[a]						
MI, stroke, or cardiovascular death	691 (7.9)	2.66	668 (7.6)	2.57	1.04 (0.93–1.15)	.51
Secondary efficacy outcomes[a]						
MI, ischemic stroke, CHD death, or ALI	588 (6.7)	2.27	572 (6.5)	2.20	1.03 (0.92–1.16)	.61
MI, ischemic stroke, cardiovascular death, or ALI	707 (8.0)	2.72	683 (7.8)	2.63	1.04 (0.94–1.15)	.50
Death						
All cause	630 (7.2)	2.37	614 (7.0)	2.31	1.03 (0.92–1.15)	.63
Cardiovascular	343 (3.9)	1.29	333 (3.8)	1.25	1.03 (0.89–1.20)	.69
Non-cardiovascular	287(3.3)	1.08	281 (3.2)	1.06	1.02 (0.87–1.21)	.78
CHD	194 (2.2)	0.73	200(2.3)	0.75	0.97 (0.80–1.18)	.94
Individual efficacy outcomes						
MI	252 (2.9)	0.96	267 (3.0)	1.02	0.94 (0.79–1.12)	.51
Stroke	184 (2.1)	0.70	159 (1.8)	0.60	1.16 (0.94–1.44)	.16
ALI	43 (0.5)	0.16	38 (0.4)	0.14	1.13 (0.73–1.75)	.58
VTE	53 (0.6)	0.20	52 (0.6)	0.20	1.01 (0.69–1.49)	.95
Cancer						
All new cancers	429 (4.9)	1.65	435 (4.9)	1.77	0.99 (0.87–1.13)	.87
GI	86 (1.0)	0.33	83 (0.9)	0.31	1.04 (0.77–1.40)	.81
Lung	73 (0.8)	0.28	77 (0.9)	0.29	0.95 (0.69–1.31)	.75
Prostate	65 (0.7)	0.25	73 (0.8)	0.28	0.89 (0.64–1.24)	.50
Skin	73 (0.8)	0.28	70 (0.8)	0.26	1.05 (0.75–1.45)	.79
Breast	9 (0.1)	0.034	18 (0.2)	0.068	0.50 (0.22–1.11)	.08
Hospitalizations						
All	3074 (35.0)	14.51	3000 (34.1)	13.96	1.04 (0.99–1.09)	.14
Cardiovascular	1721 (19.6)	7.26	1644 (18.7)	6.86	1.06 (0.99–1.13)	.10
Non-cardiovascular	1898 (21.6)	8.13	1901(21.6)	8.10	1.00 (0.94–1.07)	.92

ALI, acute limb ischemia; CHD, coronary heart disease; CI, confidence interval; GI, gastrointestinal; MI, myocardial infarction; od, once daily; VTE, venous thromboembolism.
[a]Defined by the cardiovascular outcomes related to aspirin rivaroxaban arms.[10]

(CIs) were obtained from stratified Cox proportional-hazards models and all reported *P* values are 2-sided.

For all other safety events, the number of participants who experienced an outcome in the pantoprazole vs placebo group were summarized and the OR was calculated using logistic regression and 2-sided 5% type I error. The summary measure for these events was OR rather than HR, as the precise time point of the event was not captured but simply whether or not a pre-defined adverse event had occurred at each 6-month time point. No adjustment was made for multiple testing. Safety outcomes were evaluated using an intention-to-treat principle and a sensitivity analysis of the safety outcomes was also conducted, excluding those who permanently discontinued pantoprazole or placebo therapy during the trial. Number needed to harm was calculated using the Newcombe Wilson method.[24]

Analyses were conducted using SAS software, version 9.4 of the SAS System for SunOS (SAS Institute, Cary, NC).

Results

There were 17,598 participants recruited between March 2013 and May 2016 and randomized to pantoprazole 40 mg or placebo. The main reason for exclusion from the PPI part of the trial was that patients were considered to have a clinical need for PPI (based on their physicians' judgment) at the time of randomization (Figure 1). Those that were excluded from the trial because of continuing need for PPI were similar in all baseline characteristics to those that were enrolled into the PPI randomized trial apart from a higher proportion had a medical history of peptic ulcer disease (Supplementary Table 2).

Baseline characteristics are summarized in Table 1. There were 8791 participants randomized to pantoprazole 40 mg once daily and 8807 were randomized to placebo. Mean age of participants was 67.6 years, 13,792 (78%) were male, 4074 (23%) were current smokers, 872 (5%) were taking non-steroidal anti-inflammatory drugs, and 2.6% had a history of peptic ulcer disease. One hundred and thirty-four (0.8%) participants were taking PPI at the start of the trial and randomized to pantoprazole or placebo (Table 1). Median follow-up was 3.01 years (interquartile range, 2.49–3.59 years; range, 2 days to 5 years and 1 month), accruing 53,152 patient-years of follow-up; 1884 (21%) participants in the pantoprazole group and 1975

(22%) in the placebo group discontinued the medication permanently. Median time to permanent discontinuation was 338 days (interquartile range, 109–679 days) and the reasons are described in Supplementary Table 3. In those that continued their medication, 295 (3.63%) participants in the PPI group took their medication for <80% of the time compared with 288 (3.53%) in the placebo group.

Cardiovascular and Mortality Safety Outcomes

There was no significant difference in the primary efficacy outcome of the rivaroxaban/aspirin trial[21] for the composite outcome of myocardial infarction, stroke, or cardiovascular death (HR, 1.04; 95% CI, 0.93–1.15) (Table 2 and Figure 2) with pantoprazole compared to placebo. There was no statistically significant difference in the secondary cardiovascular efficacy outcomes of the rivaroxaban/aspirin trial[22] and no difference between pantoprazole and placebo when myocardial infarction (HR, 0.94; 95% CI, 0.79–1.12), stroke (HR, 1.16; 95% CI, 0.94–1.44), and acute limb ischemia (HR, 1.13; 95% CI, 0.73–1.75) were considered separately (Table 2 and Figure 3). Hospitalization rates (HR, 1.04; 95% CI, 0.99–1.09) and all-cause mortality (HR, 1.03; 95% CI, 0.92–1.15) were also similar in the pantoprazole and placebo arms (Table 2).

Other Prespecified Safety Outcomes

There were 864 new cancer diagnoses during follow-up in participants randomized to pantoprazole or placebo. One hundred and sixty-nine cancers were from the gastrointestinal tract, with 86 in the pantoprazole group and 83 in the placebo group (Table 2). There was no statistically significant difference in overall cancer rates (HR, 0.99; 95% CI, 0.87–1.13) or in any of the primary sites of cancer between the 2 groups (Table 2). There was no statistically significant difference between pantoprazole and placebo in the proportion of participants who experienced prespecified non-cardiovascular events of interest that are associated with PPI use in observational studies[8]

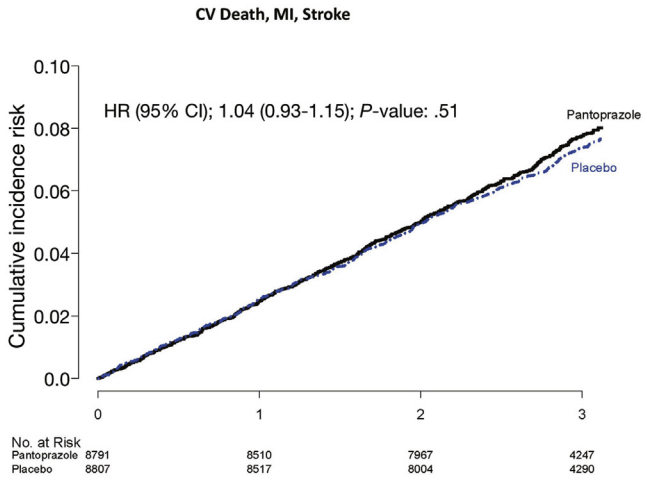

Figure 2. Cumulative incidence of combined cardiovascular death, myocardial infarction, and stroke in the pantoprazole vs placebo arm.

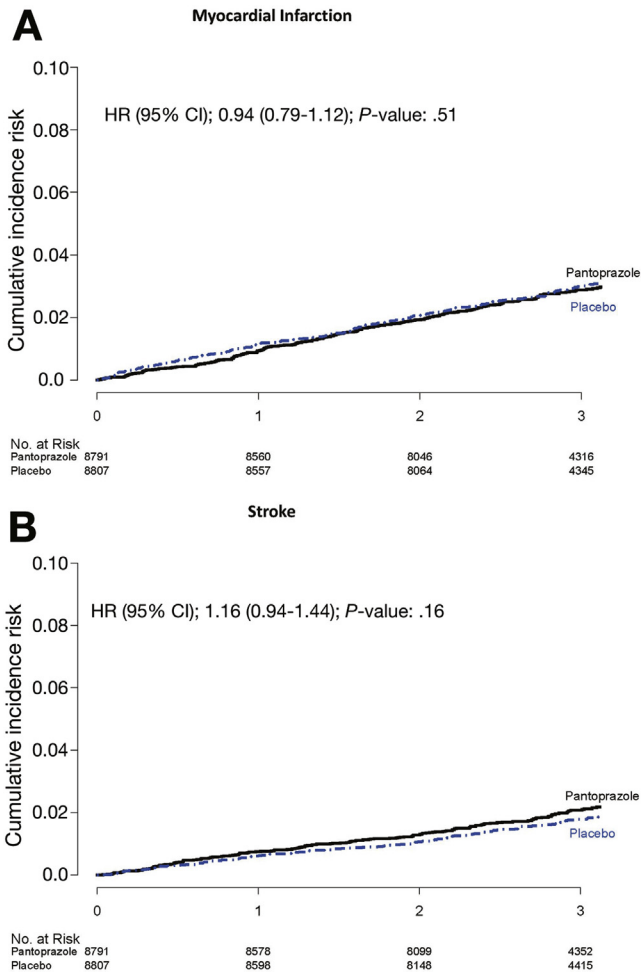

Figure 3. Cumulative incidence of individual cardiovascular events in the pantoprazole vs placebo arm.

(Table 3), including pneumonia, fracture, new diagnosis of diabetes mellitus, chronic kidney disease, dementia, chronic obstructive lung disease, gastric atrophy. However, enteric infections were more frequent in the pantoprazole group (OR, 1.33; 95% CI, 1.01–1.75) (Table 3). The number needed to harm for enteric infections was 301 (95% CI, 152–9190) after a median of 3 years of PPI use. Results were similar when participants who permanently discontinued pantoprazole or placebo were excluded from the analysis (Table 4). There were 134 (0.8%) participants that were on PPI before the start of the trial. They may have been self-selected to be tolerant of PPI, so this group was removed in a sensitivity analysis and this gave similar results (Supplementary Table 4). Patients with dementia, severe chronic obstructive pulmonary disease, and glomerular filtration rate of 15 mL/min were excluded from participating in the trial. Diabetes mellitus was not excluded and those that already have the disease cannot develop new-onset diabetes so the denominator is falsely increased in the baseline analysis. Excluding this group did not change the estimate of effect of PPI vs placebo (OR, 1.15; 95% CI, 0.89–1.50; $P = .28$). Excluding those with a glomerular filtration rate <30 mL/min at baseline also did

Table 3. Other Prespecified Safety Outcomes

Outcome	Incident events, n (%)		Pantoprazole, 40 mg od, vs placebo	
	Pantoprazole, 40 mg od (n = 8791)	Placebo (n = 8807)	OR (95% CI)	*P* value
Gastric atrophy	19 (0.2)	26 (0.3)	0.73 (0.40–1.32)	.30
Clostridium difficile	9 (0.1)	4 (<0.1)	2.26 (0.70–7.34)	.18
Other enteric infection	119 (1.4)	90 (1.0)	1.33 (1.01–1.75)	.04
Chronic kidney disease	184 (2.1)	158 (1.8)	1.17 (0.94–1.45)	.15
Dementia	55 (0.6)	46 (0.5)	1.20 (0.81–1.78)	.36
Pneumonia	318 (3.6)	313 (3.6)	1.02 (0.87–1.19)	.82
Fracture	203 (2.3)	211 (2.4)	0.96 (0.79–1.17)	.71
COPD	146 (1.7)	124 (1.4)	1.18 (0.93–1.51)	.17
Diabetes mellitus	513 (5.8)	532 (6.0)	0.96 (0.85–1.09)	.56

COPD, chronic obstructive pulmonary disease; od, once daily.

not impact on the risk of chronic renal disease (OR, 1.20; 95% CI, 0.96–1.51; $P = .11$).

Discussion

To our knowledge, this is the largest PPI trial for any indication and the first prospective randomized trial to evaluate the many long-term safety concerns related to PPI therapy. It is reassuring that there was no evidence for harm for most of these events other than an excess of enteric infections. This is in contrast to systematic reviews of observational studies that report the association of PPI therapy with harms such as pneumonia,[25] fracture,[26] and cerebrovascular events.[27] Biologically plausible mechanisms have been advanced to suggest these associations are causal, such as a PPI causing a change in the upper gastrointestinal tract microbiome, leading to pneumonia if aspirated[28]; inhibition of calcium absorption leading to increased risk of fracture[29]; and cardiovascular events may relate to PPIs reducing the activity of nitric oxide synthase.[30]

A well-known maxim of epidemiology is that association is not causation[31] and these data suggest that most of these associations relate to residual confounding or biases that are inherent in observational studies.[9] A significant proportion of patients are prescribed PPI therapy inappropriately[32] and, in these cases, it is reasonable to advocate strategies to discontinue acid suppression.[33] However, when there is a clinical need for PPI therapy,[3–6] these data suggest that the benefits are likely to outweigh any putative risks.

We found a statistically significant increased risk of enteric infections in those allocated to PPI, although the risk is lower than estimated by systematic reviews of observational studies.[13] The data in the current randomized trial were not adjusted for multiple testing, so this result should be interpreted with caution. The risk of PPI therapy and enteric infection, however, has biologic plausibility, as acid secretion protects against ingestion of organisms causing enteric infection. This is the only association where past observational studies were conducted to specifically test this hypothesis[34] rather than analyses of administrative databases or re-analyses of large cohort studies testing other primary hypotheses. The number needed to harm in this analysis is >300 with 3 years of PPI use, so the benefits are likely to outweigh the harms even for this adverse event.

There are some potential limitations of this trial. Despite the fact that our study is by far the largest placebo-controlled trial evaluating a PPI, the number of events for some of the adverse outcomes are small. This issue is

Table 4. Other Prespecified Safety Outcomes Excluding Those That Permanently Discontinued Pantoprazole or Placebo

Outcomes	Incident events, n (%)		Pantoprazole, 40 mg od, vs placebo	
	Pantoprazole, 40 mg od (n = 6947)	Placebo (n = 6868)	OR (95% CI)	*P* value
Gastric atrophy	10 (0.1)	24 (0.2)	0.71 (0.31–1.59)	.40
Clostridium difficile	5 (<0.1)	2 (<0.1)	2.48 (0.48–12.8)	.28
Other enteric infection	60 (0.9)	42 (0.6)	1.42 (0.95–2.10)	.08
Chronic kidney disease	104 (1.5)	98 (1.4)	1.05 (0.80–1.39)	.73
Dementia	24 (0.3)	22 (0.3)	1.08 (0.60–1.93)	.80
Pneumonia	203 (2.9)	185 (2.7)	1.09 (0.89–1.33)	.41
Fracture	136 (2.0)	150 (2.2)	0.89 (0.71–1.13)	.35
COPD	94 (1.4)	83 (1.2)	1.12 (0.83–1.51)	.45
Diabetes mellitus	393 (5.7)	423 (6.2)	0.91 (0.79–1.05)	.21

COPD, chronic obstructive pulmonary disease; od, once daily.

exemplified by the outcomes *C difficile* and gastric atrophy, where the number of events was modest even in this large trial. The incidence of gastric atrophy is likely to be underestimated in this trial as it relies on participants being referred for endoscopy and having gastric biopsy, and this is not mandated for all participants. It is somewhat reassuring that the proportion of gastric atrophy cases was similar between the 2 groups, but as the number of participants with gastric atrophy was small, this may have biased the results toward the null. Gastric atrophy is a risk factor for B-12 deficiency and gastric cancer. These adverse events have also been associated with PPI therapy[35] and so these associations are not supported by these randomized data, although a small effect cannot be excluded. There was an apparent excess of *C difficile*–associated diarrhea observed in our trial, but given the low numbers, this needs to be interpreted cautiously. Even if the excess of these events is real, the rarity of these events with >53,000 patient-years of follow-up suggests that any potential adverse effect will be low in terms of absolute excess of these events. We separated *C difficile*–associated diarrhea from other enteric infections, as the former is caused in the community primarily by disruption of existing gut microbiota by antibiotics or diseases such as ulcerative colitis, whereas the latter is transmitted by ingestion of infected food or drink. Previous studies have also taken the approach of evaluating *C difficile*–associated diarrhea and other enteric infections separately.[13] These adverse events were obtained mainly by patient interview every 6 months. Although participants were specifically asked about these events, it is possible that there was some misclassification. As this was a double-blind randomized trial, misclassification would have been similar in both arms, but this may have biased results toward the null. Previous studies that have reported an association between PPI and adverse events[11,12,14,17,18] have usually relied on administrative databases, which are likely to be at least as inaccurate as direct participant interview, so this is unlikely to be the explanation for our negative findings.

Furthermore, cardiovascular outcomes were independently adjudicated and, as this trial was conducted in cardiovascular centers, it is highly unlikely that significant misclassification occurred. Cardiovascular outcomes showed very similar results to other outcomes in this trial, again supporting the belief that misclassification is unlikely to explain the lack of association between PPIs and most of the harms evaluated. However, as other outcomes relied on researcher interview with the participant every 6 months, it is possible that there was some non-differential misclassification for these outcomes that can bias results toward the null.

It is always possible that PPIs are associated with a more modest risk of long-term adverse effects than currently suggested by observational studies. Such a possibility can never be excluded no matter how large the sample size of the trial. It is reassuring, however, that the HRs and ORs reported in this trial are lower than the lower end of the 95% CI of the observational data for pneumonia,[23] fracture,[26] cardiovascular disease,[27] chronic renal disease,[16] dementia,[17] and all-cause mortality.[18] Some data suggest adverse events associated with PPI therapy are not seen until after 5 years of therapy[36] and this trial had a mean follow-up of 3 years and a maximum follow-up of 5 years, which was achieved in only a small proportion of patients. However, all adverse events have studies that report observing an excess of events after 1 year of PPI therapy[17,18,23,26,27,37] and almost all patients in the COMPASS trial exceeded this time frame. There is also no evidence of time effects seen in the cumulative incidence of risk of cardiovascular events with PPI therapy compared with placebo.

In conclusion, these data suggest PPI therapy is safe for up to a median of 3 years. As with all drugs, PPI therapy should only be used when the benefits are expected to outweigh the risks and should be used according to recommended dose and duration of treatment.[38] However, this trial suggests that limiting prescription of PPI therapy because of concerns of long-term harm is not appropriate.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2019.05.056.

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Conflicts of interest

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Supplementary Table 1. Power Calculations for Each Adverse Event Evaluated in the Trial

Adverse event	OR
Enteric infection	1.62
Chronic kidney disease	1.41
Dementia	2.06
Pneumonia	1.27
Fracture	1.35
COPD	1.49
Diabetes mellitus	1.20

NOTE. The OR of a given adverse event with PPI vs placebo that the trial had 80% power and 5% significance level to detect assuming the proportions for that adverse event seen in the trial.
COPD, chronic obstructive pulmonary disease.

Supplementary Table 2. Baseline Characteristics of Those Not Randomized to Pantoprazole or Placebo

Factor	All patients (n = 27,395)	Pantoprazole, 40 mg od (n = 8791)	Placebo (n = 8807)	Not randomized to pantoprazole or placebo (n = 9797)
Age, *y*, mean (SD)	68.2 (7.9)	67.6 (8.1)	67.7 (8.1)	69.3 (7.5)
Sex, n (% *male*)	21,377 (78.0)	6854 (78.0)	6938 (78.8)	7585 (77.4)
BMI, kg/m^2, mean (SD)	28.3 (4.7)	28.3 (4.7)	28.4 (4.7)	28.3 (4.7)
Total cholesterol, *mmol/L*, mean (SD)	4.2 (1.1)	4.3 (1.1)	4.2 (1.1)	4.1 (1.0)
Race, n (%)				
Caucasian	17,027 (62.2)	5265 (59.9)	5267 (59.8)	6495 (66.3)
Afro-Caribbean	262 (1.0)	97 (1.1)	108 (1.2)	57 (0.6)
Asian	4269 (15.6)	1363 (15.5)	1384 (15.7)	1522 (15.5)
Other	5837 (21.3)	2066 (23.5)	2048 (23.3)	1723 (17.6)
Current smoker, n (%)	5867 (21.4)	2064 (23.5)	2010 (22.8)	1793 (18.3)
Hypertension, n (%)	20,647 (75.4)	6671 (75.9)	670.3 (76.1)	7273 (74.2)
Peptic ulcer disease history, n (%)	1238 (4.5)	228 (2.6)	222 (2.5)	788 (8)
Inflammatory bowel disease, n (%)	216 (0.8)	37 (0.4)	56 (0.6)	123 (1.3)
ACE inhibitor, n (%)	19,523 (71.3)	6269 (71.3)	6286 (71.4)	6968 (71.1)
Diuretic, n (%)	8141 (29.7)	2572 (29.3)	2522 (28.6)	3047 (31.1)
Lipid-lowering agent, n (%)	24,607 (89.8)	7775 (88.4)	7823 (88.8)	9009 (92)
Calcium channel blocker, n (%)	7272 (26.5)	2237 (25.4)	2265 (25.7)	2270 (28.3)
β-blocker, n (%)	19,192 (70.1)	6137 (69.8)	6122 (69.5)	6933 (70.8)
NSAID, n (%)	1468 (5.4)	425 (4.8)	447 (5.1)	596 (6.1)
Hypoglycemic agent, n (%)	8561 (31.3)	2785 (31.7)	2784 (31.6)	2992 (30.5)

ACE, angiotensin converting enzyme; BMI, body mass index; NSAID, non-steroidal anti-inflammatory drug; od, once daily.

Supplementary Table 3. Reasons for Discontinuing Pantoprazole or Placebo

Characteristic	Pantoprazole, n (%) (n = 8791)	Placebo, n (%) (n = 8807)
Permanent discontinuation of drug	1884 (21.4)	1975 (22.4)
Reason		
Serious adverse event	78 (0.9)	66 (0.75)
Participant decision not due to side effect	913 (10.4)	911 (10.3)
Bleeding	80 (0.9)	80 (0.9)
Upper GI	20 (0.2)	27 (0.3)
Other	60 (0.7)	52 (0.6)
Physician decision not due to other event	302 (3.4)	297 (3.4)
Use of open-label study drug	296 (3.4)	346 (3.9)
Non-serious adverse event	213 (2.4)	250 (2.8)
Missing	2 (0.02)	1 (0.01)

GI, gastrointestinal.

Supplementary Table 4. Other Prespecified Safety Outcomes With Those That Were Already on Proton Pump Inhibitors Before Randomization Excluded

	Incident events, n (%)		Pantoprazole, 40 mg od, vs placebo	
Outcomes	Pantoprazole, 40 mg od (n = 8735)	Placebo (n = 8729)	OR (95% CI)	*P* value
Gastric atrophy	19 (0.2)	25 (0.3)	0.76 (0.42–1.32)	.37
Clostridium difficile	7 (<0.1)	4 (<0.1)	1.75 (0.51–5.99)	.37
Other enteric infection	118 (1.4)	85 (1.0)	1.39 (1.05–1.84)	.02
Chronic kidney disease	183 (2.1)	158 (1.8)	1.16 (0.94–1.44)	.18
Dementia	55 (0.6)	46 (0.5)	1.20 (0.81–1.78)	.36
Pneumonia	318 (3.6)	309 (3.5)	1.03 (0.88–1.21)	.72
Fracture	201 (2.3)	209 (2.4)	0.96 (0.79–1.17)	.68
COPD	146 (1.7)	124 (1.4)	1.18 (0.93–1.51)	.17
Diabetes mellitus	508 (5.8)	531 (6.0)	0.95 (0.84–1.08)	.45

COPD, chronic obstructive pulmonary disease; od, once daily.