Do proton pump inhibitors increase mortality? A systematic review and in-depth analysis of the evidence

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Abstract

Aims: Proton pump inhibitors (PPIs) were primarily approved for short term use (2 to 8 weeks). However, PPI use continues to expand. Widely believed to be safe, we reviewed emerging evidence on increased mortality with PPI long-term use. Methods: We searched MEDLINE, Embase and Cochrane Central for evidence from systematic reviews (SR) and primary studies reporting all-cause mortality in adults treated with a PPI for any indication (duration > 12 weeks) compared to patients without PPI treatment (no use, placebo or H2RA use). Data was synthesized, analysed, critically examined and interpreted herein. Results: From 1304 articles, one systematic review (SR) was identified that reported on all-cause mortality. The SR pooled 3 observational studies with data to 1 year: odds ratio, 95% confidence interval (CI) 1.53-1.84. A randomized controlled trial (RCT), the COMPASS (Cardiovascular Outcomes for People Using Anticoagulant Strategies) RCT with data to 3 years: hazard ratio (HR) 1.03, 95% CI 0.92-1.15. The US Veterans Affairs cohort study using a large national dataset with data to 10 years; HR 1.17, 95% CI (1.10-1.24), (NNH) 22. The most common causes of death were from cardiovascular and chronic kidney diseases, with an excess death of 15 and 4 per 1000 patients, respectively over 10-year period. Conclusions: Harms arising from real world medication use are best evaluated using a pharmacovigilance 'convergence of proof' approach using data from a variety of sources and varied study designs. Careful appraisal of the totality of available evidence leads to the conclusion that long-term PPI utilization increases mortality

What this Study Adds

- This article represents an in-depth systematic review and analysis of the best available evidence linking long-term PPI use to mortality.
- We have highlighted the importance of using a modern standard of pharmacovigilance research framework for evaluating the serious adverse events associated with medications.
- Pooled results from 3 observational studies found that long-term PPI exposure was associated with an increased risk of all-cause mortality. The greater the PPI exposure, the stronger the association.
- A 10-year observational study of 214,467 people found that PPI exposure was associated with an increased risk of all-cause mortality.
- The COMPASS, RCT did not find increased mortality after 3-year PPI exposure in 17, 598 people.
- The RCT findings because of its smaller sample size and shorter duration are not inconsistent with findings from the observational studies.

Introduction

Prescription proton pump inhibitors (PPIs) are primarily approved for short-term use (2 to 8 weeks) for peptic ulcer disease (PUD), reflux esophagitis and non-ulcer dyspepsia [1]. Longer-term indications include gastric bleeding, severe esophagitis or Barrett's esophagus or to prevent gastric damage associated with

adverse effects of other drugs. However, these long-term indications only account for a small proportion of long-term PPI use in Canada, which exceeds 10% of the adult population [2,3].

The short-term benefits of PPIs as a drug class are not disputed[4,5]. However, the belief that the positive net benefit to harm ratio with short-term treatment extends to long-term use (greater than 12 weeks) has been challenged by post-market analyses[6-9].

Health Canada [10] has issued warnings for a number of adverse events and drug interactions that were not recognized when the first PPIs were approved 30 years ago: hypomagnesemia accompanied by hypocalcemia and hypokalemia (2011), *clostridium difficile*associated diarrhea (2012), bone fractures (2013), subacute cutaneous lupus erythematosus (2017) as well as new drug interactions with clopidogrel (2009) and methotrexate (2012). There are US Food and Drug Administration warnings for PPI use and risk of increased risk of bone fractures, *clostridium difficult* infection (*CDI*) and profound hypomagnesemia.

A number of professional associations and independent drug bulletins recommend reducing PPI exposure and provide tools for de-prescribing[11,12]. Encouraging restraint has yet to achieve a measurable impact on long-term PPI prescribing for the common indications. Is the evidence of harms sufficient that we should intensify efforts to constrain new prescriptions and to deprescribe for long-term users?

Recently in our 2016 systematic review, we reported on the comparative effectiveness of PPIs, benefits and harms, as well as evidence for considering deprescribing [4,5]. In many clinical settings, we do not know whether the benefits of long-term PPI use outweigh the harms. Harms were underreported in RCTs that directly compared different PPIs. Mortality, SAE, and withdrawal due to adverse events were not reported [4,5]. Longer duration, head-to-head comparative RCTs specifically designed to monitor adverse effects have not been conducted.

Recent evidence from a clinical trial [13] has raised doubts on a growing consensus from observational studies and systematic reviews of observational studies that PPI exposure is associated with increased risk of death; the risk increases with increased exposure[14-16]. Therefore, the aim of this review is to summarize and critically examine evidence from systematic reviews and primary studies reporting all-cause mortality.

Methods

Searching strategy

Recently in our 2016 systematic review, mortality outcome was not reported in RCTs that directly compared different PPIs[4,5]. An updated search was performed by information specialist from January 2014-the date of our last comprehensive search and PPI class review to January 2020 in the following databases: PubMed, MEDLINE, EMBASE (through Ovid), the Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Database of Systematic Reviews. The combination of the following medical subheadings (MeSH) and key words was used for database searching: proton pump inhibitors or PPI and adverse events or esomeprazole or pantoprazole or omeprazole or rabeprazole or lansoprazole and any indications. Alternative spellings and abbreviations of the above key words were also considered with no limitation on the language or the publishing date.

Inclusion criteria

Systematic reviews (with or without meta-analysis) or primary studies were included that met the following criteria: (Cochrane 'PICOS' format):

P - adults aged 18 years or older

I - PPI therapy for any indication for duration of more than 12 weeks

C – Non-use or histamine type-2 receptor antagonist (H2RA) use

O – All-cause mortality

Primary studies were sought and included that had not been available by SR search cut-off dates up to January 2020.

Data extraction and synthesis

Two investigators (MBE and CJG) independently selected eligible systematic review. Disagreement was resolved by discussion with another investigator (VM). Data on all-cause mortality was sought, synthesized, analysed, critically examined and interpreted from systematic reviews and primary studies. We extracted odds ratio (ORs), relative risk (RRs), or hazard ratios (HRs) from the included studies with 95% CI. We did not reanalyze the authors' original data or conduct new meta-analyses by combining studies.

Harm outcome hierarchy

The Therapeutics Initiative analyses all available evidence for harms according to a consistent hierarchy of harm outcomes, ranked by clinical importance starting with all-cause mortality, cause specific mortality, total serious adverse events, and other adverse events. For this study we limited our reporting of findings to all-cause mortality and cause specific mortality.

Results

Three recent studies reporting on all-cause mortality with PPI use were identified that met our inclusion criteria; each having a different study design [17-19]. One systematic review out of 103 was identified that specifically included all-cause mortality as an outcome in its protocol. A randomized controlled trial (RCT) and a longitudinal cohort study that were published after the date of our search for SRs met our inclusion criteria. Figure 1 shows selection process and provides the reasons why some articles were excluded. Table 1 provides detailed characteristics of the included studies. Supplementary file shows a bibliography sorted by harm type.

Table 1. Characteristics of included studies

Author Year (Reference)	n. of Patients	Study design n. of studies	PICO	Exposure to PPI	Length of follow up (maximum)
Shiraev 2018[17]	22,427	Systemic review of 3 cohort (prospective and retrospective)	P: elderly > 65 years 90% of patients were on ASA I: PPIs users C: non-PPIs users O: all-cause mortality and CV events	Less than 1 year	1 year
Xie 2019[18]	214,467	A longitudinal observational cohort study PPIs (n=157,625) H2RAs (n=56,842)	P: elderly > 65 years, men, white I: PPIs user C: H2Ras users O: all-cause mortality, CV and kidney diseases specific mortality	4.6 years (median)	10 years

Author Year (Reference)	n. of Patients	Study design n. of studies	PICO	Exposure to PPI	Length of follow up (maximum)
Moayyedi 2019 [19]	17, 598	RCT Harm outcomes were secondary outcomes	P: elderly > 65 years, stable CV disease I: PPIs users C: placebo O: all-cause mortality	Less than 3 years	3 years

P: population, I: intervention, C: comparator, O: outcome, n: number, PPI; proton pump inhibitor, H2RA: histamin-2 receptor antagonist, CV: cardiovascular, RCT: randomized controlled trial, ASA: acetylsalicylic acid.

The Shiraev 2018 SR pooled all-cause mortality data from 3 published observational studies [17]. Eighty-nine percent of the data was from Charlot et al, 2011, a study of Danish patients following their first myocardial infarction (19,925 of the 22,427 patients in Shiraev 2018 [20]. The pooled mortality rate was higher among PPI users compared with non-PPI users (OR = 1.68; 95% CI: 1.53 to 1.84) (Table 2). In Charlot et al, 2011 mortality was increased during 1-year follow-up in people taking PPIs (HR = 2.38; 95% CI: 2.12-2.67).

Xie et al, 2019 conducted a longitudinal cohort study emulating a clinical trial using administrative data from the United States' Veterans Affairs (VA) national database [18]. New users of acid suppressing medication were identified between July 2002 and June 2004 and followed via from their medical records for 10 years. The cohort included 214,467 US veterans (mean age of 65), who newly started taking PPIs (n=157,625) or H2RAs (n=56,842). The risk of death was higher with PPI versus H2RA users (HR = 1.17; 95% CI: 1.10 to 1.24). Event rates were 59,771 per 157,625 (37.9%) for PPIs vs 20,287 per 56,842 (35.7%) for H2RAs (Table 2).

A RCT, COMPASS (Cardiovascular Outcomes for People Using Anticoagulant Strategies) Moayyedi et al, 2019, conducted a second randomization of participants with heart and peripheral artery disease who were first randomized to rivaroxaban plus ASA or ASA alone. A subgroup without an indication for PPI use or PPI use on entry into the trial was secondarily randomized to receive pantoprazole 40 mg daily vs. placebo. A total of 17,598 participants had no approved indication for PPI treatment; data on adverse events were collected in interviews every 6 months from 580 centers in 33 countries without further verification. The death rates were 630 per 8791 (7.2%) for pantoprazole vs 614 per 8807 (7.0%) for placebo (HR = 1.03; CI: 0.92 to 1.15) (Table 2)[19].

Table 2. All-cause mortality estimates during long-term use of PPI (> 12 weeks)

Type of study (Reference)	Deaths n/N (%)	Association (95% Confidence Interval) NNH
Systematic review and meta-analysis of 3 observational studies [17] Median follow up 1 year	PPI: 765/4,775 (16%) Non-PPI users: 1,794/17,652 (10%)	OR 1.68 (1.53–1.84)
US Veterans Affairs longitudinal cohort study [18] new users of PPI vs. H2RA Median follow up 10 years	PPI: 59,771/157,625 (37.9%) H2RA: 20,287/56,842 (35.7%)	HR 1.17 (1.10-1.24) 45.20 excess deaths/1,000 (28.20–61.40)

Type of study (Reference)	Deaths n/N (%)	Association (95% Confidence Interval) NNH
COMPASS RCT [19] Pantoprazole 40mg/d vs. placebo Median follow up 3 years	PPI: 630/8791 (7.2%) Placebo: 614/8807 (7.0%)	HR 1.03 (0.92–1.15)

PPPI: proton pump inhibitor, H2RA: histamin-2 receptor antagonist, n: number, OR: odds ratio, HR: hazard ratio, CI: confidence interval, NNH: number needed to harm, COMPASS: Cardiovascular Outcomes for People Using Anticoagulant Strategies, RCT: randomized controlled trial,

Appraisal of included studies: The included studies used different study designs and can be evaluated using the three sets of quality criteria appropriate for their respective design. Such heterogeneity is appropriate for considerations of medication harm in the real world. Each publication has been peered reviewed and meets sufficient criteria to be valid for the research question, methods and findings presented.

Common to all the included studies is the challenge of misclassification of drug use. Prescription data may not truly reflect drug consumption. Users may have stopped taking PPIs or H2RAs or started taking PPI as over-the-counter medications during the follow up period.

Findings for all included studies may be subject to bias by indication if patients who are more ill are more likely to be prescribed PPI therapy. The logic is that people who are prescribed PPIs are sicker and what has caused them to be sick (and then die) is the residual confounder that also caused them to be prescribed a PPI. Healthy populations were not however well represented in the study populations of any of the analyses and each demonstrated that the control population was comparable on comorbidities as well as characteristics such as age and sex.

The representativeness across all included studies is problematic as the populations were primarily Caucasian. It is known that up to 20% of Asians (vs 3% Caucasians) have low CYP2C19 enzyme activity and are therefore poor metabolisers of PPIs with a doubling of plasma PPI levels and therefore greater exposure [21,22].

Each study also has limitations within the respective study design. These are highlighted here.

Systematic review : The pooled analysis by SR by Shiraev 2018 included studies if they "examined death or atherosclerotic events (including myocardial infarct, stroke, or peripheral arterial events), and compared a group exposed to PPIs with a control group (not exposed to PPIs), in any group of patients" [21]. The search cut-off date of October 2016 was not inclusive of more recent studies including the 2019 studies included in this review. The Danish national health set study that dominates the Shiraev 2018 pooled analysis is limited to a study population after a first heart attack[20]. The advantage of analyses representative of a geographical population being inclusive of all health care transactions in a publicly funded health care system is the real-world perspective.

RCT: There are several reasons for cautious interpretation of the COMPASS trial results. Serious harms such as cardiovascular disease, kidney diseases or cancers develop over relatively long time periods because of the slow onset. The duration of exposure and follow-up and consistency with the VA cohort means that serious but relatively rare harm may not have been detected. The authors recognized that low event rates for some outcomes limited their ability "to exclude a modest risk increase" from pantoprazole. Of the three included studies the COMPASS trial was the only one with potential conflict of interest due to funding of the research and investigators. There is also the challenge of consistently detecting adverse events with a multi-site, multi-country interview protocol on a 6-monthly schedule.

The COMPASS trial is also not consistent with other RCTs which show a clear positive reduction of GI complications in patients taking PPI and no clinical effects on cardiovascular events [3,23-25]. Surprisingly, COMPASS found no benefit of using pantoprazole to prevent upper GI bleeding in this population. The

COMPASS effectiveness trial in people using antithrombotic drugs (14), have yet to prove that net benefits exceed harms during long-term use in older people. The data confirmed that no benefit of using pantoprazole that would prevent upper GI bleeding in the selected population. This raises questions on the role of PPIs in the in the prevention of bleeding associated with antithrombotic therapy?

Interpretation

The VA cohort study found an excess of deaths in its sample that was twelve times as many participants as the COMPASS RCT and follow-up that was over three times longer. Furthermore, the Shiraev 2018 SR pooled analysis was heavily weighted by a study using the Danish national level administrative data collected from routine care transactions. It would be difficult to create an RCT of an adverse drug event on the scale of either study.

The median exposure to PPI was longer than in the COMPASS RCT (4.6 years vs $<$ 3 years). With only 3 years of follow-up, COMPASS did not have statistical power to detect 10% increases in risk for several of its pre-specified outcomes. For example, COMPASS's point estimate hazard ratio of 1.17 (0.94 to 1.45) for chronic kidney disease was similar to the VA's hazard ratio of 1.16 (1.01 to 1.33) for acute kidney injury.

In the COMPASS RCT, pantoprazole increased enteric infections (mostly *C. difficile)* with an odds ratio of 1.33 (1.01–1.75), absolute risk increase 0.4%. However, the incident rates for most serious harm, such as cardiovascular disease, hospitalizations, chronic kidney disease or dementia, were consistently higher among pantoprazole users compared to placebo group. The COMPASS authors admit this limitation, yet conclude perhaps inappropriately that PPIs "are not associated with any long-term harm" [13]

The Xie et al, 2019 analysis using VA cohort data went farther than detecting a mortality difference between a new PPI user group and a new H2Ra user group. They traced excess deaths to the underlying cause of death using ICD-10 (international classification of diseases, 10th revision) codes. Table 3 provides cause specific mortality from cardiovascular disease and chronic kidney disease from Xie et al, 2019[18]. The cardiovascular disease outcome findings from the COMPASS RCT which were available are provided for comparison[13]. Cause specific mortality data is consistent with the overall data analysis as well as consistent with findings of SRs that report on cardiovascular [21] and kidney disease[26]. This consistency is an indication of the study's internal validity – the findings are consistent within the study. And the study is consistent with other data which is an indication of external validity – that the findings may be applicable beyond this study population.

There were 17.47 excess deaths from cardiovascular diseases per 1000 patients (95% CI: 5.47-28.80), NNH of 58, and 6.25 excess deaths from chronic kidney diseases per 1000 patients (95% CI: 3.22-9.24) in the Xie et al., 2019 study (Table 3) during 10 years of follow up[18]. Moayyedi et al, 2019 did not find an association between PPI therapy and an increased risk of death due cardiovascular causes (HR = 1.03; 95% CI: 0.89-1.20) compared with placebo however there was an overlap in confidence intervals and the COMPASS RCT was shorter in duration and follow-up[19].

Table 3. Effect estimates for cause specific mortality with PPI use (> 12 weeks)

Author, Year (Reference)	Death %	Association (95% Confidence Interval) NNH
Cardiovascular disease	**Cardiovascular disease**	**Cardiovascular disease**
Shiraev 2018[21]	PPI: 2.4% Control: 1.8%	OR 1.54 (1.11-2.13)
Xie 2019 [18]	PPI: 8.87% H2RA: 7.33%	HR 1.25 (1.10-1.44) 15.48 excess deaths/1,000 (5.02–25.19)
Moayyedi 2019 [19]	PPI:7.9% Placebo:7.5%	HR 1.04 (0.93–1.15)
Chronic kidney disease	**Chronic kidney disease**	**Chronic kidney disease**
Xie 2019 [18]	PPI: 0.86 % H2RA: 0.44%	HR 2.02 (1.31-3.00) 4.19 excess deaths/1,000 (1.56-6.58)

PPPI; proton pump inhibitor, H2RA: histamin-2 receptor antagonist, HR: hazard ratio, CI: confidence interval, NNH: number needed to harm.

The Bradford-Hill criteria provide another framework used to guide an evaluation of the causal association between drugs in the post market period and adverse events. Originally developed to examine the causal relationships between public health exposures such as smoking and air pollution (which cannot ethically be randomized) and poor health outcomes it is also a useful framework for evaluating the harm profile of drugs. One of the Bradford-Hill criteria is biologic plausibility – there is a biological explanation for how the 'exposure' could cause the 'harm' from what is known.

Xie et al, 2019 report on what may be a universal mechanism of harm with PPI use and one that is consistent with their findings of specific but varied causes of increased mortality. When scientists at the Centre for Cardiovascular Regeneration in Huston, Texas, cultured microvascular epithelial cells they aged faster in media with clinically significant amounts of the PPI esomeprazole [27]. The endothelial cells that line blood and lymph vessels are present throughout the body. Basic science studies showed that exposure to PPIs impaired endothelial lysosomal acidification, enzyme activity and proteostasis resulting in endothelial dysfunction. Moreover, the telomere length was shortened (a possible sign of aging) in the esomeprazole treated group. Xie et al, 2019 also points out that there are two general biological mechanisms by which PPI use can be linked to excess deaths: worsening of pre-existing diseases (ex. existing cardiovascular and kidney disease) or the occurrence of new disease states [18]. This is only one avenue by which long-term PPI use may adversely affect human health. Also plausible are hypomagnesemia, drug interactions, reduced absorption of selected nutrients, increased gastric microbiota and small intestine bacterial overgrowth, reduced immune response, tubular-interstitial inflammation, increased bone turnover and accumulation of amyloid in the brain [28].

PPIs use was also significantly associated with renal insufficiency even after adjusting for acute interstitial nephritis (AIN) in the Xie et al, 2019 VA cohort analysis. AIN is a drug reaction known to be caused by PPI [29]. SR of observational studies have found PPIs to be associated with chronic kidney disease (CKD)[30]. The finding of continued renal insufficiency even after adjustment suggested the existence of unrecognized AKI or chronic latent renal injury[18].

Limitations

An evidence-based approach to interpretation of clinical trial data turns first to the hierarchy of evidence. RCTs are higher on the hierarchy than observational studies because randomization provides powerful protection against known and unknown confounders that observational studies do not. Given that the COMPASS findings were from an RCT and found no increase in all-cause mortality and the observational studies found an increase in all-cause mortality with PPI use, the hierarchy of evidence points to the interpretation that the RCT findings should be accepted and the observational findings understood as being most likely explained by an unidentified confounder[31].

Pharmacovigilance – "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem"[32]. challenges the use of the hierarchy of evidence for evaluating drug risk:

[N]one of the methods ... (experimental data, clinical trials, spontaneous notifications, case–control studies, cohort studies and data mining) should be considered as definitive for evaluating drug risk. It is only the **convergence of proofs** which allows final conclusions and decisions in pharmacovigilance. Thus, the notion of 'levels of evidence', widely used for evaluating drug efficacy, cannot be applied in the field of [Adverse Drug Reactions] ADRs; all methods are of interest for evaluation of ADRs [33].

Insisting on RCT evidence for fatal and serious adverse events from medication use in real-life populations contravenes modern standards in pharmacovigilance that are more directly applicable to the evaluation of the serious adverse events associated with medications.

Discussion

Ethical constraints on designing RCTs to investigate the harms associated with drugs have driven innovation in observational study design. Studies like Xie et al, 2019 replicate the safety features of RCTs including comparable selection criteria for inclusion in the cohort, exposure definitions, covariate choices, outcome definitions and analytic strategies [34]. Older observational studies that use datasets to look for associations between the independent and dependant variables using factorial analyses are primitive by comparison. Clinicians are correct in being skeptical of associations that are in the range of OR and HR less than 2 given the vulnerability of such analyses to unrecognized confounders. In evaluating clinical data, analyses have "found little evidence that estimates of treatment effects in observational studies reported after 1984 are either consistently larger than or qualitatively different from those obtained in RCTs" [35]. The difficulties of capturing the harms of pharmaceutical use under routine clinical practice conditions are recognized to be even more difficult to capture under the 'ideal' conditions of the RCT [36]. Contemporary observational studies using the administrative datasets of large integrated health care systems provide advantages over RCTs of investigating rate but serious adverse events.

To identify and control for unknown confounders, Xie et al, in an earlier 2017 study controlled for known risk factors including age, race, gender, estimated glomerular filtration rate (eGFR), number of serum creatinine measurements, number of hospitalisations, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, cancer, gastroesophageal reflex disease, upper GI tract bleeding, ulcer disease, H. pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma. Then they tested for an uncontrolled confounder that would explain the finding of increased mortality using a rule-out and external adjustment approach[37] . They determined that a confounder would have to be twice as likely in PPI users (OR 2.0) and the HR of death associated with this uncontrolled confounder exceed 4.0 to explain their finding of excess mortality with PPI use. They concluded:

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 . . .) and strength (HR 4 or more . . .) 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 [38](p.6)

Additional features like propensity score analysis and using physician preferences as a calibration check on the analysis also provide important safeguards.

The 95% CI provides more accurate representation of reality than single point estimate. COMPASS researchers interpret their findings to 'suggest PPI therapy is safe for up to a median of 3 years [13]. They report being reassured that the HRs and ORs from their study 'are lower than the lower end of the 95% CI' reported for all-cause mortality in the Xie et al, 2017 initial analysis [38]. However, the Xie et al., 2019 VA cohort study findings are not inconsistent with the COMPASS trial findings [18]. There is an overlap in the 95% confidence intervals between VA cohort (1.10 to 1.24) and COMPASS trial (0.92–1.15). The upper bound of the COMPASS trial 95% confidence interval virtually equals the point estimate of the cohort study of 1.15 to 1.17 (Figure 2). Thus, the data among mortality studies are not discordant but rather convergent. The results also show that the longer the duration of exposure to PPI, the greater the risk of death. There was a graded relation between duration of exposure and risks of all-cause mortality, death due to cardiovascular diseases, cancers, and kidney diseases [18]. This suggests that had the COMPASS RCT continued through to 10 years of follow-up the confidence interval would have approached the VA cohort findings. Duration of use and study follow-up could explain the seeming discordant findings.

Conclusions and implications for practice

Our findings and analysis of interpretive frameworks demonstrates the pharmacovigilance principle that no one study or pooled analysis of studies can adequately determine whether the harm risk of drug therapy is real. A convergence of proof using data from various sources and study designs is needed. Considering the data from the COMPASS RCT together with the pharmaco-epidemiology observational studies leads

us to conclude that on balance, it is likely that long-term PPI use increases all-cause mortality. Given the high prevalence of long-term PPI utilization, this message needs to be conveyed to health professionals and patients.

Competing interests: None declared.

Contributors: The authors are a group of Clinician-scientists (Ben-Eltriki, Green, Musini, Bassett and Wright), medical researcher and epidemiologist (Maclure) as well as Cochrane Hypertension authors and reviewers (Musini, Bassett and Wright). The authors are experts in analyzing clinical trials of drugs, and clarifying the state of scientific evidence regarding effectiveness and safety of drug therapy. All authors participated in the study design. Mohamed Ben-Eltriki and Carolyn Green screened studies for eligibility, performed data extraction, assessed the risk of bias, performed data analysis. All authors interpreted the data analysis and assessed the certainty of evidence. Mohamed Ben-Eltriki and Carolyn Green wrote the first draft of the manuscript, and all other authors revised the manuscript.

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Figure legends

Figure 1: The Flow chart of study selection for all-cause mortality with PPI use

Figure 2: PPIs: All-cause mortality - COMPASS trial vs VA cohort results

Appendices: A list of our finding of 103 recent systematic reviews of specific harms associated with PPIs sorted by harm type.

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