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Complete List of Authors:	Xie, Yan; VA Saint Louis Health Care System, Clinical Epidemiology Center Bowe, Benjamin; VA Saint Louis Health Care System, Clinical Epidemiology Center Li, Tingting; VA Saint Louis Health Care System, Clinical Epidemiology Center; Washington University in Saint Louis School of Medicine, Internal Medicine Xian, Hong; VA Saint Louis Health Care System, Clinical Epidemiology Center; Saint Louis University, School of Public Health, Department of Biostatistics Yan, Yan; VA Saint Louis Health Care System, Clinical Epidemiology Center; Washington University in Saint Louis School of Medicine, Public Health Sciences Al-Aly, Ziyad; VA Saint Louis Health Care System, Clinical Epidemiology Center; Washington University in Saint Louis School of Medicine, Internal Medicine
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Excess Risk of Death among Users of Proton Pump Inhibitors: A longitudinal observational cohort study of United States Veterans

Yan Xie MPH[1], Benjamin Bowe MPH[1], Tingting Li MD[1,2], Hong Xian PhD[1,3], Yan Yan MD, PhD[1,4], and Ziyad Al-Aly MD[1,2,5,6]

[1]Clinical Epidemiology Center, Research and Education Service, VA Saint Louis Health Care System, Saint Louis, Missouri

[2]Department of Medicine, Washington University School of Medicine, Saint Louis, Missouri

[3]Department of Biostatistics, College for Public Health and Social Justice, Saint Louis University, Saint Louis, Missouri

[4]Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, Saint Louis, Missouri

[5]Renal Section, Medicine Service, VA Saint Louis Health Care System, Saint Louis, Missouri

[6]Institute for Public Health, Washington University School of Medicine, Saint Louis, Missouri

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Corresponding Author:

Ziyad Al-Aly, M.D.
Clinical Epidemiology Center
VA Saint Louis Health Care System
915 North Grand Boulevard, 151-JC
Saint Louis, MO 63106
Telephone: (314) 289-6333
E-mail: zalaly@gmail.com

Abstract:

Objective: Proton pump inhibitors (PPI) are widely used; and their use is associated with increased risk of adverse events. However, whether PPI use is associated with excess risk of death is unknown. We aimed to examine the association between PPI use and risk of all-cause mortality.

Design: Longitudinal observational cohort study

Setting: US Department of Veterans Affairs

Participants: Primary cohort of new users of PPI or Histamine H2 receptor antagonists (H2 blockers) (N=349,312); additional cohorts included PPI versus no PPI (N=3,288,092), and PPI versus no PPI and no H2 blockers (N=2,887,030).

Main outcome measures: Risk of death.

Results: Over a median follow-up of 5.71 years (IQR: 5.11-6.37), PPI use was associated with increased risk of death compared to H2 blockers use (HR=1.25; CI=1.23-1.28). Risk of death associated with PPI use was higher in analyses adjusted for high-dimensional propensity score (HR=1.16; CI=1.13-1.18); two-stage residual inclusion estimation (HR=1.21; CI=1.16-1.26); and in 1:1 time-dependent propensity score matched cohort (HR=1.34 CI=1.29-1.39). The risk of death was increased when considering PPI use versus no PPI (HR=1.15; CI=1.14-1.15), and PPI use versus no PPI and no H2 blockers (HR= 1.23; CI=1.22-1.24). Risk of death associated with PPI use was increased among participants without gastrointestinal conditions: PPI versus H2 blockers (HR=1.24; CI=1.21-1.27); PPI use versus no PPI (HR=1.19; CI=1.18-1.20); and PPI use versus no PPI and no H2 blockers (HR=1.22; CI=1.21-1.23). Among new PPI users, there was a graded association between duration of exposure and risk of death.

Conclusions: The results suggest excess risk of death among PPI users; risk is also increased among those without gastrointestinal conditions and with prolonged duration of use. Limiting PPI use and duration to instances where it is medically indicated may be warranted.

Strength and limitations:

- The results from this large national observational cohort study suggest that Proton Pump Inhibitors (PPI) use is associated with increased risk of death.
- Risk of death is increased among those with no documented medical indication for PPI use.
- A graded association was observed between duration of PPI use and risk of death in that more prolonged exposure was associated with higher risk of death.
- Exercising pharmacovigilance and limiting PPI use to instances and durations where it is medically necessary may be a meritorious approach.
- Limitations of this study include its observational nature, and that majority of cohort participants were while males.

Introduction:

Proton pump inhibitors (PPI) are widely prescribed and are also available for sale over the counter without prescription in several countries(1, 2). Several observational studies suggest that PPI use is associated with increased risk of a number of adverse health outcomes(1). A number of studies have shown that PPI use is associated with significant risk of acute interstitial nephritis(3-5). Recent studies established an association between exposure to PPI and risk of chronic kidney disease (CKD), kidney disease progression, and end stage renal disease (ESRD)(2, 6, 7). Results from a large prospective observational German cohort suggest that patients receiving PPI had a higher risk of incident dementia(8). Several reports highlighted a rare but potentially fatal risk of hypomagnesemia among users of PPI(9-11). PPI use has been associated with increased risk of both incident and recurrent Clostridium difficile infections(12). Several observational analyses have shown that PPI use was also associated with increased risk of osteoporotic fractures including hip and spine fractures(13, 14). Less convincing -and to some extent inconsistent- evidence suggests a relationship between PPI use and risks of community acquired pneumonia and cardiovascular events(15-17). Emerging -and far from conclusive- *in vitro* evidence suggests that PPI results in inhibition of lysosomal acidification and impairment of proteostasis leading to increased oxidative stress, endothelial dysfunction, telomere shortening and accelerated senescence in human endothelial cells(18). The experimental work provides a putative mechanistic link to explain some of the adverse events associated with PPI use(18).

The adverse outcomes associated with PPI use are serious and each is independently associated with higher risk of mortality. Evidence from several small cohort studies of older adults who were recently discharged from

the hospital, or institutionalized in long term care facilities suggests inconsistently that PPI use may be associated with increased risk of 1-year mortality(19-22). Whether PPI use is associated with excess risk of death is not known and has not been examined in large epidemiologic studies spanning a sufficiently long duration of follow up. We hypothesized that owing to the consistently observed associations between PPI use and risk of adverse health outcomes, PPI use is associated with excess risk of death, and that the risk of death would be more pronounced with increased duration of use. We therefore used the Department of Veterans Affairs national databases to build a longitudinal cohort of incident users of acid suppression therapy including PPI and Histamine H2 receptor antagonists (H2 blockers) to examine the association between PPI use and risk of all-cause mortality, and to determine whether risk of death is increased with prolonged duration of use.

Methods:

Cohort participants:

Primary cohort:

Using administrative data from the United States Department of Veterans Affairs (VA), we identified patients who received an outpatient H2 blockers or PPI prescription between October 01, 2006 and September 30, 2008 (n=1,762,908). In order to select new users of acid suppression therapy (incident user design), we excluded 1,356,948 patients who received any outpatient H2 blockers or PPI prescriptions between October 01, 1998 and September 30, 2006. To account for patients' kidney function, only patients with at least one outpatient serum creatinine value before first acid suppression therapy prescription were selected in the cohort, yielding an analytic cohort of 349,312 patients. Patients whose first acid suppression therapy was PPI (n=275,977) were considered to be in the PPI group during follow-up. Patients who received H2 blockers as their first acid suppression therapy (n=73,335) served as the reference group before they received any PPI prescription. Within the reference group, those who received a PPI prescription later (n=33,136) were considered to be in the PPI group from the date of their first PPI prescription until the end of follow-up(23). Time zero (T0) for primary cohort was defined as first acid suppression therapy prescription date.

Secondary cohorts:

We additionally built two secondary cohorts to examine the association of PPI use and risk of death in a) PPI versus no PPI users, and b) PPI versus non users of acid suppression therapy. Patients with no PPI prescription between October 01, 1998 and September 30, 2006, and with at least one outpatient eGFR value before October 01, 2006 were selected to evaluate the risk of death associated with PPI use versus no PPI use (n=3,288,092). Patients with no PPI prescription between October 01, 1998 and September 30, 2006, with no H2 blockers before first PPI prescription and at least one outpatient eGFR value before October 01, 2006 were selected to evaluate the risk of death associated with PPI use versus no acid suppression therapy (n=2,887,030). T0 for secondary cohorts was defined as October 01, 2006.

Patients in both primary and secondary cohorts were followed until September 30, 2013 or death. The study was approved by the Institutional Review Board of the VA Saint Louis Health Care System, Saint Louis, MO.

Data Sources:

We used the Department of Veterans Affairs databases including inpatient and outpatient medical SAS datasets (that include utilization data related to all inpatient and outpatient encounters within the VA system) to ascertain detailed patient demographic characteristics and comorbidity information based on inpatient and outpatient encounters(2). The VA Managerial Cost Accounting System Laboratory Results (a comprehensive database that includes VA-wide results for selected laboratory tests obtained in the clinical setting) provided information on outpatient and inpatient laboratory results. The VA Corporate Data Warehouse Production Outpatient Pharmacy domain provided information on outpatient prescriptions. The VA Vital Status and Beneficiary Identification Records Locator Subsystem (BIRLS) files provided demographic characteristics and death.

Primary Predictor Variable: PPI use was the primary predictor. Once cohort participants received PPI prescription, they were considered with effect of PPI until the end of follow up. Medications that contain esomeprazole, lansoprazole, omeprazole, pantoprazole or rabeprazole were counted as PPI. Medications including ranitidine, cimetidine, and famotidine were counted as H2 blockers.

Outcome: The primary outcome in survival analyses was time to death. Death information is routinely collected by the Veterans Benefit Administration for all United States Veterans.

Covariates:

Covariates included age, race, gender, eGFR, number of outpatient serum creatinine measurements, number of hospitalizations, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, cancer, hepatitis C, HIV, dementia and diseases associated with acid suppression therapy use such as gastroesophageal reflux disease (GERD), upper gastrointestinal (GI) tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma(24-27). eGFR was calculated using the abbreviated four-variable Chronic Kidney Disease Epidemiology Collaboration equation based on age, sex, race, and outpatient serum creatinine(28). Race/ethnicity was categorized as white, black, or other (Latino, Asian, Native American, or other racial/ethnic minority groups). Comorbidities except for hepatitis C and HIV were assigned on the basis of relevant ICD-9-CM diagnostic and procedures codes and CPT codes in the VA Medical SAS datasets(2, 29-32). Hepatitis C and HIV were assigned based on laboratory results.

Baseline covariates were ascertained from October 01, 1998 till T0. All covariates except for age, race and gender covariates values were treated as time-varying covariates where they were additionally assessed until date of first PPI prescription in those patients who did not have PPI prescription at T0. Any comorbidity occurring during the assessment period was considered present during the remaining follow-up. eGFR was the outpatient eGFR value within and most proximate to the end of the assessment period. Number of outpatient serum creatinine measurements and number of hospitalizations were accumulated during the assessment period.

Statistical Analysis:

Means, standard deviations and t-tests are presented for normally distributed continuous variables; medians, interquartile ranges and Wilcoxon-Mann-Whitney tests are presented for non-normally distributed continuous variables; counts, percentages and Chi-square tests are presented for categorical variables. Incident rates per

100 person-years were computed for death and confidence intervals were estimated based on the normal distribution. Simon and Makuch method for survival curves was used for time-dependent covariates(33).

Cox regression models with time-dependent covariates were used in the assessment of the association between PPI exposure and risk of death where patients could switch from H2 blockers to PPI in the models. In order to account for potential delayed effect of PPI, patients were considered to have the effect of PPI from the first PPI prescription till end of follow up. In addition, time dependent Cox models were conducted in subgroups where patients had no GI conditions, and where patients had no GI conditions except for GERD.

Because exposure in this observational cohort is time-dependent, we undertook 1:1 propensity score matching for the primary cohort where time-dependent propensity scores were calculated based on time-dependent Cox regression with all covariates(34)(details are provided in supplemental methods).

In order to optimize control of confounding, we additionally built high-dimensional propensity score adjusted survival models following the multistep algorithm described by Schneeweiss et al(35)(details are provided in supplemental methods). We also applied two-stage residual inclusion estimation based on instrumental variable approach (Supplemental methods)(36).

In addition, we evaluated the association between duration of PPI prescription and risk of death among new users of PPI. Duration was defined in cumulative days of use and categorized as ≤30, 31-90, 91-180, 181-360, 361-720, where ≤30 days considered as the reference group. To avoid immortal time bias (by definition, cohort participants must be alive to receive prescription hence introducing a bias commonly referred to as immortal time bias), time of cohort entry was defined as the date of last PPI prescription plus days' supply (37, 38). In order to ensure sufficient length of follow up time following T0, we excluded cohort participants with cumulative duration of exposure exceeding 720 days (because of limited overall cohort timeline, and because T0 starts at the end of last prescription, those with long exposure will necessarily have limited follow up time). In regression analyses, a 95% confidence interval (CI) of a hazard ratio (HR) that does not include unity was considered statistically significant. All analyses were performed using SAS Enterprise Guide version 7.1.

Sensitivity Analysis:

In order to further evaluate the consistency and robustness of study findings, we examined the observed associations in a less contemporary cohort (dating back to an era where PPI prescription and use were far less frequent) of patients without acid suppression therapy prescriptions between October 01, 1998 and September 30, 2000 (washout period) and with acid suppression therapy prescription between October 01, 2000 and September 30, 2002 and at least one outpatient serum creatinine value before that. Patients in this cohort were followed till September 30, 2007 or death. To examine the impact of potential residual confounding on study results, we conducted additional sensitivity analyses as described by Schneeweiss(39): a) we used the rule-out approach to identify the strength of the residual confounding that could fully explain the association observed in primary analyses; and b) applied an external adjustment approach using external information (prevalence and risk estimates from published literature) to evaluate potential net confounding bias due to unmeasured confounders(2, 39-42). Methods are described elegantly by Schneeweiss(39).

We conducted additional sensitivity analyses which included hemoglobin as a covariate in cohort participants with available data. We also undertook analyses in those with and without cardiovascular disease. Finally, and in order to ascertain the specificity of the findings, we examined the association between PPI exposure and the risk of a motor vehicle accident as a tracer outcome where a priori knowledge suggests an association is not likely to exist.

Patient involvement:

No patients were involved in developing the hypothesis, the specific aims, or the research questions, nor were they involved in developing plans for design or implementation of the study. No patients were involved in the interpretation of study results, or write up of the manuscript. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results:

The demographic and health characteristics of the overall primary cohort of new users of acid suppression therapy (n=349,312), by type of acid suppressant drug at time of cohort entry (H2 blockers n=73,335; PPI

n=275,977), and those who were ever exposed to PPI (n=309,113) are provided in table 1. There were significant baseline differences in that cohort participants who were treated with PPI were older, and were more likely to have comorbid conditions including diabetes, hypertension, cardiovascular disease, and hyperlipidemia. Cohort participants treated with PPI were also more likely to have upper gastrointestinal tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma (table 1). Survival curves for PPI and H2 blockers were presented in figure 1.

Association between PPI use and risk of death:

Among new users of acid suppression therapy (N=349,312), and over a median follow up of 5.71 years (IQR: 5.11 – 6.37), where exposure was treated as time-dependent covariate; PPI use was associated with increased risk of death compared to H2 blockers use (HR=1.25; CI=1.23-1.28) (table 2). Among new users of acid suppression therapy (N=349,312); in high-dimensional propensity score adjusted models, new PPI users had increased risk of death compared to new users of H2 blockers (HR=1.16; CI=1.13-1.18); based on two-stage residual inclusion estimation, risk of death was higher in new users PPI when compared to new users of H2 blockers (HR=1.21; CI=1.16-1.26). In a 1:1 time-dependent propensity score matched cohort of new users of PPI and H2 blockers (N=146,670), PPI users had significantly increased risk of death (HR=1.34; CI=1.29-1.39).

We examined the relationship of PPI and risk of death in secondary cohorts (as described in methods) where we considered risk associated with PPI use versus no known exposure to PPI (no PPI use +/- H2 blockers use) (N=3,288,092); the results suggest that PPI use was associated with increased risk of death (HR=1.15; CI=1.14-1.15) (table 2). Assessment of risk of death associated with PPI use versus no known exposure to any acid suppression therapy (no PPI use and no H2 blockers use) (N=2,887,070), suggests increased risk of death with PPI use (HR= 1.23; CI=1.22-1.24).

Association between PPI use and risk of death in those without gastrointestinal conditions:

We then analyzed the association between PPI use and the risk of death in cohort where we excluded participants with documented medical conditions generally considered as indications for treatment with PPI

including GERD, upper gastrointestinal tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma. The intent of this analysis was to examine the putative association of PPI use and risk of death in a lower risk cohort. Examination of risk of death associated with use of acid suppression therapy (PPI vs. H2 blockers) suggests that risk of death was increased with PPI use (HR=1.24; CI=1.21-1.27) (table 2). Examination of the risk of death associated with PPI use versus no known exposure to PPI (no PPI use +/- H2 blockers use) suggests a higher risk of death associated with PPI use (HR=1.19; CI=1.18, 1.20). Results were consistent where we examined risk of death associated with PPI use versus no known exposure to any acid suppression therapy (no PPI use and no H2 blockers use) (HR=1.22; CI=1.21-1.23). Risk of death associated with PPI use in cohort participants without GI conditions but included participants with GERD yielded consistent results (PPI vs H2 blockers (HR=1.24; CI=1.21-1.27); PPI vs no PPI (HR=1.14; CI=1.13-1.14); PPI vs no PPI and no H2 blockers (HR=1.22; CI=1.21-1.22) (table 2).

Duration of exposure and excess risk of death:

We examined the association between duration of PPI exposure and risk of death among new users of PPI (n=166,098). Compared to those exposed for ≤30 days, there was a graded association between duration of exposure and risk of death among those exposed for 31-90, 91-180, 181-360, and 361-720 days (table 3, figure 2).

Sensitivity analyses:

We tested the robustness of study results in sensitivity analyses where we built a less contemporary cohort as described in methods; demographic and health characteristics of this cohort are provided in supplemental table 1. Where exposure was treated as time-dependent, PPI use was associated with increased risk of death compared to H2 blockers use (HR=1.17; CI=1.15-1.19). In a 1:1 time-dependent propensity score matched cohort of PPI and H2 blockers, PPI users had significantly increased risk of death HR=1.21 (1.19-1.24). Furthermore, we also observed a graded association between cumulative duration of exposure to PPI and risk of death (supplemental table 2, supplemental figure 1).

To examine the potential impact of residual confounding on study results, we used rule-out and external adjustment approaches as described by Schneeweiss(39). Using the rule-out approach, we characterized a set of parameters (OR for relationship of PPI and confounder), and (HR for relationship of confounder and death) with sufficient strength to fully explain the association observed in primary analyses (supplemental figure 2). For example, if the confounder was twice as likely among PPI users (OR=2), and the HR of death associated with the uncontrolled confounder exceeded 4.0, then the uncontrolled confounder would fully explain the observed association between PPI and death (supplemental figure 2). Given that our analyses accounted for most known strong independent risk factors of death, and employed an active comparator group; to cancel the results, any uncontrolled confounder of the required prevalence (OR=2 or more in the example above), and strength (HR=4 or more in the example above) would also have to be independent of the confounders already adjusted for and is unlikely to exist; thus the results cannot be fully explained by this putative uncontrolled confounder.

External adjustment to estimate the impact of 3 unmeasured confounders including obesity, smoking, and use of therapeutics including anticoagulants, antiplatelet agents, and non-steroidal anti-inflammatory drugs shows a net confounding bias of 9.66% (supplemental figure 2). The total bias could move a null association between PPI and death from HR=1.00 to HR=1.10 (reflecting the net positive bias of 9.66% rounded up to 10.0%). The association we observed between PPI and death was 1.25>1.10, which cannot be fully due to bias of unmeasured confounding.

The association between PPI and death remained significant after additionally controlling for hemoglobin levels (HR=1.25; CI=1.23, 1.28). Risk was also increased in those with and without cardiovascular disease (HR=1.19; CI=1.15, 1.23, and HR=1.30; CI=1.27, 1.34; respectively). As a test of specificity, among users of acid suppression therapy, PPI use was not associated with increased risk of the tracer outcome of a motor vehicle accident (HR=0.99; CI= 0.89, 1.10).

Discussion:

This study provides insights into the excess risk of death associated with PPI use. In a large primary cohort of new users of acid suppression therapy followed for a median of 5.71 years, we show a significant association between PPI use and risk of all-cause mortality, risk was increased among those with no documented medical indications for PPI use, and with prolonged duration of use. The results were consistent in multiple analyses and robust to changes in epidemiologic design and statistical specifications, and were reproduced in an earlier and less contemporary cohort from an era where PPI use was far less frequent (43).

PPI are widely used by millions of people for indications and durations that were never tested or approved; they are available over the counter (without prescription) in several countries, and generally perceived as safe class of therapeutics; they are often overprescribed, rarely deprescribed, frequently started inappropriately during a hospital stay, and their use extended for long term duration without appropriate medical indication (44-48). Results of nationally representative data from the National Health and Nutrition Examination Survey, where analyses were weighted to represent the US adult population, showed that the use of prescription PPI increased from 3.9% to 7.8% from 1999-2000 to 2011-2012, representing a doubling of prevalence ratio(43). Studies estimate that between 53% and 69% of PPI prescriptions are for inappropriate indications(44, 49) where benefits of PPI use may not justify the risks for many users(49-51). The findings in our study highlight a potential excess risk of death among users of PPI, and in particular among cohort participants without GI comorbidities, and that risk is increased with prolonged duration of PPI exposure. While our results should not deter prescription and use of PPI where medically indicated, they may be used to encourage and promote pharmacovigilance and emphasize the need to exercise judicious use of PPI and limit use and duration of therapy to instances where there is a clear medical indication and where benefit outweighs potential risk(1). Standardized guidelines for initiating PPI prescription may lead to reduced overuse(52), regular review of prescription and over the counter medications, and deprescription where a medical indication for PPI treatment ceases to exist may be a meritorious approach(50).

The biologic mechanism underpinning the association of PPI use and risk of death is not clear. Experimental evidence in rats suggests that PPI administration limits the regenerative capacity of livers following partial hepatectomy(53). Administration of PPI upregulates expression of mRNA, protein level, and results in

increased activity of the heme oxygenase-1 enzyme in gastric and endothelial cells(54). Heme oxygenase-1 is generally seen as salutary, but its beneficial properties are vitiated at higher doses, and with sustained duration of expression(55). PPI treatment impairs lysosomal acidification and proteostasis and results in increased oxidative stress, dysfunction, telomere shortening and accelerated senescence of human endothelial cells(18, 56). Wu and collaborators undertook a systematic toxicity mechanism analysis using a high-throughput in-silico analysis of microarray data; they reported that PPI up-regulated genes in the cellular retinol metabolism pathway, and down-regulated genes in the complement and coagulation cascades pathway and that PPI may block pathways of antigen presentation, and abrogate the synthesis and secretion of cytokines and complement component proteins and coagulation factors(56, 57). How the changes in gene expression contribute to excess risk of death is not yet entirely clear. The plausible clinical course leading to heightened risk of death is likely mediated by the occurrence of one or more of the adverse events associated with PPI use (kidney disease, dementia, hypomagnesemia, Clostridium difficile infection, osteoporotic fracture, etc…). Further studies are needed to characterize the biologic mechanisms that might explain the epidemiologic findings in this report.

The constellation of findings in this report must be interpreted with the full cognizance of the observational study design where confounding by indication, and selection bias may represent limitations; we employed an analytic strategy to evaluate the risk of death among users of acid suppression therapy (PPI and H2 blockers); a class of therapeutics generally prescribed for similar indications, a strategy which may lessen but does not completely eliminate the possibility of confounding by indication bias. We additionally built time-dependent propensity score matched cohort, high dimensional propensity score adjusted models, and employed the use of instrumental variable to reduce potential confounding bias. Although we accounted for known covariates in our analyses, it is possible that there are residual confounders (either unmeasured, or unknown) that may still confound the association of PPI and risk of death. However, we evaluated the impact of residual confounding in quantitative bias analyses, and the results suggest that even with the application of unlikely (and exaggerated) set of assumptions, the risk cannot be fully explained by residual confounding. In our analyses, we defined drug exposure as having a prescription for it; since PPI (and H2 blockers) are available over the counter in the United States, it is possible that some patients in this cohort may have obtained and used PPI

without prescription. However, owing to financial considerations, this is not highly likely, and if it occurred in some patients, it will have biased the results against the primary hypothesis and resulted in underestimation of risk. The cohort included mostly older white male US Veterans which may limit the generalizability of study results to a broader population. Our datasets did not include information on the cause of death. The study has a number of strengths including the use of national large scale data from a network of integrated health systems which was captured during routine medical care which minimizes selection bias. We employed a new user (incident user) approach, and evaluated the association between PPI use and risk of death using a number of analytical approaches where we consistently found a significant association between PPI use and increased risk of death. The consistency of study findings in our report, and the growing body of evidence in the literature showing a host of adverse events associated with PPI use are compelling, and because of the high prevalence of PPI use, may have public health implications. Exercising pharmacovigilance and limiting PPI use to instances and durations to instances where it is medically indicated may be warranted.

Footnotes

Contributors: Research area and study design: YX, BB, TL, HX, YY, ZAA; data acquisition: YX, BB; data analysis and interpretation: YX, BB, TL, HX, YY, ZAA; statistical analysis: YX, BB; supervision and mentorship: ZAA. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. ZAA takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This research project was reviewed and approved by the Institutional Review Board of the VA Saint Louis Health Care System.

Data sharing: Data is available through the United States Department of Veterans Affairs.

Transparency: The lead authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Disclaimer: The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

Disclosures: None.

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Table 1: Baseline demographic and health characteristics of overall primary cohort of new users of acid suppression therapy, by type of acid suppressant at time of cohort entry, and those who were ever exposed to PPI.

		Overall cohort	New users of H2 Blockers at time of cohort entry	New users of PPI at time of cohort entry	Ever exposed to PPI [a]	P Value [b]
N		349312	73335	275977	309113	
Age (SD)		61.00 (14.92)	58.48 (15.13)	61.67 (14.79)	61.37 (14.77)	<0.001
eGFR in mL/min/1.73m^2 (SD)		76.89 (22.66)	79.64 (21.96)	76.16 (22.79)	76.60 (22.79)	<0.001
Number of outpatient serum creatinine measurements (SD)		6.85 (7.55)	6.67 (7.39)	6.89 (7.59)	7.27 (8.00)	<0.001
Number of hospitalizations (SD)		0.51 (1.39)	0.52 (1.45)	0.51 (1.37)	0.56 (1.49)	0.014
Race	White (%)	275473 (78.86)	56530 (77.08)	218943 (79.33)	244230 (79.01)	<0.001
	Black (%)	59243 (16.96)	13229 (18.04)	46014 (16.67)	52207 (16.89)	
	Other (%)	14596 (4.18)	3576 (4.88)	11020 (3.99)	12676 (4.10)	
Sex	Male (%)	326659 (93.51)	67748 (92.38)	258911 (93.82)	289233 (93.57)	<0.001
	Female (%)	22653 (6.49)	5587 (7.62)	17066 (6.18)	19880 (6.43)	
Diabetes mellitus (%)		90273 (25.84)	16758 (22.85)	73515 (26.64)	82168 (26.58)	<0.001
Hypertension (%)		225899 (64.67)	44502 (60.68)	181397 (65.73)	203700 (65.90)	<0.001
Chronic lung disease (%)		70281 (20.12)	13849 (18.88)	56432 (20.45)	64777 (20.96)	<0.001
Peripheral artery disease (%)		11439 (3.27)	2225 (3.03)	9214 (3.34)	10680 (3.46)	<0.001
Cardiovascular disease (%)		98137 (28.09)	17436 (23.78)	80701 (29.24)	89878 (29.08)	<0.001
Cerebrovascular disease (%)		1858 (0.53)	372 (0.51)	1486 (0.54)	1719 (0.56)	0.30
Dementia (%)		16421(4.70)	3115 (4.25)	13306 (4.82)	15384 (4.98)	<0.001
Hyperlipidemia (%)		200397 (57.37)	39818 (54.30)	160579 (58.19)	181524 (58.72)	<0.001
Hepatitis C (%)		5034 (1.44)	1184 (1.61)	3850 (1.40)	4444 (1.44)	<0.001
HIV (%)		114 (0.03)	38 (0.05)	76 (0.03)	113 (0.04)	0.001
Cancer (%)		49666 (14.22)	9123 (12.44)	40543 (14.69)	45633 (14.76)	<0.001
GERD (%)		100980 (28.91)	20562 (28.04)	80418 (29.14)	94517 (30.58)	<0.001
Upper GI tract bleeding (%)		9310 (2.67)	926 (1.26)	8384 (3.04)	9098 (2.94)	<0.001
Ulcer disease (%)		25626 (7.34)	3564 (4.86)	22062 (7.99)	24864 (8.04)	<0.001
H. Pylori infection (%)		3078 (0.88)	141 (0.19)	2937 (1.06)	3239 (1.05)	<0.001
Barrett's esophagus (%)		2324 (0.67)	89 (0.12)	2235 (0.81)	2382 (0.77)	<0.001
Achalasia (%)		151 (0.04)	10 (0.01)	141 (0.05)	154 (0.05)	<0.001
Stricture (%)		1992 (0.57)	132 (0.18)	1860 (0.67)	2051 (0.66)	<0.001
Esophageal		213 (0.06)	17 (0.02)	196 (0.07)	213 (0.07)	<0.001

adenocarcinoma (%)					
Years of follow up (IQR)[c]	5.71 (5.11 – 6.37)	4.38 (1.16 – 5.92)d	5.67 (5.09 – 6.34)	5.59 (4.82 – 6.28)	<0.001
Days of having related prescription during follow-up (IQR)	442 (199 – 1272)[e]	120 (60 – 400) [d]	450 (120 – 1299)	450 (120 – 1266)	<0.001
Death (%)	81463 (23.32)	9018 (12.30) [d]	67450 (24.44)	72445 (23.44)	<0.001
Incident death in 100 person years (95% CI)	4.47 (4.44 – 4.50)	3.32 (3.25 – 3.39) [d]	4.74 (4.70 – 4.77)	4.67 (4.64 – 4.71)	<0.001

a. Includes patients exposed to PPI at T0 (n=275977) and during follow-up (n=33136). Variables were measured at time of PPI exposure.
b. P value for difference between exposed to H2 at T0 and exposed to PPI at T0
c. From T0 to first occurrence of death or September 30, 2013
d. Outcome measured from T0 to first occurrence of exposure PPI, death or September 30, 2007
e. Days of having PPI or H2 blockers

Abbreviations: CI, Confidence interval; eGFR, estimated Glomerular Filtration Rate; GERD, Gastroesophageal Reflux Disease; HIV, human immunodeficiency virus; IQR, interquartile range; SD, Standard deviation

Table 2: Association between PPI use and risk of death:

Association Between PPI and Death		Reference	PPI use
PPI use VS H2 blockers use (N=349,312)	Incident rate (95% CI)	3.32 (3.25 – 3.39)	4.67 (4.64 – 4.71)
	Unadjusted HR (95% CI)	1	1.46 (1.43 – 1.49)
	Adjusted HR (95% CI)	1	1.25 (1.23 – 1.28)
High-dimensional propensity score adjusted model of new users of PPI VS H2 blockers (N=349,312)	Incident rate (95% CI)	3.32 (3.25 – 3.39)	4.74 (4.70, 4.77)
	HR (95% CI)	1	1.16 (1.13 – 1.18)
Two-stage residual inclusion estimation model of new users of PPI VS H2 blockers (N=318,960)	Incident rate (95% CI)	3.32 (3.25 – 3.39)	4.74 (4.70 – 4.77)
	HR (95% CI)	1	1.21 (1.16 – 1.26)
Time dependent propensity score matched PPI VS H2 blockers (N=146,670)	Incident rate (95% CI)	3.32 (3.25 – 3.39)	4.37 (4.30 – 4.44)
	Unadjusted HR (95% CI)	1	1.38 (1.34 – 1.42)
	Adjusted HR (95% CI)	1	1.34 (1.29 – 1.39)
PPI use VS no PPI (N=3,288,092)	Incident rate (95% CI)	3.64 (3.63 – 3.65)	5.50 (5.47 – 5.53)
	Unadjusted HR (95% CI)	1	1.47 (1.46 – 1.48)
	Adjusted HR (95% CI)	1	1.15 (1.14 – 1.15)
PPI use VS no PPI or H2 blockers (N=2,886,879)	Incident rate (95% CI)	3.47 (3.46 – 3.48)	5.50 (5.47 – 5.53)
	Unadjusted HR (95% CI)	1	1.53 (1.52 – 1.54)
	Adjusted HR (95% CI)	1	1.23 (1.22 – 1.24)
PPI VS H2 blockers in a cohort without GI conditions (N=214,521)	Incident rate (95% CI)	3.80 (3.71 – 3.89)	5.39 (5.34 – 5.44)
	Unadjusted HR (95% CI)	1	1.47 (1.43 – 1.51)
	Adjusted HR (95% CI)	1	1.24 (1.21 – 1.27)
PPI VS no PPI in a cohort without GI conditions (N=2,790,697)	Incident rate (95% CI)	3.54 (3.53 – 3.55)	5.89 (5.86 – 5.93)
	Unadjusted HR (95% CI)	1	1.62 (1.61 – 1.63)
	Adjusted HR (95% CI)	1	1.19 (1.18 – 1.20)

PPI VS no PPI or H2 blockers in a cohort without GI conditions (N=2,543,480)	Incident rate (95% CI)	3.45 (3.44 – 3.46)	5.89 (5.86 – 5.93)
	Unadjusted HR (95% CI)	1	1.65 (1.64 – 1.67)
	Adjusted HR (95% CI)	1	1.22 (1.21 – 1.23)
PPI VS H2 blockers in a cohort without GI conditions except for GERD (N=311,115)	Incident rate (95% CI)	3.30 (3.23 – 3.37)	4.51 (4.47 – 4.54)
	Unadjusted HR (95% CI)	1	1.42 (1.38 – 1.45)
	Adjusted HR (95% CI)	1	1.24 (1.21 – 1.27)
PPI VS no PPI in a cohort without GI conditions except for GERD (N=3,132,126)	Incident rate (95% CI)	3.59 (3.58 – 3.60)	5.36 (5.34 – 5.39)
	Unadjusted HR (95% CI)	1	1.45 (1.44 – 1.46)
	Adjusted HR (95% CI)	1	1.14 (1.13 – 1.14)
PPI VS no PPI or H2 blockers in a cohort without GI conditions except for GERD (N=2,678,478)	Incident rate (95% CI)	3.44 (3.44 – 3.45)	5.36 (5.34 – 5.39)
	Unadjusted HR (95% CI)	1	1.50 (1.49 – 1.51)
	Adjusted HR (95% CI)	1	1.22 (1.21 – 1.22)

a. Incident rate as incident death in 100 person years
b. All models except time dependent propensity score matched and high-dimensional propensity score adjusted models were time dependent models. Effect of PPI was treated as time dependent and was defined as once patients used PPI, they were in PPI group during the remaining follow-up.
c. Adjusted model controlling for eGFR, age, race, gender, number of serum creatinine measurements, number of hospitalizations, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, cancer, GERD, upper GI tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma, unless used in analysis inclusion criteria.
d. GI conditions include upper GI tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma

Abbreviations: CI, Confidence interval; HR, Hazard Ratio

Table 3: Duration of exposure to PPI and risk of death among new users of PPI (n=166,098)

Duration (Days)	≤ 30	31 - 90	91 - 180	181 - 360	361 - 720
N (%)	24748 (14.90)	39345 (23.69)	29334 (17.66)	33907 (20.41)	38764 (23.34)
Hazard Ratio (95%CI)	1	1.05 (1.02-1.08)	1.17 (1.13-1.20)	1.31 (1.27-1.34)	1.51 (1.47-1.56)

a. Within people exposure to PPI between 1 to 720 days
b. Model controls for eGFR, age, race, gender, number of serum creatinine measurements, number of hospitalizations, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, cancer, GERD, upper GI tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma
c. Time zero defined as date when the patients last PPI prescription ends

Figure legends:

Figure 1: Survival curves for PPI and H2 blockers

Figure 2: Duration of PPI exposure and risk of death among new PPI users (n=166,098)

Supplemental Figures:

Supplemental figure 1: Duration of PPI exposure and risk of death among new PPI users in an older (less contemporary) sensitivity cohort (n=101,109)

Supplemental figure 2: Estimation of the impact of uncontrolled confounder using the rule-out approach: To investigate the impact of potential residual confounding; rule-out approach was used, where prevalence of potential confounder was set at 30% and prevalence of exposure (PPI use) was set at 88.5% (the latter is derived from our data). The X axis describes the Odds Ratio (OR) of the association between the confounder and PPI users. The Y axis describes the Hazard Ratio (HR) of the association between the confounder and risk of death. The blue line splits the area into two: the upper right area represents all parameter combinations of OR (between PPI use and confounder) and HR (between confounder and death) that are strong enough to move the apparent HR (AHR) from 1.25 (the HR observed in our primary analysis) to 1 or lower, rejecting the hypothesis of an association between PPI use and risk of death. The corollary observation is that the area to the lower left represents all parameter combinations that would result in acceptance of the primary hypothesis. For example, the results show that for uncontrolled confounder that is twice as likely among PPI users (OR=2), the strength of the association between the uncontrolled confounder and risk of death would have to exceed 4 (HR>4) for the uncontrolled confounder to fully explain the observed association between PPI and death (where the combination of OR=2, HR>4 is in the area above the blue line).

Supplemental figure 3: External adjustment to estimate the impact of 3 unmeasured confounders: To investigate the impact of potential residual confounding, we applied external adjustment to estimate the impact of 3 unmeasured confounders including obesity, smoking, and use of therapeutics including anticoagulants, antiplatelet agents, and non-steroidal anti-inflammatory drugs. In order to generate extreme bias estimates (against the hypothesis) we assumed that users of H2 Blockers are generally healthy and have similar health characteristics as the general population. We used published estimates from external data sources as follows (2, 39-42): Prevalence of obesity 30.00%, OR for PPI and obesity=1.30, and HR for obesity and death =1.30; prevalence of smoking=24.79%, OR for PPI and smoking =1.20, and HR for smoking and death =2.80; prevalence of anticoagulants, antiplatelet, and NSAIDs use=28.85%, OR for PPI and drug =2.20, and HR for drug and death =1.30. Given the HR between each confounder and risk of death, and assuming there is no overlap in risk among confounders (which is an unlikely assumption, but one which would generate the greatest amount of bias against our hypothesis), we found a total positive bias (or net confounding bias) of 9.66% (1.47%+4.23%+3.96%). The total bias could move a null association between PPI to death from HR=1.00 to HR=1.10 (reflecting the net positive bias of 9.66% rounded up to 10.0%). The association we observed between PPI and death is 1.25 (higher than 1.10), suggesting that it cannot be fully due to bias of unmeasured confounding. (Using the curves in the figures; for obesity, when the HR=1.30, the corresponding bias=1.47%; for smoking, when the HR=2.80, the corresponding bias=4.23%; for anticoagulants, antiplatelet, and NSAIDs, when the HR=1.30, the corresponding bias=3.96%).

Supplemental table 1: Baseline demographic and health characteristics of the overall 2001 cohort of new users of acid suppression therapy, by type of acid suppressant at time of cohort entry, and those who were ever exposed to PPI.

		Overall cohort	New users of H2 Blockers at time of cohort entry	New users of PPI at time of cohort entry	Ever exposed to PPI [a]	P Value [b]
N		396884	208492	188392	293265	
Age (SD)		62.98 (13.05)	61.93 (13.24)	64.14 (12.74)	63.78 (12.81)	<0.001
eGFR in mL/min/1.73m^2 (SD)		74.74 (22.43)	76.24 (22.04)	73.09 (22.73)	73.38 (22.61)	<0.001
Number of outpatient serum creatinine measurements (SD)		3.01 (3.40)	2.95 (3.23)	3.06 (3.58)	4.52 (5.51)	<0.001
Number of hospitalizations (SD)		0.37 (0.96)	0.36 (0.95)	0.38 (0.97)	0.51 (1.30)	<0.001
Race	White (%)	318534 (80.26)	164295 (78.80)	154239 (81.87)	236930 (80.79)	<0.001
	Black (%)	58355 (14.70)	32053 (15.37)	26302 (13.96)	42498 (14.49)	
	Other (%)	19995 (5.04)	12144 (5.82)	7851 (4.17)	13837 (4.72)	
Sex	Male (%)	377769 (95.18)	197685 (94.82)	180084 (95.59)	279023 (95.14)	<0.001
	Female (%)	19115 (4.82)	10807 (5.18)	8308 (4.41)	14242 (4.86)	
Diabetes mellitus (%)		92555 (23.32)	46562 (22.33)	45993 (24.41)	74344 (25.35)	<0.001
Hypertension (%)		231296 (58.28)	119554 (57.34)	111742 (59.31)	184529 (62.92)	<0.001
Chronic lung disease (%)		75810 (19.10)	39270 (18.84)	36540 (19.40)	64254 (21.91)	<0.001
Peripheral artery disease (%)		9141 (2.30)	4646 (2.23)	4495 (2.39)	8751 (2.98)	0.001
Cardiovascular disease (%)		122301 (30.82)	59814 (28.69)	62487 (33.17)	101220 (34.51)	<0.001
Cerebrovascular disease (%)		1529 (0.39)	776 (0.37)	753 (0.40)	1419 (0.48)	0.16
Dementia (%)		12031 (3.03)	6094 (2.92)	5937 (3.15)	10615 (3.62)	<0.001
Hyperlipidemia (%)		152040 (38.31)	78546 (37.67)	73494 (39.01)	130557 (44.52)	<0.001
Hepatitis C (%)		9332 (2.35)	4832 (2.32)	4500 (2.39)	8456 (2.88)	0.14
HIV (%)		209 (0.05)	105 (0.05)	104 (0.06)	183 (0.06)	0.51
Cancer (%)		46451 (11.70)	23312 (11.18)	23139 (12.28)	39473 (13.46)	<0.001
GERD (%)		110217 (27.77)	52586 (25.22)	57631 (30.59)	114132 (38.92)	<0.001
Upper GI tract bleeding (%)		11282 (2.84)	3352 (1.61)	7930 (4.21)	12458 (4.25)	<0.001
Ulcer disease (%)		35189 (8.87)	14152 (6.79)	21037 (11.17)	37472 (12.78)	<0.001

H. Pylori infection (%)	2599 (0.65)	477 (0.23)	2122 (1.13)	3795 (1.29)	<0.001
Barrett's esophagus (%)	0 (0.00)	0 (0.00)	0 (0.00)	245 (0.08)	NA
Achalasia (%)	188 (0.05)	41 (0.02)	147 (0.08)	245 (0.08)	<0.001
Stricture (%)	2218 (0.56)	415 (0.20)	1803 (0.96)	2953 (1.01)	<0.001
Esophageal adenocarcinoma (%)	223 (0.06)	79 (0.04)	147 (0.08)	262 (0.09)	<0.001
Years of follow up (IQR)[c]	5.65 (5.05 – 6.28)	3.35 (1.01 – 5.71)[d]	5.51 (5.01 – 6.08)	5.23 (3.22 – 5.90)	<0.001
Days of having related prescription during follow-up (IQR)	587 (168 – 1423)[e]	188 (90 – 561)[d]	621 (171 – 1496)	579 (172 – 1350)	<0.001
Death (%)	102802 (25.90)	31260 (14.99)[d]	51785 (27.49)	71565 (24.40)	<0.001
Incident death in 100 person years (95% CI)	5.08 (5.05 – 5.11)	4.40 (4.35 – 4.45)[d]	5.56 (5.51 – 5.61)	5.45 (5.41 – 5.49)	<0.001

a. Includes patients exposed to PPI at T0 (n=275977) and during follow-up (n=33136). Variables were measured at time of PPI exposure.
b. P value for difference between exposed to H2 at T0 and exposed to PPI at T0
c. From T0 to first occurrence of death or September 30, 2013
d. Outcome measured from T0 to first occurrence of exposure PPI, death or September 30, 2007
e. Days of having PPI or H2 blockers

Abbreviations: CI, Confidence interval; eGFR, estimated Glomerular Filtration Rate; GERD, Gastroesophageal Reflux Disease; HIV, human immunodeficiency virus; IQR, interquartile range; NA, Not Applicable; SD, Standard deviation

Supplemental table 2: Duration of exposure to PPI and risk of death among new users of PPI in the 2001 cohort (n=101,109)

Duration (Days)	≤ 30	31 - 90	91 - 180	181 - 360	361 - 720
N (%)	15204 (15.04)	20409 (20.19)	17137 (16.95)	21586 (21.35)	26773 (26.48)
Hazard Ratio (95%CI)	1	1.04 (1.01, 1.07)	1.11 (1.08, 1.15)	1.18 (1.15. 1.22)	1.28 (1.24, 1.31)

a. Within people exposure to PPI between 1 to 720 days
b. Model controls for eGFR, age, race, gender, number of serum creatinine measurements, number of hospitalizations, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, cancer, GERD, upper GI tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma
c. Time zero defined as date when the patients last PPI prescription end

Figure 1

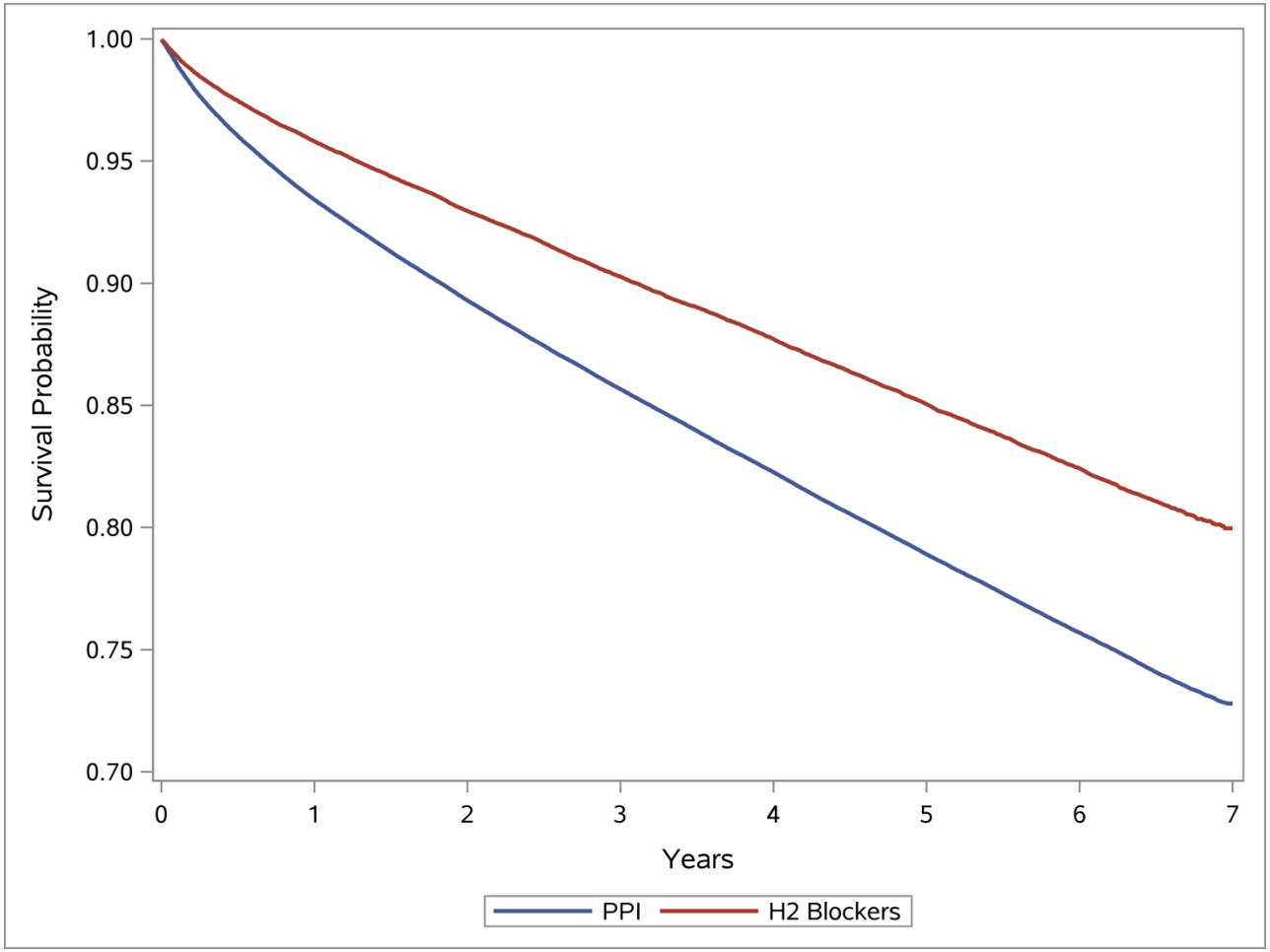
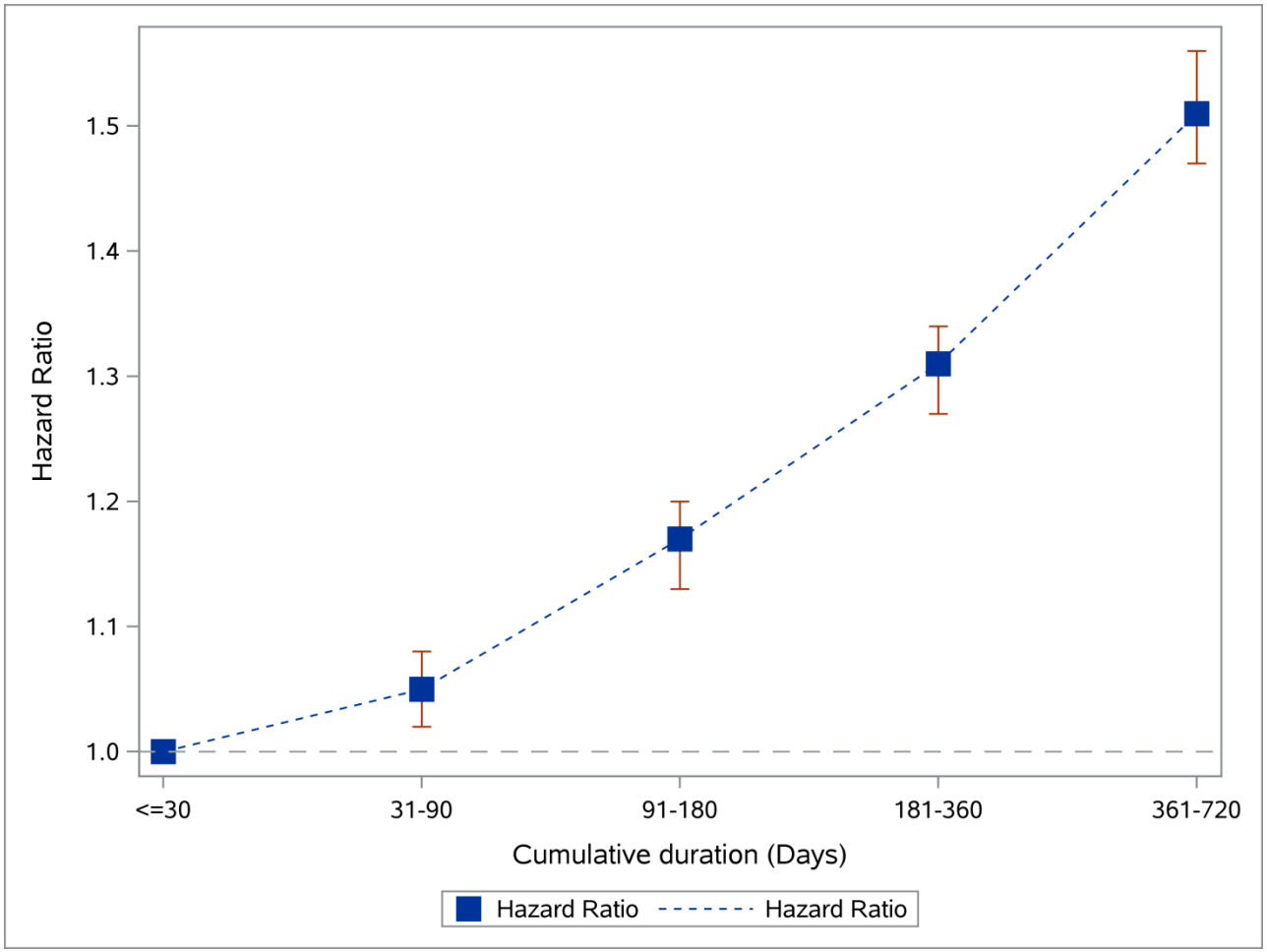
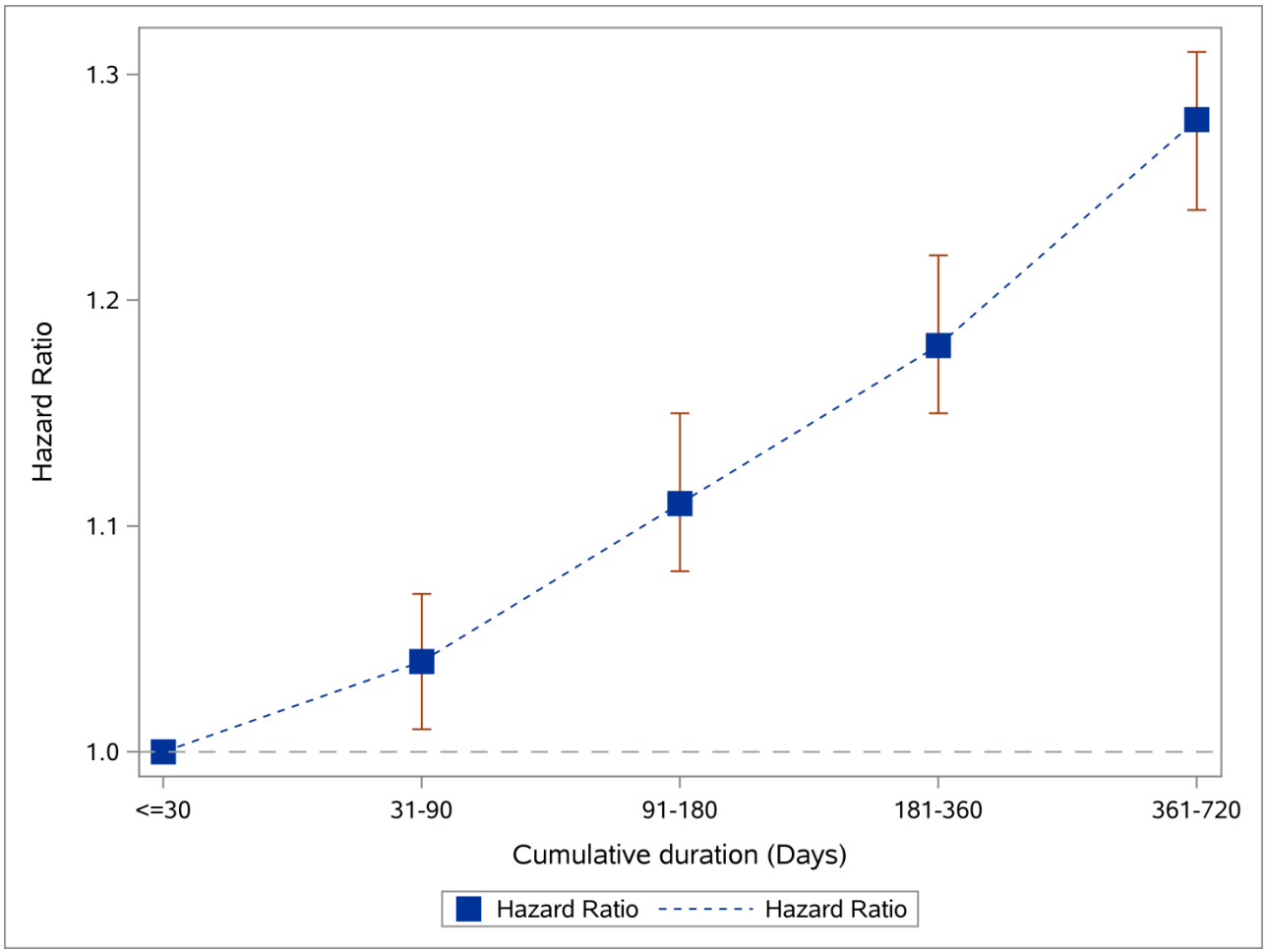

1.00
0.95
0.90
0.85
0.80
0.75
0.70
Survival Probability
0
1
2
3
4
5
6
7
Years
PPI
H2 Blockers

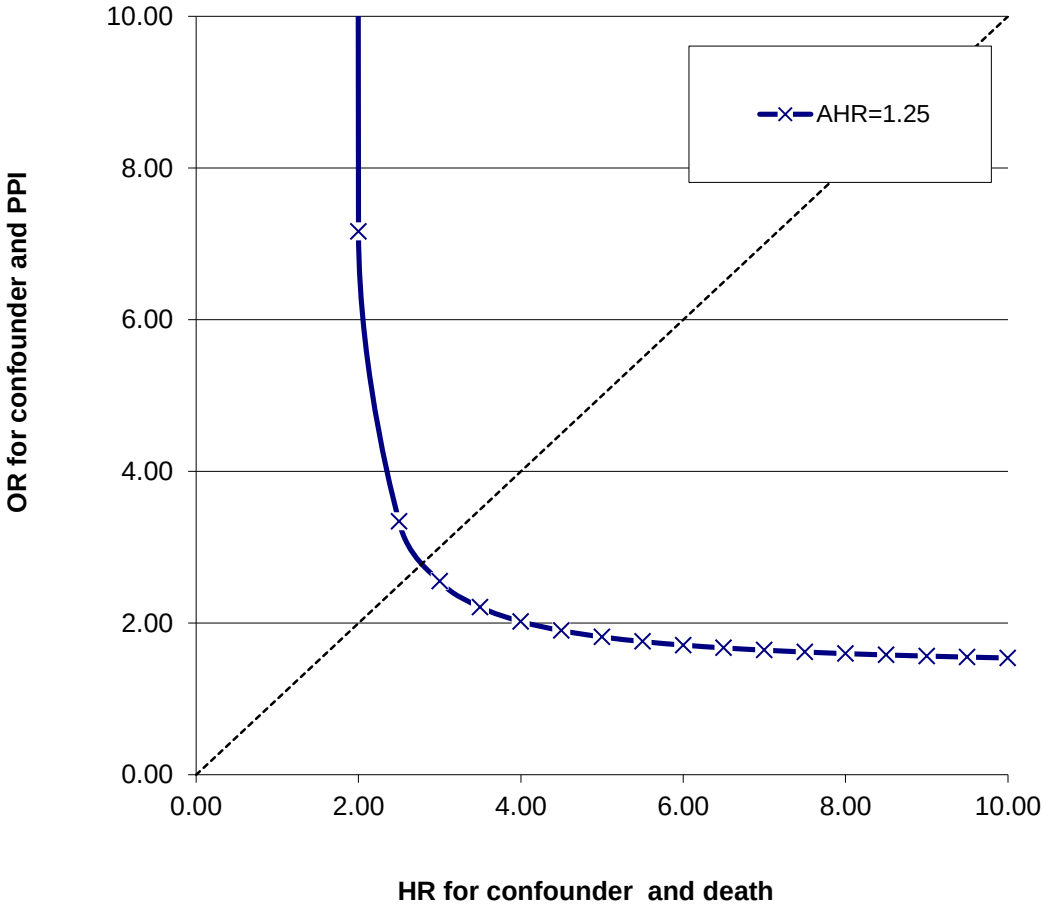
Figure 2


Hazard Ratio
1.5
1.4
1.3
1.2
1.1
1.0
<=30
31-90
91-180
181-360
361-720
Cumulative duration (Days)
Hazard Ratio
Hazard Ratio

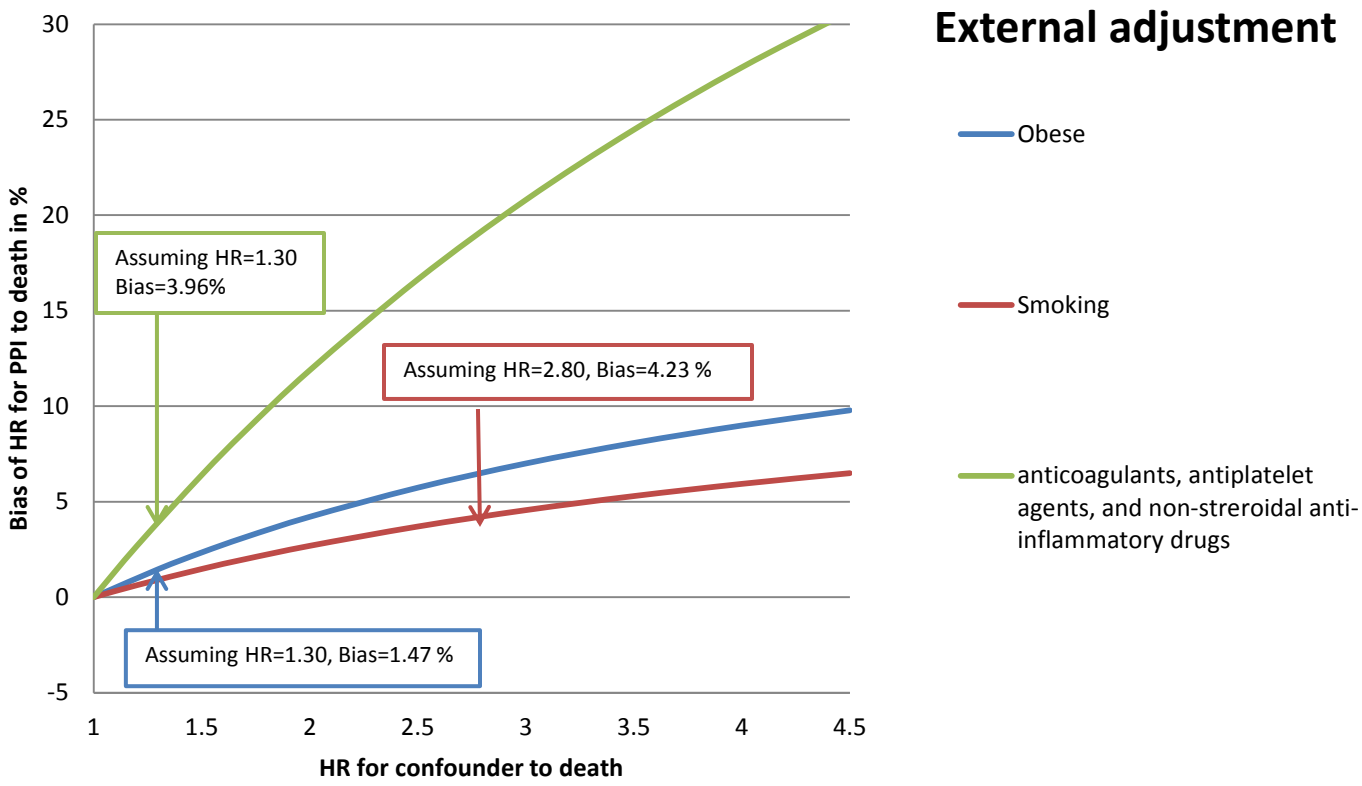
Supplemental Figure 1



Supplemental Figure 2



Supplemental Figure 3



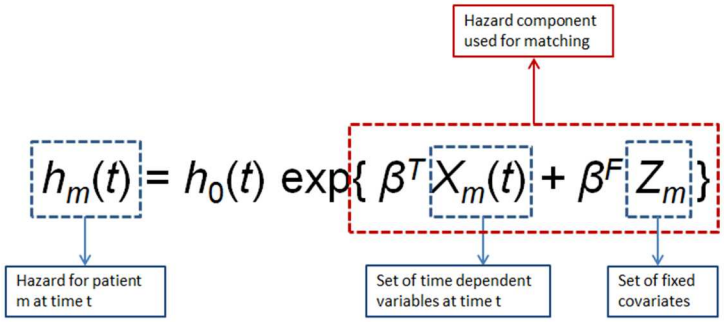
Supplemental Methods:

Time Dependent Propensity Score Matching

1. Using the primary cohort (N=349, 312), all covariates except for age, race and gender were treated as time-dependent variables from T0 till date of PPI use or end of follow up, whichever occurred first. Specifically, time-dependent eGFR indicated the eGFR at day t (where the value was equal to the outpatient eGFR measurement most close and prior to time t); time-dependent number of outpatient serum creatinine measurements and number of hospitalizations indicated the cumulative value from October 01, 1998 till day t; time-dependent disease status including diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, cancer, hepatitis C, HIV, dementia and diseases associated with acid suppression therapy use such as gastroesophageal reflux disease (GERD), upper gastrointestinal (GI) tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma indicated if participants were diagnosed with the disease between October 01, 1998 and day t.

2. Time-dependent Cox regression was applied, where time until receipt of first PPI prescription was the outcome (participants receiving PPI prescription at T0 were considered to have the event with survival time equal to 0 days). Time-dependent variables from step 1 and age, race and gender were used as predictors in the model in order to obtain parameter estimates for the predictors.

3. Every participant's hazard component at day t was computed based on the parameter estimates from step 2 and their covariate values at day t.



The hazard component was used as the time-dependent propensity score.

4. Beginning from T0 (day 0), a 1:1 sequential greedy matching without replacement was conducted. People who received PPI prescription at day t (case group at day t) were matched with people who had not yet received PPI prescription at day t (control group at day t) based on their propensity score at day

t. The order of both case and control groups was randomized before matching. A matched pair was considered successfully matched only if the propensity score difference was less than 0.2 times the standard deviation of the hazard component at time t. If no successful match was made the case in the pair was withdrawn from the further matching while the control was left in the data pool. Matching was ended when 1/ all participants in control or case group were matched or 2/ day t equaled day 1827.

5. After the matching, conditional Cox regressions stratified by matched pairs were conducted to examine the association between PPI and death.

High-dimensional propensity score:

1. Using the primary cohort (N=349,312), participants data from 1 year before T0 till T0 were collected in 5 dimensions consisting off: the first 3 digits of outpatient diagnoses ICD9 codes, the outpatient procedures CPT codes, the first 3 digits of inpatient diagnoses ICD9 codes, the first 3 digits of inpatient procedures ICD9 codes, and the outpatient drug names without dose.

2. Within each of the 5 dimensions, the top 300 most frequent items were selected, which yielded 300*5=1500 potential items.

3. For each participant, we determined if each of the 1500 potential items 1\ ever occurred, 2\ if the number of occurrences for the participant was higher than the number of occurrences in 50% of the participants and 3\ if the number of occurrences for the participant was higher than the number of occurrences in 75% of the participants. This step results in 1500*3=4500 binary potential variables. If the 50% or 75% percentile of the number of item occurrences was less than 1, then the variable were coded as 0 for all participants. If the 50% and 75% percentile of the number of item occurrences had the same value, then the 75% variable was coded as 0 for all participants.

4. Bias was calculated using formula based on apparent relative risk for each of the 4500 variables:

$$Bias=(P\_C1\ (RR\_CD-1)+1)/(P\_C0\ (RR\_CD-1)+1)\ ,\text{if } RR\_CD \geq 1$$

$$Bias=(P\_C1\ (1/RR\_CD-1)+1)/(P\_C0\ (1/RR\_CD-1)+1)\ ,\text{if } RR\_CD < 1$$

Where P_C1 indicates the prevalence of the variable in the PPI group, P_C0 indicates the prevalece of the variable in the control group, and RR_CD indicate relative risk of death associated with the variable.

5. The top 500 variables with the largest | log(bias)| value were selected as binary empirical covariates for inclusion in the propensity score modeling.

6. The 500 variables and age, gender, race, and eGFR were used to obtain propensity scores from logistic regression where the outcome was receipt of PPI or not at T0. Propensity scores were then categorized into deciles.

7. Multivariate Cox regression with an indicator for propensity score decile was used to evaluate the association between PPI and death. Patients in the control group who received PPI later were censored at the time they received PPI.

Two-stage residual inclusion estimation (Instrumental Variable):

1. Based on the primary cohort (N=349,312), for each participant, data on prescriptions by the physician who prescribed the participant the acid suppression therapy at T0 was collected from 6 months before the participant's T0 till T0.

2. For each participant, the percentage of PPIs prescribed to new acid suppression therapy users by their prescribing physician, excluding the prescription of the participant, in the 6 months prior to and including T0 was computed and used as an instrumental variable. Participants whose prescribing physician did not prescribe any other acid suppression therapy to new users in the 6 months prior to and including T0 were excluded from the analysis.

3. In order to predict the participants' possibility of receiving PPI, instrumental variable and co-variables were used in a logistic regression model where the outcome was acid suppression therapy prescription at T0.

4. Residual terms were computed as the difference between participants' real probability (1 if PPI, 0 if H2 blocker) and predicted probability.

5. Multivariate Cox regression, which included the residual term and co-variables, were conducted to evaluate the relationship between PPI and death. Patients in the control group who received PPI later were censored at the time they received PPI.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3-4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Additional matched cohort described in Supplemental methods
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7 and Supplemental methods
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	Due to the feature of VA data on death

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	information, no loss of follow-up would occur. All death data is captured by the Veterans Benefit Administration.
		(*e*) Describe any sensitivity analyses	7-8

Results			**Reported Page**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4-5
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	19-20 Table 1
		(b) Indicate number of participants with missing data for each variable of interest	see page 7 for reason
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	20 Table 1
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	19 Table 1
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	21-22 Table 2
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if	15

		applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Excess Risk of Death among Users of Proton Pump Inhibitors: A longitudinal observational cohort study of United States Veterans

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Excess Risk of Death among Users of Proton Pump Inhibitors: A longitudinal observational cohort study of United States Veterans

Yan Xie MPH[1], Benjamin Bowe MPH[1], Tingting Li MD[1,2], Hong Xian PhD[1,3], Yan Yan MD, PhD[1,4], and Ziyad Al-Aly MD[1,2,5,6]

[1]Clinical Epidemiology Center, Research and Education Service, VA Saint Louis Health Care System, Saint Louis, Missouri

[2]Department of Medicine, Washington University School of Medicine, Saint Louis, Missouri

[3]Department of Biostatistics, College for Public Health and Social Justice, Saint Louis University, Saint Louis, Missouri

[4]Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, Saint Louis, Missouri

[5]Renal Section, Medicine Service, VA Saint Louis Health Care System, Saint Louis, Missouri

[6]Institute for Public Health, Washington University School of Medicine, Saint Louis, Missouri

Running title: PPI and mortality

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Corresponding Author:

Ziyad Al-Aly, M.D.
Clinical Epidemiology Center
VA Saint Louis Health Care System
915 North Grand Boulevard, 151-JC
Saint Louis, MO 63106
Telephone: (314) 289-6333
E-mail: zalaly@gmail.com

Abstract:

Objective: Proton pump inhibitors (PPI) are widely used; and their use is associated with increased risk of adverse events. However, whether PPI use is associated with excess risk of death is unknown. We aimed to examine the association between PPI use and risk of all-cause mortality.

Design: Longitudinal observational cohort study

Setting: US Department of Veterans Affairs

Participants: Primary cohort of new users of PPI or Histamine H2 receptor antagonists (H2 blockers) (N=349,312); additional cohorts included PPI versus no PPI (N=3,288,092), and PPI versus no PPI and no H2 blockers (N=2,887,030).

Main outcome measures: Risk of death.

Results: Over a median follow-up of 5.71 years (IQR: 5.11-6.37), PPI use was associated with increased risk of death compared to H2 blockers use (HR=1.25; CI=1.23-1.28). Risk of death associated with PPI use was higher in analyses adjusted for high-dimensional propensity score (HR=1.16; CI=1.13-1.18); two-stage residual inclusion estimation (HR=1.21; CI=1.16-1.26); and in 1:1 time-dependent propensity score matched cohort (HR=1.34 CI=1.29-1.39). The risk of death was increased when considering PPI use versus no PPI (HR=1.15; CI=1.14-1.15), and PPI use versus no PPI and no H2 blockers (HR= 1.23; CI=1.22-1.24). Risk of death associated with PPI use was increased among participants without gastrointestinal conditions: PPI versus H2 blockers (HR=1.24; CI=1.21-1.27); PPI use versus no PPI (HR=1.19; CI=1.18-1.20); and PPI use versus no PPI and no H2 blockers (HR=1.22; CI=1.21-1.23). Among new PPI users, there was a graded association between duration of exposure and risk of death.

Conclusions: The results suggest excess risk of death among PPI users; risk is also increased among those without gastrointestinal conditions and with prolonged duration of use. Limiting PPI use and duration to instances where it is medically indicated may be warranted.

Strength and limitations:

- National large scale data from a network of integrated health systems
- Employed a new user design and developed a number of analytical approaches where we consistently found a significant association between PPI exposure and risk of death.
- Cohort included mostly older white male US Veterans which may limit the generalizability.
- Did not include information on the cause of death.

Introduction:

Proton pump inhibitors (PPI) are widely prescribed and are also available for sale over the counter without prescription in several countries(1, 2). Several observational studies suggest that PPI use is associated with increased risk of a number of adverse health outcomes(1). A number of studies have shown that PPI use is associated with significant risk of acute interstitial nephritis(3-5). Recent studies established an association between exposure to PPI and risk of chronic kidney disease (CKD), kidney disease progression, and end stage renal disease (ESRD)(2, 6, 7). Results from a large prospective observational German cohort suggest that patients receiving PPI had a higher risk of incident dementia(8). Several reports highlighted a rare but potentially fatal risk of hypomagnesemia among users of PPI(9-11). PPI use has been associated with increased risk of both incident and recurrent Clostridium difficile infections(12). Several observational analyses have shown that PPI use was also associated with increased risk of osteoporotic fractures including hip and spine fractures(13, 14). Less convincing -and to some extent inconsistent- evidence suggests a relationship between PPI use and risks of community acquired pneumonia and cardiovascular events(15-17). Emerging -and far from conclusive- *in vitro* evidence suggests that PPI results in inhibition of lysosomal acidification and impairment of proteostasis leading to increased oxidative stress, endothelial dysfunction, telomere shortening and accelerated senescence in human endothelial cells(18). The experimental work provides a putative mechanistic link to explain some of the adverse events associated with PPI use(18).

The adverse outcomes associated with PPI use are serious and each is independently associated with higher risk of mortality. Evidence from several small cohort studies of older adults who were recently discharged from the hospital, or institutionalized in long term care facilities suggests inconsistently that PPI use may be associated with increased risk of 1-year mortality(19-22). Whether PPI use is associated with excess risk of

death is not known and has not been examined in large epidemiologic studies spanning a sufficiently long duration of follow up. We hypothesized that owing to the consistently observed associations between PPI use and risk of adverse health outcomes, PPI use is associated with excess risk of death, and that the risk of death would be more pronounced with increased duration of use. We therefore used the Department of Veterans Affairs national databases to build a longitudinal cohort of incident users of acid suppression therapy including PPI and Histamine H2 receptor antagonists (H2 blockers) to examine the association between PPI use and risk of all-cause mortality, and to determine whether risk of death is increased with prolonged duration of use.

Methods:

Cohort participants:

Primary cohort:

Using administrative data from the United States Department of Veterans Affairs (VA), we identified patients who received an outpatient H2 blockers or PPI prescription between October 01, 2006 and September 30, 2008 (n=1,762,908). In order to select new users of acid suppression therapy (incident user design), we excluded 1,356,948 patients who received any outpatient H2 blockers or PPI prescriptions between October 01, 1998 and September 30, 2006. To account for patients' kidney function, only patients with at least one outpatient serum creatinine value before first acid suppression therapy prescription were selected in the cohort, yielding an analytic cohort of 349,312 patients. Patients whose first acid suppression therapy was PPI (n=275,977) were considered to be in the PPI group during follow-up. Patients who received H2 blockers as their first acid suppression therapy (n=73,335) served as the reference group before they received any PPI prescription. (Supplemental figure 1) Within the reference group, those who received a PPI prescription later (n=33,136) were considered to be in the PPI group from the date of their first PPI prescription until the end of follow-up(23). Time zero (T0) for primary cohort was defined as first acid suppression therapy prescription date.

Secondary cohorts:

We additionally built two secondary cohorts to examine the association of PPI use and risk of death in a) PPI versus no PPI users, and b) PPI versus non users of acid suppression therapy. Patients with no PPI prescription between October 01, 1998 and September 30, 2006, and with at least one outpatient eGFR value

before October 01, 2006 were selected to evaluate the risk of death associated with PPI use versus no PPI use (n=3,288,092) (Supplemental figure 2a). Patients with no PPI prescription between October 01, 1998 and September 30, 2006, with no H2 blockers before first PPI prescription and at least one outpatient eGFR value before October 01, 2006 were selected to evaluate the risk of death associated with PPI use versus no acid suppression therapy (n=2,887,030) (Supplemental figure 2b). T0 for secondary cohorts was defined as October 01, 2006.

Patients in both primary and secondary cohorts were followed until September 30, 2013 or death. The study was approved by the Institutional Review Board of the VA Saint Louis Health Care System, Saint Louis, MO.

Data Sources:

We used the Department of Veterans Affairs databases including inpatient and outpatient medical SAS datasets (that include utilization data related to all inpatient and outpatient encounters within the VA system) to ascertain detailed patient demographic characteristics and comorbidity information based on inpatient and outpatient encounters(2, 24). The VA Managerial Cost Accounting System Laboratory Results (a comprehensive database that includes VA-wide results for selected laboratory tests obtained in the clinical setting) provided information on outpatient and inpatient laboratory results. The VA Corporate Data Warehouse Production Outpatient Pharmacy domain provided information on outpatient prescriptions. The VA Vital Status and Beneficiary Identification Records Locator Subsystem (BIRLS) files provided demographic characteristics and death.

Primary Predictor Variable: PPI use was the primary predictor. Once cohort participants received PPI prescription, they were considered with effect of PPI until the end of follow up. Medications that contain esomeprazole, lansoprazole, omeprazole, pantoprazole or rabeprazole were counted as PPI. Medications including ranitidine, cimetidine, and famotidine were counted as H2 blockers.

Outcome: The primary outcome in survival analyses was time to death. Death information is routinely collected by the Veterans Benefit Administration for all United States Veterans.

Covariates:

Covariates included age, race, gender, eGFR, number of outpatient serum creatinine measurements, number of hospitalizations, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, cancer, hepatitis C, HIV, dementia and diseases associated with acid suppression therapy use such as gastroesophageal reflux disease (GERD), upper gastrointestinal (GI) tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma(25-28). eGFR was calculated using the abbreviated four-variable Chronic Kidney Disease Epidemiology Collaboration equation based on age, sex, race, and outpatient serum creatinine(29). Race/ethnicity was categorized as white, black, or other (Latino, Asian, Native American, or other racial/ethnic minority groups). Comorbidities except for hepatitis C and HIV were assigned on the basis of relevant ICD-9-CM diagnostic and procedures codes and CPT codes in the VA Medical SAS datasets(2, 30-33). Hepatitis C and HIV were assigned based on laboratory results.

Baseline covariates were ascertained from October 01, 1998 till T0. All covariates except for age, race and gender covariates values were treated as time-varying covariates where they were additionally assessed until date of first PPI prescription in those patients who did not have PPI prescription at T0. Any comorbidity occurring during the assessment period was considered present during the remaining follow-up. eGFR was the outpatient eGFR value within and most proximate to the end of the assessment period. Number of outpatient serum creatinine measurements and number of hospitalizations were accumulated during the assessment period.

Statistical Analysis:

Means, standard deviations and t-tests are presented for normally distributed continuous variables; medians, interquartile ranges and Wilcoxon-Mann-Whitney tests are presented for non-normally distributed continuous variables; counts, percentages and Chi-square tests are presented for categorical variables. Incident rates per 100 person-years were computed for death and confidence intervals were estimated based on the normal distribution. Simon and Makuch method for survival curves was used for time-dependent covariates(34).

Cox regression models with time-dependent covariates were used in the assessment of the association between PPI exposure and risk of death where patients could switch from H2 blockers to PPI in the models. In order to account for potential delayed effect of PPI, patients were considered to have the effect of PPI from the first PPI prescription till end of follow up. In addition, time dependent Cox models were conducted in subgroups where patients had no GI conditions, and where patients had no GI conditions except for GERD.

Because exposure in this observational cohort is time-dependent, we undertook 1:1 propensity score matching for the primary cohort where time-dependent propensity scores were calculated based on time-dependent Cox regression with all covariates(35)(details are provided in supplemental methods). After matching, all covariates except for age had an absolute standardized difference of less than 0.1, which indicated all covariates except for age were well balanced. Age had a standardized difference equal to 0.13. Doubly robust estimation was applied after matching, where all covariates were additionally controlled for in the model, to obtain an unbiased effect estimator(36).

In order to optimize control of confounding, we additionally built high-dimensional propensity score adjusted survival models following the multistep algorithm described by Schneeweiss et al(37)(details are provided in supplemental methods). We also applied two-stage residual inclusion estimation based on instrumental variable approach (Supplemental methods)(38).

In addition, we evaluated the association between duration of PPI prescription and risk of death among new users of PPI. Duration was defined in cumulative days of use and categorized as ≤30, 31-90, 91-180, 181-360, 361-720, where ≤30 days considered as the reference group. To avoid immortal time bias (by definition, cohort participants must be alive to receive prescription hence introducing a bias commonly referred to as immortal time bias), time of cohort entry was defined as the date of last PPI prescription plus days' supply (39, 40). In order to ensure sufficient length of follow up time following T0, we excluded cohort participants with cumulative duration of exposure exceeding 720 days (because of limited overall cohort timeline, and because T0 starts at the end of last prescription, those with long exposure will necessarily have limited follow up time). In

regression analyses, a 95% confidence interval (CI) of a hazard ratio (HR) that does not include unity was considered statistically significant. All analyses were performed using SAS Enterprise Guide version 7.1.

Sensitivity Analysis:

In order to further evaluate the consistency and robustness of study findings, we examined the observed associations in a less contemporary cohort (dating back to an era where PPI prescription and use were far less frequent) of patients without acid suppression therapy prescriptions between October 01, 1998 and September 30, 2000 (washout period) and with acid suppression therapy prescription between October 01, 2000 and September 30, 2002 and at least one outpatient serum creatinine value before that. Patients in this cohort were followed till September 30, 2007 or death. To examine the impact of potential residual confounding on study results, we conducted additional sensitivity analyses as described by Schneeweiss(41): a) we used the rule-out approach to identify the strength of the residual confounding that could fully explain the association observed in primary analyses; and b) applied an external adjustment approach using external information (prevalence and risk estimates from published literature) to evaluate potential net confounding bias due to unmeasured confounders(2, 41-44). Methods are described elegantly by Schneeweiss(41). In addition, to remove death events that were less likely to be related to PPI exposure, we excluded cohort participants who died within 90 days after first PPI or H2 blockers prescription.

We conducted additional sensitivity analyses which included hemoglobin as a covariate in cohort participants with available data. We also undertook analyses which stratified the cohort based on cardiovascular disease, history of pneumonia, chronic kidney disease (eGFR<60 and ≥60 mL/min/1.73m^2) or age (<65 and ≥65 years old) at T0. Finally, and in order to ascertain the specificity of the findings, we examined the association between PPI exposure and the risk of a motor vehicle accident as a tracer outcome where a priori knowledge suggests an association is not likely to exist.

Patient involvement:

No patients were involved in developing the hypothesis, the specific aims, or the research questions, nor were they involved in developing plans for design or implementation of the study. No patients were involved in the

interpretation of study results, or write up of the manuscript. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results:

The demographic and health characteristics of the overall primary cohort of new users of acid suppression therapy (n=349,312), by type of acid suppressant drug at time of cohort entry (H2 blockers n=73,335; PPI n=275,977), and those who were ever exposed to PPI (n=309,113) are provided in table 1. There were significant baseline differences in that cohort participants who were treated with PPI were older, and were more likely to have comorbid conditions including diabetes, hypertension, cardiovascular disease, and hyperlipidemia. Cohort participants treated with PPI were also more likely to have upper gastrointestinal tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma (table 1). Survival curves for PPI and H2 blockers were presented in figure 1.

Association between PPI use and risk of death:

Among new users of acid suppression therapy (N=349,312), and over a median follow up of 5.71 years (IQR: 5.11 – 6.37), where exposure was treated as time-dependent covariate; PPI use was associated with increased risk of death compared to H2 blockers use (HR=1.25; CI=1.23-1.28) (table 2). Among new users of acid suppression therapy (N=349,312); in high-dimensional propensity score adjusted models, new PPI users had increased risk of death compared to new users of H2 blockers (HR=1.16; CI=1.13-1.18); based on two-stage residual inclusion estimation, risk of death was higher in new users PPI when compared to new users of H2 blockers (HR=1.21; CI=1.16-1.26). In a 1:1 time-dependent propensity score matched cohort of new users of PPI and H2 blockers (N=146,670), PPI users had significantly increased risk of death (HR=1.34; CI=1.29-1.39).

We examined the relationship of PPI and risk of death in secondary cohorts (as described in methods) where we considered risk associated with PPI use versus no known exposure to PPI (no PPI use +/- H2 blockers use) (N=3,288,092); the results suggest that PPI use was associated with increased risk of death (HR=1.15; CI=1.14-1.15) (table 2). Assessment of risk of death associated with PPI use versus no known exposure to any

acid suppression therapy (no PPI use and no H2 blockers use) (N=2,887,070), suggests increased risk of death with PPI use (HR= 1.23; CI=1.22-1.24).

Association between PPI use and risk of death in those without gastrointestinal conditions:

We then analyzed the association between PPI use and the risk of death in cohort where we excluded participants with documented medical conditions generally considered as indications for treatment with PPI including GERD, upper gastrointestinal tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma. The intent of this analysis was to examine the putative association of PPI use and risk of death in a lower risk cohort. Examination of risk of death associated with use of acid suppression therapy (PPI vs. H2 blockers) suggests that risk of death was increased with PPI use (HR=1.24; CI=1.21-1.27) (table 2). Examination of the risk of death associated with PPI use versus no known exposure to PPI (no PPI use +/- H2 blockers use) suggests a higher risk of death associated with PPI use (HR=1.19; CI=1.18, 1.20). Results were consistent where we examined risk of death associated with PPI use versus no known exposure to any acid suppression therapy (no PPI use and no H2 blockers use) (HR=1.22; CI=1.21-1.23). Risk of death associated with PPI use in cohort participants without GI conditions but included participants with GERD yielded consistent results (PPI vs H2 blockers (HR=1.24; CI=1.21-1.27); PPI vs no PPI (HR=1.14; CI=1.13-1.14); PPI vs no PPI and no H2 blockers (HR=1.22; CI=1.21-1.22) (table 2).

Duration of exposure and excess risk of death:

We examined the association between duration of PPI exposure and risk of death among new users of PPI (n=166,098). Compared to those exposed for ≤30 days, there was a graded association between duration of exposure and risk of death among those exposed for 31-90, 91-180, 181-360, and 361-720 days (table 3, figure 2).

Sensitivity analyses:

We tested the robustness of study results in sensitivity analyses where we built a less contemporary cohort as described in methods; demographic and health characteristics of this cohort are provided in supplemental table

1. Where exposure was treated as time-dependent, PPI use was associated with increased risk of death compared to H2 blockers use (HR=1.17; CI=1.15-1.19). In a 1:1 time-dependent propensity score matched cohort of PPI and H2 blockers, PPI users had significantly increased risk of death HR=1.21 (1.19-1.24). Furthermore, we also observed a graded association between cumulative duration of exposure to PPI and risk of death (supplemental table 2, supplemental figure 3).

To examine the potential impact of residual confounding on study results, we used rule-out and external adjustment approaches as described by Schneeweiss(41). Using the rule-out approach, we characterized a set of parameters (OR for relationship of PPI and confounder), and (HR for relationship of confounder and death) with sufficient strength to fully explain the association observed in primary analyses (supplemental figure 4). For example, if the confounder was twice as likely among PPI users (OR=2), and the HR of death associated with the uncontrolled confounder exceeded 4.0, then the uncontrolled confounder would fully explain the observed association between PPI and death (supplemental figure 4). Given that our analyses accounted for most known strong independent risk factors of death, and employed an active comparator group; to cancel the results, any uncontrolled confounder of the required prevalence (OR=2 or more in the example above), and strength (HR=4 or more in the example above) would also have to be independent of the confounders already adjusted for and is unlikely to exist; thus the results cannot be fully explained by this putative uncontrolled confounder.

External adjustment to estimate the impact of 3 unmeasured confounders including obesity, smoking, and use of therapeutics including anticoagulants, antiplatelet agents, and non-steroidal anti-inflammatory drugs shows a net confounding bias of 9.66% (supplemental figure 5). The total bias could move a null association between PPI and death from HR=1.00 to HR=1.10 (reflecting the net positive bias of 9.66% rounded up to 10.0%). The association we observed between PPI and death was 1.25>1.10, which cannot be fully due to bias of unmeasured confounding.

The association between PPI and death remained significant after excluding cohort participants who died within 90 days after first PPI or H2 blockers prescription (HR=1.23; CI=1.20, 1.26), or additionally controlling for

hemoglobin levels (HR=1.25; CI=1.23, 1.28). In models stratified for the presence of cardiovascular disease, history of pneumonia, chronic kidney disease, and age at T0; there was increased risk of death associated with PPI use in those with and without cardiovascular disease (HR=1.19; CI=1.15, 1.23, and HR=1.30; CI=1.27, 1.34; respectively); with and without history of pneumonia (HR=1.39; CI=1.32, 1.45, and HR=1.21; CI=1.18, 1.24; respectively); with and without chronic kidney disease (HR=1.18; CI=1.14, 1.22, and HR=1.29; CI=1.26, 1.33; respectively); and above and below age 65 (HR=1.17; CI=1.13, 1.20, and HR=1.44; CI=1.39, 1.50; respectively). As a test of specificity, among users of acid suppression therapy, PPI use was not associated with increased risk of the tracer outcome of a motor vehicle accident (HR=0.99; CI= 0.89, 1.10).

Discussion:

This study provides insights into the excess risk of death associated with PPI use. In a large primary cohort of new users of acid suppression therapy followed for a median of 5.71 years, we show a significant association between PPI use and risk of all-cause mortality, risk was increased among those with no documented medical indications for PPI use, and with prolonged duration of use. The results were consistent in multiple analyses and robust to changes in epidemiologic design and statistical specifications, and were reproduced in an earlier and less contemporary cohort from an era where PPI use was far less frequent (45).

PPI are widely used by millions of people for indications and durations that were never tested or approved; they are available over the counter (without prescription) in several countries, and generally perceived as safe class of therapeutics; they are often overprescribed, rarely deprescribed, frequently started inappropriately during a hospital stay, and their use extended for long term duration without appropriate medical indication (46-50). Results of nationally representative data from the National Health and Nutrition Examination Survey, where analyses were weighted to represent the US adult population, showed that the use of prescription PPI increased from 3.9% to 7.8% from 1999-2000 to 2011-2012, representing a doubling of prevalence ratio(45). Studies estimate that between 53% and 69% of PPI prescriptions are for inappropriate indications(46, 51) where benefits of PPI use may not justify the risks for many users(51-53). The findings in our study highlight a potential excess risk of death among users of PPI, and in particular among cohort participants without GI comorbidities, and that risk is increased with prolonged duration of PPI exposure. While our results should not

deter prescription and use of PPI where medically indicated, they may be used to encourage and promote pharmacovigilance and emphasize the need to exercise judicious use of PPI and limit use and duration of therapy to instances where there is a clear medical indication and where benefit outweighs potential risk(1). Standardized guidelines for initiating PPI prescription may lead to reduced overuse(54), regular review of prescription and over the counter medications, and deprescription where a medical indication for PPI treatment ceases to exist may be a meritorious approach(52).

The biologic mechanism underpinning the association of PPI use and risk of death is not clear. Experimental evidence in rats suggests that PPI administration limits the regenerative capacity of livers following partial hepatectomy(55). Administration of PPI upregulates expression of mRNA, protein level, and results in increased activity of the heme oxygenase-1 enzyme in gastric and endothelial cells(56). Heme oxygenase-1 is generally seen as salutary, but its beneficial properties are vitiated at higher doses, and with sustained duration of expression(57). PPI treatment impairs lysosomal acidification and proteostasis and results in increased oxidative stress, dysfunction, telomere shortening and accelerated senescence of human endothelial cells(18, 58). Wu and collaborators undertook a systematic toxicity mechanism analysis using a high-throughput in-silico analysis of microarray data; they reported that PPI up-regulated genes in the cellular retinol metabolism pathway, and down-regulated genes in the complement and coagulation cascades pathway and that PPI may block pathways of antigen presentation, and abrogate the synthesis and secretion of cytokines and complement component proteins and coagulation factors(58, 59). How the changes in gene expression contribute to excess risk of death is not yet entirely clear. The plausible clinical course leading to heightened risk of death is likely mediated by the occurrence of one or more of the adverse events associated with PPI use (kidney disease, dementia, hypomagnesemia, Clostridium difficile infection, osteoporotic fracture, etc…). Further studies are needed to characterize the biologic mechanisms that might explain the epidemiologic findings in this report.

The constellation of findings in this report must be interpreted with the full cognizance of the observational study design where confounding by indication, and selection bias may represent limitations; we employed an analytic strategy to evaluate the risk of death among users of acid suppression therapy (PPI and H2 blockers);

a class of therapeutics generally prescribed for similar indications, a strategy which may lessen but does not completely eliminate the possibility of confounding by indication bias. We additionally built time-dependent propensity score matched cohort, high dimensional propensity score adjusted models, and employed the use of instrumental variable to reduce potential confounding bias. Although we accounted for known covariates in our analyses, it is possible that there are residual confounders (either unmeasured, or unknown) that may still confound the association of PPI and risk of death. However, we evaluated the impact of residual confounding in quantitative bias analyses, and the results suggest that even with the application of unlikely (and exaggerated) set of assumptions, the risk cannot be fully explained by residual confounding. In our analyses, we defined drug exposure as having a prescription for it; since PPI (and H2 blockers) are available over the counter in the United States, it is possible that some patients in this cohort may have obtained and used PPI without prescription. However, owing to financial considerations, this is not highly likely, and if it occurred in some patients, it will have biased the results against the primary hypothesis and resulted in underestimation of risk. The cohort included mostly older white male US Veterans which may limit the generalizability of study results to a broader population. Our datasets did not include information on the cause of death. The study has a number of strengths including the use of national large scale data from a network of integrated health systems which was captured during routine medical care which minimizes selection bias. We employed a new user (incident user) approach, and evaluated the association between PPI use and risk of death using a number of analytical approaches where we consistently found a significant association between PPI use and increased risk of death. The consistency of study findings in our report, and the growing body of evidence in the literature showing a host of adverse events associated with PPI use are compelling, and because of the high prevalence of PPI use, may have public health implications. Exercising pharmacovigilance and limiting PPI use to instances and durations to instances where it is medically indicated may be warranted.

Footnotes

Contributors: Research area and study design: YX, BB, TL, HX, YY, ZAA; data acquisition: YX, BB; data analysis and interpretation: YX, BB, TL, HX, YY, ZAA; statistical analysis: YX, BB; supervision and mentorship: ZAA. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. ZAA takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This research project was reviewed and approved by the Institutional Review Board of the VA Saint Louis Health Care System.

Data sharing: Data is available through the United States Department of Veterans Affairs.

Transparency: The lead authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Table 1: Baseline demographic and health characteristics of overall primary cohort of new users of acid suppression therapy, by type of acid suppressant at time of cohort entry, and those who were ever exposed to PPI.

		Overall cohort	New users of H2 Blockers at time of cohort entry	New users of PPI at time of cohort entry	Ever exposed to PPI [a]	P Value [b]
N		349312	73335	275977	309113	
Age (SD)		61.00 (14.92)	58.48 (15.13)	61.67 (14.79)	61.37 (14.77)	<0.001
eGFR in mL/min/1.73m^2 (SD)		76.89 (22.66)	79.64 (21.96)	76.16 (22.79)	76.60 (22.79)	<0.001
Number of outpatient serum creatinine measurements (SD)		6.85 (7.55)	6.67 (7.39)	6.89 (7.59)	7.27 (8.00)	<0.001
Number of hospitalizations (SD)		0.51 (1.39)	0.52 (1.45)	0.51 (1.37)	0.56 (1.49)	0.014
Race	White (%)	275473 (78.86)	56530 (77.08)	218943 (79.33)	244230 (79.01)	<0.001
	Black (%)	59243 (16.96)	13229 (18.04)	46014 (16.67)	52207 (16.89)	
	Other (%)	14596 (4.18)	3576 (4.88)	11020 (3.99)	12676 (4.10)	
Sex	Male (%)	326659 (93.51)	67748 (92.38)	258911 (93.82)	289233 (93.57)	<0.001
	Female (%)	22653 (6.49)	5587 (7.62)	17066 (6.18)	19880 (6.43)	
Diabetes mellitus (%)		90273 (25.84)	16758 (22.85)	73515 (26.64)	82168 (26.58)	<0.001
Hypertension (%)		225899 (64.67)	44502 (60.68)	181397 (65.73)	203700 (65.90)	<0.001
Chronic lung disease (%)		70281 (20.12)	13849 (18.88)	56432 (20.45)	64777 (20.96)	<0.001
Peripheral artery disease (%)		11439 (3.27)	2225 (3.03)	9214 (3.34)	10680 (3.46)	<0.001
Cardiovascular disease (%)		98137 (28.09)	17436 (23.78)	80701 (29.24)	89878 (29.08)	<0.001
Cerebrovascular disease (%)		1858 (0.53)	372 (0.51)	1486 (0.54)	1719 (0.56)	0.30
Dementia (%)		16421(4.70)	3115 (4.25)	13306 (4.82)	15384 (4.98)	<0.001
Hyperlipidemia (%)		200397 (57.37)	39818 (54.30)	160579 (58.19)	181524 (58.72)	<0.001
Hepatitis C (%)		5034 (1.44)	1184 (1.61)	3850 (1.40)	4444 (1.44)	<0.001
HIV (%)		114 (0.03)	38 (0.05)	76 (0.03)	113 (0.04)	0.001
Cancer (%)		49666 (14.22)	9123 (12.44)	40543 (14.69)	45633 (14.76)	<0.001
GERD (%)		100980 (28.91)	20562 (28.04)	80418 (29.14)	94517 (30.58)	<0.001
Upper GI tract bleeding (%)		9310 (2.67)	926 (1.26)	8384 (3.04)	9098 (2.94)	<0.001
Ulcer disease (%)		25626 (7.34)	3564 (4.86)	22062 (7.99)	24864 (8.04)	<0.001
H. Pylori infection (%)		3078 (0.88)	141 (0.19)	2937 (1.06)	3239 (1.05)	<0.001
Barrett's esophagus (%)		2324 (0.67)	89 (0.12)	2235 (0.81)	2382 (0.77)	<0.001
Achalasia (%)		151 (0.04)	10 (0.01)	141 (0.05)	154 (0.05)	<0.001
Stricture (%)		1992 (0.57)	132 (0.18)	1860 (0.67)	2051 (0.66)	<0.001
Esophageal		213 (0.06)	17 (0.02)	196 (0.07)	213 (0.07)	<0.001

adenocarcinoma (%)					
Years of follow up (IQR)[c]	5.71 (5.11 – 6.37)	4.38 (1.16 – 5.92)d	5.67 (5.09 – 6.34)	5.59 (4.82 – 6.28)	<0.001
Days of having related prescription during follow-up (IQR)	442 (199 – 1272)[e]	120 (60 – 400) [d]	450 (120 – 1299)	450 (120 – 1266)	<0.001
Death (%)	81463 (23.32)	9018 (12.30) [d]	67450 (24.44)	72445 (23.44)	<0.001
Incident death in 100 person years (95% CI)	4.47 (4.44 – 4.50)	3.32 (3.25 – 3.39) [d]	4.74 (4.70 – 4.77)	4.67 (4.64 – 4.71)	<0.001

a. Includes patients exposed to PPI at T0 (n=275977) and during follow-up (n=33136). Variables were measured at time of PPI exposure.
b. P value for difference between exposed to H2 at T0 and exposed to PPI at T0
c. From T0 to first occurrence of death or September 30, 2013
d. Outcome measured from T0 to first occurrence of exposure PPI, death or September 30, 2007
e. Days of having PPI or H2 blockers

Abbreviations: CI, Confidence interval; eGFR, estimated Glomerular Filtration Rate; GERD, Gastroesophageal Reflux Disease; HIV, human immunodeficiency virus; IQR, interquartile range; SD, Standard deviation

Table 2: Association between PPI use and risk of death:

Association Between PPI and Death		Reference	PPI use
PPI use VS H2 blockers use (N=349,312)	Incident rate (95% CI)	3.32 (3.25 – 3.39)	4.67 (4.64 – 4.71)
	Unadjusted HR (95% CI)	1	1.46 (1.43 – 1.49)
	Adjusted HR (95% CI)	1	1.25 (1.23 – 1.28)
High-dimensional propensity score adjusted model of new users of PPI VS H2 blockers (N=349,312)	Incident rate (95% CI)	3.32 (3.25 – 3.39)	4.74 (4.70, 4.77)
	HR (95% CI)	1	1.16 (1.13 – 1.18)
Two-stage residual inclusion estimation model of new users of PPI VS H2 blockers (N=318,960)	Incident rate (95% CI)	3.32 (3.25 – 3.39)	4.74 (4.70 – 4.77)
	HR (95% CI)	1	1.21 (1.16 – 1.26)
Time dependent propensity score matched PPI VS H2 blockers (N=146,670)	Incident rate (95% CI)	3.32 (3.25 – 3.39)	4.37 (4.30 – 4.44)
	Unadjusted HR (95% CI)	1	1.38 (1.34 – 1.42)
	Adjusted HR (95% CI)	1	1.34 (1.29 – 1.39)
PPI use VS no PPI (N=3,288,092)	Incident rate (95% CI)	3.64 (3.63 – 3.65)	5.50 (5.47 – 5.53)
	Unadjusted HR (95% CI)	1	1.47 (1.46 – 1.48)
	Adjusted HR (95% CI)	1	1.15 (1.14 – 1.15)
PPI use VS no PPI or H2 blockers (N=2,886,879)	Incident rate (95% CI)	3.47 (3.46 – 3.48)	5.50 (5.47 – 5.53)
	Unadjusted HR (95% CI)	1	1.53 (1.52 – 1.54)
	Adjusted HR (95% CI)	1	1.23 (1.22 – 1.24)
PPI VS H2 blockers in a cohort without GI conditions (N=214,521)	Incident rate (95% CI)	3.80 (3.71 – 3.89)	5.39 (5.34 – 5.44)
	Unadjusted HR (95% CI)	1	1.47 (1.43 – 1.51)
	Adjusted HR (95% CI)	1	1.24 (1.21 – 1.27)
PPI VS no PPI in a cohort without GI conditions (N=2,790,697)	Incident rate (95% CI)	3.54 (3.53 – 3.55)	5.89 (5.86 – 5.93)
	Unadjusted HR (95% CI)	1	1.62 (1.61 – 1.63)
	Adjusted HR (95% CI)	1	1.19 (1.18 – 1.20)

PPI VS no PPI or H2 blockers in a cohort without GI conditions (N=2,543,480)	Incident rate (95% CI)	3.45 (3.44 – 3.46)	5.89 (5.86 – 5.93)
	Unadjusted HR (95% CI)	1	1.65 (1.64 – 1.67)
	Adjusted HR (95% CI)	1	1.22 (1.21 – 1.23)
PPI VS H2 blockers in a cohort without GI conditions except for GERD (N=311,115)	Incident rate (95% CI)	3.30 (3.23 – 3.37)	4.51 (4.47 – 4.54)
	Unadjusted HR (95% CI)	1	1.42 (1.38 – 1.45)
	Adjusted HR (95% CI)	1	1.24 (1.21 – 1.27)
PPI VS no PPI in a cohort without GI conditions except for GERD (N=3,132,126)	Incident rate (95% CI)	3.59 (3.58 – 3.60)	5.36 (5.34 – 5.39)
	Unadjusted HR (95% CI)	1	1.45 (1.44 – 1.46)
	Adjusted HR (95% CI)	1	1.14 (1.13 – 1.14)
PPI VS no PPI or H2 blockers in a cohort without GI conditions except for GERD (N=2,678,478)	Incident rate (95% CI)	3.44 (3.44 – 3.45)	5.36 (5.34 – 5.39)
	Unadjusted HR (95% CI)	1	1.50 (1.49 – 1.51)
	Adjusted HR (95% CI)	1	1.22 (1.21 – 1.22)

a. Incident rate as incident death in 100 person years
b. All models except time dependent propensity score matched and high-dimensional propensity score adjusted models were time dependent models. Effect of PPI was treated as time dependent and was defined as once patients used PPI, they were in PPI group during the remaining follow-up.
c. Adjusted model controlling for eGFR, age, race, gender, number of serum creatinine measurements, number of hospitalizations, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, cancer, GERD, upper GI tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma, unless used in analysis inclusion criteria.
d. GI conditions include upper GI tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma

Abbreviations: CI, Confidence interval; HR, Hazard Ratio

Table 3: Duration of exposure to PPI and risk of death among new users of PPI (n=166,098)

Duration (Days)	≤ 30	31 - 90	91 - 180	181 - 360	361 - 720
N (%)	24748 (14.90)	39345 (23.69)	29334 (17.66)	33907 (20.41)	38764 (23.34)
Hazard Ratio (95%CI)	1	1.05 (1.02-1.08)	1.17 (1.13-1.20)	1.31 (1.27-1.34)	1.51 (1.47-1.56)

a. Within people exposure to PPI between 1 to 720 days
b. Model controls for eGFR, age, race, gender, number of serum creatinine measurements, number of hospitalizations, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, cancer, GERD, upper GI tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma
c. Time zero defined as date when the patients last PPI prescription ends

Figure legends:

Figure 1: Survival curves for PPI and H2 blockers

Figure 2: Duration of PPI exposure and risk of death among new PPI users (n=166,098)

Supplemental Figures:

Supplemental Figure 1: Flowchart of primary cohort

Supplemental Figure 2a: Flowchart of secondary cohort PPI vs no PPI

Supplemental Figure 2b: Flowchart of secondary cohort PPI vs no PPI no H2 blockers

Supplemental figure 3: Duration of PPI exposure and risk of death among new PPI users in an older (less contemporary) sensitivity cohort (n=101,109)

Supplemental figure 4: Estimation of the impact of uncontrolled confounder using the rule-out approach: To investigate the impact of potential residual confounding; rule-out approach was used, where prevalence of potential confounder was set at 30% and prevalence of exposure (PPI use) was set at 88.5% (the latter is derived from our data). The X axis describes the Odds Ratio (OR) of the association between the confounder and PPI users. The Y axis describes the Hazard Ratio (HR) of the association between the confounder and risk of death. The blue line splits the area into two: the upper right area represents all parameter combinations of OR (between PPI use and confounder) and HR (between confounder and death) that are strong enough to move the apparent HR (AHR) from 1.25 (the HR observed in our primary analysis) to 1 or lower, rejecting the hypothesis of an association between PPI use and risk of death. The corollary observation is that the area to the lower left represents all parameter combinations that would result in acceptance of the primary hypothesis. For example, the results show that for uncontrolled confounder that is twice as likely among PPI users (OR=2), the strength of the association between the uncontrolled confounder and risk of death would have to exceed 4 (HR>4) for the uncontrolled confounder to fully explain the observed association between PPI and death (where the combination of OR=2, HR>4 is in the area above the blue line).

Supplemental figure 5: External adjustment to estimate the impact of 3 unmeasured confounders: To investigate the impact of potential residual confounding, we applied external adjustment to estimate the impact of 3 unmeasured confounders including obesity, smoking, and use of therapeutics including anticoagulants, antiplatelet agents, and non-steroidal anti-inflammatory drugs. In order to generate extreme bias estimates (against the hypothesis) we assumed that users of H2 Blockers are generally healthy and have similar health characteristics as the general population. We used published estimates from external data sources as follows (2, 41-44): Prevalence of obesity 30.00%, OR for PPI and obesity=1.30, and HR for obesity and death =1.30; prevalence of smoking=24.79%, OR for PPI and smoking =1.20, and HR for smoking and death =2.80; prevalence of anticoagulants, antiplatelet, and NSAIDs use=28.85%, OR for PPI and drug =2.20, and HR for drug and death =1.30. Given the HR between each confounder and risk of death, and assuming there is no overlap in risk among confounders (which is an unlikely assumption, but one which would generate the greatest amount of bias against our hypothesis), we found a total positive bias (or net confounding bias) of 9.66% (1.47%+4.23%+3.96%). The total bias could move a null association between PPI to death from HR=1.00 to HR=1.10 (reflecting the net positive bias of 9.66% rounded up to 10.0%). The association we observed between PPI and death is 1.25 (higher than 1.10), suggesting that it cannot be fully due to bias of unmeasured confounding. (Using the curves in the figures; for obesity, when the HR=1.30, the corresponding bias=1.47%; for smoking, when the HR=2.80, the corresponding bias=4.23%; for anticoagulants, antiplatelet, and NSAIDs, when the HR=1.30, the corresponding bias=3.96%).

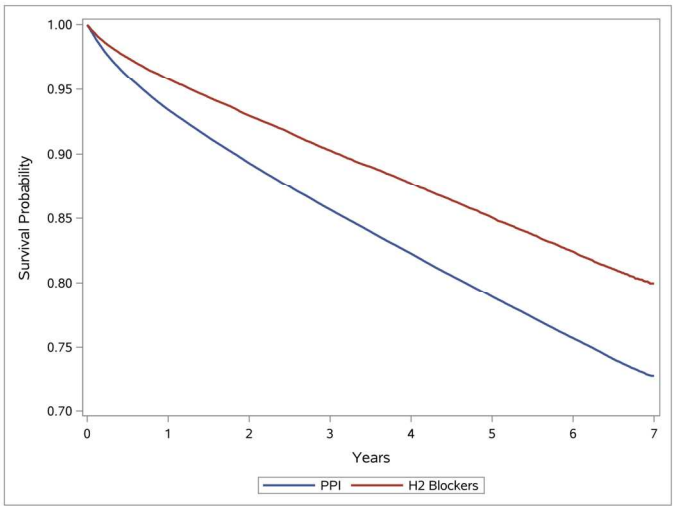

Figure 1: Survival curves for PPI and H2 blockers
Figure 1
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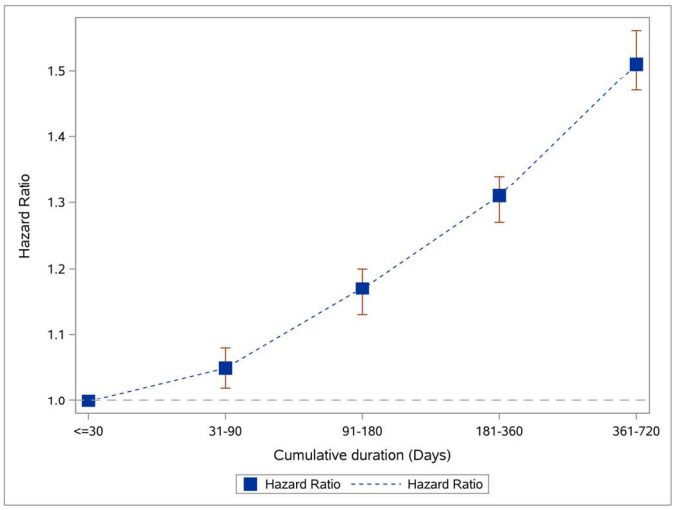

Figure 2: Duration of PPI exposure and risk of death among new PPI users (n=166,098)
Figure 2
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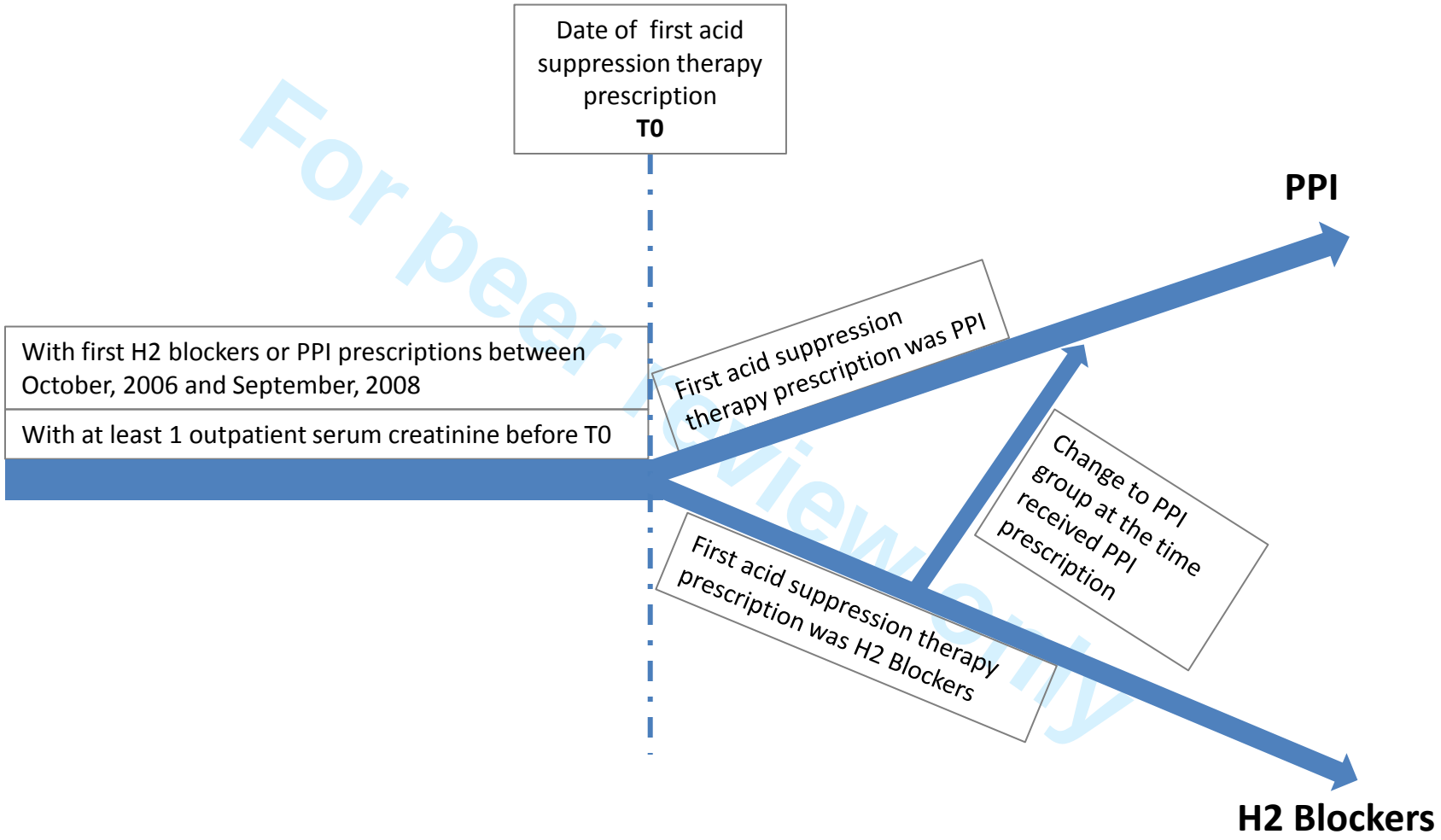
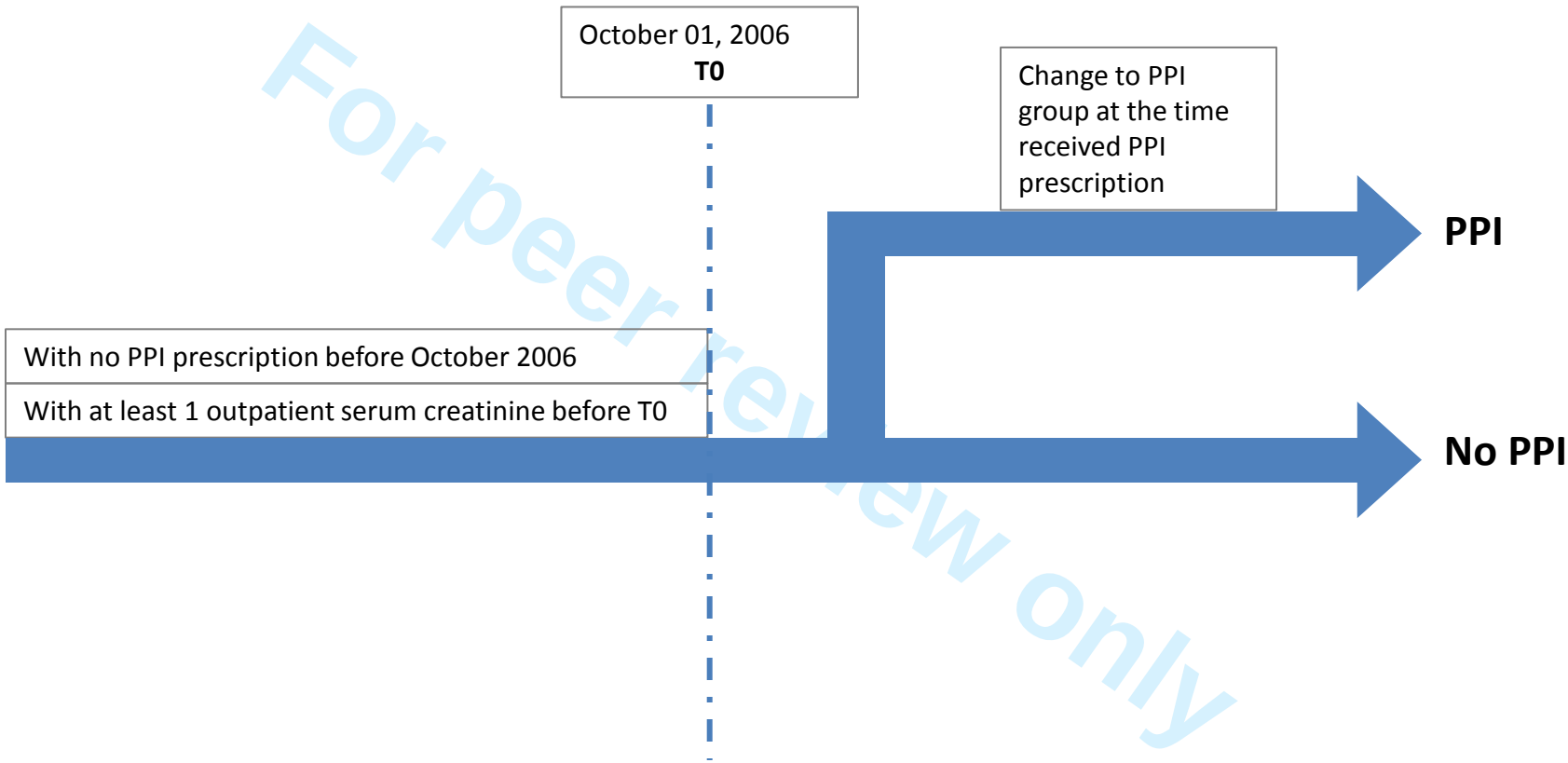
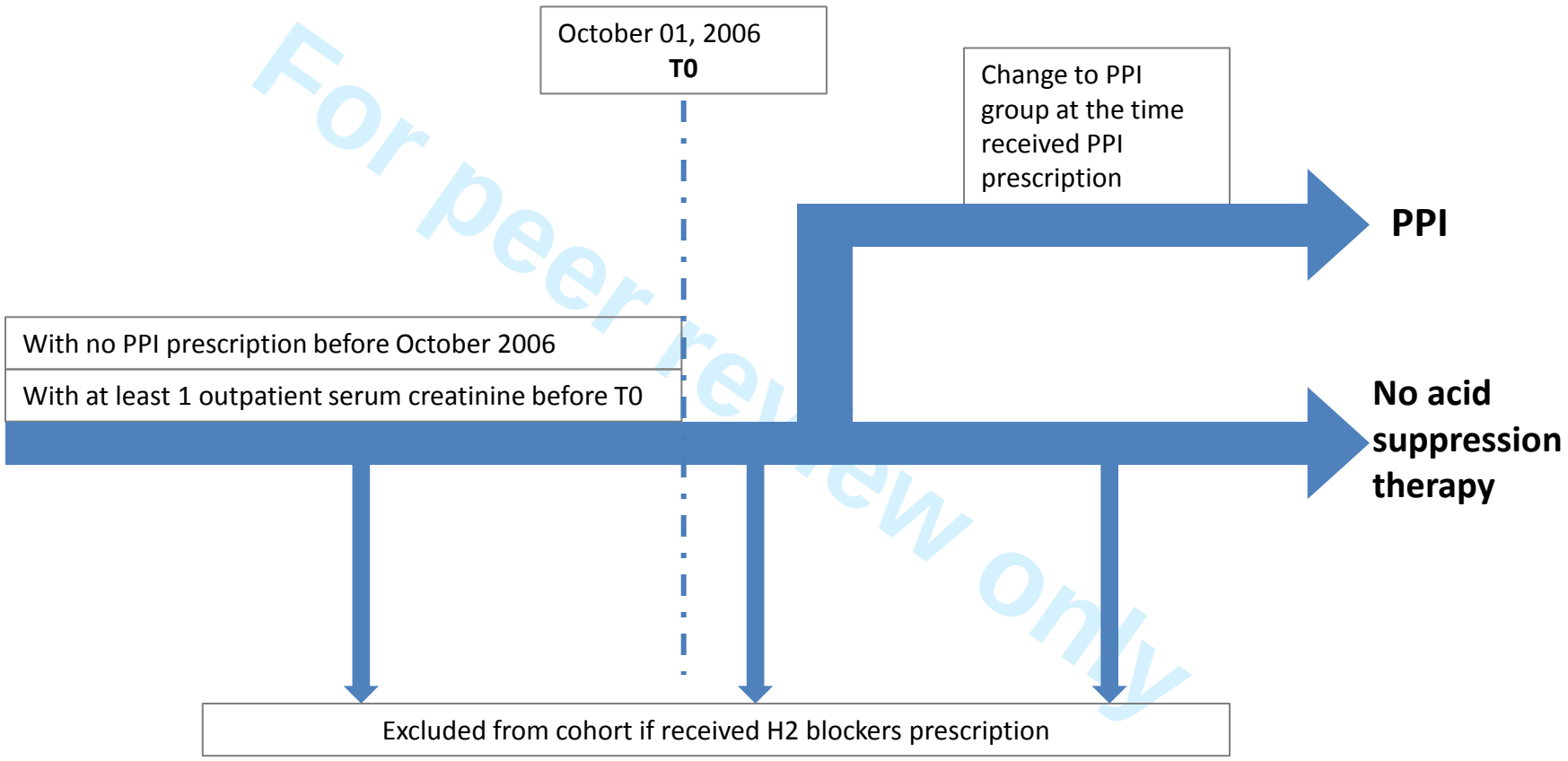
Supplemental Figure 1



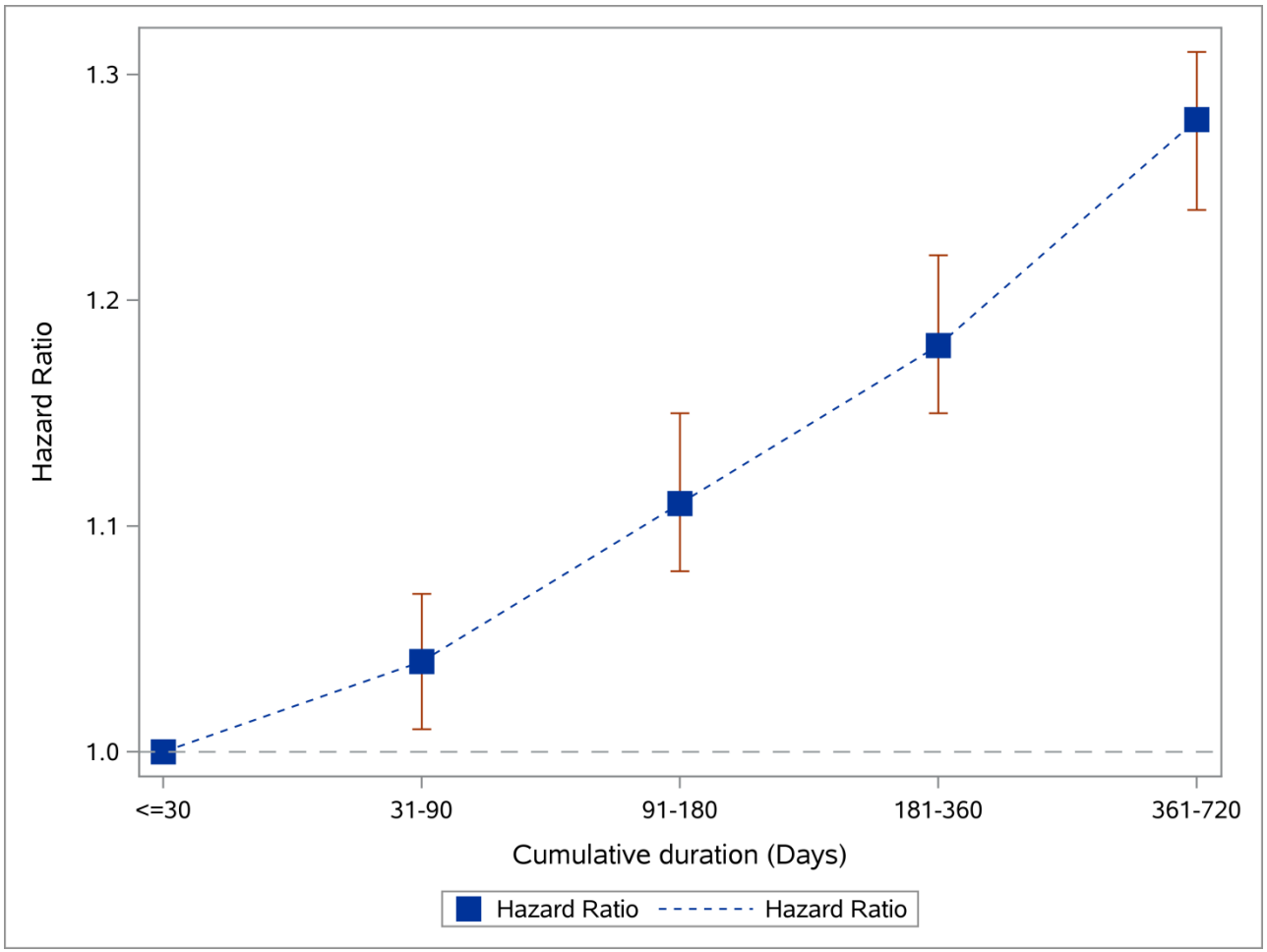
Supplemental Figure 2a



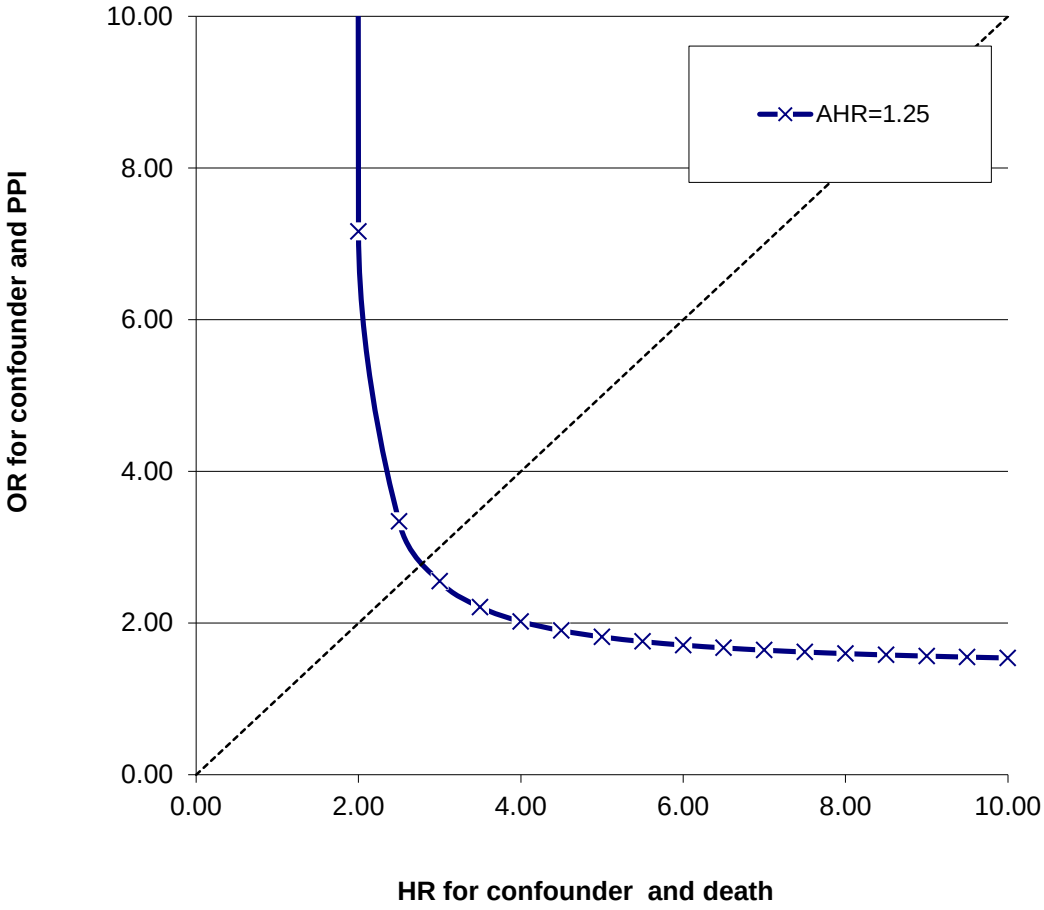
Supplemental Figure 2b



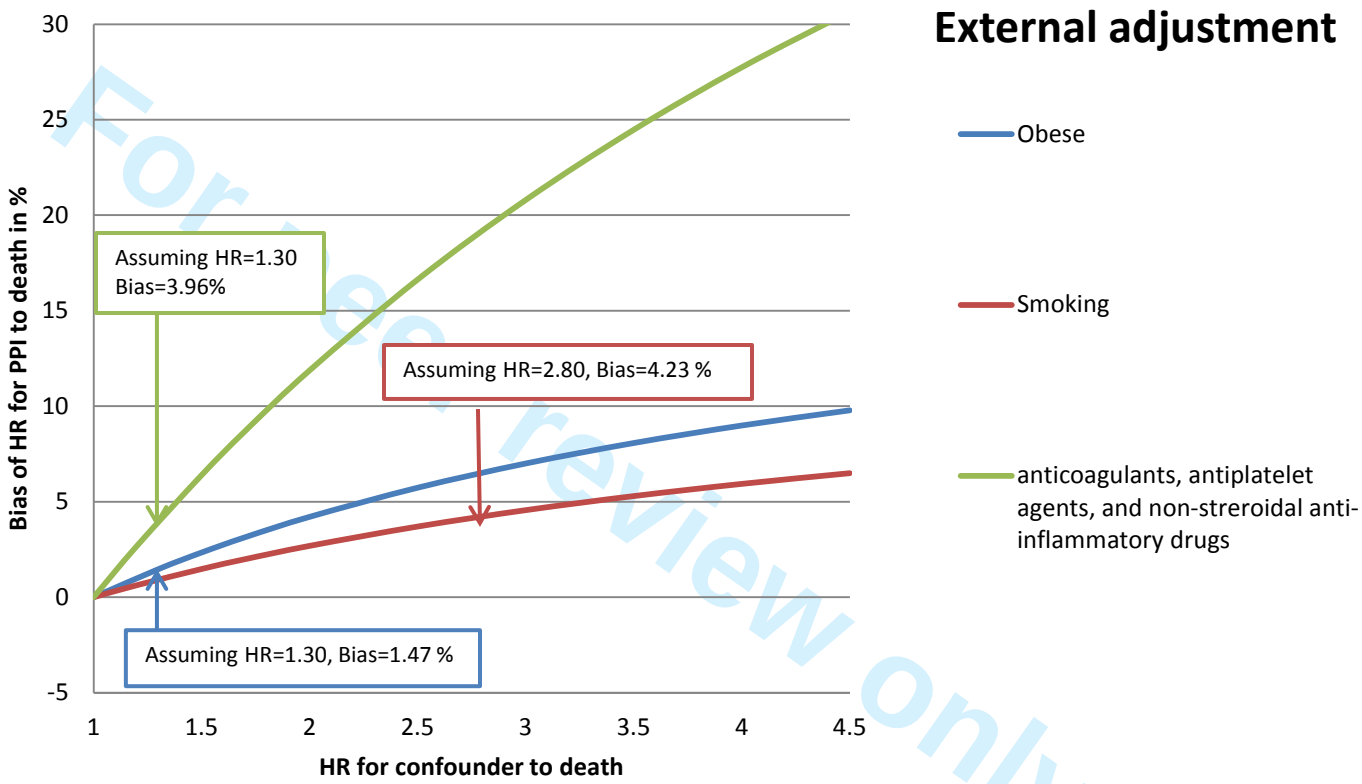
Supplemental Figure 3



Supplemental Figure 4



Supplemental Figure 5



Supplemental table 1: Baseline demographic and health characteristics of the overall 2001 cohort of new users of acid suppression therapy, by type of acid suppressant at time of cohort entry, and those who were ever exposed to PPI.

		Overall cohort	New users of H2 Blockers at time of cohort entry	New users of PPI at time of cohort entry	Ever exposed to PPI [a]	P Value [b]
N		396884	208492	188392	293265	
Age (SD)		62.98 (13.05)	61.93 (13.24)	64.14 (12.74)	63.78 (12.81)	<0.001
eGFR in mL/min/1.73m^2 (SD)		74.74 (22.43)	76.24 (22.04)	73.09 (22.73)	73.38 (22.61)	<0.001
Number of outpatient serum creatinine measurements (SD)		3.01 (3.40)	2.95 (3.23)	3.06 (3.58)	4.52 (5.51)	<0.001
Number of hospitalizations (SD)		0.37 (0.96)	0.36 (0.95)	0.38 (0.97)	0.51 (1.30)	<0.001
Race	White (%)	318534 (80.26)	164295 (78.80)	154239 (81.87)	236930 (80.79)	<0.001
	Black (%)	58355 (14.70)	32053 (15.37)	26302 (13.96)	42498 (14.49)	
	Other (%)	19995 (5.04)	12144 (5.82)	7851 (4.17)	13837 (4.72)	
Sex	Male (%)	377769 (95.18)	197685 (94.82)	180084 (95.59)	279023 (95.14)	<0.001
	Female (%)	19115 (4.82)	10807 (5.18)	8308 (4.41)	14242 (4.86)	
Diabetes mellitus (%)		92555 (23.32)	46562 (22.33)	45993 (24.41)	74344 (25.35)	<0.001
Hypertension (%)		231296 (58.28)	119554 (57.34)	111742 (59.31)	184529 (62.92)	<0.001
Chronic lung disease (%)		75810 (19.10)	39270 (18.84)	36540 (19.40)	64254 (21.91)	<0.001
Peripheral artery disease (%)		9141 (2.30)	4646 (2.23)	4495 (2.39)	8751 (2.98)	0.001
Cardiovascular disease (%)		122301 (30.82)	59814 (28.69)	62487 (33.17)	101220 (34.51)	<0.001
Cerebrovascular disease (%)		1529 (0.39)	776 (0.37)	753 (0.40)	1419 (0.48)	0.16
Dementia (%)		12031 (3.03)	6094 (2.92)	5937 (3.15)	10615 (3.62)	<0.001
Hyperlipidemia (%)		152040 (38.31)	78546 (37.67)	73494 (39.01)	130557 (44.52)	<0.001
Hepatitis C (%)		9332 (2.35)	4832 (2.32)	4500 (2.39)	8456 (2.88)	0.14
HIV (%)		209 (0.05)	105 (0.05)	104 (0.06)	183 (0.06)	0.51
Cancer (%)		46451 (11.70)	23312 (11.18)	23139 (12.28)	39473 (13.46)	<0.001
GERD (%)		110217 (27.77)	52586 (25.22)	57631 (30.59)	114132 (38.92)	<0.001

Upper GI tract bleeding (%)	11282 (2.84)	3352 (1.61)	7930 (4.21)	12458 (4.25)	<0.001
Ulcer disease (%)	35189 (8.87)	14152 (6.79)	21037 (11.17)	37472 (12.78)	<0.001
H. Pylori infection (%)	2599 (0.65)	477 (0.23)	2122 (1.13)	3795 (1.29)	<0.001
Barrett's esophagus (%)	0 (0.00)	0 (0.00)	0 (0.00)	245 (0.08)	NA
Achalasia (%)	188 (0.05)	41 (0.02)	147 (0.08)	245 (0.08)	<0.001
Stricture (%)	2218 (0.56)	415 (0.20)	1803 (0.96)	2953 (1.01)	<0.001
Esophageal adenocarcinoma (%)	223 (0.06)	79 (0.04)	147 (0.08)	262 (0.09)	<0.001
Years of follow up (IQR)[c]	5.65 (5.05 – 6.28)	3.35 (1.01 – 5.71) [d]	5.51 (5.01 – 6.08)	5.23 (3.22 – 5.90)	<0.001
Days of having related prescription during follow-up (IQR)	587 (168 – 1423)[e]	188 (90 – 561) [d]	621 (171 – 1496)	579 (172 – 1350)	<0.001
Death (%)	102802 (25.90)	31260 (14.99) [d]	51785 (27.49)	71565 (24.40)	<0.001
Incident death in 100 person years (95% CI)	5.08 (5.05 – 5.11)	4.40 (4.35 – 4.45) [d]	5.56 (5.51 – 5.61)	5.45 (5.41 – 5.49)	<0.001

a. Includes patients exposed to PPI at T0 (n=275977) and during follow-up (n=33136). Variables were measured at time of PPI exposure.
b. P value for difference between exposed to H2 at T0 and exposed to PPI at T0
c. From T0 to first occurrence of death or September 30, 2013
d. Outcome measured from T0 to first occurrence of exposure PPI, death or September 30, 2007
e. Days of having PPI or H2 blockers

Abbreviations: CI, Confidence interval; eGFR, estimated Glomerular Filtration Rate; GERD, Gastroesophageal Reflux Disease; HIV, human immunodeficiency virus; IQR, interquartile range; NA, Not Applicable; SD, Standard deviation

Supplemental table 2: Duration of exposure to PPI and risk of death among new users of PPI in the 2001 cohort (n=101,109)

Duration (Days)	≤ 30	31 - 90	91 - 180	181 - 360	361 - 720
N (%)	15204 (15.04)	20409 (20.19)	17137 (16.95)	21586 (21.35)	26773 (26.48)
Hazard Ratio (95%CI)	1	1.04 (1.01, 1.07)	1.11 (1.08, 1.15)	1.18 (1.15. 1.22)	1.28 (1.24, 1.31)

a. Within people exposure to PPI between 1 to 720 days
b. Model controls for eGFR, age, race, gender, number of serum creatinine measurements, number of hospitalizations, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, cancer, GERD, upper GI tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma
c. Time zero defined as date when the patients last PPI prescription end

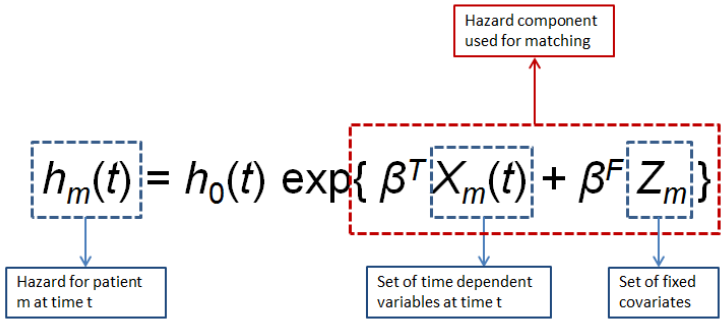
Supplemental Methods:

Time Dependent Propensity Score Matching

1. Using the primary cohort (N=349, 312), all covariates except for age, race and gender were treated as time-dependent variables from T0 till date of PPI use or end of follow up, whichever occurred first. Specifically, time-dependent eGFR indicated the eGFR at day t (where the value was equal to the outpatient eGFR measurement most close and prior to time t); time-dependent number of outpatient serum creatinine measurements and number of hospitalizations indicated the cumulative value from October 01, 1998 till day t; time-dependent disease status including diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, cancer, hepatitis C, HIV, dementia and diseases associated with acid suppression therapy use such as gastroesophageal reflux disease (GERD), upper gastrointestinal (GI) tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma indicated if participants were diagnosed with the disease between October 01, 1998 and day t.

2. Time-dependent Cox regression was applied, where time until receipt of first PPI prescription was the outcome (participants receiving PPI prescription at T0 were considered to have the event with survival time equal to 0 days). Time-dependent variables from step 1 and age, race and gender were used as predictors in the model in order to obtain parameter estimates for the predictors.

3. Every participant's hazard component at day t was computed based on the parameter estimates from step 2 and their covariate values at day t.



The hazard component was used as the time-dependent propensity score.

4. Beginning from T0 (day 0), a 1:1 sequential greedy matching without replacement was conducted. People who received PPI prescription at day t (case group at day t) were matched with people who had not yet received PPI prescription at day t (control group at day t) based on their propensity score at day

t. The order of both case and control groups was randomized before matching. A matched pair was considered successfully matched only if the propensity score difference was less than 0.2 times the standard deviation of the hazard component at time t. If no successful match was made the case in the pair was withdrawn from the further matching while the control was left in the data pool. Matching was ended when 1/ all participants in control or case group were matched or 2/ day t equaled day 1827.

5. After the matching, conditional Cox regressions stratified by matched pairs were conducted to examine the association between PPI and death.

High-dimensional propensity score:

1. Using the primary cohort (N=349,312), participants data from 1 year before T0 till T0 were collected in 5 dimensions consisting off: the first 3 digits of outpatient diagnoses ICD9 codes, the outpatient procedures CPT codes, the first 3 digits of inpatient diagnoses ICD9 codes, the first 3 digits of inpatient procedures ICD9 codes, and the outpatient drug names without dose.

2. Within each of the 5 dimensions, the top 300 most frequent items were selected, which yielded 300*5=1500 potential items.

3. For each participant, we determined if each of the 1500 potential items 1\ ever occurred, 2\ if the number of occurrences for the participant was higher than the number of occurrences in 50% of the participants and 3\ if the number of occurrences for the participant was higher than the number of occurrences in 75% of the participants. This step results in 1500*3=4500 binary potential variables. If the 50% or 75% percentile of the number of item occurrences was less than 1, then the variable were coded as 0 for all participants. If the 50% and 75% percentile of the number of item occurrences had the same value, then the 75% variable was coded as 0 for all participants.

4. Bias was calculated using formula based on apparent relative risk for each of the 4500 variables:

$$Bias=(P\_C1\ (RR\_CD-1)+1)/(P\_C0\ (RR\_CD-1)+1)\ ,\text{if } RR\_CD \geq 1$$

$$Bias=(P\_C1\ (1/RR\_CD-1)+1)/(P\_C0\ (1/RR\_CD-1)+1)\ ,\text{if } RR\_CD < 1$$

Where P_C1 indicates the prevalence of the variable in the PPI group, P_C0 indicates the prevalece of the variable in the control group, and RR_CD indicate relative risk of death associated with the variable.

5. The top 500 variables with the largest | log(bias)| value were selected as binary empirical covariates for inclusion in the propensity score modeling.

6. The 500 variables and age, gender, race, and eGFR were used to obtain propensity scores from logistic regression where the outcome was receipt of PPI or not at T0. Propensity scores were then categorized into deciles.

7. Multivariate Cox regression with an indicator for propensity score decile was used to evaluate the association between PPI and death. Patients in the control group who received PPI later were censored at the time they received PPI.

Two-stage residual inclusion estimation (Instrumental Variable):

1. Based on the primary cohort (N=349,312), for each participant, data on prescriptions by the physician who prescribed the participant the acid suppression therapy at T0 was collected from 6 months before the participant's T0 till T0.

2. For each participant, the percentage of PPIs prescribed to new acid suppression therapy users by their prescribing physician, excluding the prescription of the participant, in the 6 months prior to and including T0 was computed and used as an instrumental variable. Participants whose prescribing physician did not prescribe any other acid suppression therapy to new users in the 6 months prior to and including T0 were excluded from the analysis.

3. In order to predict the participants' possibility of receiving PPI, instrumental variable and co-variables were used in a logistic regression model where the outcome was acid suppression therapy prescription at T0.

4. Residual terms were computed as the difference between participants' real probability (1 if PPI, 0 if H2 blocker) and predicted probability.

5. Multivariate Cox regression, which included the residual term and co-variables, were conducted to evaluate the relationship between PPI and death. Patients in the control group who received PPI later were censored at the time they received PPI.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3-4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Additional matched cohort described in Supplemental methods
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7 and Supplemental methods
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	Due to the feature of VA data on death

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	information, no loss of follow-up would occur. All death data is captured by the Veterans Benefit Administration.
		(*e*) Describe any sensitivity analyses	7-8

Results			**Reported Page**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4-5
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	19-20 Table 1
		(b) Indicate number of participants with missing data for each variable of interest	see page 7 for reason
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	20 Table 1
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	19 Table 1
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	21-22 Table 2
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if	15

		applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Excess Risk of Death among Users of Proton Pump Inhibitors: A longitudinal observational cohort study of United States Veterans

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Excess Risk of Death among Users of Proton Pump Inhibitors: A longitudinal observational cohort study of United States Veterans

Yan Xie MPH[1], Benjamin Bowe MPH[1], Tingting Li MD[1,2], Hong Xian PhD[1,3], Yan Yan MD, PhD[1,4], and Ziyad Al-Aly MD[1,2,5,6]

[1]Clinical Epidemiology Center, Research and Education Service, VA Saint Louis Health Care System, Saint Louis, Missouri

[2]Department of Medicine, Washington University School of Medicine, Saint Louis, Missouri

[3]Department of Biostatistics, College for Public Health and Social Justice, Saint Louis University, Saint Louis, Missouri

[4]Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, Saint Louis, Missouri

[5]Renal Section, Medicine Service, VA Saint Louis Health Care System, Saint Louis, Missouri

[6]Institute for Public Health, Washington University School of Medicine, Saint Louis, Missouri

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Corresponding Author:

Ziyad Al-Aly, M.D.
Clinical Epidemiology Center
VA Saint Louis Health Care System
915 North Grand Boulevard, 151-JC
Saint Louis, MO 63106
Telephone: (314) 289-6333
E-mail: zalaly@gmail.com

Abstract:

Objective: Proton pump inhibitors (PPI) are widely used; and their use is associated with increased risk of adverse events. However, whether PPI use is associated with excess risk of death is unknown. We aimed to examine the association between PPI use and risk of all-cause mortality.

Design: Longitudinal observational cohort study

Setting: US Department of Veterans Affairs

Participants: Primary cohort of new users of PPI or Histamine H2 receptor antagonists (H2 blockers) (N=349,312); additional cohorts included PPI versus no PPI (N=3,288,092), and PPI versus no PPI and no H2 blockers (N=2,887,030).

Main outcome measures: Risk of death.

Results: Over a median follow-up of 5.71 years (IQR: 5.11-6.37), PPI use was associated with increased risk of death compared to H2 blockers use (HR=1.25; CI=1.23-1.28). Risk of death associated with PPI use was higher in analyses adjusted for high-dimensional propensity score (HR=1.16; CI=1.13-1.18); two-stage residual inclusion estimation (HR=1.21; CI=1.16-1.26); and in 1:1 time-dependent propensity score matched cohort (HR=1.34 CI=1.29-1.39). The risk of death was increased when considering PPI use versus no PPI (HR=1.15; CI=1.14-1.15), and PPI use versus no PPI and no H2 blockers (HR= 1.23; CI=1.22-1.24). Risk of death associated with PPI use was increased among participants without gastrointestinal conditions: PPI versus H2 blockers (HR=1.24; CI=1.21-1.27); PPI use versus no PPI (HR=1.19; CI=1.18-1.20); and PPI use versus no PPI and no H2 blockers (HR=1.22; CI=1.21-1.23). Among new PPI users, there was a graded association between duration of exposure and risk of death.

Conclusions: The results suggest excess risk of death among PPI users; risk is also increased among those without gastrointestinal conditions and with prolonged duration of use. Limiting PPI use and duration to instances where it is medically indicated may be warranted.

Strength and limitations:

- National large scale data from a network of integrated health systems
- Employed a new user design and developed a number of analytical approaches where we consistently found a significant association between PPI exposure and risk of death.
- Cohort included mostly older white male US Veterans which may limit the generalizability.
- Did not include information on the cause of death.

Introduction:

Proton pump inhibitors (PPI) are widely prescribed and are also available for sale over the counter without prescription in several countries(1, 2). Several observational studies suggest that PPI use is associated with increased risk of a number of adverse health outcomes(1). A number of studies have shown that PPI use is associated with significant risk of acute interstitial nephritis(3-5). Recent studies established an association between exposure to PPI and risk of chronic kidney disease (CKD), kidney disease progression, and end stage renal disease (ESRD)(2, 6, 7). Results from a large prospective observational German cohort suggest that patients receiving PPI had a higher risk of incident dementia(8). Several reports highlighted a rare but potentially fatal risk of hypomagnesemia among users of PPI(9-11). PPI use has been associated with increased risk of both incident and recurrent Clostridium difficile infections(12). Several observational analyses have shown that PPI use was also associated with increased risk of osteoporotic fractures including hip and spine fractures(13, 14). Less convincing -and to some extent inconsistent- evidence suggests a relationship between PPI use and risks of community acquired pneumonia and cardiovascular events(15-17). Emerging -and far from conclusive- *in vitro* evidence suggests that PPI results in inhibition of lysosomal acidification and impairment of proteostasis leading to increased oxidative stress, endothelial dysfunction, telomere shortening and accelerated senescence in human endothelial cells(18). The experimental work provides a putative mechanistic link to explain some of the adverse events associated with PPI use(18).

The adverse outcomes associated with PPI use are serious and each is independently associated with higher risk of mortality. Evidence from several small cohort studies of older adults who were recently discharged from the hospital, or institutionalized in long term care facilities suggests inconsistently that PPI use may be associated with increased risk of 1-year mortality(19-22). Whether PPI use is associated with excess risk of

death is not known and has not been examined in large epidemiologic studies spanning a sufficiently long duration of follow up. We hypothesized that owing to the consistently observed associations between PPI use and risk of adverse health outcomes, PPI use is associated with excess risk of death, and that the risk of death would be more pronounced with increased duration of use. We therefore used the Department of Veterans Affairs national databases to build a longitudinal cohort of incident users of acid suppression therapy including PPI and Histamine H2 receptor antagonists (H2 blockers) to examine the association between PPI use and risk of all-cause mortality, and to determine whether risk of death is increased with prolonged duration of use.

Methods:

Cohort participants:

Primary cohort:

Using administrative data from the United States Department of Veterans Affairs (VA), we identified patients who received an outpatient H2 blockers or PPI prescription between October 01, 2006 and September 30, 2008 (n=1,762,908). In order to select new users of acid suppression therapy (incident user design), we excluded 1,356,948 patients who received any outpatient H2 blockers or PPI prescriptions between October 01, 1998 and September 30, 2006. To account for patients' kidney function, only patients with at least one outpatient serum creatinine value before first acid suppression therapy prescription were selected in the cohort, yielding an analytic cohort of 349,312 patients. Patients whose first acid suppression therapy was PPI (n=275,977) were considered to be in the PPI group during follow-up. Patients who received H2 blockers as their first acid suppression therapy (n=73,335) served as the reference group before they received any PPI prescription. (Supplemental figure 1) Within the reference group, those who received a PPI prescription later (n=33,136) were considered to be in the PPI group from the date of their first PPI prescription until the end of follow-up(23). Time zero (T0) for primary cohort was defined as first acid suppression therapy prescription date.

Secondary cohorts:

We additionally built two secondary cohorts to examine the association of PPI use and risk of death in a) PPI versus no PPI users, and b) PPI versus non users of acid suppression therapy. Patients with no PPI prescription between October 01, 1998 and September 30, 2006, and with at least one outpatient eGFR value

before October 01, 2006 were selected to evaluate the risk of death associated with PPI use versus no PPI use (n=3,288,092) (Supplemental figure 2a). Patients with no PPI prescription between October 01, 1998 and September 30, 2006, with no H2 blockers before first PPI prescription and at least one outpatient eGFR value before October 01, 2006 were selected to evaluate the risk of death associated with PPI use versus no acid suppression therapy (n=2,887,030) (Supplemental figure 2b). T0 for secondary cohorts was defined as October 01, 2006.

Patients in both primary and secondary cohorts were followed until September 30, 2013 or death. The study was approved by the Institutional Review Board of the VA Saint Louis Health Care System, Saint Louis, MO.

Data Sources:

We used the Department of Veterans Affairs databases including inpatient and outpatient medical SAS datasets (that include utilization data related to all inpatient and outpatient encounters within the VA system) to ascertain detailed patient demographic characteristics and comorbidity information based on inpatient and outpatient encounters(2, 24). The VA Managerial Cost Accounting System Laboratory Results (a comprehensive database that includes VA-wide results for selected laboratory tests obtained in the clinical setting) provided information on outpatient and inpatient laboratory results. The VA Corporate Data Warehouse Production Outpatient Pharmacy domain provided information on outpatient prescriptions. The VA Vital Status and Beneficiary Identification Records Locator Subsystem (BIRLS) files provided demographic characteristics and death.

Primary Predictor Variable: PPI use was the primary predictor. Once cohort participants received PPI prescription, they were considered with effect of PPI until the end of follow up. Medications that contain esomeprazole, lansoprazole, omeprazole, pantoprazole or rabeprazole were counted as PPI. Medications including ranitidine, cimetidine, and famotidine were counted as H2 blockers.

Outcome: The primary outcome in survival analyses was time to death. Death information is routinely collected by the Veterans Benefit Administration for all United States Veterans.

Covariates:

Covariates included age, race, gender, eGFR, number of outpatient serum creatinine measurements, number of hospitalizations, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, cancer, hepatitis C, HIV, dementia and diseases associated with acid suppression therapy use such as gastroesophageal reflux disease (GERD), upper gastrointestinal (GI) tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma(25-28). eGFR was calculated using the abbreviated four-variable Chronic Kidney Disease Epidemiology Collaboration equation based on age, sex, race, and outpatient serum creatinine(29). Race/ethnicity was categorized as white, black, or other (Latino, Asian, Native American, or other racial/ethnic minority groups). Comorbidities except for hepatitis C and HIV were assigned on the basis of relevant ICD-9-CM diagnostic and procedures codes and CPT codes in the VA Medical SAS datasets(2, 30-33). Hepatitis C and HIV were assigned based on laboratory results.

Baseline covariates were ascertained from October 01, 1998 till T0. All covariates except for age, race and gender covariates values were treated as time-varying covariates where they were additionally assessed until date of first PPI prescription in those patients who did not have PPI prescription at T0. Any comorbidity occurring during the assessment period was considered present during the remaining follow-up. eGFR was the outpatient eGFR value within and most proximate to the end of the assessment period. Number of outpatient serum creatinine measurements and number of hospitalizations were accumulated during the assessment period.

Statistical Analysis:

Means, standard deviations and t-tests are presented for normally distributed continuous variables; medians, interquartile ranges and Wilcoxon-Mann-Whitney tests are presented for non-normally distributed continuous variables; counts, percentages and Chi-square tests are presented for categorical variables. Incident rates per 100 person-years were computed for death and confidence intervals were estimated based on the normal distribution. Simon and Makuch method for survival curves was used for time-dependent covariates(34).

Cox regression models with time-dependent covariates were used in the assessment of the association between PPI exposure and risk of death where patients could switch from H2 blockers to PPI in the models. In order to account for potential delayed effect of PPI, patients were considered to have the effect of PPI from the first PPI prescription till end of follow up. In addition, time dependent Cox models were conducted in subgroups where patients had no GI conditions, and where patients had no GI conditions except for GERD.

Because exposure in this observational cohort is time-dependent, we undertook 1:1 propensity score matching for the primary cohort where time-dependent propensity scores were calculated based on time-dependent Cox regression with all covariates(35)(details are provided in supplemental methods). After matching, all covariates except for age had an absolute standardized difference of less than 0.1, which indicated all covariates except for age were well balanced. Age had a standardized difference equal to 0.13. Doubly robust estimation was applied after matching, where all covariates were additionally controlled for in the model, to obtain an unbiased effect estimator(36).

In order to optimize control of confounding, we additionally built high-dimensional propensity score adjusted survival models following the multistep algorithm described by Schneeweiss et al(37)(details are provided in supplemental methods). We also applied two-stage residual inclusion estimation based on instrumental variable approach (Supplemental methods)(38).

In addition, we evaluated the association between duration of PPI prescription and risk of death among new users of PPI. Duration was defined in cumulative days of use and categorized as ≤30, 31-90, 91-180, 181-360, 361-720, where ≤30 days considered as the reference group. To avoid immortal time bias (by definition, cohort participants must be alive to receive prescription hence introducing a bias commonly referred to as immortal time bias), time of cohort entry was defined as the date of last PPI prescription plus days' supply (39, 40). In order to ensure sufficient length of follow up time following T0, we excluded cohort participants with cumulative duration of exposure exceeding 720 days (because of limited overall cohort timeline, and because T0 starts at the end of last prescription, those with long exposure will necessarily have limited follow up time). In

regression analyses, a 95% confidence interval (CI) of a hazard ratio (HR) that does not include unity was considered statistically significant. All analyses were performed using SAS Enterprise Guide version 7.1.

Sensitivity Analysis:

In order to further evaluate the consistency and robustness of study findings, we examined the observed associations in a less contemporary cohort (dating back to an era where PPI prescription and use were far less frequent) of patients without acid suppression therapy prescriptions between October 01, 1998 and September 30, 2000 (washout period) and with acid suppression therapy prescription between October 01, 2000 and September 30, 2002 and at least one outpatient serum creatinine value before that. Patients in this cohort were followed till September 30, 2007 or death. To examine the impact of potential residual confounding on study results, we conducted additional sensitivity analyses as described by Schneeweiss(41): a) we used the rule-out approach to identify the strength of the residual confounding that could fully explain the association observed in primary analyses; and b) applied an external adjustment approach using external information (prevalence and risk estimates from published literature) to evaluate potential net confounding bias due to unmeasured confounders(2, 41-44). Methods are described elegantly by Schneeweiss(41). In addition, to remove death events that were less likely to be related to PPI exposure, we excluded cohort participants who died within 90 days after first PPI or H2 blockers prescription.

We conducted analyses based on a three level classification of exposure, where patient's status at time t could be current use (using PPI or finished last PPI prescription within 90 days before t), past use (used PPI after T_0 but finished more than 90 days before t), and never use. We conducted additional sensitivity analyses which included hemoglobin as a covariate in cohort participants with available data. We also undertook analyses which stratified the cohort based on cardiovascular disease, history of pneumonia, chronic kidney disease (eGFR<60 and ≥60 mL/min/1.73m^2) or age (<65 and ≥65 years old) at T0. Finally, and in order to ascertain the specificity of the findings, we examined the association between PPI exposure and the risk of a motor vehicle accident as a tracer outcome where a priori knowledge suggests an association is not likely to exist.

Patient involvement:

No patients were involved in developing the hypothesis, the specific aims, or the research questions, nor were they involved in developing plans for design or implementation of the study. No patients were involved in the interpretation of study results, or write up of the manuscript. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results:

The demographic and health characteristics of the overall primary cohort of new users of acid suppression therapy (n=349,312), by type of acid suppressant drug at time of cohort entry (H2 blockers n=73,335; PPI n=275,977), and those who were ever exposed to PPI (n=309,113) are provided in table 1. There were significant baseline differences in that cohort participants who were treated with PPI were older, and were more likely to have comorbid conditions including diabetes, hypertension, cardiovascular disease, and hyperlipidemia. Cohort participants treated with PPI were also more likely to have upper gastrointestinal tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma (table 1). Survival curves for PPI and H2 blockers were presented in figure 1.

Association between PPI use and risk of death:

Among new users of acid suppression therapy (N=349,312), and over a median follow up of 5.71 years (IQR: 5.11 – 6.37), where exposure was treated as time-dependent covariate; PPI use was associated with increased risk of death compared to H2 blockers use (HR=1.25; CI=1.23-1.28) (table 2). Among new users of acid suppression therapy (N=349,312); in high-dimensional propensity score adjusted models, new PPI users had increased risk of death compared to new users of H2 blockers (HR=1.16; CI=1.13-1.18); based on two-stage residual inclusion estimation, risk of death was higher in new users PPI when compared to new users of H2 blockers (HR=1.21; CI=1.16-1.26). In a 1:1 time-dependent propensity score matched cohort of new users of PPI and H2 blockers (N=146,670), PPI users had significantly increased risk of death (HR=1.34; CI=1.29-1.39).

We examined the relationship of PPI and risk of death in secondary cohorts (as described in methods) where we considered risk associated with PPI use versus no known exposure to PPI (no PPI use +/- H2 blockers use) (N=3,288,092); the results suggest that PPI use was associated with increased risk of death (HR=1.15; CI=1.14-1.15) (table 2). Assessment of risk of death associated with PPI use versus no known exposure to any acid suppression therapy (no PPI use and no H2 blockers use) (N=2,887,070), suggests increased risk of death with PPI use (HR= 1.23; CI=1.22-1.24).

Association between PPI use and risk of death in those without gastrointestinal conditions:

We then analyzed the association between PPI use and the risk of death in cohort where we excluded participants with documented medical conditions generally considered as indications for treatment with PPI including GERD, upper gastrointestinal tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma. The intent of this analysis was to examine the putative association of PPI use and risk of death in a lower risk cohort. Examination of risk of death associated with use of acid suppression therapy (PPI vs. H2 blockers) suggests that risk of death was increased with PPI use (HR=1.24; CI=1.21-1.27) (table 2). Examination of the risk of death associated with PPI use versus no known exposure to PPI (no PPI use +/- H2 blockers use) suggests a higher risk of death associated with PPI use (HR=1.19; CI=1.18, 1.20). Results were consistent where we examined risk of death associated with PPI use versus no known exposure to any acid suppression therapy (no PPI use and no H2 blockers use) (HR=1.22; CI=1.21-1.23). Risk of death associated with PPI use in cohort participants without GI conditions but included participants with GERD yielded consistent results (PPI vs H2 blockers (HR=1.24; CI=1.21-1.27); PPI vs no PPI (HR=1.14; CI=1.13-1.14); PPI vs no PPI and no H2 blockers (HR=1.22; CI=1.21-1.22) (table 2).

Duration of exposure and excess risk of death:

We examined the association between duration of PPI exposure and risk of death among new users of PPI (n=166,098). Compared to those exposed for ≤30 days, there was a graded association between duration of exposure and risk of death among those exposed for 31-90, 91-180, 181-360, and 361-720 days (table 3, figure 2).

Sensitivity analyses:

We tested the robustness of study results in sensitivity analyses where we built a less contemporary cohort as described in methods; demographic and health characteristics of this cohort are provided in supplemental table 1. Where exposure was treated as time-dependent, PPI use was associated with increased risk of death compared to H2 blockers use (HR=1.17; CI=1.15-1.19). In a 1:1 time-dependent propensity score matched cohort of PPI and H2 blockers, PPI users had significantly increased risk of death HR=1.21 (1.19-1.24). Furthermore, we also observed a graded association between cumulative duration of exposure to PPI and risk of death (supplemental table 2, supplemental figure 3).

To examine the potential impact of residual confounding on study results, we used rule-out and external adjustment approaches as described by Schneeweiss(41). Using the rule-out approach, we characterized a set of parameters (OR for relationship of PPI and confounder), and (HR for relationship of confounder and death) with sufficient strength to fully explain the association observed in primary analyses (supplemental figure 4). For example, if the confounder was twice as likely among PPI users (OR=2), and the HR of death associated with the uncontrolled confounder exceeded 4.0, then the uncontrolled confounder would fully explain the observed association between PPI and death (supplemental figure 4). Given that our analyses accounted for most known strong independent risk factors of death, and employed an active comparator group; to cancel the results, any uncontrolled confounder of the required prevalence (OR=2 or more in the example above), and strength (HR=4 or more in the example above) would also have to be independent of the confounders already adjusted for and is unlikely to exist; thus the results cannot be fully explained by this putative uncontrolled confounder.

External adjustment to estimate the impact of 3 unmeasured confounders including obesity, smoking, and use of therapeutics including anticoagulants, antiplatelet agents, and non-steroidal anti-inflammatory drugs shows a net confounding bias of 9.66% (supplemental figure 5). The total bias could move a null association between PPI and death from HR=1.00 to HR=1.10 (reflecting the net positive bias of 9.66% rounded up to 10.0%). The association we observed between PPI and death was 1.25>1.10, which cannot be fully due to bias of unmeasured confounding.

In analyses where time-dependent exposure was classified as current use (within 90 days), past use (use prior to 90 days), and never use of PPI; compared to use of H2 blockers and never use of PPI (the reference group), current use of PPI and past use of PPI were associated with increased in risk of death (HR=1.23; CI=1.21-1.26, and HR=1.53; CI=1.50, 1.57, respectively).

The association between PPI and death remained significant after excluding cohort participants who died within 90 days after first PPI or H2 blockers prescription (HR=1.23; CI=1.20, 1.26), or additionally controlling for hemoglobin levels (HR=1.25; CI=1.23, 1.28). In models stratified for the presence of cardiovascular disease, history of pneumonia, chronic kidney disease, and age at T0; there was increased risk of death associated with PPI use in those with and without cardiovascular disease (HR=1.19; CI=1.15, 1.23, and HR=1.30; CI=1.27, 1.34; respectively); with and without history of pneumonia (HR=1.39; CI=1.32, 1.45, and HR=1.21; CI=1.18, 1.24; respectively); with and without chronic kidney disease (HR=1.18; CI=1.14, 1.22, and HR=1.29; CI=1.26, 1.33; respectively); and above and below age 65 (HR=1.17; CI=1.13, 1.20, and HR=1.44; CI=1.39, 1.50; respectively). As a test of specificity, among users of acid suppression therapy, PPI use was not associated with increased risk of the tracer outcome of a motor vehicle accident (HR=0.99; CI= 0.89, 1.10).

Discussion:

This study provides insights into the excess risk of death associated with PPI use. In a large primary cohort of new users of acid suppression therapy followed for a median of 5.71 years, we show a significant association between PPI use and risk of all-cause mortality, risk was increased among those with no documented medical indications for PPI use, and with prolonged duration of use. The results were consistent in multiple analyses and robust to changes in epidemiologic design and statistical specifications, and were reproduced in an earlier and less contemporary cohort from an era where PPI use was far less frequent (45).

PPI are widely used by millions of people for indications and durations that were never tested or approved; they are available over the counter (without prescription) in several countries, and generally perceived as safe

class of therapeutics; they are often overprescribed, rarely deprescribed, frequently started inappropriately during a hospital stay, and their use extended for long term duration without appropriate medical indication (46-50). Results of nationally representative data from the National Health and Nutrition Examination Survey, where analyses were weighted to represent the US adult population, showed that the use of prescription PPI increased from 3.9% to 7.8% from 1999-2000 to 2011-2012, representing a doubling of prevalence ratio(45). Studies estimate that between 53% and 69% of PPI prescriptions are for inappropriate indications(46, 51) where benefits of PPI use may not justify the risks for many users(51-53). The findings in our study highlight a potential excess risk of death among users of PPI, and in particular among cohort participants without GI comorbidities, and that risk is increased with prolonged duration of PPI exposure. While our results should not deter prescription and use of PPI where medically indicated, they may be used to encourage and promote pharmacovigilance and emphasize the need to exercise judicious use of PPI and limit use and duration of therapy to instances where there is a clear medical indication and where benefit outweighs potential risk(1). Standardized guidelines for initiating PPI prescription may lead to reduced overuse(54), regular review of prescription and over the counter medications, and deprescription where a medical indication for PPI treatment ceases to exist may be a meritorious approach(52).

The biologic mechanism underpinning the association of PPI use and risk of death is not clear. Experimental evidence in rats suggests that PPI administration limits the regenerative capacity of livers following partial hepatectomy(55). Administration of PPI upregulates expression of mRNA, protein level, and results in increased activity of the heme oxygenase-1 enzyme in gastric and endothelial cells(56). Heme oxygenase-1 is generally seen as salutary, but its beneficial properties are vitiated at higher doses, and with sustained duration of expression(57). PPI treatment impairs lysosomal acidification and proteostasis and results in increased oxidative stress, dysfunction, telomere shortening and accelerated senescence of human endothelial cells(18, 58). Wu and collaborators undertook a systematic toxicity mechanism analysis using a high-throughput in-silico analysis of microarray data; they reported that PPI up-regulated genes in the cellular retinol metabolism pathway, and down-regulated genes in the complement and coagulation cascades pathway and that PPI may block pathways of antigen presentation, and abrogate the synthesis and secretion of cytokines and complement component proteins and coagulation factors(58, 59). How the changes in gene expression

contribute to excess risk of death is not yet entirely clear. The plausible clinical course leading to heightened risk of death is likely mediated by the occurrence of one or more of the adverse events associated with PPI use (kidney disease, dementia, hypomagnesemia, Clostridium difficile infection, osteoporotic fracture, etc…). Further studies are needed to characterize the biologic mechanisms that might explain the epidemiologic findings in this report.

The constellation of findings in this report must be interpreted with the full cognizance of the observational study design where confounding by indication, and selection bias may represent limitations; we employed an analytic strategy to evaluate the risk of death among users of acid suppression therapy (PPI and H2 blockers); a class of therapeutics generally prescribed for similar indications, a strategy which may lessen but does not completely eliminate the possibility of confounding by indication bias. We additionally built time-dependent propensity score matched cohort, high dimensional propensity score adjusted models, and employed the use of instrumental variable to reduce potential confounding bias. Although we accounted for known covariates in our analyses, it is possible that there are residual confounders (either unmeasured, or unknown) that may still confound the association of PPI and risk of death. However, we evaluated the impact of residual confounding in quantitative bias analyses, and the results suggest that even with the application of unlikely (and exaggerated) set of assumptions, the risk cannot be fully explained by residual confounding. In our analyses, we defined drug exposure as having a prescription for it; since PPI (and H2 blockers) are available over the counter in the United States, it is possible that some patients in this cohort may have obtained and used PPI without prescription. However, owing to financial considerations, this is not highly likely, and if it occurred in some patients, it will have biased the results against the primary hypothesis and resulted in underestimation of risk. The cohort included mostly older white male US Veterans which may limit the generalizability of study results to a broader population. Our datasets did not include information on the cause of death. The study has a number of strengths including the use of national large scale data from a network of integrated health systems which was captured during routine medical care which minimizes selection bias. We employed a new user (incident user) approach, and evaluated the association between PPI use and risk of death using a number of analytical approaches where we consistently found a significant association between PPI use and increased risk of death. The consistency of study findings in our report, and the growing body of evidence in

the literature showing a host of adverse events associated with PPI use are compelling, and because of the high prevalence of PPI use, may have public health implications. Exercising pharmacovigilance and limiting PPI use to instances and durations to instances where it is medically indicated may be warranted.

Footnotes

Contributors: Research area and study design: YX, BB, TL, HX, YY, ZAA; data acquisition: YX, BB; data analysis and interpretation: YX, BB, TL, HX, YY, ZAA; statistical analysis: YX, BB; supervision and mentorship: ZAA. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. ZAA takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained.

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Ethical approval: This research project was reviewed and approved by the Institutional Review Board of the VA Saint Louis Health Care System.

Data sharing: Data is available through the United States Department of Veterans Affairs.

Transparency: The lead authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Table 1: Baseline demographic and health characteristics of overall primary cohort of new users of acid suppression therapy, by type of acid suppressant at time of cohort entry, and those who were ever exposed to PPI.

		Overall cohort	New users of H2 Blockers at time of cohort entry	New users of PPI at time of cohort entry	Ever exposed to PPI [a]	P Value [b]
N		349312	73335	275977	309113	
Age (SD)		61.00 (14.92)	58.48 (15.13)	61.67 (14.79)	61.37 (14.77)	<0.001
eGFR in mL/min/1.73m^2 (SD)		76.89 (22.66)	79.64 (21.96)	76.16 (22.79)	76.60 (22.79)	<0.001
Number of outpatient serum creatinine measurements (SD)		6.85 (7.55)	6.67 (7.39)	6.89 (7.59)	7.27 (8.00)	<0.001
Number of hospitalizations (SD)		0.51 (1.39)	0.52 (1.45)	0.51 (1.37)	0.56 (1.49)	0.014
Race	White (%)	275473 (78.86)	56530 (77.08)	218943 (79.33)	244230 (79.01)	<0.001
	Black (%)	59243 (16.96)	13229 (18.04)	46014 (16.67)	52207 (16.89)	
	Other (%)	14596 (4.18)	3576 (4.88)	11020 (3.99)	12676 (4.10)	
Sex	Male (%)	326659 (93.51)	67748 (92.38)	258911 (93.82)	289233 (93.57)	<0.001
	Female (%)	22653 (6.49)	5587 (7.62)	17066 (6.18)	19880 (6.43)	
Diabetes mellitus (%)		90273 (25.84)	16758 (22.85)	73515 (26.64)	82168 (26.58)	<0.001
Hypertension (%)		225899 (64.67)	44502 (60.68)	181397 (65.73)	203700 (65.90)	<0.001
Chronic lung disease (%)		70281 (20.12)	13849 (18.88)	56432 (20.45)	64777 (20.96)	<0.001
Peripheral artery disease (%)		11439 (3.27)	2225 (3.03)	9214 (3.34)	10680 (3.46)	<0.001
Cardiovascular disease (%)		98137 (28.09)	17436 (23.78)	80701 (29.24)	89878 (29.08)	<0.001
Cerebrovascular disease (%)		1858 (0.53)	372 (0.51)	1486 (0.54)	1719 (0.56)	0.30
Dementia (%)		16421(4.70)	3115 (4.25)	13306 (4.82)	15384 (4.98)	<0.001
Hyperlipidemia (%)		200397 (57.37)	39818 (54.30)	160579 (58.19)	181524 (58.72)	<0.001
Hepatitis C (%)		5034 (1.44)	1184 (1.61)	3850 (1.40)	4444 (1.44)	<0.001
HIV (%)		114 (0.03)	38 (0.05)	76 (0.03)	113 (0.04)	0.001
Cancer (%)		49666 (14.22)	9123 (12.44)	40543 (14.69)	45633 (14.76)	<0.001
GERD (%)		100980 (28.91)	20562 (28.04)	80418 (29.14)	94517 (30.58)	<0.001
Upper GI tract bleeding (%)		9310 (2.67)	926 (1.26)	8384 (3.04)	9098 (2.94)	<0.001
Ulcer disease (%)		25626 (7.34)	3564 (4.86)	22062 (7.99)	24864 (8.04)	<0.001
H. Pylori infection (%)		3078 (0.88)	141 (0.19)	2937 (1.06)	3239 (1.05)	<0.001
Barrett's esophagus (%)		2324 (0.67)	89 (0.12)	2235 (0.81)	2382 (0.77)	<0.001
Achalasia (%)		151 (0.04)	10 (0.01)	141 (0.05)	154 (0.05)	<0.001
Stricture (%)		1992 (0.57)	132 (0.18)	1860 (0.67)	2051 (0.66)	<0.001
Esophageal		213 (0.06)	17 (0.02)	196 (0.07)	213 (0.07)	<0.001

adenocarcinoma (%)					
Years of follow up (IQR)[c]	5.71 (5.11 – 6.37)	4.38 (1.16 – 5.92)d	5.67 (5.09 – 6.34)	5.59 (4.82 – 6.28)	<0.001
Days of having related prescription during follow-up (IQR)	442 (199 – 1272)[e]	120 (60 – 400) [d]	450 (120 – 1299)	450 (120 – 1266)	<0.001
Death (%)	81463 (23.32)	9018 (12.30) [d]	67450 (24.44)	72445 (23.44)	<0.001
Incident death in 100 person years (95% CI)	4.47 (4.44 – 4.50)	3.32 (3.25 – 3.39) [d]	4.74 (4.70 – 4.77)	4.67 (4.64 – 4.71)	<0.001

a. Includes patients exposed to PPI at T0 (n=275977) and during follow-up (n=33136). Variables were measured at time of PPI exposure.
b. P value for difference between exposed to H2 at T0 and exposed to PPI at T0
c. From T0 to first occurrence of death or September 30, 2013
d. Outcome measured from T0 to first occurrence of exposure PPI, death or September 30, 2007
e. Days of having PPI or H2 blockers

Abbreviations: CI, Confidence interval; eGFR, estimated Glomerular Filtration Rate; GERD, Gastroesophageal Reflux Disease; HIV, human immunodeficiency virus; IQR, interquartile range; SD, Standard deviation

Table 2: Association between PPI use and risk of death:

Association Between PPI and Death		Reference	PPI use
PPI use VS H2 blockers use (N=349,312)	Incident rate (95% CI)	3.32 (3.25 – 3.39)	4.67 (4.64 – 4.71)
	Unadjusted HR (95% CI)	1	1.46 (1.43 – 1.49)
	Adjusted HR (95% CI)	1	1.25 (1.23 – 1.28)
High-dimensional propensity score adjusted model of new users of PPI VS H2 blockers (N=349,312)	Incident rate (95% CI)	3.32 (3.25 – 3.39)	4.74 (4.70, 4.77)
	HR (95% CI)	1	1.16 (1.13 – 1.18)
Two-stage residual inclusion estimation model of new users of PPI VS H2 blockers (N=318,960)	Incident rate (95% CI)	3.32 (3.25 – 3.39)	4.74 (4.70 – 4.77)
	HR (95% CI)	1	1.21 (1.16 – 1.26)
Time dependent propensity score matched PPI VS H2 blockers (N=146,670)	Incident rate (95% CI)	3.32 (3.25 – 3.39)	4.37 (4.30 – 4.44)
	Unadjusted HR (95% CI)	1	1.38 (1.34 – 1.42)
	Adjusted HR (95% CI)	1	1.34 (1.29 – 1.39)
PPI use VS no PPI (N=3,288,092)	Incident rate (95% CI)	3.64 (3.63 – 3.65)	5.50 (5.47 – 5.53)
	Unadjusted HR (95% CI)	1	1.47 (1.46 – 1.48)
	Adjusted HR (95% CI)	1	1.15 (1.14 – 1.15)
PPI use VS no PPI or H2 blockers (N=2,886,879)	Incident rate (95% CI)	3.47 (3.46 – 3.48)	5.50 (5.47 – 5.53)
	Unadjusted HR (95% CI)	1	1.53 (1.52 – 1.54)
	Adjusted HR (95% CI)	1	1.23 (1.22 – 1.24)
PPI VS H2 blockers in a cohort without GI conditions (N=214,521)	Incident rate (95% CI)	3.80 (3.71 – 3.89)	5.39 (5.34 – 5.44)
	Unadjusted HR (95% CI)	1	1.47 (1.43 – 1.51)
	Adjusted HR (95% CI)	1	1.24 (1.21 – 1.27)
PPI VS no PPI in a cohort without GI conditions (N=2,790,697)	Incident rate (95% CI)	3.54 (3.53 – 3.55)	5.89 (5.86 – 5.93)
	Unadjusted HR (95% CI)	1	1.62 (1.61 – 1.63)
	Adjusted HR (95% CI)	1	1.19 (1.18 – 1.20)

PPI VS no PPI or H2 blockers in a cohort without GI conditions (N=2,543,480)	Incident rate (95% CI)	3.45 (3.44 – 3.46)	5.89 (5.86 – 5.93)
	Unadjusted HR (95% CI)	1	1.65 (1.64 – 1.67)
	Adjusted HR (95% CI)	1	1.22 (1.21 – 1.23)
PPI VS H2 blockers in a cohort without GI conditions except for GERD (N=311,115)	Incident rate (95% CI)	3.30 (3.23 – 3.37)	4.51 (4.47 – 4.54)
	Unadjusted HR (95% CI)	1	1.42 (1.38 – 1.45)
	Adjusted HR (95% CI)	1	1.24 (1.21 – 1.27)
PPI VS no PPI in a cohort without GI conditions except for GERD (N=3,132,126)	Incident rate (95% CI)	3.59 (3.58 – 3.60)	5.36 (5.34 – 5.39)
	Unadjusted HR (95% CI)	1	1.45 (1.44 – 1.46)
	Adjusted HR (95% CI)	1	1.14 (1.13 – 1.14)
PPI VS no PPI or H2 blockers in a cohort without GI conditions except for GERD (N=2,678,478)	Incident rate (95% CI)	3.44 (3.44 – 3.45)	5.36 (5.34 – 5.39)
	Unadjusted HR (95% CI)	1	1.50 (1.49 – 1.51)
	Adjusted HR (95% CI)	1	1.22 (1.21 – 1.22)

a. Incident rate as incident death in 100 person years
b. All models except time dependent propensity score matched and high-dimensional propensity score adjusted models were time dependent models. Effect of PPI was treated as time dependent and was defined as once patients used PPI, they were in PPI group during the remaining follow-up.
c. Adjusted model controlling for eGFR, age, race, gender, number of serum creatinine measurements, number of hospitalizations, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, cancer, GERD, upper GI tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma, unless used in analysis inclusion criteria.
d. GI conditions include upper GI tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma

Abbreviations: CI, Confidence interval; HR, Hazard Ratio

Table 3: Duration of exposure to PPI and risk of death among new users of PPI (n=166,098)

Duration (Days)	≤ 30	31 - 90	91 - 180	181 - 360	361 - 720
N (%)	24748 (14.90)	39345 (23.69)	29334 (17.66)	33907 (20.41)	38764 (23.34)
Hazard Ratio (95%CI)	1	1.05 (1.02-1.08)	1.17 (1.13-1.20)	1.31 (1.27-1.34)	1.51 (1.47-1.56)

a. Within people exposure to PPI between 1 to 720 days
b. Model controls for eGFR, age, race, gender, number of serum creatinine measurements, number of hospitalizations, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, cancer, GERD, upper GI tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma
c. Time zero defined as date when the patients last PPI prescription ends

Figure legends:

Figure 1: Survival curves for PPI and H2 blockers

Figure 2: Duration of PPI exposure and risk of death among new PPI users (n=166,098)

Supplemental Figures:

Supplemental Figure 1: Flowchart of primary cohort

Supplemental Figure 2a: Flowchart of secondary cohort PPI vs no PPI

Supplemental Figure 2b: Flowchart of secondary cohort PPI vs no PPI no H2 blockers

Supplemental figure 3: Duration of PPI exposure and risk of death among new PPI users in an older (less contemporary) sensitivity cohort (n=101,109)

Supplemental figure 4: Estimation of the impact of uncontrolled confounder using the rule-out approach: To investigate the impact of potential residual confounding; rule-out approach was used, where prevalence of potential confounder was set at 30% and prevalence of exposure (PPI use) was set at 88.5% (the latter is derived from our data). The X axis describes the Odds Ratio (OR) of the association between the confounder and PPI users. The Y axis describes the Hazard Ratio (HR) of the association between the confounder and risk of death. The blue line splits the area into two: the upper right area represents all parameter combinations of OR (between PPI use and confounder) and HR (between confounder and death) that are strong enough to move the apparent HR (AHR) from 1.25 (the HR observed in our primary analysis) to 1 or lower, rejecting the hypothesis of an association between PPI use and risk of death. The corollary observation is that the area to the lower left represents all parameter combinations that would result in acceptance of the primary hypothesis. For example, the results show that for uncontrolled confounder that is twice as likely among PPI users (OR=2), the strength of the association between the uncontrolled confounder and risk of death would have to exceed 4 (HR>4) for the uncontrolled confounder to fully explain the observed association between PPI and death (where the combination of OR=2, HR>4 is in the area above the blue line).

Supplemental figure 5: External adjustment to estimate the impact of 3 unmeasured confounders: To investigate the impact of potential residual confounding, we applied external adjustment to estimate the impact of 3 unmeasured confounders including obesity, smoking, and use of therapeutics including anticoagulants, antiplatelet agents, and non-steroidal anti-inflammatory drugs. In order to generate extreme bias estimates (against the hypothesis) we assumed that users of H2 Blockers are generally healthy and have similar health characteristics as the general population. We used published estimates from external data sources as follows (2, 41-44): Prevalence of obesity 30.00%, OR for PPI and obesity=1.30, and HR for obesity and death =1.30; prevalence of smoking=24.79%, OR for PPI and smoking =1.20, and HR for smoking and death =2.80; prevalence of anticoagulants, antiplatelet, and NSAIDs use=28.85%, OR for PPI and drug =2.20, and HR for drug and death =1.30. Given the HR between each confounder and risk of death, and assuming there is no overlap in risk among confounders (which is an unlikely assumption, but one which would generate the greatest amount of bias against our hypothesis), we found a total positive bias (or net confounding bias) of 9.66% (1.47%+4.23%+3.96%). The total bias could move a null association between PPI to death from HR=1.00 to HR=1.10 (reflecting the net positive bias of 9.66% rounded up to 10.0%). The association we observed between PPI and death is 1.25 (higher than 1.10), suggesting that it cannot be fully due to bias of unmeasured confounding. (Using the curves in the figures; for obesity, when the HR=1.30, the corresponding bias=1.47%; for smoking, when the HR=2.80, the corresponding bias=4.23%; for anticoagulants, antiplatelet, and NSAIDs, when the HR=1.30, the corresponding bias=3.96%).

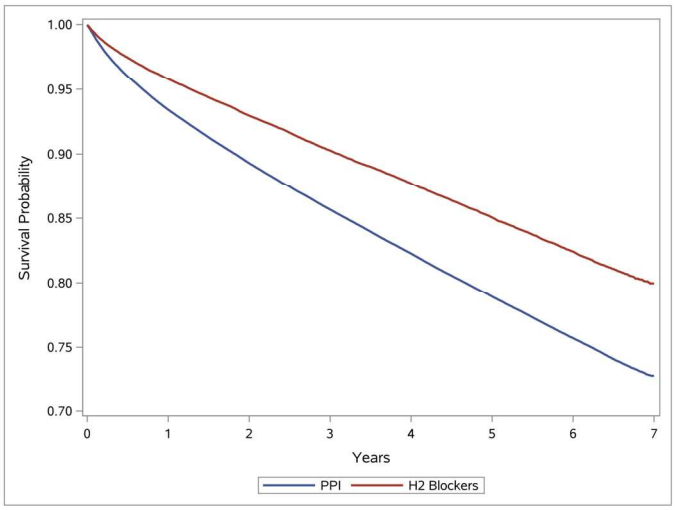


Figure 1: Survival curves for PPI and H2 blockers
Figure 1
190x142mm (300 x 300 DPI)

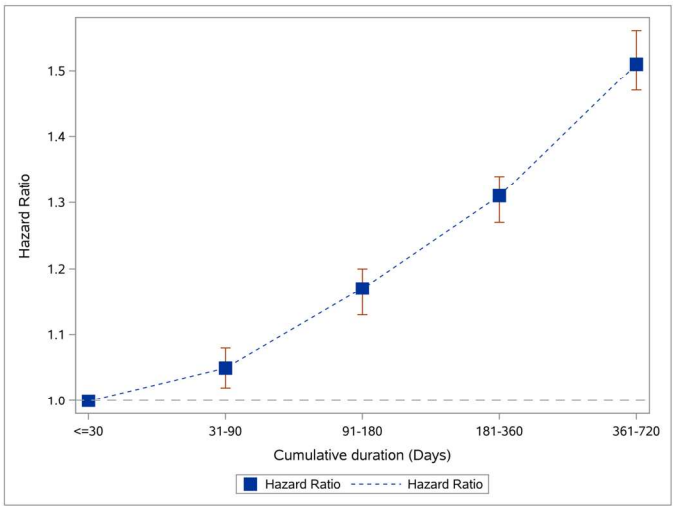
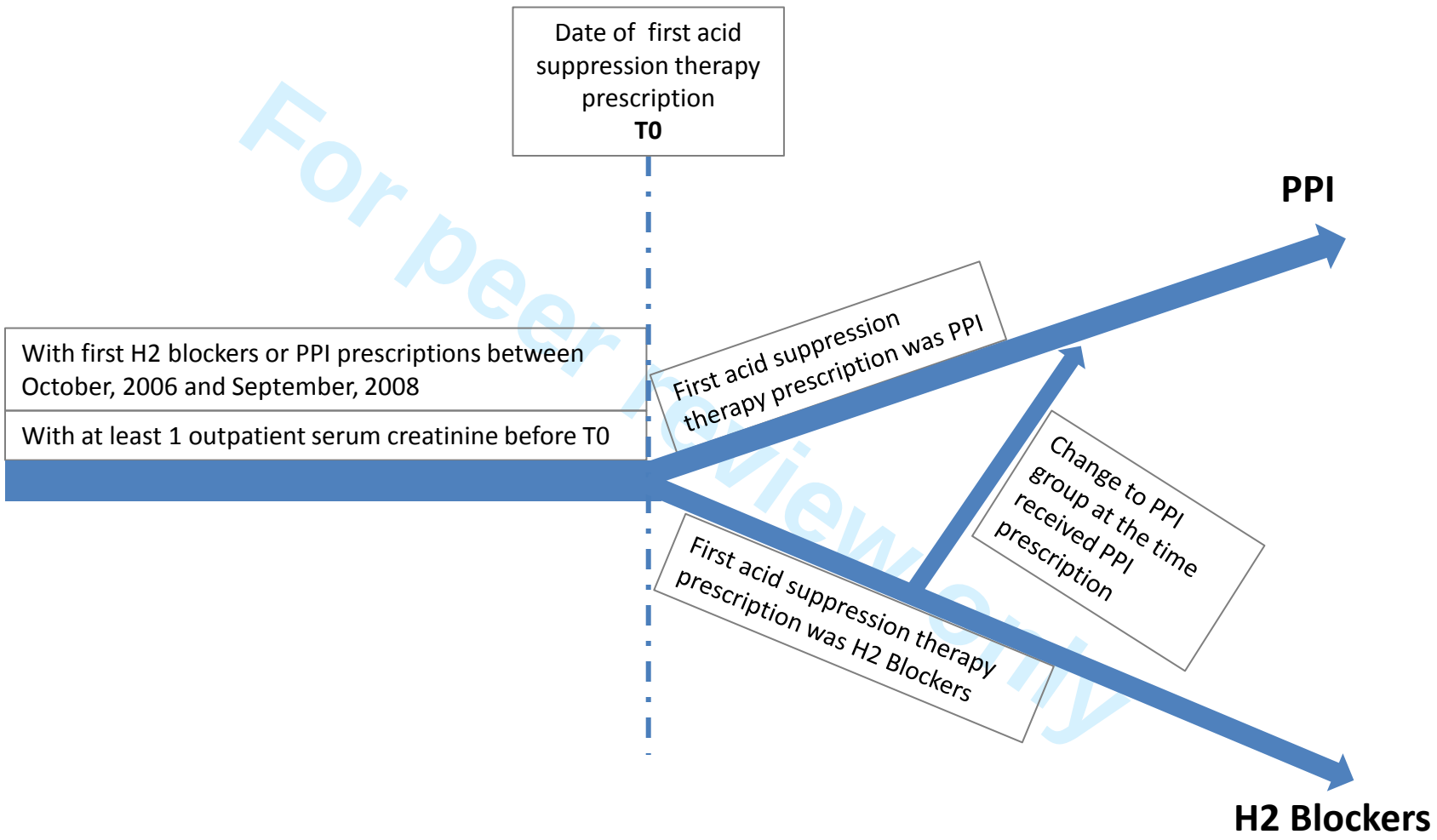


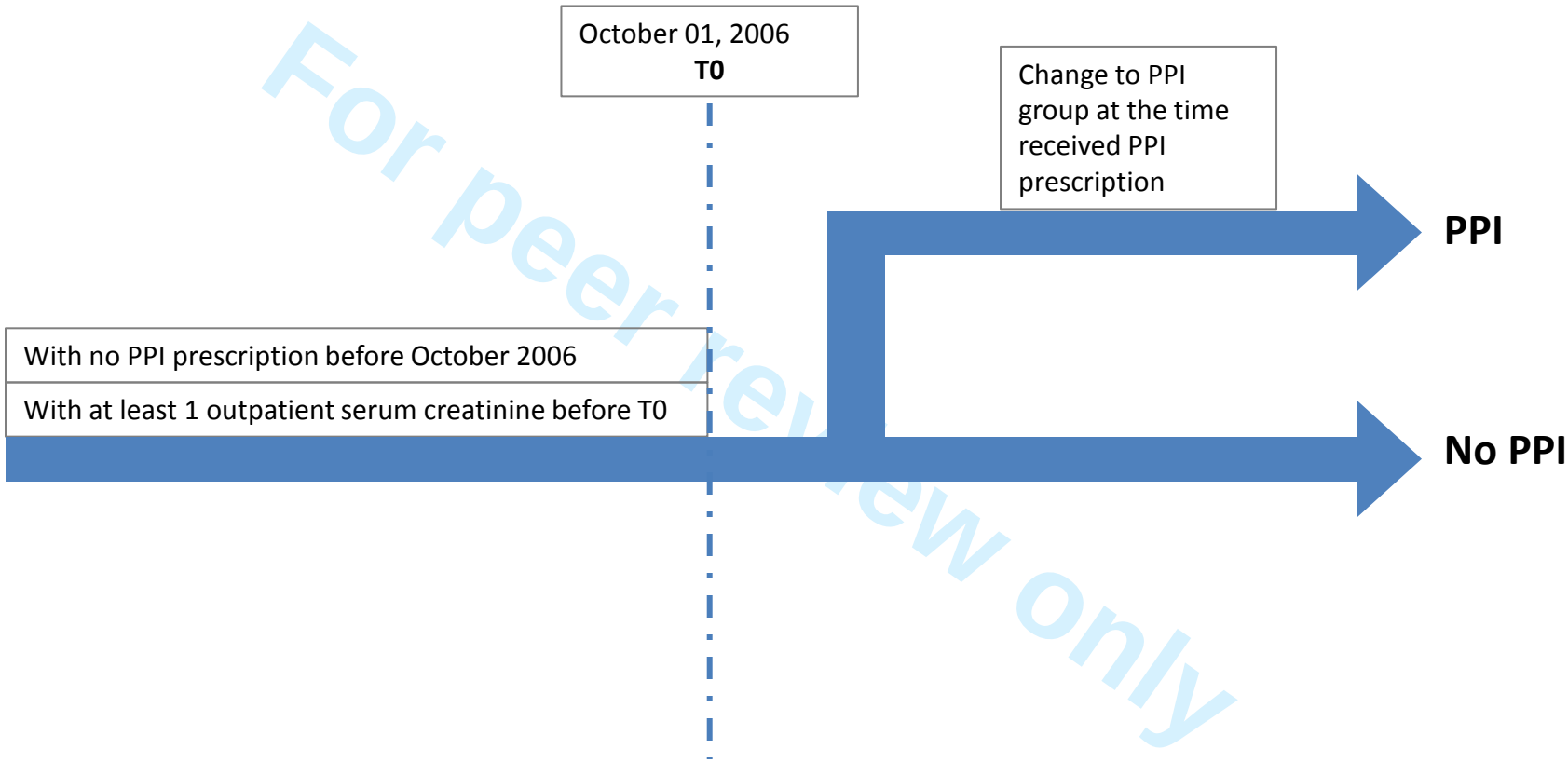
Figure 2: Duration of PPI exposure and risk of death among new PPI users (n=166,098)
Figure 2
190x142mm (300 x 300 DPI)

BMJ Open

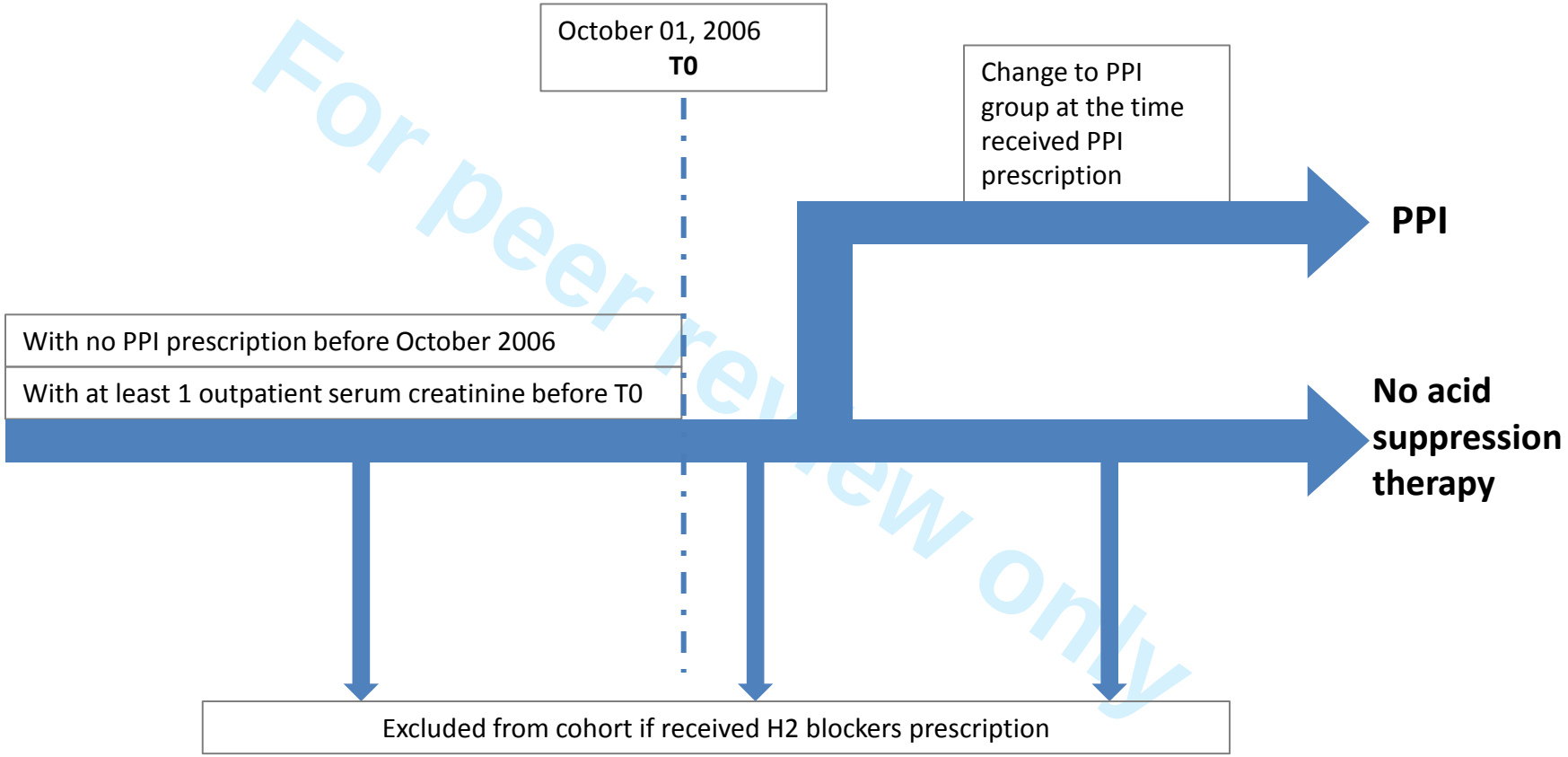
Supplemental Figure 1



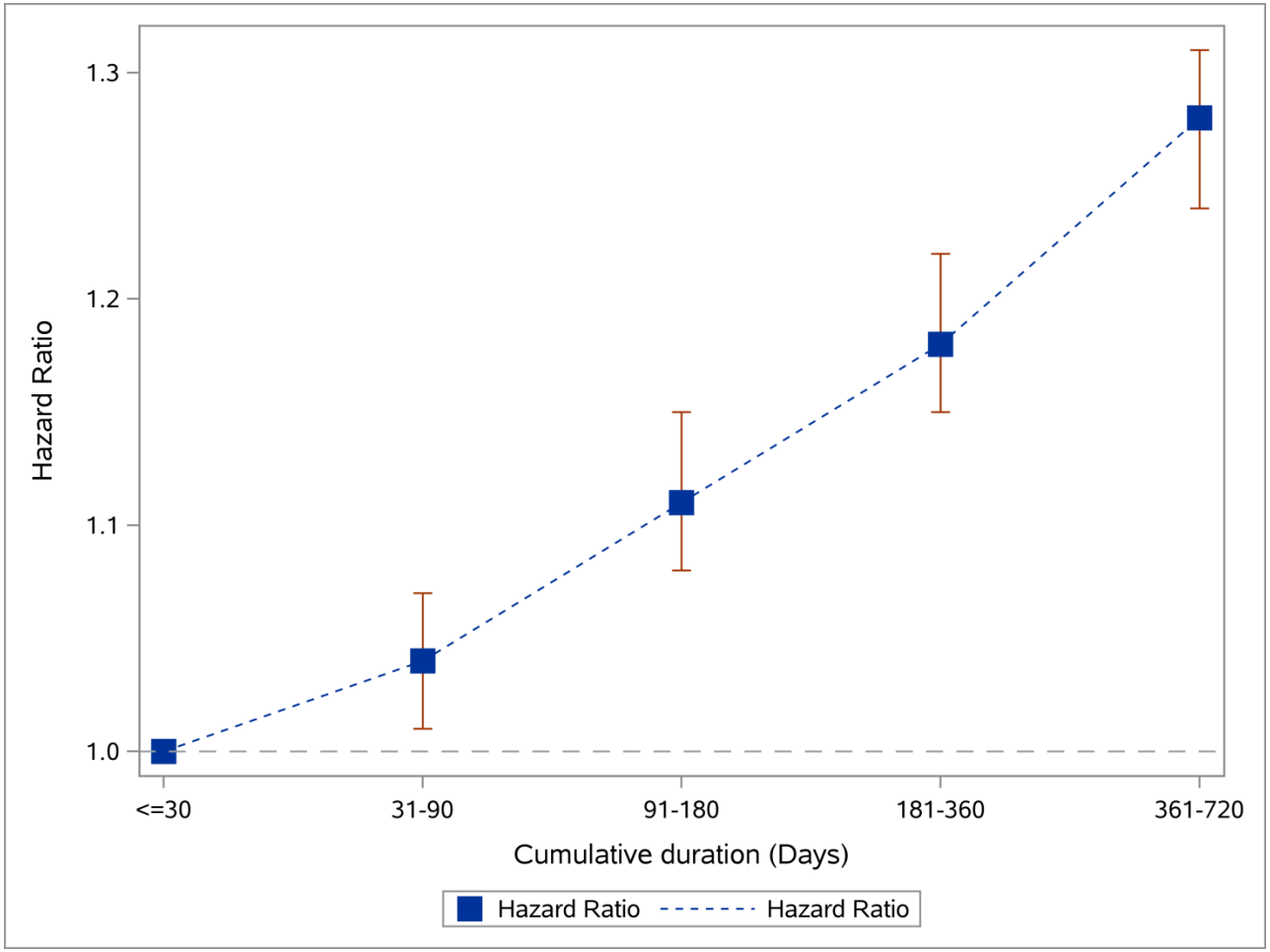
Supplemental Figure 2a



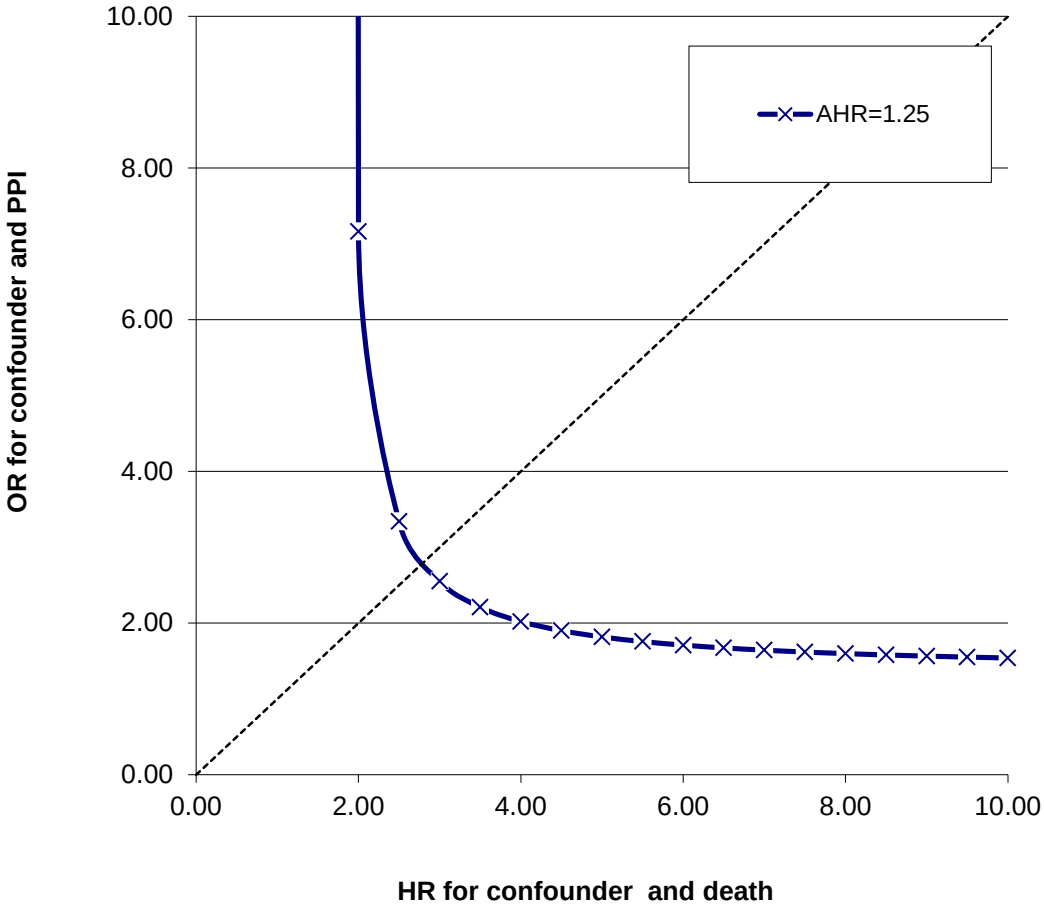
Supplemental Figure 2b



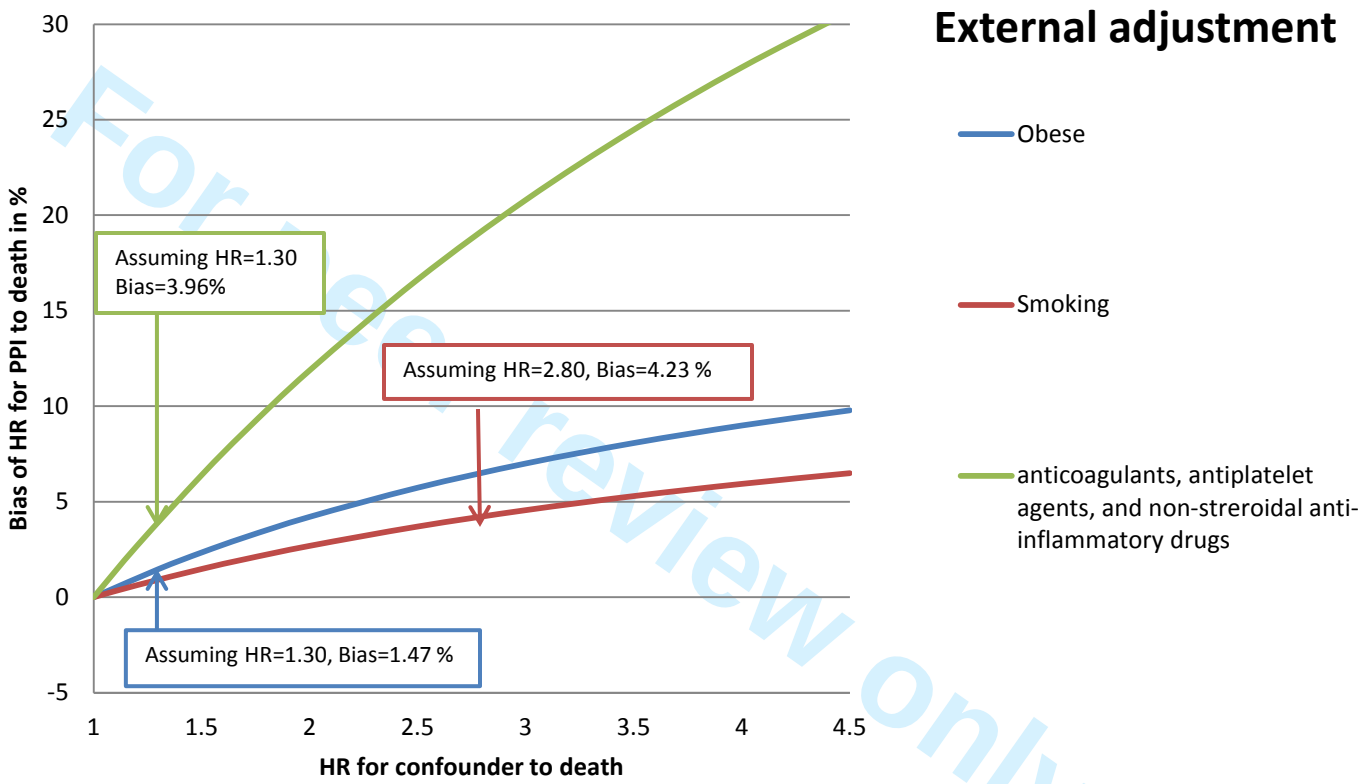
Supplemental Figure 3



Supplemental Figure 4



Supplemental Figure 5



Supplemental table 1: Baseline demographic and health characteristics of the overall 2001 cohort of new users of acid suppression therapy, by type of acid suppressant at time of cohort entry, and those who were ever exposed to PPI.

		Overall cohort	New users of H2 Blockers at time of cohort entry	New users of PPI at time of cohort entry	Ever exposed to PPI [a]	P Value [b]
N		396884	208492	188392	293265	
Age (SD)		62.98 (13.05)	61.93 (13.24)	64.14 (12.74)	63.78 (12.81)	<0.001
eGFR in mL/min/1.73m^2 (SD)		74.74 (22.43)	76.24 (22.04)	73.09 (22.73)	73.38 (22.61)	<0.001
Number of outpatient serum creatinine measurements (SD)		3.01 (3.40)	2.95 (3.23)	3.06 (3.58)	4.52 (5.51)	<0.001
Number of hospitalizations (SD)		0.37 (0.96)	0.36 (0.95)	0.38 (0.97)	0.51 (1.30)	<0.001
Race	White (%)	318534 (80.26)	164295 (78.80)	154239 (81.87)	236930 (80.79)	<0.001
	Black (%)	58355 (14.70)	32053 (15.37)	26302 (13.96)	42498 (14.49)	
	Other (%)	19995 (5.04)	12144 (5.82)	7851 (4.17)	13837 (4.72)	
Sex	Male (%)	377769 (95.18)	197685 (94.82)	180084 (95.59)	279023 (95.14)	<0.001
	Female (%)	19115 (4.82)	10807 (5.18)	8308 (4.41)	14242 (4.86)	
Diabetes mellitus (%)		92555 (23.32)	46562 (22.33)	45993 (24.41)	74344 (25.35)	<0.001
Hypertension (%)		231296 (58.28)	119554 (57.34)	111742 (59.31)	184529 (62.92)	<0.001
Chronic lung disease (%)		75810 (19.10)	39270 (18.84)	36540 (19.40)	64254 (21.91)	<0.001
Peripheral artery disease (%)		9141 (2.30)	4646 (2.23)	4495 (2.39)	8751 (2.98)	0.001
Cardiovascular disease (%)		122301 (30.82)	59814 (28.69)	62487 (33.17)	101220 (34.51)	<0.001
Cerebrovascular disease (%)		1529 (0.39)	776 (0.37)	753 (0.40)	1419 (0.48)	0.16
Dementia (%)		12031 (3.03)	6094 (2.92)	5937 (3.15)	10615 (3.62)	<0.001
Hyperlipidemia (%)		152040 (38.31)	78546 (37.67)	73494 (39.01)	130557 (44.52)	<0.001
Hepatitis C (%)		9332 (2.35)	4832 (2.32)	4500 (2.39)	8456 (2.88)	0.14
HIV (%)		209 (0.05)	105 (0.05)	104 (0.06)	183 (0.06)	0.51
Cancer (%)		46451 (11.70)	23312 (11.18)	23139 (12.28)	39473 (13.46)	<0.001
GERD (%)		110217 (27.77)	52586 (25.22)	57631 (30.59)	114132 (38.92)	<0.001

Upper GI tract bleeding (%)	11282 (2.84)	3352 (1.61)	7930 (4.21)	12458 (4.25)	<0.001
Ulcer disease (%)	35189 (8.87)	14152 (6.79)	21037 (11.17)	37472 (12.78)	<0.001
H. Pylori infection (%)	2599 (0.65)	477 (0.23)	2122 (1.13)	3795 (1.29)	<0.001
Barrett's esophagus (%)	0 (0.00)	0 (0.00)	0 (0.00)	245 (0.08)	NA
Achalasia (%)	188 (0.05)	41 (0.02)	147 (0.08)	245 (0.08)	<0.001
Stricture (%)	2218 (0.56)	415 (0.20)	1803 (0.96)	2953 (1.01)	<0.001
Esophageal adenocarcinoma (%)	223 (0.06)	79 (0.04)	147 (0.08)	262 (0.09)	<0.001
Years of follow up (IQR)[c]	5.65 (5.05 – 6.28)	3.35 (1.01 – 5.71) [d]	5.51 (5.01 – 6.08)	5.23 (3.22 – 5.90)	<0.001
Days of having related prescription during follow-up (IQR)	587 (168 – 1423)[e]	188 (90 – 561) [d]	621 (171 – 1496)	579 (172 – 1350)	<0.001
Death (%)	102802 (25.90)	31260 (14.99) [d]	51785 (27.49)	71565 (24.40)	<0.001
Incident death in 100 person years (95% CI)	5.08 (5.05 – 5.11)	4.40 (4.35 – 4.45) [d]	5.56 (5.51 – 5.61)	5.45 (5.41 – 5.49)	<0.001

a. Includes patients exposed to PPI at T0 (n=275977) and during follow-up (n=33136). Variables were measured at time of PPI exposure.
b. P value for difference between exposed to H2 at T0 and exposed to PPI at T0
c. From T0 to first occurrence of death or September 30, 2013
d. Outcome measured from T0 to first occurrence of exposure PPI, death or September 30, 2007
e. Days of having PPI or H2 blockers

Abbreviations: CI, Confidence interval; eGFR, estimated Glomerular Filtration Rate; GERD, Gastroesophageal Reflux Disease; HIV, human immunodeficiency virus; IQR, interquartile range; NA, Not Applicable; SD, Standard deviation

Supplemental table 2: Duration of exposure to PPI and risk of death among new users of PPI in the 2001 cohort (n=101,109)

Duration (Days)	≤ 30	31 - 90	91 - 180	181 - 360	361 - 720
N (%)	15204 (15.04)	20409 (20.19)	17137 (16.95)	21586 (21.35)	26773 (26.48)
Hazard Ratio (95%CI)	1	1.04 (1.01, 1.07)	1.11 (1.08, 1.15)	1.18 (1.15. 1.22)	1.28 (1.24, 1.31)

a. Within people exposure to PPI between 1 to 720 days
b. Model controls for eGFR, age, race, gender, number of serum creatinine measurements, number of hospitalizations, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, cancer, GERD, upper GI tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma
c. Time zero defined as date when the patients last PPI prescription end

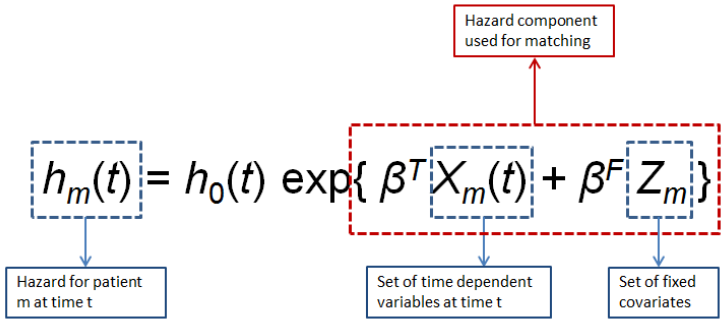
Supplemental Methods:

Time Dependent Propensity Score Matching

1. Using the primary cohort (N=349, 312), all covariates except for age, race and gender were treated as time-dependent variables from T0 till date of PPI use or end of follow up, whichever occurred first. Specifically, time-dependent eGFR indicated the eGFR at day t (where the value was equal to the outpatient eGFR measurement most close and prior to time t); time-dependent number of outpatient serum creatinine measurements and number of hospitalizations indicated the cumulative value from October 01, 1998 till day t; time-dependent disease status including diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, cancer, hepatitis C, HIV, dementia and diseases associated with acid suppression therapy use such as gastroesophageal reflux disease (GERD), upper gastrointestinal (GI) tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma indicated if participants were diagnosed with the disease between October 01, 1998 and day t.

2. Time-dependent Cox regression was applied, where time until receipt of first PPI prescription was the outcome (participants receiving PPI prescription at T0 were considered to have the event with survival time equal to 0 days). Time-dependent variables from step 1 and age, race and gender were used as predictors in the model in order to obtain parameter estimates for the predictors.

3. Every participant's hazard component at day t was computed based on the parameter estimates from step 2 and their covariate values at day t.



The hazard component was used as the time-dependent propensity score.

4. Beginning from T0 (day 0), a 1:1 sequential greedy matching without replacement was conducted. People who received PPI prescription at day t (case group at day t) were matched with people who had not yet received PPI prescription at day t (control group at day t) based on their propensity score at day

t. The order of both case and control groups was randomized before matching. A matched pair was considered successfully matched only if the propensity score difference was less than 0.2 times the standard deviation of the hazard component at time t. If no successful match was made the case in the pair was withdrawn from the further matching while the control was left in the data pool. Matching was ended when 1/ all participants in control or case group were matched or 2/ day t equaled day 1827.

5. After the matching, conditional Cox regressions stratified by matched pairs were conducted to examine the association between PPI and death.

High-dimensional propensity score:

1. Using the primary cohort (N=349,312), participants data from 1 year before T0 till T0 were collected in 5 dimensions consisting off: the first 3 digits of outpatient diagnoses ICD9 codes, the outpatient procedures CPT codes, the first 3 digits of inpatient diagnoses ICD9 codes, the first 3 digits of inpatient procedures ICD9 codes, and the outpatient drug names without dose.

2. Within each of the 5 dimensions, the top 300 most frequent items were selected, which yielded 300*5=1500 potential items.

3. For each participant, we determined if each of the 1500 potential items 1\ ever occurred, 2\ if the number of occurrences for the participant was higher than the number of occurrences in 50% of the participants and 3\ if the number of occurrences for the participant was higher than the number of occurrences in 75% of the participants. This step results in 1500*3=4500 binary potential variables. If the 50% or 75% percentile of the number of item occurrences was less than 1, then the variable were coded as 0 for all participants. If the 50% and 75% percentile of the number of item occurrences had the same value, then the 75% variable was coded as 0 for all participants.

4. Bias was calculated using formula based on apparent relative risk for each of the 4500 variables:

$$Bias=(P\_C1\ (RR\_CD-1)+1)/(P\_C0\ (RR\_CD-1)+1)\ ,\text{if } RR\_CD \geq 1$$

$$Bias=(P\_C1\ (1/RR\_CD-1)+1)/(P\_C0\ (1/RR\_CD-1)+1)\ ,\text{if } RR\_CD < 1$$

Where P_C1 indicates the prevalence of the variable in the PPI group, P_C0 indicates the prevalece of the variable in the control group, and RR_CD indicate relative risk of death associated with the variable.

5. The top 500 variables with the largest | log(bias)| value were selected as binary empirical covariates for inclusion in the propensity score modeling.

6. The 500 variables and age, gender, race, and eGFR were used to obtain propensity scores from logistic regression where the outcome was receipt of PPI or not at T0. Propensity scores were then categorized into deciles.

7. Multivariate Cox regression with an indicator for propensity score decile was used to evaluate the association between PPI and death. Patients in the control group who received PPI later were censored at the time they received PPI.

Two-stage residual inclusion estimation (Instrumental Variable):

1. Based on the primary cohort (N=349,312), for each participant, data on prescriptions by the physician who prescribed the participant the acid suppression therapy at T0 was collected from 6 months before the participant's T0 till T0.

2. For each participant, the percentage of PPIs prescribed to new acid suppression therapy users by their prescribing physician, excluding the prescription of the participant, in the 6 months prior to and including T0 was computed and used as an instrumental variable. Participants whose prescribing physician did not prescribe any other acid suppression therapy to new users in the 6 months prior to and including T0 were excluded from the analysis.

3. In order to predict the participants' possibility of receiving PPI, instrumental variable and co-variables were used in a logistic regression model where the outcome was acid suppression therapy prescription at T0.

4. Residual terms were computed as the difference between participants' real probability (1 if PPI, 0 if H2 blocker) and predicted probability.

5. Multivariate Cox regression, which included the residual term and co-variables, were conducted to evaluate the relationship between PPI and death. Patients in the control group who received PPI later were censored at the time they received PPI.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3-4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Additional matched cohort described in Supplemental methods
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7 and Supplemental methods
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	Due to the feature of VA data on death

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	information, no loss of follow-up would occur. All death data is captured by the Veterans Benefit Administration.
		(*e*) Describe any sensitivity analyses	7-8

Results			**Reported Page**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4-5
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	19-20 Table 1
		(b) Indicate number of participants with missing data for each variable of interest	see page 7 for reason
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	20 Table 1
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	19 Table 1
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	21-22 Table 2
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if	15

		applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.