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

Moayyedi, Paul; Eikelboom, John W; Bosch, Jackie; Connolly, Stuart J; Dyal, Leanne; Shestakovska, Olga; Leong, Darryl; Anand, Sonia S; Störk, Stefan; Branch, Kelley R H; Bhatt, Deepak L; Verhamme, Peter B; O'Donnell, Martin; Maggioni, Aldo P; Lonn, Eva M; Piegas, Leopoldo S; Ertl, Georg; Keltai, Matyas; Bruns, Nancy Cook; Muehlhofer, Eva; Dagenais, Gilles R; Kim, Jae-Hyung; Hori, Masatsugu; Steg, P Gabriel; Hart, Robert G; Diaz, Rafael; Alings, Marco; Widimsky, Petr; Avezum, Alvaro; Probstfield, Jeffrey; Zhu, Jun; Liang, Yan; Lopez-Jaramillo, Patricio; Kakkar, Ajay K; Parkhomenko, Alexander N; Ryden, Lars; Pogosova, Nana; Dans, Antonio L; Lanas, Fernando; Commerford, Patrick J; Torp-Pedersen, Christian; Guzik, Tomek J; Vinereanu, Dragos; Tonkin, Andrew M; Lewis, Basil S; Felix, Camilo; Yusoff, Khalid; Metsarinne, Kaj P; Fox, Keith A A; Yusuf, Salim; COMPASS Investigators

Published in:
Gastroenterology

DOI (link to publication from Publisher):
10.1053/j.gastro.2019.05.056

Publication date:
2019

Document Version
Accepted author manuscript, peer reviewed version

Accepted Manuscript

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

Paul Moayyedi, MB ChB., PhD, John W. Eikelboom, M.B., B.S., Jackie Bosch, Ph.D., Stuart J. Connolly, M.D., Leanne Dyal, M.Sc, Olga Shestakovska, M.Sc., Darryl Leong, M.B., B.S, Sonia S. Anand, M.D, Stefan Störk, M.D, Kelley R.H. Branch, M.D, Deepak L. Bhatt, M.D., Peter B. Verhamme, M.D, Martin O'Donnell, Ph.D, Aldo P. Maggioni, M.D, Eva M. Lonn, M.D., Leopoldo S. Piegas, M.D, Georg Ertl, M.D, Matyas Keltai, M.D, Nancy Cook Bruns, M.D, Eva Muehlhofer, M.D, Gilles R. Dagenais, M.D., Jae-Hyung Kim, Ph.D, Masatsugu Hori, M.D, P. Gabriel Steg, M.D, Robert G. Hart, M.D, Rafael Diaz, M.D, Marco Alings, Ph.D, Petr Widimsky, M.D, Alvaro Avezum, Ph.D, Jeffrey Probstfield, M.D., Jun Zhu, M.D., Yan Liang, M.D., Patricio Lopez-Jaramillo, Ph.D, Ajay K. Kakkar, M.B., B.S, Alexander N. Parkhomenko, Ph.D, Lars Ryden, M.D, Nana Pogosova, Ph.D, Antonio L. Dans, M.D, Fernando Lanas, Ph.D, Patrick J. Commerford, M.B., Ch.B, Christian Torp-Pedersen, M.D, Tomek J. Guzik, Ph.D., Dragos Vinereanu, Ph.D, Andrew M. Tonkin, M.D, Basil S. Lewis, M.D, Camilo Felix, M.D, Khalid Yusoff, M.B., B.S, Kaj P. Metsarinne, Ph.D, Keith A.A. Fox, M.B., Ch.B., Salim Yusuf, D.Phil, for the COMPASS investigators

PII: S0016-5085(19)40974-8
DOI: https://doi.org/10.1053/j.gastro.2019.05.056
Reference: YGAST 62685

To appear in: *Gastroenterology*
Accepted Date: 21 May 2019

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

Paul Moayyedi, MB ChB., PhD., John W. Eikelboom, M.B., B.S., Jackie Bosch, Ph.D., Stuart J. Connolly, M.D., Leanne Dyal M.Sc., Olga Shestakovska, M.Sc., Darryl Leong, M.B., B.S., Sonia S. Anand, M.D., Stefan Störk, M.D., Kelley R.H. Branch, M.D., Deepak L. Bhatt, M.D., Peter B. Verhamme, M.D., Martin O'Donnell, Ph.D., Aldo P. Maggioni, M.D., Eva M. Lonn, M.D., Leopoldo S. Piegas, M.D., Georg Ertl, M.D., Matyas Keltai, M.D., Nancy Cook Bruns, M.D., Eva Muehlhofer M.D., Gilles R. Dagenais, M.D., Jae□Hyung Kim, Ph.D., Masatsugu Hori, M.D., P. Gabriel Steg, M.D., Robert G. Hart, M.D., Rafael Diaz, M.D., Marco Alings, Ph.D., Petr Widimsky, M.D., Alvaro Avezum, Ph.D., Jeffrey Probstfield, M.D., Jun Zhu, M.D., Yan Liang, M.D., Patricio Lopez□Jaramillo, Ph.D., Ajay K. Kakkar, M.B., B.S., Alexander N. Parkhomenko, Ph.D., Lars Ryden, M.D., Nana Pogosova, Ph.D., Antonio L. Dans, M.D., Fernando Lanas, Ph.D., Patrick J. Commerford, M.B., Ch.B., Christian Torp□Pedersen, M.D., Tomek J. Guzik, Ph.D., Dragos Vinereanu, Ph.D., , Andrew M. Tonkin, M.D., Basil S. Lewis, M.D., Camilo Felix, M.D., Khalid Yusoff, M.B., B.S., Kaj P. Metsarinne, Ph.D., Keith A.A. Fox, M.B., Ch.B., and Salim Yusuf, D.Phil. for the COMPASS investigators

The authors' affiliations are as follows: The Population Health Research Institute, McMaster University and Hamilton Health Sciences,
Hamilton, ON (P.M, J.W.E., S.J.C., J.B., R.G.H., O.S., E.M.L., S.S.A., D.L., S.Y.), and Institut Universitaire de Cardiologie et de Pneumologie de
Quebec, Quebec, QC (G.R.D.) — both in Canada; Estudios Clinicos Latino America and Instituto Cardiovascular de Rosario, Rosario,
Argentina (R.D.); Amphia Ziekenhuis and Werkgroep Cardiologische Centra Nederland (WCN), Utrecht, the Netherlands (M.A.); Cardiocenter,
University Hospital Kralovske Vinohrady and Third Faculty of Medicine, Charles University, Prague, Czech Republic (P.W.); Osaka
International Cancer Institute, Osaka, Japan (M.H.); Instituto Dante Pazzanese de Cardiologia (A.A.), and Hospital do Coracao (L.S.P.), Sao
Paulo; University of Washington Medical Center (K.R.H.B.) and University of Washington (J.P.), Seattle; Brigham and Women's Hospital
Heart and Vascular Center, Harvard Medical School, Boston (D.L.B.); FuWai Hospital, Beijing (J.Z., Y.L.); National Association of Hospital
Cardiologists Research Center (ANMCO), Florence, Italy (A.P.M.); Research Institute, Fundaciun Oftalmoligica de Santander (FOSCAL)–
Bucaramanga, Bucaramanga, Colombia (P.L.-J.); National University of Ireland, Galway (M.O.); Thrombosis Research Institute and University
College London, London (A.K.K.), Centre for Cardiovascular Science, University of Edinburgh, Edinburgh (K.A.A.F.), and University
of Glasgow, Glasgow (T.J.G.) — all in the United Kingdom; Collegium Medicum Jagiellonian University, Krakow, Poland (T.J.G);
Institute of Cardiology, Kiev, Ukraine (A.N.P.); University of Würzburg and University Hospital, Würzburg (G.E., S.S.), and Bayer, Leverkusen

(N.C.B., E.L) — all in Germany; Semmelweis University, Budapest, Hungary (M.K.); Karolinska Institutet, Stockholm (L.R.);
National Research Center for Preventative Medicine, Moscow (N.P.); University of Philippines, Manila (A.L.D.); Universidad de La Frontera,
Temuco, Chile (F.L.); University of Cape Town, Cape Town, South Africa (P.J.C.); University of Aalborg, Copenhagen (C.T.-P.); University
of Leuven, Leuven, Belgium (P.B.V.); University of Medicine and Pharmacology, Carol Davila University and Emergency Hospital, Bucharest,
Romania (D.V.); Catholic University of Korea, Seoul, South Korea (J.-H.K.); Monash University, Melbourne, VIC, Australia (A.M.T.); Lady
Davis Carmel Medical Center, Haifa, Israel (B.S.L.); Facultad de Ciencias de la Salud Eugenio Espejo–Universidad Tecnoligica Equinoccial,
Quito, Ecuador (C.F.); Universiti Teknologi Mara, Selangor, Malaysia (K.Y.); Universit. Paris Diderot, Hopital Bichat, Assistance Publique–
Hopitaux de Paris, Paris (P.G.S.); and Turku University Central Hospital and Turku University, Turku, Finland (K.P.M.).

Corresponding author: Paul Moayyedi, Population Health Research Institute, McMaster University and Hamilton Health Sciences, David Brailey Research Bldg., Hamilton General Hospital, 237 Barton St. E., Hamilton, ON L8L 2X2, Canada. Fax 905 521 4958. E-mail moayyep@mcmaster.ca

Word Count = 2861
Abstract word count = 252

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, JW Eikelboom, J Bosch, SJ 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. JW Eikelboom and S Yusuf were involved in obtaining funding and N. Cook Bruns, E. Muehlhofer were involved with the decision to provide support from Bayer AG.

Funding
Bayer AG

Conflicts of interest

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, receiving lecture fees and consulting fees from Bristol-Myers Squibb, Pfizer, Portola Pharmaceuticals,

Boehringer Ingelheim, Servier, Daiichi Sankyo, and Medtronic; Dr. Hart, 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, receiving grant support from the Population Health Research Institute; Dr. Alings, receiving consulting fees from Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, and Sanofi-Aventis; Dr. Lonn, receiving consulting fees from Bayer, Amgen, Sanofi, Novartis, and Servier; Dr. Anand, receiving consulting fees and lecture fees from Bayer and Novartis; Dr. Avezum, receiving consulting fees from Boehringer Ingelheim; Dr. Branch, receiving grant support from Astellas and serving on an advisory board for Janssen; Dr. Bhatt, 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 coinvestigator 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, receiving lecture fees from Bayer, Boehringer Ingelheim, and Sanofi; Dr. Liang, receiving lecture fees from Bayer, Boehringer Ingelheim, and Sanofi; Dr. Maggioni, receiving fees for serving as a study committee member from Novartis, Bayer, Fresenius Medical Care, and Cardiorentis; Dr. Kakkar, 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, receiving grant support and honoraria from AstraZeneca and honoraria from Sanofi/Regeneron Pharmaceuticals; Dr. Parkhomenko, receiving grant support and honoraria from Pfizer, Bayer, Janssen, AstraZeneca, Sanofi, and Merck Sharp & Dohme; Dr. Störk, 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, receiving lecture fees from Pfizer and Boehringer Ingelheim; Dr. Torp-Pedersen, receiving grant support from Biotronik; Dr. Verhamme, 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, receiving grant support, lecture fees, and consulting fees from Boehringer Ingelheim, Pfizer, and Novartis and grant support and lecture fees from Servier; Dr. Lewis, receiving lecture fees and honoraria from Pfizer/Bristol-Myers Squibb; Dr. Steg, 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, being employed by Bayer; and Dr. Yusuf, receiving grant support and honoraria from Bayer, Boehringer Ingelheim, Astra-Zeneca, Bristol-Myers Squibb, and Cadila Pharmaceuticals. No other potential conflict of interest relevant to this article was reported.

Abstract

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 3x2 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% CI, 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 identifier: NCT01776424 (https://clinicaltrials.gov/ct2/show/NCT01776424)

KEY WORDS: reflux, thrombosis, CVD, bacteria

Introduction

Proton pump inhibitors (PPI) are one of the most widely used classes of drugs in the United States (1). PPIs are the most effective drugs for treating gastro-esophageal reflux disease (GERD) (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 suggests that high dose PPI therapy may reduce high-grade dysplasia and esophageal adenocarcinoma in patients with Barrett's esophagus (6). Acid secretion returns towards normal within 12-24 hours of discontinuation of therapy, so PPIs are often used long term, particularly in patients with GERD symptoms (2). Acid related conditions such as dyspepsia and GERD occur in over 25% of the population (7, 8) and, given that most patients take PPI therapy long term, it is not surprising that the US spends over $5 billion annually on these drugs (9). Omeprazole was the first PPI to be developed and this 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* (*C. difficile*) associated diarrhea (14), cerebrovascular events (15), chronic renal failure (16), dementia (17) and all-cause mortality (18). These papers 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 for differences in known and unknown confounders (20). There is equipoise between concerns regarding the long-term safety of PPI therapy versus their efficacy in treating acid related diseases. We have previously reported that rivaroxaban 2.5mg 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 GI 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 Anticoagulant Strategies (COMPASS) trial is a 3-by-2 partial factorial, multicenter, double-blind, randomized placebo-controlled trial, evaluating patients with stable atherosclerotic vascular disease. The detailed study design has been published (22). Participants were randomized to rivaroxaban 2.5 mg twice daily with aspirin 100mg once daily, rivaroxaban 5mg

twice daily alone or aspirin 100mg once daily alone to compare the primary outcome of cardiovascular death, stroke or myocardial infarction in these three arms. All participants who were not already taking a PPI at baseline (64%) were randomized to receive either pantoprazole 40mg 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 three years (22) and the protocol is available in the Supplementary Appendix. 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.

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 PPI. 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 two cardiovascular beds and/or had two additional risk factors (see Supplementary Appendix). Patients were randomized to receive pantoprazole 40mg 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 Appendix. Following randomization participants were seen at one month, 6 months and then at 6-month intervals for three 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 (e.g. myocardial infarction, stroke, cardiovascular death, coronary heart disease 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, *Clostridium 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 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 event rate was very small the smallest effect size that could be detected related to pneumonia with an 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 these calculations assumed the proportions seen in the placebo group with 80% power and 5% type 1 error.

All events occurring in the randomized participants are included in the intention to treat (ITT) analysis utilizing the time to the first occurrence of the cardiovascular events, mortality, cancer and hospitalizations for pantoprazole versus placebo from the time of randomization until the date of formal trial termination. Differences in rates between pantoprazole 40 mg o.d vs. pantoprazole placebo were evaluated using a log-rank test stratified by antithrombotic study treatment (three strata levels: rivaroxaban 2.5 mg b.i.d + aspirin 100 mg o.d; rivaroxaban 5 mg b.i.d + aspirin placebo; rivaroxaban placebo + aspirin 100 mg o.d), conducted at a two-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 (HR) and 95% confidence intervals (CI) were obtained from stratified Cox proportional-hazards models and all reported P values are two-sided.

For all other safety events, the number of participants who experienced an outcome in the pantoprazole versus placebo group were summarized and the odds ratio (OR) was calculated using logistic regression and two-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 predefined 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 Inc, Cary, NC, USA).

Results

17,598 participants were recruited between March 2013 and May 2016 and randomized to pantoprazole 40mg 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 past medical history of peptic ulcer disease (Supplementary Table 2).

Baseline characteristics are summarized in Table 1. 8,791 participants were randomized to pantoprazole 40mg once daily and 8,807 were randomized to placebo. The mean age of participants was 67.6 years, 13792 (78%) were male, 4074 (23%) were current smokers, 872 (5%) were taking non-steroidal anti-inflammatory drugs and 2.6% had a past history of peptic ulcer disease. One hundred and thirty-five (0.8%) participants were taking PPI at the start of the trial and randomized to pantoprazole or placebo (Table 1). The median follow-up was 3.01 years (inter-quartile range (IQR) = (2.49 to 3.59), range 2 days to five years one month) thus accruing 53,152 patient-years of follow up, 1,884 participants (21%) in the pantoprazole group and 1,975 (22%) in the placebo group permanently discontinued the medication. The median time to permanent discontinuation was 338 days (IQR = (109 to 679)) and the reasons are described in Supplementary Table 3. In those that continued their medication, 295 participants (3.63%) 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 to 1.15) (Table 2, 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 to 1.12), stroke (HR = 1.16; 95% CI = 0.94 to 1.44), and acute limb ischemia (HR = 1.13; 95% CI = 0.73 to 1.75) were considered separately (Table 2, Figure 3). Hospitalization rates (HR = 1.04; 95% CI = 0.99 to 1.09) and all-cause mortality (HR = 1.03; 95% CI = 0.92 to 1.15) were also similar in the pantoprazole and placebo arms (Table 2).

Other pre-specified 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 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 to 1.13) or in any of the primary sites of cancer between the two groups (Table 2). There was no statistically significant difference between pantoprazole and placebo in the proportion of participants who experienced pre-specified non-cardiovascular events of interest that are associated with PPI use in observational studies (8) (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 to 1.75) (Table 3). The number

needed to harm for enteric infections was 301 (95% CI 152 to 9,190) after a median of three 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 were removed in a sensitivity analysis and this gave similar results (Supplementary Table 4). Patients with dementia, severe COPD and glomerular filtration rate (GFR) of 15ml/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 versus placebo (OR = 1.15; 95% CI = 0.89 to 1.50, p=0.28). Excluding those with a GFR <30ml/min at baseline did also not impact on the risk of chronic renal disease (OR = 1.20; 95% CI = 0.96 to 1.51 p=0.11).

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 (26), fracture (26) and cerebrovascular events (27). Biologically plausible mechanisms have been advanced to suggest

these associations are causal such as a PPIs 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 over 300 with three 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 exemplified by the outcomes *Clostridium difficile* and gastric atrophy, where the number of events were 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 were similar between the two groups but as the number of participants with gastric atrophy was small this may have biased the results towards the null. Gastric atrophy is a risk factor for B12 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 over 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 mainly obtained by patient interview every six 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 will have been similar in both arms, but this may have biased results towards the null. Previous studies that have reported an association between PPI and adverse event (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 PPI 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 towards 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 hazard ratios and odds ratios 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 five years of therapy (36) and this trial had a mean follow up of three years and a maximum follow up of 5 years that was achieved in only a small proportion of patients. However, all adverse events have studies that report observing an excess of events after one 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 three 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.

References

1. Kantor ED, Rehm CD, Haas JS, et al. Trends in Prescription Drug Use Among Adults in the United States From 1999-2012. JAMA 2015; 314: 1818–1831.
2. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol 2013; 108: 308-28.
3. Miner PB, Allgood LD, Grender JM. Comparison of gastric pH with omeprazole magnesium 20.6mg (Prilosec OTC) o.m. famotidine 10mg (Pepcid AC) b.d. and famotidine 20mg b.d. over 14 days treatment. Aliment Pharmacol Ther 2007; 25: 103-9.
4. Moayyedi P, Lacy BE, Andrews CN, Enns RA, Howden CW, Vakil N. ACG and CAG clinical guideline: management of dyspepsia. Am J Gastroenterol 2017; 112: 988-1038.
5. Fallone CA, Chiba N, van Zanten SV, Fischbach L, Gisbert JP, et al. The Toronto Consensus for the Treatment of *Helicobacter pylori* Infection in Adults. Gastroenterology 2016; 151: 51-69.
6. Jankowski JA, de Caestecker J, Love SB et al. Esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomised factorial trial. Lancet 2018; 392: 400-8.
7. Ford AC, Marwaha A, Sood R, Moayyedi P. Global prevalence of, and risk factors for, uninvestigated dyspepsia: a meta-analysis. Gut 2015; 64: 1049-57.
8. Moayyedi P, Axon AT. Review article: gastro-oesophageal reflux disease – the extent of the problem. Aliment Pharmacol Thher 2005; 22 Suppl 1: 11-9.

9. Johansen ME, Huerta TR, Richardson CR. National Use of Proton Pump Inhibitors From 2007 to 2011. JAMA Intern Med 2014; 174: 1856-8.
10. WHO Model List of Essential Medicines 20th Edition. http://www.who.int/medicines/publications/essentialmedicines/en/ - accessed 17th January 2019
11. Laheij RJ, Sturkenboom MC, Hassing RJ, et al. Risk of community-acquired pneumonia and use of gastric acid suppressive drugs. JAMA 2004; 292: 1955–60.
12. Yang YX, Lewis JD, Epstein S, et al. Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA 2006; 296:2947–2953.
13. Leonard J. Marshall JK. Moayyedi P. Systematic review of the risk of enteric infection in patients taking acid suppression. American Journal of Gastroenterology 2007; 102: 2047-56.
14. Dial S, Delaney JAC, Barkun AN et al. Use of gastric acid-suppressive agents and the risk of community-acquired Clostridium difficile-associated disease. JAMA 2005; 294: 2989-95.
15. Charlot M, Grove EL, Hansen PR et al. Proton pump inhibitor use and risk of adverse cardiovascular events in aspirin treated patient with first time myocardial infarction: a nationwide propensity score matched analysis. BMJ 2011; 342: d2690.
16. Lazarus B, Chen Y, Wilson FP, Sang Y, Chang AR et al. Proton pump inhibitor use and risk of chronic kidney disease. JAMA Intern Med 2016; 176: 238-46.

17. Gomm W, von Holt K, Thome F, Broich K, Maier W et al. Association of proton pump inhibitors with risk of dementia: a pharmacoepidemiological claims data analysis. JAMA Neurol 2016; 73: 410–16.
18. Xie Y, Bowe B, Li T, Xian H, Yan Y, Al-Aly Z. Risk of death among users of proton pump inhibitors: a longitudinal observational cohort study of United States veterans. BMJ Open 2017; 7 (6): e015735.
19. Vaezi M, Yang Y-X, Howden CW. Complications of proton pump inhibitor therapy. Gastroenterology 2017; 153: 35-48.
20. Moayyedi P, Leontiadis GI. The risks of PPI therapy. Nature Reviews of Gastroenterology & Hepatology 2012; 9: 132-9.
21. Eikelboom JW, Connolly SJ, Bosch J et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med 2017; 377: 1319-30.
22. Bosch J, Eikelboom JW, Connolly SJ et al. Rationale, design and baseline characteristics of participants in the Cardiovascular Outcomes for People Using Anticoagulant Strategies (COMPASS) trial. Can J Cardiol 2017; 33: 1027-35.
23. Herzig SJ. Howell MD. Ngo LH. Marcantonio ER. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. JAMA 2009; 301: 2120-8.
24. Newcombe RG. Interval estimation for the difference between independent proportions: Comparison of eleven methods. Statistics in Medicine 1998; 17: 873-890.

25. Zedtwitz-Liebenstein K, Wenisch C, Patruta S, et al. Omeprazole treatment diminishes intra- and extracellular neutrophil reactive oxygen production and bactericidal activity. Crit Care Med. 2002; 30: 1118–22.

26. Nassar Y, Richter S. Proton-pump inhibitor use and fracture risk: an updated systematic review and meta-analysis. J Bone Metab 2018; 25: 141-51.

27. Batchelor R, Kumar R, Gilmartin-Thomas JFM et al. Systematic review with meta-analysis: risk of adverse cardiovascular events with proton pump inhibitors independent of clopidogrel. Aliment Pharmcol Ther 2018; 48: 780-96.

28. Savarino V, Di Mario F, Scarpignato C. Proton pump inhibitors in GORD. An overview of their pharmacology, efficacy and safety. Pharmacol Res. 2009; 59: 135–153.

29. O'Connell MB, Madden DM, Murray AM, Heaney RP, Kerzner LJ. Effects of proton pump inhibitors on calcium carbonate absorption in women: a randomized crossover trial. Am J Med. 2005; 118: 778–781.

30. Ghebremariam YT, LePendu P, Lee JC, et al. Unexpected effect of proton pump inhibitors: elevation of the cardiovascular risk factor asymmetric dimethylarginine. Circulation. 2013; 128: 845–853.

31. Altman N, Krzywinski M. Association, correlation and causation. Nature Methods 2015; 12: 899-900.

32. Heidelbaugh J.J., Goldberg K.L., Inadomi J.M. Magnitude and economic impact of overutilization of antisecretory therapy in the ambulatory care setting. Am J Manag Care 2010; 16: e228–e234

33. Boghossian TA, Rashid FJ, Thompson W et al. Deprescribing versus continuation of chronic proton pump inhibitor use in adults. Cochrane Database Systematic Reviews 2017 March 16: CD011969: DOI:10.1002/14651858.CD011969.pub2

34. Neal, KR, Scott, HM, Slack, RCB, Logan RF. Omeprazole as a risk factor for *Campylobacter* gastroenteritis: Case-control study. BMJ 1996; 312: 414–415.

35. Cheung KS, Chan EW, Wong AYS, Chen L, Wong ICK, Leung WK. Long-term proton pump inhibitors and risk of gastric cancer development after treatment for *Helicobacter pylori*: a population-based study. Gut 2018; 67: 28-35.

36. Targownik LE, Lix LM, Metge CJ, Prior HJ, Leung S, Leslie WD. Use of proton pump inhibitors and risk of osteoporosis-related fractures. CMAJ 2008; 179: 319-26.

37. Xie Y, Bowe B, Li T, et al. Proton pump inhibitors and risk of incident CKD and progression to ESRD. J. Am. Soc. Nephrol. 2016; 27: 3153–63.

38. Moayyedi P, Yuan Y, Leontiadis G. Canadian Association of Gastroenterology position statement: Hip fracture and proton pump inhibitor therapy – a 2013 update. Canadian Association of Gastroenterology 2013; 27: 593-5.

Figure 1. Consort diagram

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

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

Table 1. Baseline characteristics of participants

Characteristic	Pantoprazole (N = 8791)	Placebo (N = 8807)
Age (years)	67.6 ± 8.1	67.7 ± 8.1
Female sex- no. (%)	1937 (22)	1869 (21)
Race – no. (%)		
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 – no. (%)		
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	28.3 ± 4.7	28.4 ± 4.7
Smoking status – no. (%)		
Current	2064 (23.5)	2010 (23)
Former	3764 (43)	3808 (43)

Never	2693 (34)	2989 (34)
Previous MI – no. (%)	5403 (61.5)	5404 (61)
Previous stroke – no. (%)	350 (4)	366 (4)
Previous cancer – no. (%)	450 (5)	491 (6)
Previous peptic ulcer – no. (%)	228 (3)	222 (2.5)
Inflammatory bowel disease – no (%)	37 (0.4)	56 (0.6)
Diverticulitis - no. (%)	131 (1.5)	120 (1.4)
Liver disease – no. (%)	85 (1)	83 (1)
Diabetes – no. (%)	3363 (38)	3369 (38)
Heart failure – no. (%)	2181 (25)	2138 (24)
Estimated GFR – no. (%) *<30 ml/min* *30 to <60 ml/min* *≥ 60 ml/min*	 75 (0.9) 1878 (21) 6838 (78)	 77 (0.9) 1917 (22) 6810 (77)
Medication – no. (%) *Taking PPI at start of trial* *NSAIDs* *SSRIs* *Hypoglycemic agents* *ACE inhibitor/ARBs*	 56 (0.6) 425 (5) 257 (3) 2785 (32) 6269 (71)	 78 (0.9) 447 (5) 258 (3) 2784 (32) 6286 (71)

Beta blockers	6137 (70)	6122 (70)
Calcium channel blockers	2237 (25)	2265 (26)
Lipid lowering agents	7775 (88)	7823 (89)
Diuretics	2572 (29)	2522 (29)

NSAID = non-steroidal anti-inflammatory drug
SSRI = selective serotonin re-uptake inhibitor
ACE = angiotensin converting enzyme
ARB = angiotensin receptor blockers

Table 2. Cardiovascular events, cancers and hospitalizations.

Outcome	Pantoprazole 40mg od (N=8791)		Placebo (N= 8807)		Pantoprazole versus placebo	
	No. of first events (%)	Annual rate (%/yr)	No. of first events (%)	Annual rate (%/yr)	Hazard ratio (95% CI)	P value
Primary efficacy outcome						
MI, stroke or cardiovascular death	691 (7.9)	2.66	668 (7.6)	2.57	1.04 (0.93 to 1.15)	0.51
Secondary efficacy outcomes						
MI, ischemic stroke, CHD death or ALI	588 (6.7)	2.27	572 (6.5)	2.20	1.03 (0.92 to 1.16)	0.61
MI, ischemic stroke, cardiovascular death or ALI	707 (8.0)	2.72	683 (7.8)	2.63	1.04 (0.94 to 1.15)	0.50
Death						
All cause	630 (7.2)	2.37	614 (7.0)	2.31	1.03 (0.92 to 1.15)	0.63
Cardiovascular	343 (3.9)	1.29	333 (3.8)	1.25	1.03 (0.89 to 1.20)	0.69
Non-cardiovascular	287(3.3)	1.08	281 (3.2)	1.06	1.02 (0.87 to 1.21)	0.78
CHD	194 (2.2)	0.73	200(2.3)	0.75	0.97 (0.80 to 1.18)	0.94
Individual efficacy outcomes						
MI	252 (2.9)	0.96	267 (3.0)	1.02	0.94 (0.79 to 1.12)	0.51
Stroke	184 (2.1)	0.70	159 (1.8)	0.60	1.16 (0.94 to 1.44)	0.16
ALI	43 (0.5)	0.16	38 (0.4)	0.14	1.13 (0.73 to 1.75)	0.58
Venous thromboembolism	53 (0.6)	0.20	52 (0.6)	0.20	1.01 (0.69 to 1.49)	0.95
Cancer						
All new cancers	429 (4.9)	1.65	435 (4.9)	1.77	0.99 (0.87 to 1.13)	0.87
GI	86 (1.0)	0.33	83 (0.9)	0.31	1.04 (0.77 to 1.40)	0.81
Lung	73 (0.8)	0.28	77 (0.9)	0.29	0.95 (0.69 to 1.31)	0.75
Prostate	65 (0.7)	0.25	73 (0.8)	0.28	0.89 (0.64 to 1.24)	0.50
Skin	73 (0.8)	0.28	70 (0.8)	0.26	1.05 (0.75 to 1.45)	0.79
Breast	9 (0.1)	0.034	18 (0.2)	0.068	0.50 (0.22 to 1.11)	0.08
Hospitalizations						
All	3074 (35.0)	14.51	3000 (34.1)	13.96	1.04 (0.99 to 1.09)	0.14
Cardiovascular	1721 (19.6)	7.26	1644 (18.7)	6.86	1.06 (0.99 to 1.13)	0.10
Non-cardiovascular	1898 (21.6)	8.13	1901(21.6)	8.10	1.00 (0.94 to 1.07)	0.92

* Defined by the cardiovascular outcomes related to aspirin rivaroxaban arms (10)
yr = year
CI = confidence interval
MI = myocardial infarction
CAD = Coronary Heart Disease
ALI = Acute limb ischemia
GI = gastrointestinal

Table 3. Other pre-specified safety outcomes

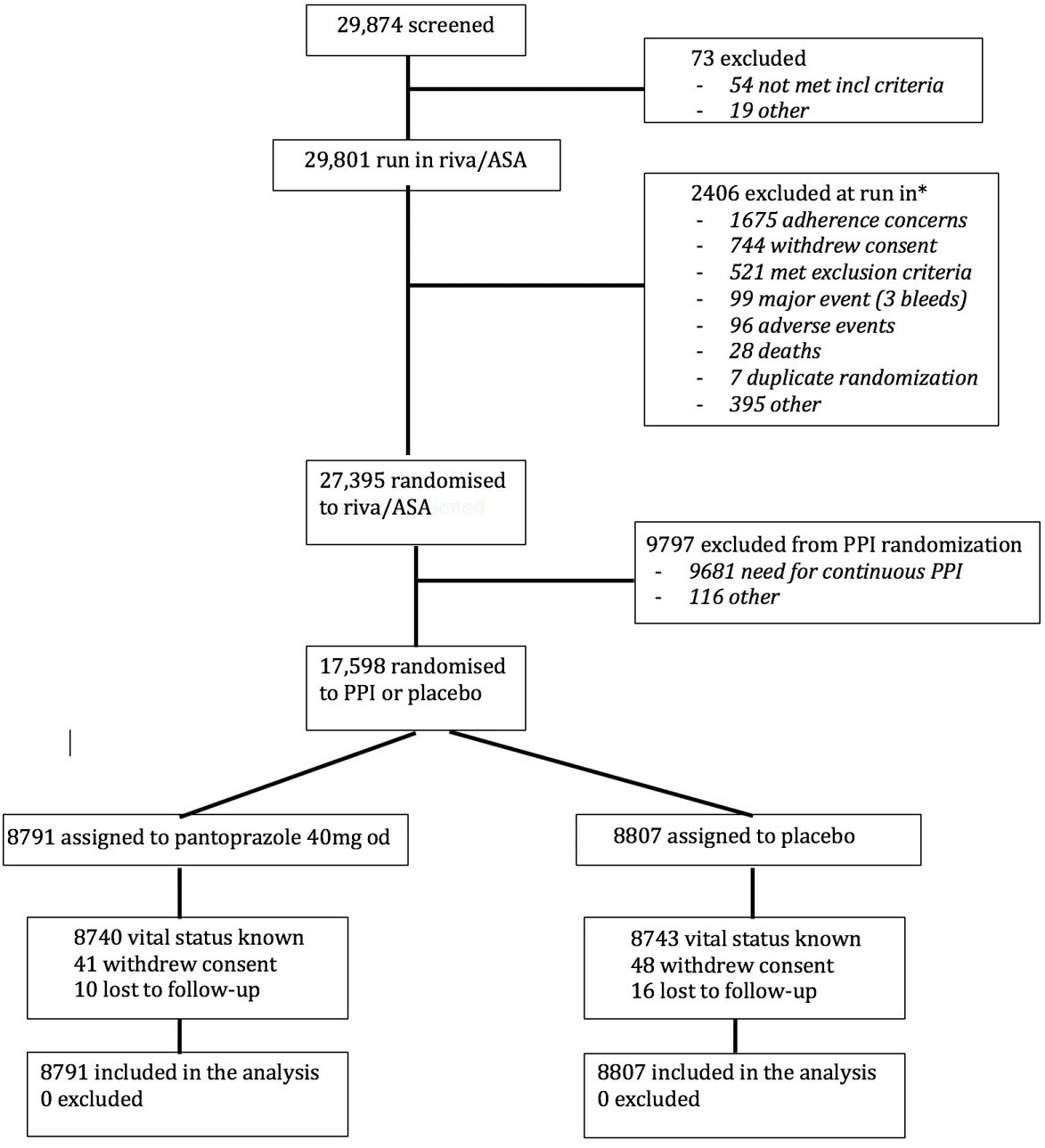
Outcomes	Pantoprazole 40 mg od (N=8791)	Placebo (N=8807)	Pantoprazole 40mg od versus placebo	
	no. of incident events (%)	no. of incident events (%)	Odds ratio (95% CI)	P value
Gastric atrophy	19 (0.2)	26 (0.3)	0.73 (0.40 to 1.32)	0.30
Clostridium difficile	9 (0.1)	4 (<0.1)	2.26 (0.70 to 7.34)	0.18
Other enteric infection	119 (1.4)	90 (1.0)	1.33(1.01 to 1.75)	0.04
Chronic kidney disease	184 (2.1)	158 (1.8)	1.17 (0.94 to 1.45)	0.15
Dementia	55 (0.6)	46 (0.5)	1.20 (0.81 to 1.78)	0.36
Pneumonia	318 (3.6)	313 (3.6)	1.02 (0.87 to 1.19)	0.82
Fracture	203 (2.3)	211 (2.4)	0.96 (0.79 to 1.17)	0.71
COPD	146 (1.7)	124 (1.4)	1.18 (0.93 to 1.51)	0.17
Diabetes mellitus	513 (5.8)	532 (6.0)	0.96 (0.85 to 1.09)	0.56

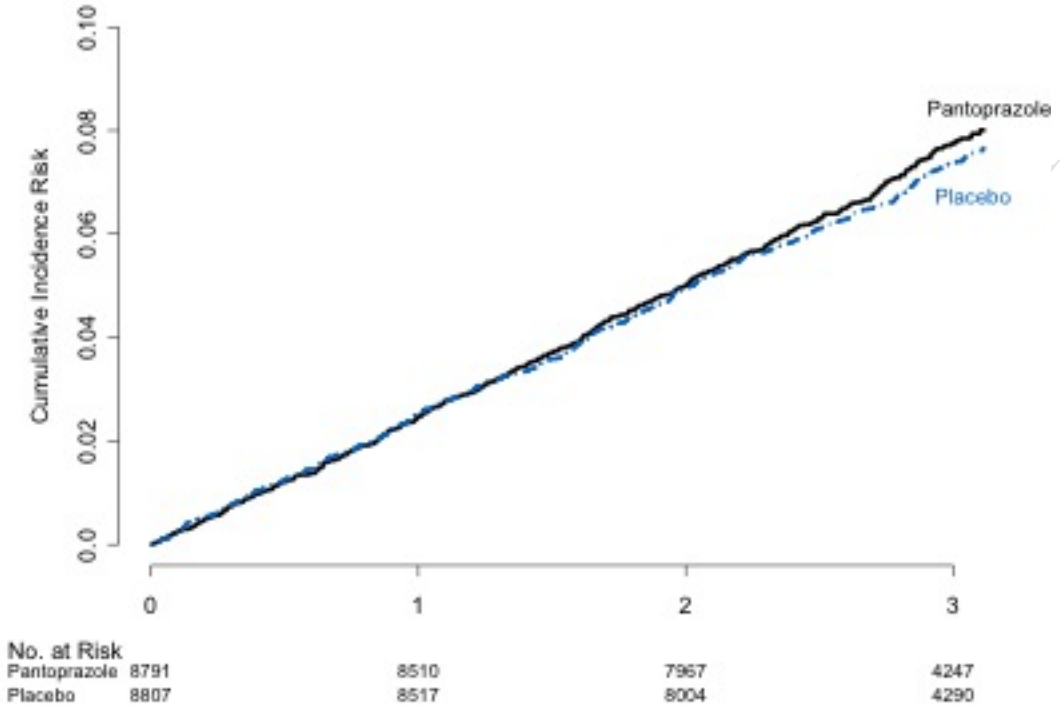
CI = confidence interval
COPD = chronic obstructive pulmonary disease

Table 4. Other prespecified safety outcomes excluding those that permanently discontinued pantoprazole or placebo

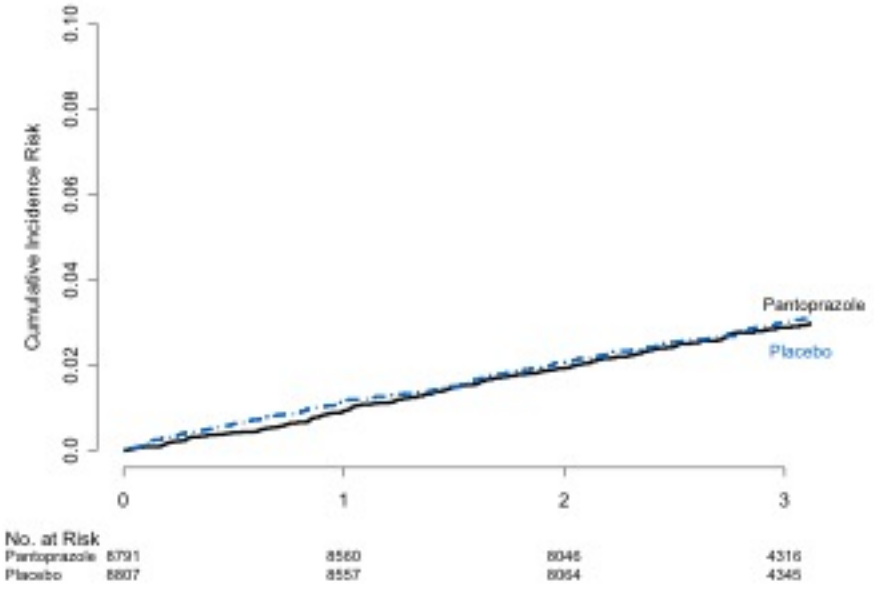
Outcomes	Pantoprazole 40 mg od (N=6947)	Placebo (N=6868)	Pantoprazole 40mg od versus placebo	
	no. of incident events (%)	no. of incident events (%)	Odds ratio (95% CI)	P value
Gastric atrophy	10 (0.1)	24 (0.2)	0.71 (0.31 to 1.59)	0.40
Clostridium difficile	5 (<0.1)	2 (<0.1)	2.48 (0.48 to 12.8)	0.28
Other enteric infection	60 (0.9)	42 (0.6)	1.42 (0.95 to 2.10)	0.08
Chronic kidney disease	104 (1.5)	98 (1.4)	1.05 (0.80 to 1.39)	0.73
Dementia	24 (0.3)	22 (0.3)	1.08 (0.60 to 1.93)	0.80
Pneumonia	203 (2.9)	185 (2.7)	1.09 (0.89 to 1.33)	0.41
Fracture	136 (2.0)	150 (2.2)	0.89 (0.71 to 1.13)	0.35
COPD	94 (1.4)	83 (1.2)	1.12 (0.83 to 1.51)	0.45
Diabetes mellitus	393 (5.7)	423 (6.2)	0.91 (0.79 to 1.05)	0.21

CI = confidence interval
COPD = chronic obstructive pulmonary disease

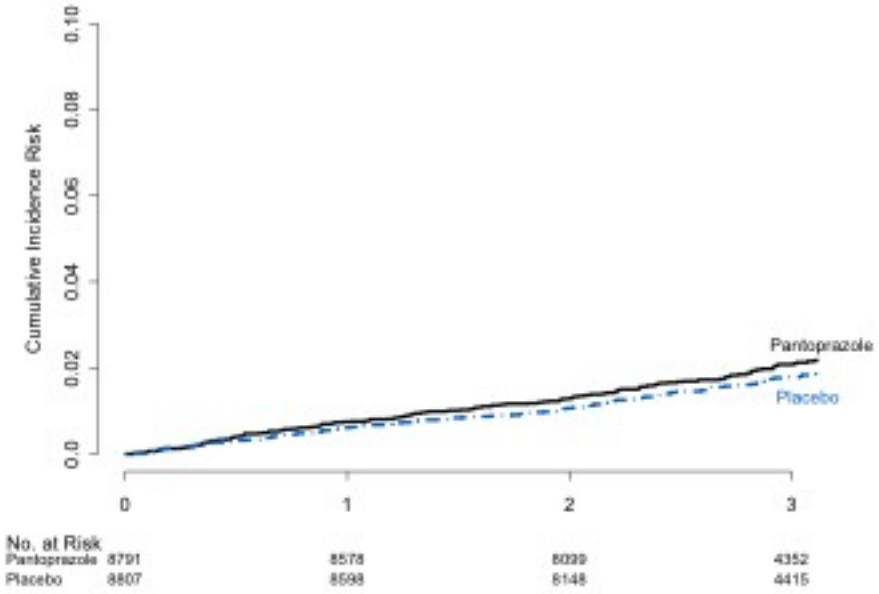




a) Myocardial infarction



b) Stroke



What you need to know

Evidence before this study
Observational studies have raised concerns that proton pump inhibitors may be associated with increased risk of pneumonia, fracture, clostridium difficile associated diarrhoea, 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 long-term harm and therefore the benefits are likely to outweigh the risks of these medications provided they are used for clinically appropriate indications.

Lay summary

Concerns have been raised regarding the long-term safety of acid suppressing medications, proton pump inhibitors. 17,598 participants were randomized to the proton pump inhibitor pantoprazole 40mg daily or placebo and followed up for three years. There was a slight increased risk of enteric infection in patients taking proton pump inhibitors. There was, however, no difference in pneumonia, fracture, clostridium difficile associated diarrhoea, cardiovascular disease, chronic renal disease, dementia and all-cause mortality in patients taking proton pump inhibitors.