Gastroenterology 2019;157:403–412

CLINICAL AT

Pantoprazole to Prevent Gastroduodenal Events in Patients Receiving Rivaroxaban and/or Aspirin in a Randomized, Double-Blind, Placebo-Controlled Trial

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BACKGROUND & AIMS: Antiplatelets and anticoagulants are associated with increased upper gastrointestinal bleeding. We evaluated whether proton pump inhibitor therapy could reduce this risk. **METHODS:** We performed a 3 × 2 partial factorial double-blind trial of 17,598 participants with stable cardiovascular disease and peripheral artery disease. Participants were randomly assigned to groups given pantoprazole 40 mg daily or placebo, as well as rivaroxaban 2.5 mg twice daily with aspirin 100 mg once daily, rivaroxaban 5 mg twice daily, or aspirin 100 mg alone. The primary outcome was time to first upper gastrointestinal event, defined as a composite of overt bleeding, upper gastrointestinal bleeding from a gastroduodenal lesion or of unknown origin, occult bleeding, symptomatic gastroduodenal ulcer or ≥5 erosions, upper gastrointestinal obstruction, or perforation. **RESULTS:** There was no significant difference in upper gastrointestinal events between the pantoprazole group (102 of 8791 events) and the placebo group (116 of 8807 events) (hazard ratio, 0.88; 95% confidence interval [CI], 0.67–1.15). Pantoprazole significantly reduced bleeding of gastroduodenal lesions (hazard ratio, 0.52; 95% confidence interval, 0.28–0.94; $P = .03$); this reduction was greater when we used a post-hoc definition of bleeding gastroduodenal lesion (hazard ratio, 0.45; 95% confidence interval, 0.27–0.74), although the number needed to treat still was high (n = 982; 95% confidence interval, 609–2528). **CONCLUSIONS:** In a randomized placebo-controlled trial, we found that routine use of proton pump inhibitors in patients receiving low-dose anticoagulation and/or aspirin for stable cardiovascular disease does not reduce upper gastrointestinal events, but may reduce bleeding from gastroduodenal lesions. ClinicalTrials.gov ID: NCT01776424.

Keywords: Heart Disease Prevention; Thrombosis; Stomach; Drug.

CLINICAL AT

Aspirin is effective in preventing cardiovascular morbidity and mortality,[1] and a significant proportion of people over the age of 45 years use it regularly.[2] Anticoagulants are commonly used to prevent thromboembolic events in patients with venous thromboembolism or atrial fibrillation, with new oral anticoagulants (NOACs) overtaking the prescription of vitamin K antagonists for these indications in the United States and several other countries.[3] Gastrointestinal (GI) bleeding is one of the most common adverse events in patients treated with antiplatelet or anticoagulant therapy.[4] Epidemiologic data suggest that patients taking cardioprotective aspirin have a 2-fold increased risk of upper GI complications, and patients taking vitamin K antagonists have a similar increased risk.[5] Combining vitamin K antagonists and nonsteroidal anti-inflammatory drugs can increase the risk of upper GI complications further, with 1 study suggesting a 12-fold increase in risk.[5] NOACs are also associated with an increased risk of GI bleeding,[4] and some NOACs are associated with a greater risk of GI bleeding than vitamin K antagonists.[6]

With increasing long-term use of antiplatelet and antithrombotic therapy, it would be important to prevent GI bleeding and related complications. Randomized trials suggest that proton pump inhibitors (PPIs) prevent gastroduodenal ulcers and reduce the risk of peptic ulcer bleeding related to the use of nonsteroidal anti-inflammatory drugs.[7] There is, however, a paucity of randomized data relating to patients taking aspirin for cardioprotection. A randomized trial suggested that PPIs protect against peptic ulcer diagnosed at endoscopy in patients taking aspirin,[8] but this does not relate to complicated peptic ulcer disease. A further randomized trial showing that PPI therapy prevented GI events in patients taking dual antiplatelet therapy,[9] but this trial was stopped early for administrative reasons when only a modest number of events had accrued, and so the apparent benefits may have been inflated. There are also no randomized trial data on PPIs reducing the risk of upper GI complications related to anticoagulant therapy.[10] Guidelines suggest that patients receiving the combination of antiplatelet and anticoagulant therapy should receive PPIs to reduce the risk of upper GI bleeding.[11] However, as stated, there are no randomized data to support the use of PPI therapy in patients taking oral anticoagulants, and a paucity of data relating to aspirin.

We have previously reported that rivaroxaban 2.5 mg twice daily with aspirin 100 mg once daily reduced cardiovascular outcomes in patients with stable cardiovascular disease or peripheral artery disease, but significantly increased major GI bleeding events.[12] This finding has the potential to widen the indications for NOACs and underscores the importance of evaluating whether PPIs may reduce the risks of GI bleeding and thereby minimize the risk of upper GI complications related to the use of antiplatelet anticoagulant therapy or the combination of both. We assessed the impact of PPI in reducing upper GI complications for aspirin alone, anticoagulants alone, or the combination, as both aspirin and anticoagulant therapy are associated with a similar risk of upper GI complications[5] and the combination has an even higher risk. We therefore evaluated whether the PPI pantoprazole is effective in preventing upper GI events in individuals receiving aspirin, rivaroxaban, or the combination as part of the COMPASS (Cardiovascular Outcomes for People Using Anticoagulant Strategies) trial.

WHAT YOU NEED TO KNOW

BACKGROUND & CONTEXT

Upper gastrointestinal bleeding mainly relates to peptic ulcer disease and this may be prevented by proton pump inhibitor therapy. There have been no randomised trials evaluating the efficacy of proton pump inhibitor therapy in patients taking new anticoagulant therapies

NEW FINDINGS

Pantoprazole 40mg daily did not reduce the overall risk of upper gastrointestinal events in patients taking rivaroxaban and/or aspirin for stable cardiovascular disease but may reduce the risk of peptic ulcer disease events including bleeding from a gastroduodenal lesion.

LIMITATIONS

Low risk gastrointestinal bleeding patients were evaluated and a composite end-point was chosen for upper gastrointestinal tract complications.

IMPACT

Routine use of proton pump inhibitor therapy is not warranted in patients starting low dose anticoagulants and/or aspirin. These drugs may be appropriate for patients at high risk of peptic ulcer disease.

Methods

Trial Design

The design of the COMPASS trial has been published previously.[11] This is a 3 × 2 partial factorial, multicenter, double-blind, randomized placebo-controlled trial, evaluating patients with stable atherosclerotic vascular disease.[10] 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. In addition, all participants with no clinical need for a PPI (64%) were randomized to receive either pantoprazole 40 mg or matching placebo once daily. The rivaroxaban part of the trial was stopped in response to recommendations by the data monitoring committee at a planned interim analysis for overwhelming

Abbreviations used in this paper: **CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; NOAC, new oral anticoagulant; NNT, number needed to treat; PPI, proton pump inhibitor.**

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0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2019.04.041

efficacy of the rivaroxaban 2.5 mg and aspirin combination arm compared to aspirin alone in reducing major cardiovascular events.[12] Participants had been followed up for a mean of 23 months at this point and all patients continued on at least taking aspirin for the remainder of the trial. The pantoprazole part of the trial was continued as planned for a mean follow-up of 3 years.[13] Participants in the PPI arms were recruited from 580 centers in 33 countries and all relevant authorities and research ethics boards approved the trial. Written informed consent was obtained from all of the participants. Bayer AG sponsored the trial, but 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. All authors had access to study data and reviewer and approved the final manuscript. The protocol is available in the Supplementary Material.

Randomization, Concealment of Allocation, and Blinding

All participants were randomly assigned to receive low-dose rivaroxaban 2.5 mg twice a day with aspirin 100 mg once daily, rivaroxaban 5 mg twice a day alone, or aspirin 100 mg once daily alone stratified by center and use of PPI. Eligible participants were further randomized 1:1 to receive pantoprazole (40 mg once daily) or matched placebo stratified by center and antithrombotic treatment arm. 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 pantoprazole allocation until database closure.

Trial Population, Intervention, and Follow-Up

Participants were eligible if they had stable coronary or peripheral arterial disease. Patients with coronary artery disease under the age of 65 years were additionally required to have arterial disease involving 2 vascular beds or 2 additional risk factors.[10] Patients were randomized to receive pantoprazole 40 mg once daily or placebo, except if they had a clinical need for long-term PPI therapy. 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 or anticoagulant therapy, or known hypersensitivity to any of the study drugs.[13] Previous peptic ulcer disease or nonsteroidal anti-inflammatory use were not exclusion criteria. After randomization, participants were seen at 1 month, 6 months, and then at 6-month intervals until the end of the study.

Outcomes

The primary efficacy outcome for the randomized comparison of pantoprazole vs placebo was time to first upper GI clinical event. This was defined from a previous study[9] as a composite of overt bleeding (hematemesis and/or melena) with a gastroduodenal lesion (peptic ulcer or neoplasia confirmed by endoscopy or radiology) that is bleeding at the time of the procedure, overt upper GI bleeding of unknown origin (patient presents with hematemesis with or without melena that was thought by the attending clinician to relate to the upper GI tract), occult bleeding (drop in the hemoglobin of $\geq$2 g/dL), symptomatic gastroduodenal ulcer with at least 3 days of GI pain, or at least 5 gastroduodenal erosions (confirmed by endoscopy) with at least 3 days of GI pain, upper GI obstruction, or perforation. This definition is similar to the end point definition in the COGENT (Clopidogrel and the Optimization of Gastrointestinal Events Trial) study, which previously reported that PPI significantly reduced the composite of these upper GI events. We also evaluated a less stringent definition of peptic ulcer events to explore the impact that changing the definition of events might have on conclusions (but this was post-hoc after the results of the above analyses were known to the first and last authors).

Sample Size Calculations and Statistical Analyses

A sample size of 16,440 participants randomized in a 1:1 ratio to pantoprazole or placebo would have 99% power at 5% type I error level to detect a relative risk reduction of 50%, assuming an annual incidence risk of 1.6%–2% in the control arm with a 20% discontinuation rate. This magnitude of effect had been observed in a previous moderate-sized trial.[6]

All events occurring in the randomized participants are included in the intention-to-treat analysis utilizing the time to the first occurrence of primary outcome for pantoprazole vs placebo from the time of randomization until the date of formal trial termination. The superiority statistical hypothesis for pantoprazole 40 mg once daily vs pantoprazole placebo comparison was tested using a log-rank test stratified by antithrombotic study treatment (3 strata levels: rivaroxaban 2.5 mg twice a day + aspirin 100 mg once daily; rivaroxaban 5 mg twice a day + aspirin placebo; rivaroxaban placebo + aspirin 100 mg once daily) and 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 2 PPI study groups (pantoprazole/pantoprazole placebo). Hazard ratios (HRs) and 95% confidence intervals (CIs) were obtained from stratified Cox proportional hazards models and all reported *P* values are 2-sided.

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 flow of participants through the trial is described in Supplementary Figure 1. The main reason for exclusion from the PPI arm of the trial was that patients were considered to have a clinical need for PPI based on their physicians' judgment at the time of enrollment (Supplementary Figure 1). Mean age of participants was 67.6 years, 13,792 (78%) were male, 4074 (23%) were current smokers, 872 (5%) were taking nonsteroidal anti-inflammatory drugs, 515 (3%) were taking selective serotonin reuptake inhibitors, and 228 (2.6%) had a history of peptic ulcer disease. Baseline characteristics were similar between both randomized groups and are summarized in Table 1. Those not randomized to pantoprazole or placebo had baseline characteristics similar to those that were randomized (Supplementary Table 2). There were 8791 participants randomized to pantoprazole 40 mg once daily and

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
Median (Q1, Q3)	68 (64, 73)	68 (64, 73)
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, kg/m^2, 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 (%)		
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; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; Q, quartile; SSRI, selective serotonin reuptake inhibitor.

8807 allocated to placebo. The mean follow-up was 3.02 years (SD, 0.80 year; range, 2 days to 5 years and 1 month), thus accruing 53,152 patient-years of follow-up. Eighteen hundred and eighty-four (21%) participants in the pantoprazole group and 1975 (22%) in the placebo group permanently discontinued the medication and the reasons are described in Supplementary Table 1. For those who permanently discontinued pantoprazole/placebo, the median time to permanent discontinuation was 338 days (interquartile range, 109–679 days).

Primary Efficacy Outcome

The primary efficacy outcome, clinically significant upper GI events, occurred in 102 of 8791 (1.2%) participants in the pantoprazole arm and 116 of 8807 (1.3%) participants in the placebo arm (HR, 0.88; 95% CI, 0.67–1.15) (Table 2 and Figure 1). Event rates in those not randomized were similar to those randomized, with 128 of 9797 (event rate = 0.6% per year) having a GI event in those not randomized to PPI or placebo. Evaluating the components of the upper GI bleeding events, there was a reduction in the gastroduodenal bleeding events in the pantoprazole arm compared to the placebo arm (HR, 0.52; 95% CI, 0.28–0.94; nominal *P* value = .03) (Table 2 and Figure 1) with no difference in overt or occult upper GI bleeding events between the 2 groups (Table 2). The number needed to treat (NNT) was 1770 (95% CI, 933.5–17,111) for pantoprazole to prevent 1 overt bleeding gastroduodenal lesion compared to placebo each year. There was no statistically significant difference in painful upper GI ulcer/erosions, upper GI obstruction, or perforation events between the 2 groups (Table 2). There was no statistically significant interaction among pantoprazole, aspirin, and/or rivaroxaban for clinically upper GI events (Supplementary Table 3). The primary outcome and individual components of that outcome for the aspirin alone, rivaroxaban alone, and rivaroxaban combined with aspirin groups are described in Supplementary Tables 4–6. The effects were similar in various subgroups, with no evidence of statistical interactions (Figure 2).

Post-Hoc Efficacy Outcome

Upper GI events as defined in the study protocol were uncommon in this trial and, therefore, we explored whether this related to the narrow definition of an event. In a post-hoc analysis, we broadened the definition of upper GI events related to gastroduodenal ulcers. The post-hoc outcomes were defined before analyses were conducted and, therefore, specified without knowledge of what the results would be. Bleeding of gastroduodenal lesions was redefined as an ulcer seen at endoscopy in a patient with upper GI bleeding of gastroduodenal origin with no requirement for the lesion to be actively bleeding at the time of endoscopy. In addition, we changed the requirement for documented pain when ulcer/erosions were diagnosed at endoscopy or other imaging. Also, in this analysis, an upper GI event remained uncommon (Table 3). However, pantoprazole was associated with a lower risk of redefined bleeding of gastroduodenal lesions as in the primary analysis (HR, 0.45; 95% CI, 0.27–0.74) (Table 3 and Figure 3) with an NNT of 982 (95% CI, 609–2528). Furthermore, in this post-hoc analysis, pantoprazole was also associated with a lower risk of peptic ulcer (HR, 0.46; 95% CI, 0.25–0.83) (NNT = 1397; 95% CI, 804–5312) and erosions (HR, 0.33; 95% CI, 0.13–0.84) (NNT = 2214; 95% CI, 1230–11,099) when the requirement of 5 days of pain before peptic ulcer and/or erosions at endoscopy was removed (Table 3). When all post-hoc gastroduodenal ulcer complications were combined,

Table 2. Primary Efficacy Outcome of Clinically Significant Upper Gastrointestinal Event

Outcome	Pantoprazole, 40 mg od (n = 8791)		Pantoprazole placebo (n = 8807)		Pantoprazole vs placebo	
	First events, n (%)	Annual rate, %/y	First events, n (%)	Annual rate, %/y	HR (95% CI)	*P* value
Upper GI event[a]	102 (1.2)	0.39	116 (1.3)	0.44	0.88 (0.67–1.15)	.35
Overt bleeding of gastroduodenal origin confirmed by endoscopy or radiography	16[b] (0.2)	0.060	31 (0.4)	0.12	0.52 (0.28–0.94)	.03
Overt upper GI bleeding of unknown origin	50 (0.6)	0.19	46 (0.5)	0.17	1.09 (0.73–1.63)	.68
Bleeding of presumed occult upper GI tract origin with documented decrease in Hb ≥2 g/dL	10 (0.1)	0.038	10 (0.1)	0.034	1.00 (0.42–2.40)	.99
Symptomatic gastroduodenal ulcer	8 (<0.1)	0.030	17 (0.2)	0.064	0.47 (0.20–1.09)	.07
GI pain with underlying multiple gastroduodenal erosions	4 (<0.1)	0.015	7 (<0.1)	0.026	0.57 (0.17–1.95)	.37
Upper GI obstruction or perforation	21 (0.2)	0.079	16 (0.2)	0.064	1.32 (0.69–2.52)	.41

Hb, hemaglobin; od, once daily.
[a]Composite of overt bleeding of gastroduodenal origin confirmed by endoscopy or radiography, overt upper GI bleeding of unknown origin, bleeding of presumed occult upper GI tract origin with documented decrease in Hb of 2 g/dL, symptomatic gastroduodenal ulcer, GI pain with underlying multiple gastroduodenal erosions, and upper GI obstruction/perforation.
[b]Includes 1 gastric cancer in the pantoprazole group, no upper GI cancers in the placebo group.

pantoprazole reduced events by >50% (HR, 0.44; 95% CI, 0.31–0.63) with an NNT of 498 (95% CI, 348–876).

Discussion

This is the largest PPI trial and the first to evaluate whether PPI therapy can prevent clinically significant upper GI events in patients receiving anticoagulation with or without aspirin therapy. The data suggest that routine use of PPI therapy is not warranted for patients receiving low-dose rivaroxaban with or without aspirin for the prevention of atherothrombotic events in patients with stable coronary artery disease or symptomatic peripheral artery disease, as there was no overall impact on clinical upper GI events or upper GI bleeding. This is in contrast to previous systematic reviews of randomized trials reporting that PPIs were associated with a 50%–70% reduction in bleeding and symptomatic peptic ulcers related to nonsteroidal anti-inflammatory drugs,[7,14] including in the critical care setting.[15] However, the patient populations differed, and systematic reviews can overestimate treatments effects due to small study bias and selective publication of results that fit in with "group thinking" and expectations.[7]

Our primary GI outcome (an expanded composite) was based on what was used in the COGENT trial,[9] which demonstrated a large effect of PPI in reducing upper GI complications. There was no significant impact of PPI on this predefined primary composite GI outcome. However, PPI therapy did reduce bleeding gastroduodenal lesions by approximately 50% (HR, 0.52; 95% CI, 0.28–0.94), which is consistent with previous data regarding PPI reducing peptic ulcer complications related to nonsteroidal anti-inflammatory drugs.[14] This raises the possibility that PPI therapy may reduce overt gastroduodenal bleeding, although as this is only 1 component of the primary outcome and $P = .03$, this needs to be considered as hypothesis-generating. Furthermore, our definition of gastroduodenal bleeding was very stringent, and events were only included if the lesion was bleeding at the time of endoscopy. If a broader definition was used, more events were recorded, with a similar pattern toward benefit and with narrower CIs (HR, 0.45; 95% CI, 0.27–0.74). PPI therapy has been shown to reduce ulcer relapse in other settings,[16] so it is perhaps surprising that they did not significantly reduce symptomatic peptic ulcer disease in this trial, although the overall rate of this event was low (0.4% per year). This may relate to the definition requiring pain to be present for 3 days before diagnosis. The pantoprazole group did have a lower incidence of overall peptic ulcer disease and erosions compared to placebo in an exploratory post-hoc analysis, which is consistent with prior studies.

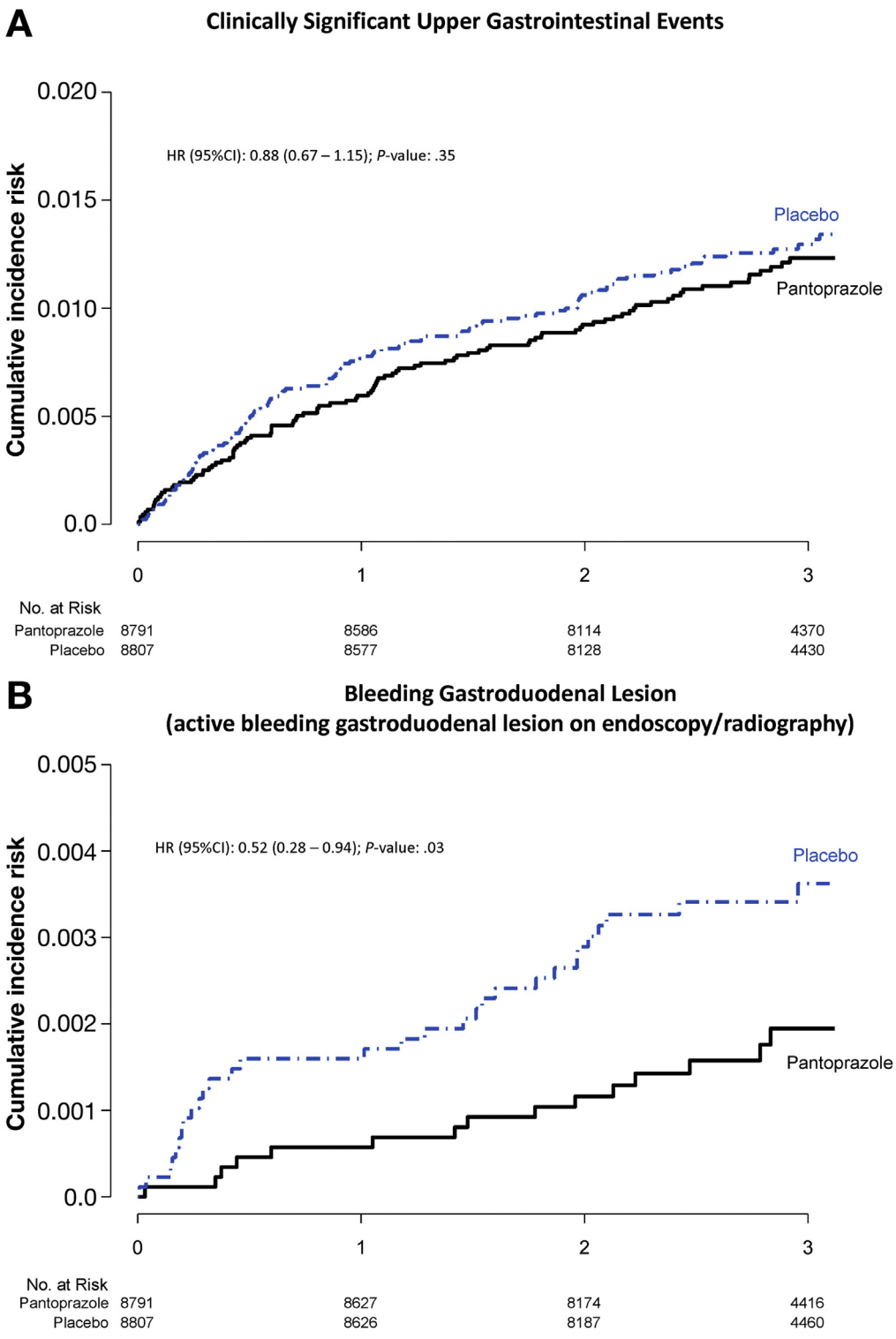

Figure 1. Cumulative incidence of upper GI events in the pantoprazole vs placebo arm.

It is therefore possible that PPIs might be beneficial for patients at particularly high risk for peptic ulcer disease who are also taking aspirin and/or anticoagulants. We evaluated factors that could be associated with increased risk of peptic ulcer disease in subgroup analyses. There was no significant difference seen in any subgroup, although in many subgroups there was insufficient power, despite this being the largest trial to evaluate PPI therapy to reduce clinically significant upper GI events. For example, patients with previous peptic ulcer disease had greater benefit from pantoprazole therapy, but with only 10 events (3 in the pantoprazole group vs 7 in the placebo group) in the peptic ulcer group it is difficult to draw any conclusions from this, but it indicates that the rate of GI complications is very low in the population studied.

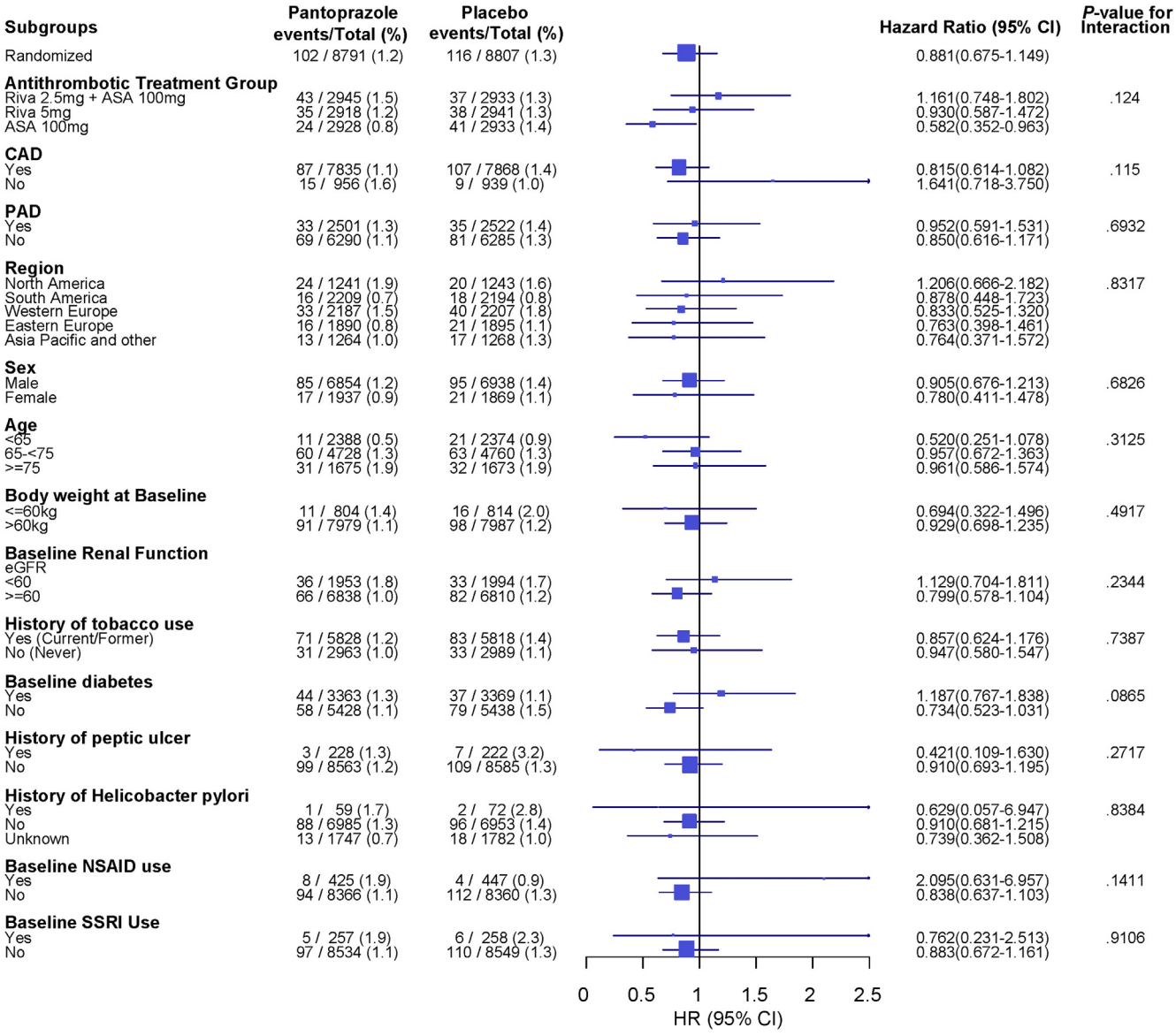

Figure 2. Subgroup analyses of pantoprazole vs placebo for the primary outcome of clinically significant upper GI event.

Table 3. Post-Hoc Outcomes Related to Gastroduodenal Ulcer and Erosions

Outcome	Pantoprazole, 40 mg od (n = 8791)		Pantoprazole placebo (n = 8807)		Pantoprazole vs placebo	
	First events, n (%)	Annual rate, %/y	First events, n (%)	Annual rate, %/y	HR (95% CI)	*P* value
Overt bleeding of gastroduodenal origin confirmed by endoscopy or radiography with no need for active bleeding at time of investigation	22[a] (0.3)	0.083	49[a] (0.6)	0.18	0.45 (0.27–0.74)	.001
Gastroduodenal ulcer without the need for symptoms prior to diagnosis	16 (0.2)	0.060	35 (0.4)	0.13	0.46 (0.25–0.83)	.01
Multiple gastroduodenal erosions without the need for symptoms prior to diagnosis	6 (<0.1)	0.023	18 (0.2)	0.068	0.33 (0.13–0.84)	.01
Combination of all post-hoc gastroduodenal ulcer/erosion outcomes	42 (0.5)	0.16	95 (1.1)	0.36	0.44 (0.31–0.63)	<.0001

od, once daily.
[a]Includes 2 gastric cancers in the pantoprazole group and 1 gastric cancer in the placebo group.

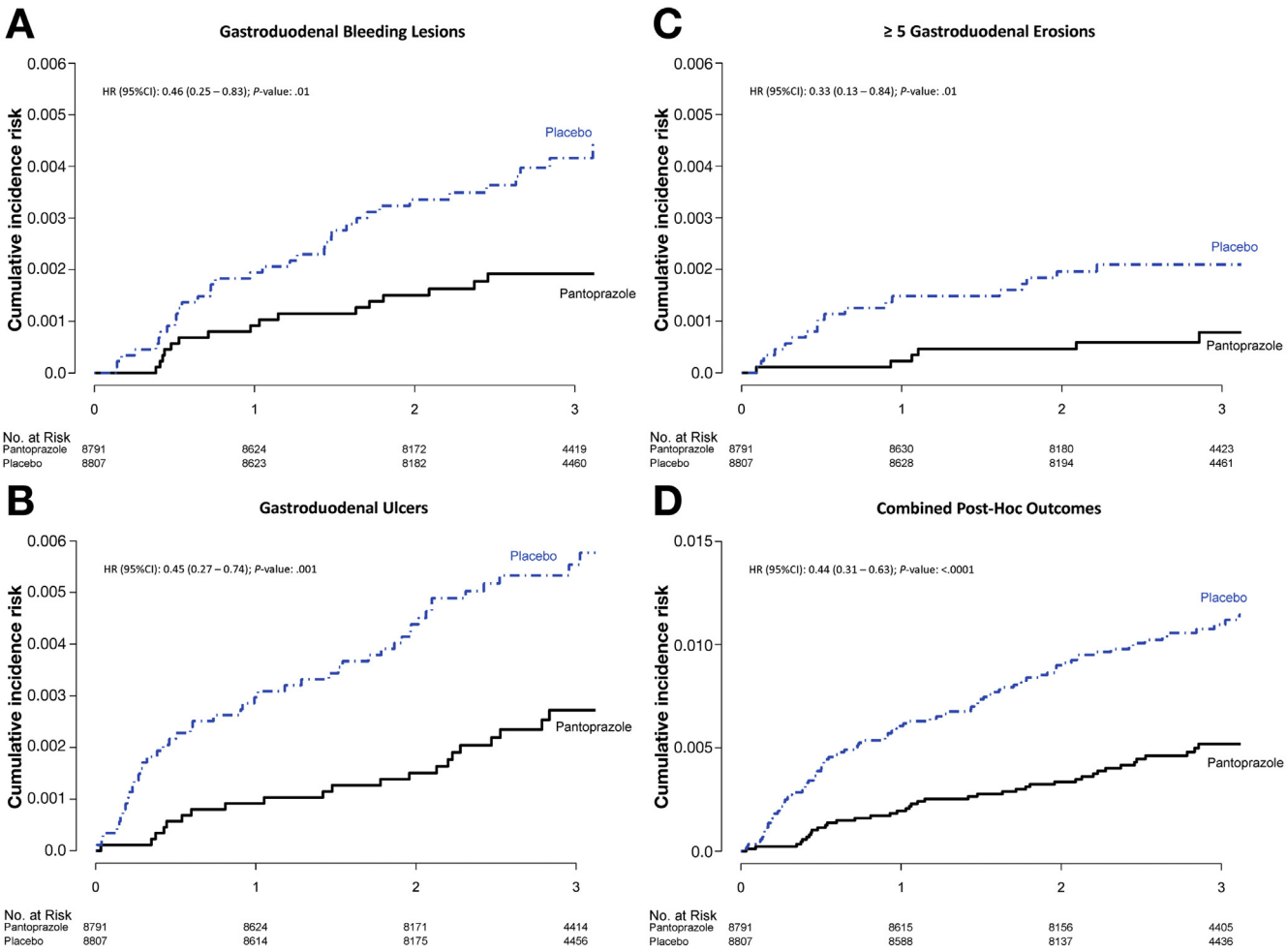

Figure 3. Cumulative incidence of events using the post-hoc definitions of gastroduodenal lesions in the pantoprazole vs placebo arm.

It is noteworthy that patients in our study had stable cardiovascular disease and so had been receiving aspirin long-term before enrollment into this study. Patients were excluded if they were already taking PPI therapy and those at high risk of peptic ulcer disease may already have been prescribed these drugs. This may also explain why our finds differed from the OBERON trial, which evaluated the impact of PPI therapy vs placebo in participants commencing aspirin therapy.[8] This trial mandated that participants had endoscopies during follow-up and is therefore not analogous to our study. Nevertheless, this trial reported that 7.4% developed peptic ulcer within 6 months, but all participants enrolled were aspirin-naïve and had previous uncomplicated peptic ulcer disease.[8] This further emphasizes that our trial enrolled a population at low risk for upper GI complications.

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 bleeding upper GI events was small. Therefore, the CIs for the effect of PPI therapy are wide and so a modest effect of a 20% relative risk reduction on peptic ulcer bleeding may have gone undetected in our trial. However, the number of events in this trial (n = 218) is several times the number of GI events in most previous trials (an average of 6 events).[7] In this trial, the NNT for PPIs to prevent peptic ulcer disease or erosions was approximately 500, even with a relaxed post-hoc definition. The NNT will be lower in higher-risk populations, which includes increasing age over 65 years,[17] *Helicobacter pylori* infection,[18] nonsteroidal anti-inflammatory use,[19] smoking,[20] and past peptic ulcer disease,[21] particularly complicated peptic ulcer disease.[22] As yet, however, there is no validated risk calculator that gives the absolute risk of developing peptic ulcer disease analogous to risk calculators used to determine risk of cardiovascular disease.[23] These are urgently needed so we can identify which patients may benefit from PPI therapy to prevent peptic ulcer disease complications.[23]

In conclusion, there is no benefit in routinely giving PPI therapy to patients with stable cardiovascular disease deemed to be at low risk of GI events and needing anticoagulant therapy or aspirin. PPI therapy reduces the risk of peptic ulcer complications and PPI therapy may be warranted in patients at high risk for this event. This is hypothesis-generating and needs to be evaluated in future studies.

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.2019.04.041.

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Received February 24, 2019. Accepted April 25, 2019.

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Acknowledgments
Author contributions: All authors were involved in data acquisition, general design of the trial, interpretation of the data and critical revision of the manuscript. L. Dyal and O. Shestakovska were involved with the primary analysis of the data. P. Moayyedi, J.W. Eikelboom, J. Bosch, S.J. Connolly, and S. Yusuf were involved in the initial draft of the manuscript. P. Moayyedi, J.W. Eikelboom, J. Bosch, S.J. Connolly, N. Cook Bruns, E.

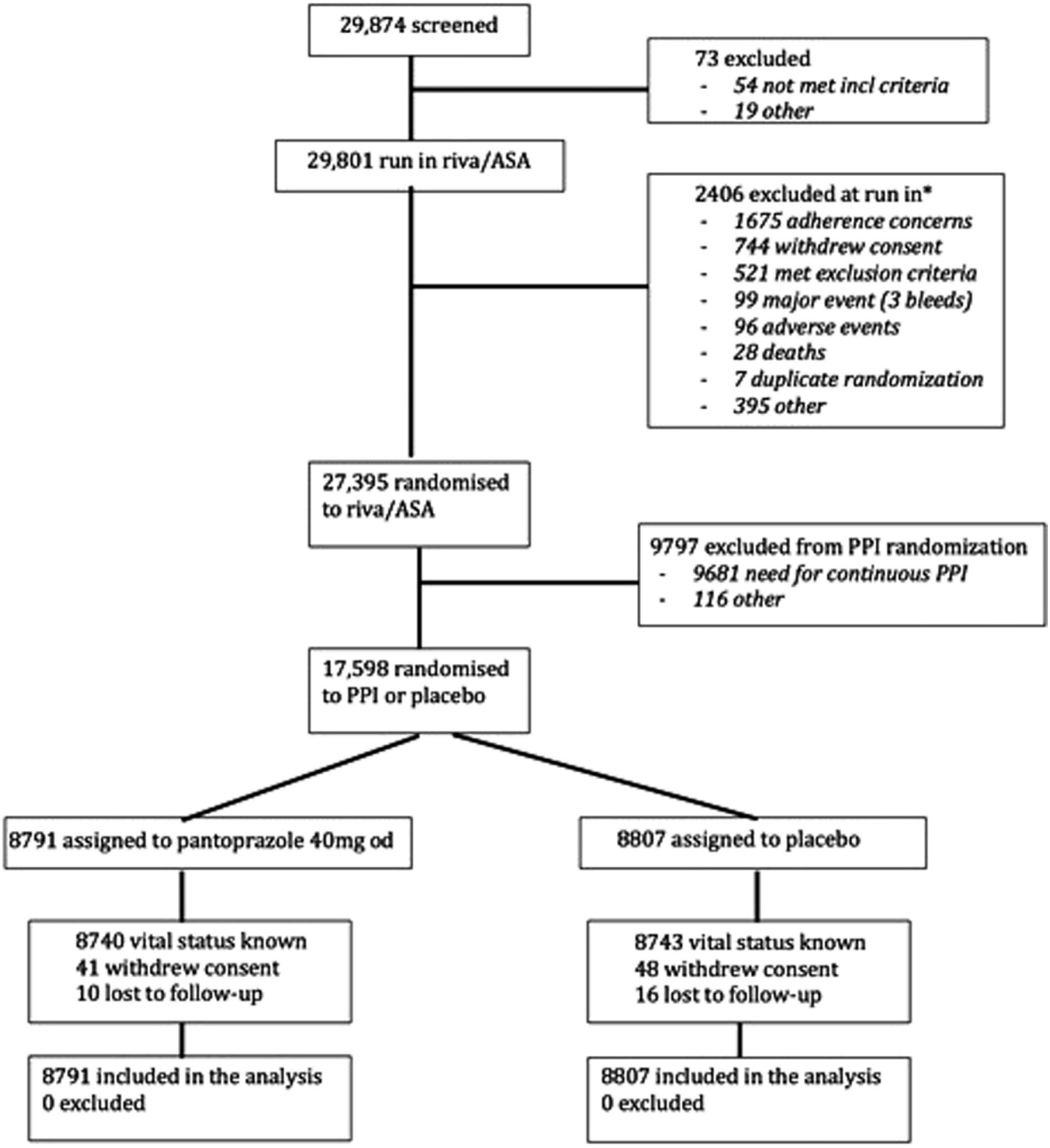
Muehlhofer and S. Yusuf were involved with the design of this aspect of the trial. J.W. Eikelboom and S. Yusuf were involved in obtaining funding and N. Cook Bruns and E. Muehlhofer were involved with the decision to provide support from Bayer AG.

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 is receiving lecture fees and consulting fees from Bristol-Myers Squibb, Pfizer, Portola Pharmaceuticals, Boehringer Ingelheim, Servier, Daiichi Sankyo, and Medtronic. Dr Hart is 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 is receiving grant support from the Population Health Research Institute. Dr Alings is receiving consulting fees from Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, and Sanofi-Aventis. Dr Lonn is receiving consulting fees from Bayer, Amgen, Sanofi, Novartis, and Servier. Dr Anand is receiving consulting fees and lecture fees from Bayer and Novartis. Dr Avezum is receiving consulting fees from Boehringer Ingelheim. Dr Branch is receiving grant support from Astellas and serving on an advisory board for Janssen. Dr Bhatt is 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 (US 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 is receiving lecture fees from Bayer, Boehringer Ingelheim, and Sanofi. Dr Liang is receiving lecture fees from Bayer, Boehringer Ingelheim, and Sanofi. Dr Maggioni is receiving fees for serving as a study committee member from Novartis, Bayer, Fresenius Medical Care, and Cardiorentis. Dr Kakkar is 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 is receiving grant support and honoraria from AstraZeneca and honoraria from Sanofi/Regeneron Pharmaceuticals. Dr Parkhomenko is receiving grant support and honoraria from Pfizer, Bayer, Janssen, AstraZeneca, Sanofi, and Merck Sharp & Dohme. Dr Störk is 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 is receiving lecture fees from Pfizer and Boehringer Ingelheim. Dr Torp-Pedersen is receiving grant support from Biotronik. Dr Verhamme is receiving grant support, lecture fees, and consulting fees from Bayer HealthCare, Boehringer Ingelheim, Daiichi Sankyo, Pfizer, and Brisol-Myers Squibb, grant support from Sanofi and Leo Pharma, and consulting fees from Portola Pharmaceuticals. Dr Vinereanu is receiving grant support, lecture fees, and consulting fees from Boehringer Ingelheim, Pfizer, and Novartis and grant support and lecture fees from Servier. Dr Lewis is receiving lecture fees and honoraria from Pfizer/Bristol-Myers Squibb. Dr Steg is 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 is 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 study was funded by Bayer AG.



Supplementary Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram.

Supplementary Table 1. 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)

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

Characteristic	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, male, n (%)	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, nonsteroidal anti-inflammatory drug; od, once daily.

Supplementary Table 3. Subgroup Analysis of Impact of Pantoprazole or Placebo According to Aspirin/Rivaroxaban Randomization for Clinically Significant Upper Gastrointestinal Adverse Event

	Pantoprazole, 40 mg od			Placebo			Pantoprazole vs placebo	
Antithrombotic treatment group	Total	Events	n/100 py	Total	Events	n/100 py	HR (95% CI)	*P* value for interaction
Rivaroxaban 2.5 mg + aspirin 100 mg	2954	43	0.49	2933	37	0.42	1.16 (0.75–1.80)	.124
Rivaroxaban 5 mg	2918	35	0.40	2941	38	0.43	0.93 (0.60–1.47)	—
Aspirin 100 mg	2928	24	0.27	2933	41	0.47	0.58 (0.35–0.96)	—

od, once daily; py, patient-years.

Supplementary Table 4. Subgroup Analysis of Impact of Pantoprazole or Placebo in the Aspirin Alone Arm for Clinically Significant Upper Gastrointestinal Adverse Event

	Pantoprazole, 40 mg od (n = 2982)		Pantoprazole placebo (n = 2933)		Pantoprazole vs placebo	
Outcome	First events, n (%)	Annual rate, %/*y*	First events, n (%)	Annual rate, %/*y*	HR (95% CI)	*P* value
Upper GI event[a]	24 (0.8)	0.27	41 (1.4)	0.47	0.58 (0.35–0.96)	0.03
Overt bleeding of gastroduodenal origin confirmed by endoscopy or radiography	5 (0.2)	0.057	8 (0.3)	0.091	0.62 (0.20–1.90)	0.40
Overt upper GI bleeding of unknown origin	10 (0.3)	0.11	18 (0.6)	0.21	0.55 (0.26–1.20)	0.13
Bleeding of presumed occult upper GI tract origin with documented decrease in Hb ≥2 g/dL	5 (0.2)	0.057	2 (<0.1)	0.023	2.48 (0.48–12.8)	0.26
Symptomatic gastroduodenal ulcer	0	0	5 (0.2)	0.057	NA	NA
GI pain with underlying multiple gastroduodenal erosions	1 (<0.1)	0.011	3 (0.1)	0.034	0.33 (0.03–3.20)	0.32
Upper GI obstruction or perforation	5 (0.2)	0.057	7 (0.2)	0.080	0.71 (0.23–2.54)	0.56

Hb, hemoglobin; NA, not applicable; od, once daily.
[a]Composite of overt bleeding of gastroduodenal origin confirmed by endoscopy or radiography, overt upper GI bleeding of unknown origin, bleeding of presumed occult upper GI tract origin with documented decrease in Hb of 2 g/dL, symptomatic gastroduodenal ulcer, GI pain with underlying multiple gastroduodenal erosions, upper GI obstruction/perforation.

Supplementary Table 5. Subgroup Analysis of Impact of Pantoprazole or Placebo in the Rivaroxaban Alone Arm for Clinically Significant Upper Gastrointestinal Adverse Event

Outcome	Pantoprazole, 40 mg od (n = 2918)		Pantoprazole placebo (n = 2941)		Pantoprazole vs placebo	
	First events, n (%)	Annual rate, %/y	First events, n (%)	Annual rate, %/y	HR (95% CI)	*P* value
Upper GI event[a]	35 (1.2)	0.40	38 (1.3)	0.43	0.93 (0.60 to 1.47)	.76
Overt bleeding of gastroduodenal origin confirmed by endoscopy or radiography	3 (0.1)	0.034	12 (0.4)	0.14	0.25 (0.07 to 0.89)	.02
Overt upper GI bleeding of unknown origin	18 (0.6)	0.21	12 (0.4)	0.14	1.52 (0.73 to 3.15)	.26
Bleeding of presumed occult upper GI tract origin with documented decrease in Hb $\geq$2 g/dL	3 (0.1)	0.034	5 (0.2)	0.056	0.61 (0.14 to 2.53)	.49
Symptomatic gastroduodenal ulcer	4 (0.1)	0.045	5 (0.2)	0.056	0.81 (0.22 to 3.01)	.75
GI pain with underlying multiple gastroduodenal erosions	0	0	3 (0.1)	0.034	NA	NA
Upper GI obstruction or perforation	7 (0.2)	0.080	2 (<0.1)	0.023	3.53 (0.73 to 17.0)	.09

NA, not applicable.
[a]Composite of overt bleeding of gastroduodenal origin confirmed by endoscopy or radiography, overt upper GI bleeding of unknown origin, bleeding of presumed occult upper GI tract origin with documented decrease in Hb of 2 g/dL, symptomatic gastroduodenal ulcer, GI pain with underlying multiple gastroduodenal erosions, upper GI obstruction/perforation

Supplementary Table 6. Subgroup Analysis of Impact of Pantoprazole or Placebo in the Rivaroxaban Combined With Aspirin Arm for Clinically Significant Upper Gastrointestinal Adverse Event

	Pantoprazole, 40 mg od (n = 2945)		Pantoprazole placebo (n = 2933)		Pantoprazole vs placebo	
Outcome	First events, n (%)	Annual rate, %/y	First events, n (%)	Annual rate, %/y	HR (95% CI)	*P* value
Upper GI event[a]	43 (1.5)	0.49	37 (1.3)	0.42	1.16 (0.75–1.80)	.50
Overt bleeding of gastroduodenal origin confirmed by endoscopy or radiography	8 (0.3)	0.090	11 (0.4)	0.12	0.73 (0.29–1.80)	.49
Overt upper GI bleeding of unknown origin	22 (0.7)	0.25	16 (0.5)	0.18	1.37 (0.72–2.61)	.33
Bleeding of presumed occult upper GI tract origin with documented decrease in Hb $\geq$2 g/dL	2 (<0.1)	0.022	2 (<0.1)	0.022	1.00 (0.14–7.07)	.99
Symptomatic gastroduodenal ulcer	4 (0.1)	0.045	7 (0.2)	0.079	0.57 (0.17–1.94)	.36
GI pain with underlying multiple gastroduodenal erosions	3 (0.1)	0.034	1 (<0.1)	0.011	2.98 (0.31–28.7)	.32
Upper GI obstruction or perforation	9 (0.3)	0.10	8 (0.3)	0.090	1.13 (0.44–2.93)	.80

Hb, hemoglobin.
[a]Composite of overt bleeding of gastroduodenal origin confirmed by endoscopy or radiography, overt upper GI bleeding of unknown origin, bleeding of presumed occult upper GI tract origin with documented decrease in Hb of 2 g/dL, symptomatic gastroduodenal ulcer, GI pain with underlying multiple gastroduodenal erosions, upper GI obstruction/perforation.