Comprehensive Safety Evaluation of Proton Pump Inhibitors

by

Ahmed Ullah Mishuk

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Approved by

Jingjing Qian, Chair, Associate Professor of Health Outcomes Research and Policy
Li Chen, Assistant Professor of School of Medicine, Indiana University
Philippe Gaillard, Associate Professor of Mathematics and Statistics
Salisa Westrick, Professor of Health Outcomes Research and Policy

Abstract

Objective: This study1) examined trends in proton pump inhibitor (PPI) use and associated healthcare spending among the U.S. population, 2) identified adverse outcomes associated with PPI use, and 3) conducted a systematic review and meta-analysis to examine the association between PPIs and myocardial infarction (MI) and gastric cancer (GC).

Methods: The 2002-2017 Medical Expenditure Panel Survey was used to examine PPI use and spending trend and multivariable model was used to identify patient factors associated with PPI use. The 2004-2019 U.S FDA Adverse Event Reporting System (FAERS) data were analyzed and safety signals of MI, chronic kidney disease (CKD), and GC were evaluated using disproportionality analyses. A 5% random sample of the 2013-2016 Medicare administrative claims data was used to assess the associations of MI, CKD, and heart failure (HF) with PPI use employing a new user cohort design. Finally, clinical trials and observational studies were included to assess the associations between PPIs with MI and GC.

Results: Trends in prescription PPI use increased significantly in 2002-2017, overall and in patient subgroups. Individuals who were aged >25, female, non-Hispanic Whites, residing in the Northeast, with low income, having public or private health insurance, obese or overweight, having poor health status, and having more comorbidities had higher likelihoods of using PPIs. The FAERS analyses identified disproportionate signals in CKD and GC AEs reporting. The reporting for CKD AEs might be impacted by publication bias. The Medicare claims data analyses found a

decreased risk of MI for new users of PPI compared to H2 blocker, while associations in risk of CKD and HF with PPI use were observed. For individual PPIs, only pantoprazole users showed an increase in the risk of MI compared to omeprazole users. Finally, meta-analysis found no association between PPI use and risk of MI or GC among RCTs, but significant associations appeared after adding evidence from observational studies.

Conclusion: Prescription PPI use increased significantly among U.S population. Findings of this study suggested no or limited risk of MI with PPI use. Further longitudinal studies are warranted to investigate the association between PPI use and GC.

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List of Abbreviations

AEs	Adverse events
AHR	Adjusted Hazard ratio
AHRQ	Agency for Healthcare Research and Quality
AOR	Adjusted Odds ratio
CCI	Charlson comorbidity score
CI	Confidence interval
CKD	Chronic kidney disease
CPI	Consumer price index
EPHPP	Effective public health practice project
ESRD	End stage renal disease
FAERS	FDA adverse event reporting system
GC	Gastric cancer
GEE	Generalized estimating equation
GERD	Gastroesophageal reflux disease
H2RA	Histamine 2 receptor antagonists
HF	Heart failure
HR	Hazard ratio
HRQoL	Health-related quality of Life
ICD	International Classification of Disease
IRR	Incidence rate ratio
LIS	Low income subsidiary
MEPS	Medical expenditure panel survey
MI	Myocardial infarction
OR	Odds ratio
OTC	Over-the-counter
PPI	Proton pump inhibitor
RCT	Randomized controlled trials
ROR	Reporting odds ratio

Chapter 1
Introduction

1.0 Overview

In western countries, gastroesophageal reflux disease (GERD) is the most common upper gastrointestinal disease where 10-20% of the total population experience GERD symptoms weekly.[1,2] The frequent backflow of food, acid, and pepsin into the esophagus is the major contributing factor of GERD, and frequent heartburn, acid ingestion, and bitter taste in the mouth which are the main symptoms of GERD.[3] For almost 70% of patients, heartburn is the most reliable symptom to establish GERD diagnosis, and once the cardiac cause has been ruled out, chest pain is also indicative of GERD.[4,5]

Across the world, GERD is one of the most common digestive disorder contributing to serious harm, burden, and economic consequences on the individuals.[6] In addition to the economic burden, GERD also impacts patient's health-related quality of life (HRQoL).[7-9] For instance, GERD has been reported to be associated with meaningful impairment in HRQoL in the dimensions of vitality, eating/drinking, and emotional well-being; however, impairment in physical functioning was not associated with GERD.[7]

Medications such as antacids and alginates are used to relieve GERD symptoms, and these medications are recommended to use after each meal and before going to sleep.[10-12] At present, different acid suppressive agents are used in the

GERD treatment to relieve and prevent the recurrence of symptoms.[13] Compared to antacids, Histamine 2 receptor antagonists (H2RAs), otherwise referred to as H2 blockers, work better to decrease the acid secretion after a meal. However, they are not effective enough to heal the esophagitis, and their use cannot prevent relapse among the patients suffering from GERD.[14,15] At present, Proton Pump Inhibitors (PPI) are the most common and most potent acid-suppressive medications which work by inhibiting the final step of acid secretion.[16] PPIs were first introduced in the 1980"s and demonstrated better efficacy than H2 blockers.[17] Currently, six PPIs are commercially available in the U.S. (omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, and rabeprazole) in various doses and dosage forms.[18] Although all PPIs are not the same and have some variations in their pharmacokinetic properties, they share a similar mechanism of action.[19,20]

PPIs played a revolutionary role in the medical approach to treat the gastrointestinal disorders[21], however, the rate of inappropriate use of PPIs are increasing alarmingly[22]. Inappropriate PPIs use also associated with increased health care costs. For example, in 2014, Ladd et al., identified about $12,272 and $59,272 as the estimated cost of inappropriate PPIs use in inpatient and outpatient settings, respectively, among 419 patients[21]. Both brand and generic PPIs have the same mechanism of action, and evidence is very little regarding the therapeutic benefit of more expensive PPIs, compared to inexpensive PPIs. However, a recent study using the National Ambulatory Medical Care Survey (NAMCS) found that from 2002–2009 both branded esomeprazole and generic omeprazole had a significant increase in use among U.S. population. Increased use of branded PPIs can play a vital role in

increasing the associated healthcare expenditures, thus appropriate use of PPIs and promoting the least costly or generic version of PPIs can help to reduce the healthcare cost associated with PPIs use. Identifying the different PPIs use trends, different factors related to PPIs use, and their associated cost among the U.S. population will inform us better regarding the need to promote low cost PPIs among the U.S. population.

Generally, acid suppressive agents such as H2 blockers and PPIs are considered safe, but recent evidence suggests otherwise. A case-control study in the UK, published in 2005, identified an association between community-acquired C difficile and the use of PPIs.[23] Several other adverse events (AEs), such as community-acquired pneumonia (CAP), have been found to be associated with the use of PPIs, but the associations of these AEs with H2 blockers were not observed.[24,25] Several studies have been conducted among non-U.S. populations, and these studies identified associations between PPIs and potential AEs such as acute kidney disease, chronic kidney disease, pneumonia, bone fractures, cardiovascular events, and enteric infections.[26-28] Given the prevalent use of PPIs, the emerging concerns with the safety profile of PPIs need to be closely examined and monitored.

1.1 Significance of the studies on PPI(s)

In the U.S., (PPIs are among the highest-selling classes of drugs with an annual sale of $9.5 billion in fiscal year 2012.[29] Across the world, as well as in the U.S., inappropriate PPIs usage and high cost PPIs usage are contributing to the increased healthcare spending associated with PPIs use.[30] PPIs utilization pattern and associated spending with the brand and generic version of PPIs can inform use better

to have specific policies to reduce the cost associated with PPIs use. PPIs are generally considered safe, and short-term use of PPIs are usually well tolerated. However, there is some evidence indicating that long-term use of PPIs among older adults is associated with some AEs such as bone fractures, Clostridium difficile infection and acute interstitial nephritis.[31,32] While existing evidence provides a strong argument for the association between several AEs and PPI use, for some AEs such as myocardial infarction (MI), chronic kidney disease (CKD), and gastric cancer (GC), more evidence is required to confirm any causal relation. For example, animal models indicates the link between PPI use and cardiovascular AEs such as MI[33], however existing observational studies provide mixed evidence.[34,35] Existing studies evaluating the association between MI, GC, and PPI use are also prone to protopathic bias, thus leading to the erroneous conclusion that PPIs are responsible for MI and GC.[36] Published studies investigating the associations between PPI use and AEs were either conducted among non-U.S. populations[37-45] or had small sample sizes[46-52] and weak study design.[47,53] Large population-based studies examining patterns and economic burdens of PPI use and its association with AEs among the U.S. population are warranted.

1.2 Objective

The overall objective of this dissertation project was to understand the utilization of PPIs, and systematically and comprehensively assess the safety of post-marketing use of PPIs among the real-world population.

1.3 Specific Aims

1.3.1 Aim 1. To examine trends in PPIs use and associated healthcare spending among the U.S. population.

We used the 2002-2017 MEPS (Medical Expenditure Panel Survey) data to examine trends in PPI use and associated healthcare spending (i.e., total annual expenditures, total out-of-pocket (OOP) expenditures, and the amount paid by private and public insurance on overall PPIs, brand, generic as well as individual PPIs). Trends were examined in different patient subgroups by age, sex, race/ethnicity, income, and education. PPIs use trends by overall, brand, generic, and specific PPIs provided a comprehensive scenario regarding the utilization of PPIs among the U.S. population. Finally, patient demographic, medical condition, and prescribed medicine information were assessed in the generalized multivariable models with generalized estimating equation (GEE) to identify factors associated with PPI use among the U.S. population.

1.3.2 Aim 2. To identify adverse outcomes associated with PPI Use: retrospective analyses of the U.S. FDA Adverse Events Reporting System (FAERS) and Medicare claims data

In this aim, first, we used the publicly available FAERS data from January 1, 2004, to June 30, 2019, to identify potential safety signals for PPIs, focusing on CKD, MI, and GC. The influence of key publications on spontaneous reporting for PPIs were evaluated by identifying AE reports with PPIs in the FEARS data during the entire study period, as well as before and after the availability of key publications. In the

second part of aim 2, we used the 5% random sample of the 2013-2016 Medicare administrative claims data to assess the associations of MI, CKD, and heart failure (HF) with the use of PPIs. We compared the risk of these AEs among new users of PPI with new users of H2 blockers, long time PPI users with short term PPI users, long term PPI users with long term H2 blocker users, and individual PPI users with omeprazole users.

1.3.3 Aim 3. To assess the association between PPIs and MI and GC: a systematic review and meta-analysis.

We conducted a comprehensive systematic review focusing on AEs (MI, GC) associated with the use of PPIs. This systematic review and meta-analysis evaluated the most up-to-date evidence to assess the association between PPIs and MI and GC by including both clinical trials and observational studies. Subgroup analyses based on the study design and comparator group further helped understand potential associations.

1.4 Innovation

This project is innovative in the use of multiple data sources and study designs to evaluate the safety profile of PPIs. Findings from this research provided empirical evidence to build up the comprehensive post-marketing safety evaluation of PPIs use using both population-level data and existing published literature. First, this study is unique in that we identified the risk factors associated with the use of PPI from the multiple national data sources representing the U.S. population. Specifically, we used the 2002-2017 MEPS data to examine the use patterns and healthcare spending of PPI among the general U.S. civilian noninstitutionalized population, and we further

used both the FAERS (2004-2019Q1Q2) and Medicare administrative claims data (2013-2016) to investigate real-world AEs (MI, GC, CKD, HF) associated with PPI use. This study is unique as in this study, we also evaluated the impact of research findings on AE reporting and then by observing the Influence of key publications on spontaneous reporting for AEs with PPIs. To our best knowledge, no other existing study has explored the influence of publication bias on AEs reporting for PPIs.

While focusing on specific safety portfolio of PPIs, this project is also innovative and impactful in the sense that it used different levels of evidence in the pharmacovigilance system. No work has been published regarding the comprehensive systematic review of PPI-related AEs. In Aim 3, we conducted a comprehensive systematic review focusing on AEs (MI and GC) associated with the use of PPIs. We evaluated the most up-to-date evidence in the association between PPIs with MI and GC by including both clinical trials and observational studies. To our knowledge, no published systematic review and meta-analyses evaluated the relationship between GC and PPI use. Similarly, for MI risk with PPI use, we did not find any published systematic review and meta-analysis, including both RCTs and observational studies. This dissertation project provided the opportunity to understand how post-marketing safety signals in pharmaceutical products differ across study designs and how signals evolve over time as we learn more about use patterns and unanticipated risks. Finally, findings from this study could help pharmaceutical regulatory authorities improve their existing pharmacovigilance system for prescription products.

Chapter 2

Literature Review

2.0 Gastrointestinal Disorders

The human gastrointestinal (GI) tract is comprised of the esophagus, stomach, and intestines, joined in a long, twisting tube from the mouth to the anus and divided into the upper and lower gastrointestinal tracts.[54] Every part of the GI tract- esophagus, stomach, small intestine, and large intestine, contributes to the digestion of food through sensation and motility.[43] For example, glands present in the stomach produces gastric acid and enzymes that help to break down the food, and then stomach muscles' motility helps to mix these broken food particles with digestive juice.[37]

Gastric acid is a digestive fluid secreted from the parietal cells of the stomach, plays a vital role in human physiology to maintain the normal function of the upper gastrointestinal tract.[55] While gastric acid facilitates the digestion of the food[56], it also plays a vital role in protecting the body from food or waterborne diseases by acting against the ingested pathogens.[57] Although gastric acid has a beneficial impact on human physiology and immunity, the imbalance in gastric acid secretion can lead to various gastrointestinal tract (GIT) disorders.[58] For example, heartburn is a frequent symptom of low gastric acid secretion, and infection with Helicobacter pylori (*H. pylori*) can take place when gastric acid secretion is altered.[59] In addition to heartburn and infection, GERD results due to the reflux of gastric contents to the esophagus due to imbalance in an imbalance in the gastric acid content of the stomach.[60] Among different gastric acid-related diseases, around 10-20% of adults in western countries

are affected by GERD, contributing to economic burden and decreased quality of life among affected individuals.[1,61-63]

2.1 Gastroesophageal reflux disease (GERD)

GERD is a long-term condition where stomach contents return to the esophagus, resulting in symptoms such as the taste of acid in the back of the mouth, heartburn, bad breath, chest pain, vomiting, breathing problems, and wearing away of the teeth or complications such as esophagitis, esophageal strictures, and Barrett's esophagus.[64] According to the Montreal consensus, “GERD is a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications”.[65] GERD can be classified into two types: 1) non-erosive reflux disease (NERD) and 2) erosive reflux disease (ERD), based on the presence or absence of esophagus mucosal damage on endoscopy.[66] Symptoms of GERD can be classified as typical and atypical. Typical symptoms include heartburn and regurgitation, whereas cough, asthma, hoarseness, chronic laryngitis, throat-clearing, chest pain, dyspepsia, and nausea are the atypical symptoms of GERD.[67,68]

2.2 Prevalence GERD

GERD is a prevalent acid-related disorder, affecting a vast number of people across the world. In Western Europe and North America, the prevalence of at least weekly heartburn and/or regurgitation is 10-20%; however, in Asia, the prevalence is lower, in the range of 2-5%.[1,69] In the U.S., the prevalence of GERD among whites is equivalently high compared to blacks, even though whites are affected more by esophageal adenocarcinoma than blacks.[70,71] The prevalence of GERD is higher among males than females. For example, a recently published meta-analysis found the

male/female ratio in the prevalence of GERD was 1.57/1 (95%CI: 1.40-1.76).[72] The GERD prevalence is higher among those with older age and lower socioeconomic status.[73] Existing evidence found that older patients (≥65 years) have more severe gastroesophageal reflux (Grade III/IV esophagitis: 20.8% of elderly patients vs. 3.4% of younger patients) compared to younger patients.[74]

2.3 Burden of GERD

For the U.S. population, gastrointestinal disorders are a significant source of healthcare expenditure.[61] In the U.S., about 60 to 70 million individuals are affected by GIT diseases every year.[75] Hospitalization, ambulatory care visits, and deaths are associated with GIT diseases, and healthcare spending on GIT diseases has been estimated as $142 billion per year.[76] Among various GIT disorders, GERD has a substantial impact on patient's financial burden, quality of life, and productivity.[77] For example, the cost of treating patients with GERD has been reported to be about two times more expensive than treating comparable patients without GERD.[78] Patients with GERD also had poorer health status, lower physical activity, and higher rates of obesity, along with a significantly higher rate of depression and anxiety than the comparable patients without GERD.[78] Although GERD is associated with reduced quality of life, GERD is not associated with a patient's survival.[79] The economic burden of GERD has also increased over time. In 2009, GERD was the most common GIT diagnosis in the U.S, and during the 1990s, GERD had an annual direct cost of $9.3 billion, which increased to $12 billion in 2004[75,76] and further increased to $18.1 billion in 2015.[80] In the United Kingdom the cost of GERD was about £0.75 billion (equivalent to $0.98 billion) in 2004, and in Sweden, a total of $258 million was attributed to direct

cost and $166 million was attributed to indirect cost for dyspepsia, peptic ulcer disease, and GERD in 1997.[81,82]

2.4 Diagnosis of GERD

Generally, the diagnosis of GERD among adults can be established with the symptoms of heartburn and regurgitation.[83] While objective testing for GERD is uncommon in primary medical practice[84], poor predictors of GERD such as hurt burn can predict GERD.[85,86] A GERD diagnosis can also be predicted with the symptom of chest pain; once cardiac causes are eliminated.[87] Endoscopy is another procedure to diagnose GERD, but the sensitivity is low since over 60% of patients suffer from NERD.[88] Another approach to GERD diagnosis is the use of an acid-suppressive agent, usually a PPI in patients with atypical symptoms—such as dyspepsia, epigastric pain, nausea, bloating, and eructation.[87,89] Diagnosis of GERD can be confirmed if the symptoms are relieved with the use of an acid-suppressive agent such as a PPI. However, this diagnostic procedure should not be considered as a definitive method to diagnose GERD.[5,90-92]

2.5 Treatment of GERD

Several treatment strategies, including pharmacological, behavioral, and surgical treatment options, are available to treat GERD.[89]

Change in lifestyle is the first line therapy for GERD and has been considered to lead to desired outcomes.[67,93] For example, weight loss has been documented as an effective option to relieve GERD symptoms among patients who are either overweight or have normal body mass index (BMI) with recent weight gain.[94] Weight gain has been found to be positively associated with the initiation or exacerbation of GERD symptoms

among women,[95] thus, reducing weight has been recommended to relieve GERD symptoms among patients who are overweight or have gained weight recently.[96] Dietary modification such as reducing the intake of fat, chocolate, alcohol, citrus and tomato products, coffee, tea, and large meals has been recommended by the National Institutes of Health and the American College of Gastroenterology for patients with GERD, however, published studies are not available to support these recommendations.[97]

Several pharmacological treatment options are available to manage GERD. Acid suppression is considered as a major pharmacological option in the treatment of GERD.[96] Acid suppression can be achieved through different medications such as antacids, histamine-receptor antagonists (H2RAs), or proton-pump inhibitors (PPIs).[93,96] Several antacids such as sodium bicarbonate, calcium carbonate, magnesium hydroxide, and aluminum hydroxide are available as OTCs and relieve heartburn by neutralizing acid in the esophagus without providing any significant effect on gastric pH.[98,99] Although antacids provide rapid relief from GERD symptoms, their activity does not last long enough and does not alter gastric pH significantly. Thus antacids do not provide prevention from subsequent reflux episodes.[100]

Gastric acid suppression and an increase in gastric pH can be achieved using H2RAs or PPIs.[101] H2RAs decrease gastric acid secretion by blocking the histamine at the histamine H2 receptors of gastric parietal cells.[101] PPIs also decrease gastric acid secretion by inhibiting the H+-K+-ATPase (proton pump) in the gastric parietal cells.[102] Although acid suppression can be achieved through H2RAs or PPIs, PPIs are two times more effective compared to H2RAs.[103] PPIs inhibit the H+-K+-ATPase (proton

pump) in the gastric parietal cells, thus suppresses the gastric acid and shows maximum effectiveness when administered 1 hour prior to the first meal of the day.[102] Another option to get relief from the GERD is antireflux surgery. Surgical therapy in the management of GERD is becoming popular as it has been found to be superior over pharmacological treatment.[104]

Although PPIs are considered as first-line therapy choice for pharmacological treatment of GERD[105], surgery is becoming a popular option among patients with different complications.[106] The most common surgical procedure for the management of GERD is fundoplication, which has proven to produce significantly less acidic content, high level of patient satisfaction, increased quality of life, and is curative in 85%-93% of cases of GERD.[106-108]

Patients suffering from chronic GERD might feel less comfortable to take PPIs for a long period of time due to various reasons such as cost or potential adverse events.[109,110] In addition, for GERD patients who are not responding to single or multiple doses of PPI, anti-reflux surgery is considered as a rational approach to achieving a disease-free state.[111] Due to these reasons, patients might grow a strong inclination towards the surgical treatment option. Although the surgical procedure provides superiority over pharmacological therapy in terms of healing and patient satisfaction,[91,106,107] surgery offers no advantages when symptoms can be fully relieved with pharmacological therapy. In addition, patients might still need reoperation or pharmacological therapy even after having a successful surgery.[109,112-114] For example, long-term follow-up studies have found that 52% of patients returned to pharmacological treatment within 3-5 years after having a successful antireflux

surgery.[115] Furthermore, quality of life can be impaired as antireflux surgery is associated with different adverse events such as dysphagia, bloating, an inability to burp, and excessive flatulence.[116,117] Due to these reasons, effective counseling between patient and physician is needed to identify the potential benefits of surgery over pharmacological therapy.[106,110]

2.6 PPI vs. H2RAS

Rapid and complete relief from the symptoms is the therapeutic goal among patients suffering from acid-related diseases. The main objective of pharmacological treatment of acid-related disease is to increase gastric $p^{H,}$ thus providing relief from the symptoms. Increase in gastric acid p^{H} can be obtained through competing with the H2-receptors on the parietal cells or by inhibiting the gastric H,K-ATPase.[118,119] Currently, histamine (H2) receptor antagonists (H2RAs) are available to block H2-receptors, and PPIs are available to inhibit the gastric H,K-ATPase, thus increase gastric p^{H}, and results in symptoms relief in acid-related disorders. Although H2RAs have pharmacological properties to increase gastric p^{H}, they do not provide optimum acid suppression. In addition, chronic use of H2RAs can develop tolerances, thus do not manage acid-related disorders, especially GERD effectively.[17,118-120] The tolerance phenomenon of H2RAS is a weakened acid suppression property that takes place within two weeks of repetitive administration, which is considered as a short-term remedy option in acid-related disorders.[121,122] On the other hand, inhibiting the final step of acid secretion (H,K-ATPase) is more effective than blocking H2-receptors.[123] PPIs have a low tolerance phenomena, thus they provide long-term acid inhibition particularly when the administration is taking place during daytime.[124] Use of PPI

inhibits the gastric acid secretion through blocking of H,K-ATPase and maintaining the intragastric p^H>4 for between 15 and 21 hours daily, while it is 8 hours per day for H2RAs.[18,125]

2.7 Mechanism of Action of PPI

PPIs are the derivatives of benzimidazole, which includes both pyridine and benzimidazole moiety linked by a methylsulfinyl group[18], activated in the acidic environment of the stomach.[126,127] PPIs are acid labile weak bases, protonated to the nitrogens on either side of the sulfinyl group in the acidic environment of the gastric glands.[128,129] Once the PPI is activated through the addition of two protons,[91,92] it forms disulfide bonds by binding to CYS molecules on the ATPase of H+/K+-ATPase enzyme, thus inactivating the proton pump and resulting in the reduction of gastric acid secretion.[130]

2.8 Indications of PPI

Several clinical trials and observational studies provide substantial evidence to validate the effectiveness of PPIs in the management of acid-related disorders. According to the recommendation of the American Gastroenterological Association, for short term and long term management, PPIs should be prescribed to patients with GERD, erosive esophagitis, and peptic stricture.[131]

Table 2.1 Best Practice Advice From the American Gastroenterological Association for PPI use

Best Practice Advice	Condition	Recommendation
1	GERD and acid-related complications (i.e., erosive esophagitis or peptic stricture).	PPI for short-term healing, maintenance of healing, and long-term symptom control.
2	Uncomplicated GERD. Respond to short-term PPIs.	Should attempt to stop or reduce the dose.
3	Barrett's esophagus and symptomatic GERD.	Should take a long-term PPI.
4	Asymptomatic patients with Barrett's esophagus	Should take a long-term PPI.
5	High risk for ulcer-related bleeding from NSAIDs	Should take a PPI with NSAIDs.
6	Long-term PPI use	Periodic evaluation of the dose of long-term PPIs to use a minimum effective dose.
7	Long-term PPI users	Should not routinely use probiotics to prevent infection.
8	Long-term PPI use	Should not routinely raise the consumption of calcium, vitamin B12 or magnesium beyond the Recommended Dietary Allowance (RDA).
9	Long-term PPI use	Should not routinely screen or monitor bone mineral density, serum creatinine, magnesium, or vitamin B12. Rationale: There is no evidence for or against dedicated testing for patients taking long-term PPIs. Such screening (eg, for iron or vitamin B12 deficiency) can be offered but is of no proven benefit.
10	Specific PPI formulations	Potential risk factor should not be used to select a specific PPI formulation.

2.9 PPI Efficacy Comparison:

Suppressing the acid secretion and increasing the gastric p^H more than 4 to 16 hours/day results in the healing of reflux esophagitis.[132] Usually, all PPIs have a good

ability to suppress gastric acid suppression as they are used at different doses.[133] Although it is difficult to establish the comparative effectiveness profile of different PPIs due to their usage at different doses, several studies have tried to find the answer.[134-143] For example, studies found that esomeprazole (40 mg) provides better acid suppression compared with rabeprazole (20 mg), omeprazole (20 mg), lansoprazole (30 mg), and pantoprazole (40 mg).[135,136] Among patients with GERD, who do not have any erosions, esomeprazole, pantoprazole, and rabeprazole have comparable efficacy, while to relieve GERD symptoms completely, all PPIs are equally effective when comparable doses are used.[144]

2.10 Available PPIs in the U.S.

As of October 2020, six PPIs have been approved in the U.S. in various formulations to treat acid-related diseases.[18] Although all PPIs have a similar mechanism of action, three PPIs (omeprazole, esomeprazole, and lansoprazole) are available as Over-the-counter (OTC), whereas the other three PPIs (dexlansoprazole, pantoprazole, and rabeprazole) are not available as OTC. All six PPIs have available generics from different manufacturers except for dexlansoprazole (Table 2).[18,145-155]

Table 2. 2- Approved PPIs in the U.S.[18]

PPI	Dosage form	Availability		
		Brand	Generic	OTC
Omeprazole	Oral	√	√	√
Esomeprazole	Oral, IV	√	√	√
Pantoprazole	Oral, IV	√	√	×
Rabeprazole	Oral	√	√	×
Lansoprazole	Oral, IV	√	√	√
Dexlansoprazole	Oral	√	×	×

IV= Intravenous

Not all PPIs are indicated to manage the same acid-related disorders. The U.S. Food and Drug Administration (FDA) provides specific guidance regarding the indication of each PPI based on disease condition. Table 2.3 provides the FDA approved PPI dosages for treating different kinds of acid-related diseases.[156]

Table 2.3: FDA approved dosage for different kinds of acid-related diseases for PPIs

PPI	Indication	Dosage
Omeprazole	Short-term treatment of DU	20 mg, Once daily.
	H. pylori eradication to reduce the risk of recurrence in DU	Triple Therapy: 20 mg twice a day for 10 days. Dual Therapy: 40 mg Once daily for 2 weeks.
	Healing of EE	20 mg Once daily for 4 to 8 weeks.
	Maintenance of healing after treatment of EE	20 mg Once daily.
	Symptomatic (non-erosive) GERD	20 mg Once daily, up to 4 weeks.
	Heartburn	20 mg once a daily for 14 days.
	Pathological hypersecretory conditions	60 mg once daily.
	Short-term treatment of benign GU	40 mg Once daily for 4 to 8 weeks.
Esomeprazole	H. pylori eradication to reduce the risk of recurrence in DU	Triple therapy: 40 mg Once daily for 10 days.
	Healing of EE	20 mg or 40 mg Once daily for 4 to 8 weeks.
	Maintenance of healing after EE treatment	20 mg Once daily.
	Symptomatic (non-erosive) GERD	20 mg Once daily for 4 weeks.
	Risk reduction of NSAID-associated GU	20 mg or 40 mg once a day for up to 6 months.
	Pathological hypersecretory conditions	40 mg twice a day.
Lansoprazole	Short-term treatment of DU	15 mg Once daily for 4 weeks
	Maintenance of healing after DU treatment	15 mg Once daily.
	H. pylori eradication to reduce the risk of recurrence of DU	Triple Therapy: 30 mg twice a day for 2 weeks. Dual Therapy: 30 mg 3 times a day for 2 weeks.

	Healing of EE	30 mg once a day for up to 8 weeks.
	GERD, symptomatic (non-erosive)	15 mg Once daily up to 8 weeks.
	Short-term treatment of benign GU	30 mg once daily up to 8 weeks.
	Healing of NSAID associated GU	30 mg once daily up to 8 weeks.
	Risk reduction of NSAID-associated GU	15 mg once daily up to 12 weeks.
	Heartburn	15 mg once daily for 14 days.
	Pathological hypersecretory conditions	60 mg once a daily.
Pantoprazole	Healing of EE	40 mg once a day for up to 8 weeks.
	Maintenance of healed EE	40 mg once a day.
	Pathological hypersecretory conditions	40 mg twice a day.
Rabeprazole	Short term treatment of DU	20 mg once daily for 4 weeks.
	H. pylori eradication to reduce the risk of recurrence of DU	Triple Therapy: 20 mg twice a day for 7 days.
	GERD, healing of erosive or ulcerative	20 mg once daily for 4 to 8 weeks.
	GERD, maintenance of healing of erosive or ulcerative	20 mg once daily.
	GERD, symptomatic (non-erosive)	20 mg once daily for 4 weeks.
	Pathological hypersecretory conditions	260 mg once daily.
Dexlansoprazole	Healing of EE	60 mg once daily for up to 8 weeks.
	Maintenance of healing after EE treatment	30 mg once daily.
	GERD, symptomatic (non-erosive)	30 mg once daily for 4 weeks.

DU = duodenal ulcer, EE = erosive esophagitis, GERD = gastroesophageal reflux disease
GU = gastric ulcer, OTC = over the counter, NSAID = nonsteroidal anti-inflammatory drug

2.11 Use of PPI across the U.S

PPIs are the most widely prescribed drugs by a wide range of physicians in the U.S.[157] In the U.S. PPIs are account for more than $10 billion in annual health care costs.[157] and more than 15 million people in the U.S. used either brand or generic

versions of any of the six approved PPIs.[158] In 2013, omeprazole had the highest market share of 52.9% compared to other PPIs, whereas Aciphex (rabeprazole sodium) was the leading PPI by generating a revenue of $692.9 million in the U.S. At present, most PPIs are available in generic forms, therefore the overall use of brand name PPIs is decreasing due to the increased availability of generic PPI formulations.[157] One major reason for using generic PPIs over the branded PPIs is the low price of generic PPIs. For example, in 2013, the estimated cost for 3 months' supply of Prilosec (20 mg omeprazole, 42 tablets) was $390, while at the same time online generic formulations of 20 mg omeprazole were available with a cost between $13-16 for 28 tablets.[157] Although information regarding the overall use of PPIs are available in the literature, knowledge gap exists regarding proportions of the use of brand and generic PPIs in different settings of the U.S.[159] To this date, one study sought to identify the association of different factors with PPI use and found that compared to HMO visits, patient visits at academic medical centers (Incidence rate ratio (IRR)=4.2, 95% CI=2.2-8.0), physician-owned practices (IRR=3.9, 95% CI=2.1-7.1), and community health centers (IRR=3.6, 95% CI=1.9-6.6) were strongly associated with brand name only PPIs.[160]

2.12 Inappropriate Use of PPIs

Although PPIs show effectiveness to manage acid-related disorders and the FDA has well defined approved indications for PPIs[126], inappropriate use of PPIs exist in different settings.[161-167] For example, studies found that, in ambulatory settings, 36-39% patients lack an indication for PPI use.[165,166] While during hospital discharge, up to 69% of patients were prescribed PPI inappropriately. [167] Inappropriate PPI use has

both health and financial consequences. Recently, several studies have been conducted to identify the relationship between different AEs and long-term PPI use. Although the use of PPIs is well recognized as effective treatment options, overutilization can take place due to lack of monitoring and reevaluation of patients' medical condition.[167] This can result in increased PPI use that might not be needed for patients, which might increase the possibility of acquiring different AEs such as acute kidney disease, chronic kidney disease, pneumonia, bone fractures, cardiovascular events, and enteric infections.[31,32,34,140-146] In the U.S., more than $10 billion in annual expenditures are attributed to the use of PPIs, but in many cases, PPI use takes place without any proper indication.[61] For example, a retrospective cohort study in the U.S., conducted in a Veteran Administration hospital, found that 36% of patients had no documented indication for PPI therapy.[165] For PPIs prescribed without proper indication, significant prescription spending can be saved with rationale use of PPI.[168]

2.13 Safety Concerns with PPI Use

Although PPIs are considered a safe class of drugs, several studies have identified potential AEs after short- and long-term exposure. Although short-term use of PPIs are well tolerated, long-term use of PPIs among older adults has been reported to be associated with AEs such as bone fractures, clostridium difficile infection and acute interstitial nephritis etc.[31,32] Potential consequences of overutilization of PPI use can include malabsorption of vitamins and minerals, drug interaction, and even increased risks of infection, fracture, cardiac infarction, dementia, and renal complications.[41,169-174]

2.13.1 Fracture

Several studies have identified the association between risk of fracture and PPI use. A recently published meta-analysis systematically evaluated the use of PPI and risk of fractures. Different types of fractures have been assessed for their relationship with the use of PPI. For example, this meta-analysis sought to identify the possible association between PPI use and hip fracture and demonstrated the pooled risk estimation (Risk Ratio (RR) = 1.26, 95 % CI=1.16–1.36) from 15 studies, indicating a positive association between the use of PPI and hip fractures.[175] This study also identified associations with risk of spine and any-site fracture and found that PPI use moderately increased the risk of both spine and any-site fracture.[175] Although studies have identified the associations between fractures and PPI use, the responsible biological mechanism is still unknown.[175] A potential mechanism for risk of fracture is hypothesized that PPI reduces the absorption of calcium thus results in decreased bone mineral density, however, existing evidence shows mixed support for this hypothesis.[175] While one study identified the reduced absorption of calcium among postmenopausal women when omeprazole is taken with food, other randomized clinical trials did not find any reduction of calcium absorption with the use of omeprazole.[176,177]

2.13.2 Hypomagnesemia

Use of PPIs has also been linked with hypomagnesemia. Hypomagnesemia is an electrolyte disturbance when the magnesium level is lower than 0.66 mmol/L (1.6 mg/dL).[178] Several studies have been conducted to assess the relationship between hypomagnesemia and use of PPI. In 2015, Cheungpasitporn et al. identified 9

observational studies and performed a meta-analysis and found that the risk of hypomagnesemia was higher (RR=1.43 and 95% CI=1.08-1.88) among patients using PPI.[179]

2.13.3 Vitamin B12 and Iron Deficiency

The associations between vitamin B12 deficiency and iron deficiency with the use of PPI have been explored in many studies. Existing evidence for vitamin B12 deficiency and use of PPI is mixed by the duration of PPI use. Specifically, short-term use of PPIs was found to be associated with decreased absorption of vitamin B12,[180] but for patients using PPI continuously for 3-5 years, the association with vitamin B12 absorption was not found.[181] Iron deficiency was also explored in a few studies, and a significant decrease in mean hemoglobin and hematocrit has been observed among patient using PPIs.[182] For both vitamin B12 and iron deficiency, the possible biological mechanism is the malabsorption due to the use of PPIs.[159] However, the limited number of studies warrants further research to explore the causality between these associations.

2.13.4 Infection

Gastric acid not only helps to digest food but also plays a vital role in the body's defense system against pathogens ingested with foods and drinks.[182] Under lower pH conditions (e.g., <4), gastric acid works as potent bactericidal. Almost half of the ingested bacteria can escape when the gastric pH is more than 4.[183] Thus, suppressing gastric acid secretion and initiating a state of hypochlorhydria may increase the risk of bacterial infection.[184] PPIs have the ability to increase gastric pH to more than 4 and can keep this increased pH for a prolonged period of time. With

increased pH, ingested bacteria can escape due to less bactericidal effect of gastric acid and can disrupt the natural gut bacteria ecology.[183,185] Relationship between PPI use and infection has also been explored and documented in different studies. Existing evidence indicates that suppression of gastric acid secretion induces intestinal pathogen colonization from the stomach to lower respiratory tract.[172] This pathogen colonization along with the regurgitation develops pneumonia.[186,187] Previous studies have been conducted to explore the association between PPI use and pneumonia and those studies found that PPI users are at an increased risk of pneumonia compared to the non-users.[188-195] The same biological mechanism also explains the relationship between PPI use and enteric infections.

Existing evidence indicates a possible association between PPI use and enteric infections. For example, the association between Salmonella infections and PPI therapy has been assessed from two case-control studies with a RR ranging from 4.2-8.3.[196,197] Similarly risk for *C. jejuni* diarrhea was also observed among PPI users compared to non-users with a RR ranging between 4.3-11.7.[196,198,199] Among different types of enteric infections, the association between PPIs and C. difficile was examined extensively. For example, Janarthanan et al. included 17 case-control and 6 cohort studies and compiled a total of 288,620 study participants in a meta-analysis, and they found a positive association between C. difficile and PPI therapy (RR=1.69; 95%CI=1.40–1.97).[200] Similar findings were also observed in another meta-analysis combining 30 case-control and 12 cohort studies (pooled odds ratio= 1.74 and 95%CI=1.47–2.85 based on a total of 313,000 study participants) for developing CDI among PPI users.[159,201] A plausible biological mechanism for this acid rebound

phenomenon can be attributed to the compensatory gastrin release due to the stimulation of long-term increased gastric pH.[127]

2.13.5 Acid Rebound

Although PPIs decrease gastric acid secretion, findings from long-term physiological studies have shown that the capacity to secrete gastric acid increases after discontinuation of long-term PPI use.[202,203] A plausible biological mechanism for this acid rebound phenomenon can be attributed to compensatory gastrin release due to the stimulation of long-term increased gastric pH.[127] A few studies have been conducted to observe this physiological phenomenon and found that withdrawal of PPI treatment increases the acid-related symptoms among healthy subjects.[204,205]

2.13.6 Dementia and Cognitive Impairment

Recent pharmacoepidemiologic studies have found an increased risk of dementia and cognitive impairment associated with the use of PPIs.[40,41] In a systematic review, Batchelor et al. identified 4 studies assessing the risk of dementia with PPI use and 7 studies exploring cognitive impairment among the PPI users.[206] The authors reported positive associations between PPI use and dementia, as well as between PPI use and cognitive impairment. However, for cognitive impairment, the majority of the studies were case reports.[206]

2.13.7 Neoplasia

Due to the compensatory increased gastric secretion after the constant elevation of pH in the stomach, the trophic effect of gastrin is a concern regarding the development of gastric polyps, gastric cancer, carcinoids, and colorectal cancer.[159,207]

Although some case reports and case series studies have identified the increased fundic gland polyps (FGPs) with the use of PPIs, one case-control study did not find any association of FGPs with short or long-term PPI use.[208,209] Risk of atrophic gastritis followed by intestinal metaplasia and gastric cancer has received considerable attention recently. Although studies suggest an increased risk of atrophic gastritis among PPI users, existing evidence is insufficient to support the transformation of atrophic gastritis into malignant diseases.[159,210,211] While a high level of gastrin exerts the trophic effect of colon cells in vitro,[130] several long-term European studies did not identify an increased risk of colorectal cancer due to the use of PPI.[212,213]

2.13.8 Kidney Diseases

Recently concerns with the use of acid-suppressive drugs and kidney diseases have been raised, and several population-based studies have been conducted to explore the potential relationship. For acute interstitial nephritis (AIN), PPI users had a higher risk of developing this disease compared to non-PPI users. However, existing evidence has substantial heterogeneity.[214-216] Risk of acute kidney injury (AKI) was evaluated in several studies. However, evidence was mixed regarding its association with PPI use.[217-219] Risk of chronic kidney (CKD) disease with PPI therapy was also explored, and like AKI, existing evidence for CKD is also mixed. While some studies identified no association,[53,218,219] one study identified a positive association between PPI use and CKD (OR=1.10 and 95% CI=1.05-1.16).[220] In addition to PPI use, the relationship of doses of PPIs and the risk of developing kidney diseases was also explored by several studies. Existing evidence indicates the association of increased doses of PPI with the increased risk of developing renal diseases.[173,219]

2.13.9 Gastric Cancer

Limited existing evidence suggest the association between PPI use and gastric cancer (GC). It is suspected that hypergastrinemia caused by profound acid suppression caused by PPIs could be a responsible factor for the increased risk of GC among PPI users.[221] At present, one meta-analysis evaluated the association between PPI use and the risk of GC, but it only synthesized the findings from observational studies.[222] This meta-analysis identified one cohort and three case-control studies and found that PPI use might increase the risk of GC by 43% (OR: 1.43; 95% CI: 1.23 - 1.66).[222] While this meta-analysis provided valuable information on the risk of GC and PPI use, the included observational studies are susceptible to several biases, such as protopathic bias.[223] A significant proportion of patients with early GC experience typical dyspeptic symptoms and use PPI to control these dyspeptic symptoms.[224] Thus protopathic bias may lead to the erroneous conclusion that PPIs are responsible for GC.[224,225]

2.13.10 Myocardial Infarction

A novel mechanism of PPI use and increased risk of MI follows the hypothesis that PPI use increases levels of asymmetrical dimethylarginine (ADMA) by inhibiting dimethylarginine dimethylaminohydrolase (DDAH), causing the blockade of vascular nitric oxide synthase activity, and enhanced contractility with loss of normal relaxation.[226,227] Several studies support this hypothesis of PPI use and MI mechanism.[228,229] For example, Ghebremariam et al., found that cellular ADMA levels increased with the use of PPI in animal and ex vivo human models.[228] In another study, baseline ADMA levels predicted cardiovascular death among patients with coronary

diseases.[229] Similarly, ADMA concentrations were associated with increased risk of cardiovascular death among patients who were free from cardiovascular disease at baseline.[230] These evidence indicated a theoretical plausibility of PPI induced CV, but this mechanism has not been validated in human coronary diseases. Several clinical trials and observational studies also explored the risk of MI with the use of PPIs and presented mixed results.[34,35] For example, Landi et al found decreased risk of MI among PPI users compared with H2 blocker users at 3 months post initiation and the early onset association disappeared after 12 months of treatment initiation whereas in 2013 Juurlink et al. suggested that PPI was associated with a higher risk of acute myocardial infarction.[34,231]

2.14 Knowledge Gaps in AEs Associated with PPI Use

Existing studies provide limited information regarding the association between PPIs use and potential AEs such as MI and GC. While the available studies provide important evidence in PPIs use and AEs, the studied populations mainly resided in the European countries and the evidence is very limited for the U.S. population. Those studies conducted among the U.S. population either have weaker study designs or have small sample sizes. In addition, most of the studies that evaluated the safety profile of PPIs focused on the overall PPIs use instead of individual PPIs, and very few studies were conducted among the U.S. population. Therefore, existing evidence in the association between PPIs use and potential AEs has limited generalizability for both different PPIs and the U.S. population.

In addition, existing evidence in long-term PPI use and associated potential harm remains limited. Not all physicians perceive the risk of long-term PPI use in the

same magnitude. For example, a survey conducted by the State University of New York at Stony Brook found that primary care physicians (PCPs) were more concerned regarding AEs associated with long-term PPI use, whereas the majority of gastroenterologists did not have any concerns regarding the long-term PPI use.[232] Although some physicians perceived potential harm of long-term PPI use, inappropriate use of PPI still exists in different healthcare settings.[161-167] According to the peptic ulcer disease guideline, "Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease," [5] PPI therapy should be discontinued after short-term therapy (4 to 12 weeks)[22]. However, discontinuation should not take place if patients are receiving maintenance therapy on half of the short-term therapy dose, usually after healing of reflux esophagitis or erosive esophagitis.[233-235] Although appropriate acute and maintenance use of PPI is supported by evidence-based treatment guideline[233], overuse and inappropriate use are very common in the U.S.,[161-167], which is mainly due to an inadequate re-evaluation of the need for continuation of PPI treatment or consideration of on-demand and step-down PPI therapy.[30] While studies suggest short-term PPIs use is safe; the evidence is different for long term use of PPIs. Long-term PPIs use defined as the use of PPIs for more than 12 weeks in a year[236,237], and long term PPIs use has found to be associated with several AEs such as nephritis, malabsorption of vitamins and minerals, drug interaction, increased risks of infection, fracture, cardiac infarction, dementia, and renal complications.[31,32,41,169-174] The comparative safety profile of all available PPIs has remained understudied for long term PPIs use. Comprehensive evaluation of long term use of all available PPIs can

provide fundamental evidence on the safety of PPIs use and guide clinical practice in optimizing PPI treatment.

2.15 Rationale for This Study

PPIs are generally considered as safe drugs. However, several studies identified the association of PPIs and potential AEs such as acute kidney disease, chronic kidney disease, pneumonia, bone fractures, cardiovascular events, and enteric infections.[27,28,41,169-174,238] While existing evidence provides a strong argument for the association between several AEs and PPI use, for some AEs such as Myocardial infarction (MI), Chronic kidney disease (CKD), gastric cancer (GC), more information is required to confirm any causal relation. Additionally, most published studies focused on overall PPI use and did not differentiate and evaluated the safety profile of individual PPIs. With the consideration of selection and evaluation of all the PPIs based on their safety profiles, comparing and contrasting their associated AEs with each other as well as with the H2 blocker (as control product), findings of this study can close the knowledge gap regarding the associations between PPIs and potential AEs such as MI, CKD, GC by different PPIs and among different subgroups of populations.

In this study, we first examined the utilization patterns of PPI and associated healthcare spending in the U.S. population. Findings in distributions of PPI use (i.e., overall PPIs use: PPIs users and non-users, PPIs use among patients with esophageal diseases, individual PPIs use, branded and generic PPIs), factors associated with PPIs use, and cost associated with PPI use will provide a thorough assessment of PPI use and economic burden among the U.S. population overtime, which in turn, will guide

policymakers to improve the cost-effectiveness assessment and appropriate use of PPIs.

Next, in aim 2, both the spontaneous FAERS and Medicare administrative claims data were analyzed to evaluate the safety profile of PPIs. In aim 2 we first identified potential safety signals for PPIs using the FDA Adverse Event Reporting System (FAERS) data, focusing on CKD, MI, and GC. Furthermore, the influence of important research findings on AE reporting was tested during the entire study period, as well as before and after the availability of key publications. Then we used the 5% random sample of the 2013-2016 Medicare administrative claims data to assess the associations of MI, CKD, and HF with PPI use. In this aim, we assessed the safety of over new users of PPIs, long-term PPI use, short term PPI use, and individual PPI use to build real-world evidence in safety of PPI use, thus guide clinical practice in optimizing PPI treatment.

Finally, a comprehensive systematic review of existing clinical trials and observational studies were conducted to evaluate the safety of PPI use by a different focusing on the risk of MI, GC and PPI use. Subgroup analyses based on the study design and comparator group further help understand potential associations. We believe the comprehensive systematic evaluation quantified and compared risks associated with PPI use across hierarchical evidence. Findings will help pharmaceutical regulatory authorities such as the U.S. Food and Drug Administration (FDA) improve their existing pharmacovigilance system for drug products including PPIs.

2.16 Overall Contribution

The study is innovative and impactful in the aspect of the post-marketing pharmacovigilance of PPI use among the U.S. population. In aim 1, the longitudinal utilization patterns and associated healthcare cost with the use of PPIs informed the burdens of PPIs among the U.S. population. In aim 2, findings could inform us regarding the safety signals for MI, CKD, and GC for PPI and the influence of publications on the reporting of these AEs. Furthermore, these signals were further assessed using the 5% random sample of the 2013-2016 Medicare administrative claims data employing a new user cohort design. In Aim 3, the comprehensive systematic review and meta-analysis focusing on AEs (MI, GC) associated with the use of PPIs characterized risks associated with PPI use across RCTs and observational studies. This systematic review and meta-analysis evaluated the most up-to-date evidence to assess the association between PPIs and MI and GC. Findings could help drug regulatory authorities evaluate and improve their current post-marketing surveillance system regarding PPI use and risk. This systematic review approach along with the secondary data analysis of multiple population-based datasets is unique and well-suited to answer research questions regarding PPI use and safety among the U.S. population.

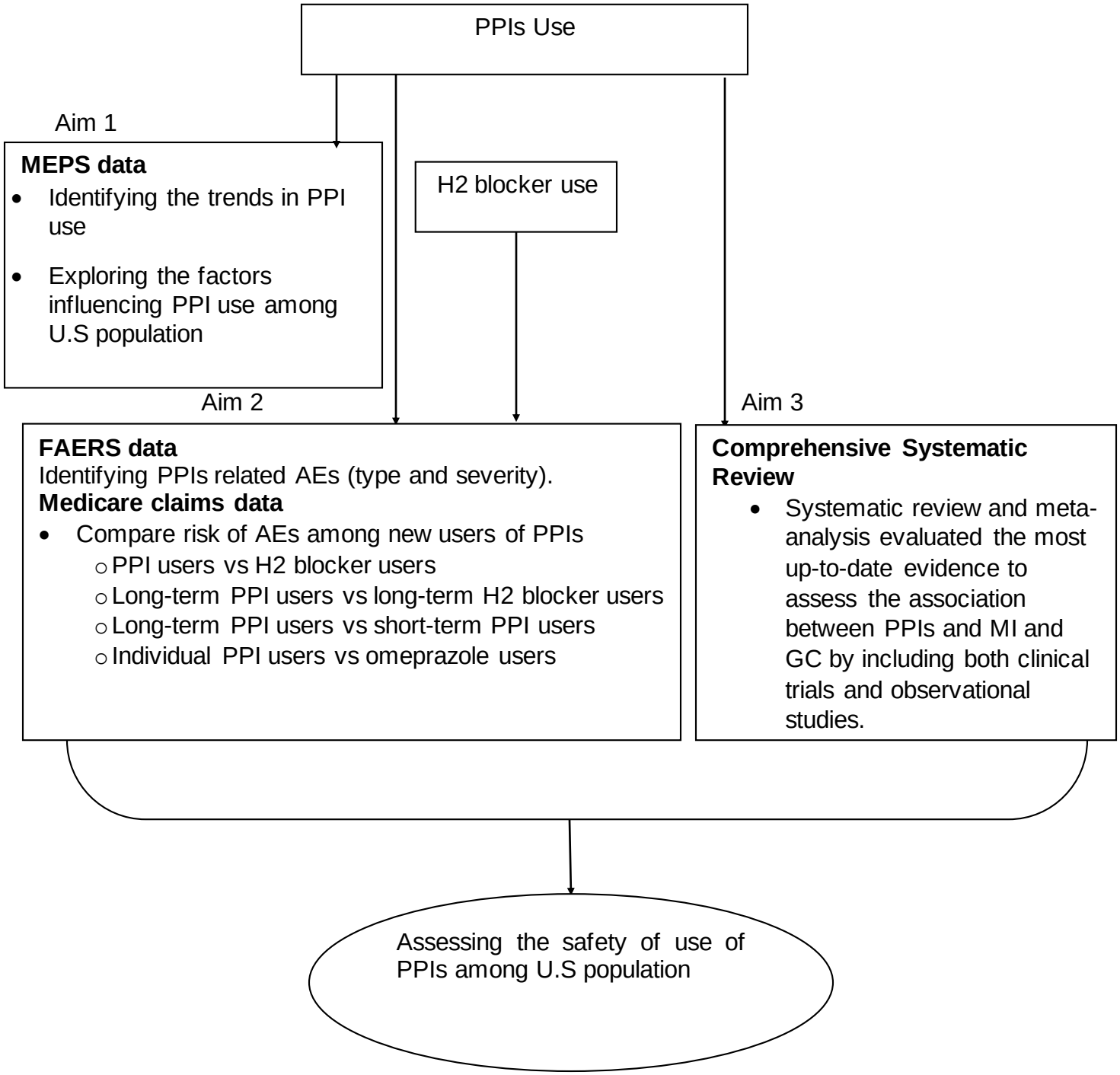
Chapter 3

Methods

3.1 Overview

The goal of this research is to systematically and comprehensively assess the safety of post-marketing use of PPIs among the real-world population living in the U.S. In this study, we described the trends in PPI use, expenditure and reported AEs among the U.S. population. Through FAERS analyses, we evaluated the safety signals of MI, CKD, and GC for PPI use and assessed how the publication of important research findings might have influenced the reporting of these AEs. We further assessed how the use of long-term, short-term, and individual PPIs influenced the incidence of AEs such as MI, HF, and GC among real-world population using the 5% random sample of the Medicare claims data. Finally, we conducted a comprehensive systematic review and meta-analyses of existing evidence to assess the association between PPI use and MI and GC by including both clinical trials and observational studies. Data from the Medical Expenditure Panel Survey (MEPS), FDA Adverse Event Reporting System (FAERS), and Medicare claims were used to document the safety of post-marketing use of PPIs among the real-world population living in the U.S.

Figure 3.1: Conceptual model of ensuring the safety of PPI use



3.2 Approach

3.2.1 Specific Aim1: To examine trends in PPIs use and associated healthcare spending among the U.S. population.

3.2.1.1 Data source and study population

The Medical Expenditure Panel Survey (MEPS) is a set of large-scale national representative surveys of families and individuals, their medical providers, and employers across the U.S.[239] The MEPS is designed and sponsored by the Agency for Healthcare Research and Quality (AHRQ) and serves as the major data source measuring the use and payment for medical care, health insurance, and out-of-pocket spending of U.S. citizens.

MEPS is a multi-stage probability survey, which collects data on the health services that Americans use, frequency and cost of use, and costs associated and payment of the services, as well as data on the private health insurance available to the U.S. civilian non-institutionalized population. The probability sampling of MEPS provides national level so that national level estimations can be made. The MEPS data are publicly available online at http://meps.ahrq.gov/mepsweb/. The most recently available annual MEPS data is 2017.

The MEPS has two major components, 1) The Household Component (HC) and 2) The Insurance Component (IC). The HC collects data from a sample of families and individuals in selected communities across the U.S., drawn from nationally representative subsamples of households that participated in the prior year's National Health Interview Survey (NHIS). Private and public employers provide data to the IC

data files. MEPS also has the Medical Provider Component (MPC), covering hospitals, physicians, home health care providers, and pharmacies identified by MEPS-HC respondents. To this date, MEPS has a total of 53,1415 individual participants from 2002-2017 containing age groups under 5 to 65 years and above (Table 3.1).[240]

Table 3.1: MEPS-HC Unweighted Sample Sizes by age group

Year	All persons (Having positive weight)	Under 5	5-17	18-24	25-44	45-64	65+	MEPS-HC Full-year overall response rate
2002	37,418	2,849	8,250	3,463	10,264	8,268	4,324	64.7%
2003	32,681	2,638	7,359	3,072	8,873	7,028	3,711	64.5%
2004	32,737	2,609	7,200	3,080	8,821	7,280	3,747	63.1%
2005	32,320	2,559	7,132	3,032	8,554	7,340	3,703	61.3%
2006	32,577	2,559	7,074	2,976	8,323	7,728	3,917	58.3%
2007	29,370	2,201	6,296	2,679	7,537	7,106	3,551	56.9%
2008	31,262	2,540	6,594	3,073	8,278	7,374	3,403	59.3%
2009	34,920	2,791	7,259	3,433	9,154	8,399	3,884	57.2%
2010	31,228	2,317	6,393	3,010	8,093	7,695	3,720	53.5%
2011	33,622	2,525	6,861	3,265	8,835	8,080	4,056	54.9%
2012	37,182	2,723	7,697	3,679	9,827	8,937	4,319	56.3%
2013	35,068	2,531	7,369	3,460	9,291	8,430	3,987	52.8%
2014	33,162	2,336	6,939	3,197	8,791	7,897	4,002	48.5%
2015	33,893	2,244	6,958	3,119	8,925	8,275	4,372	47.7%
2016	33,259	2,158	6,692	3,005	8,525	8,233	4,646	46.0%
2017	30,716	1,899	5,974	2,575	7,682	7,699	4,887	44.2%

The MEPS has been used to identify health care services, drug utilization and expenditures associated with different disease state, healthcare settings and health condition.[241,242] In 2017, Salami et al. used the MEPS data to identify the statin use and expenditure among U.S adults.[243] MEPS data also has been used to identify the differences of health care utilization and cost among different subgroups of age, gender, race/ethnicity.[244]

In this study, the MEPS data from 2002-2017 were used to examine PPI use and associated expenditure among U.S. adults. The MEPS Household Components' full-year consolidated, medical conditions, and prescribed medicines files for each year from 2002 to 2017 were merged to create annual files with sociodemographic characteristics, medical conditions, and medication use and expenditures. Data in each 2-year cycle were pooled, and the person-level weight was adjusted to reflect the mean annual population size and medication use and expenditures of the two years in each cycle.

3.2.1.2 Study design and study sample

Serial cross-sectional analyses of U.S adults using MEPS data from 2002-2017 were performed. In this study, we included respondents of all ages regardless of gender, educational status, marital status, insurance status, and race-ethnic background. We excluded MEPS respondents who were in-scope for the survey for only part of the year. In MEPS data, some respondents can be in-scope for the survey for part of the year. These persons included those who had some periods of time in the year living in an institution (e.g., nursing home or prison), were in the military, or were not in the U.S., as well as newborn (or adopted) into MEPS sample households or died during the year. [245] They were considered respondents to the survey and are included in MEPS data files with positive person weights, but no data were collected for the periods they were not in-scope and their annual data for variables like health care utilization and expenditures reflect only the part of the year they were in-scope for the survey. [245] MEPS variables: inscop31, inscop42, inscop53, begrfy31, perwtXXf,

inscopXX, panelXX (XX=02……15) were used to identify MEPS respondents who were in-scope for the survey for only part of the year. [245]

Ideally, in a survey, a selected sample is a miniature of the population it came from. However, non-response is a real life problem in survey research and it may cause some groups to be over- or under-represented.[246] Weighting adjustment is a commonly applied method to adjust this issue. In MEPS, person weight is used to compensate for oversampling and non-response. Final person weight>0 indicates the person selected and in-scope for survey, and Weight = 0 indicates person not in-scope for survey but living in household with in-scope person(s). These out of scope individuals are active duty military personnel and certain individuals (died, new born, institutionalized, military, moved within U.S., out of country) who first joined a MEPS household after MEPS households had been selected.[247] Out of scope individuals in MEPS survey might stay in the in scope domain partially, however data were be collected for the period while they are in out of scope domain.[152] For the out of scope individuals of a MEPS year, annual data for variables like health care utilization and expenditures does not provide complete information[152], thus including them gives a biased result. Therefore, we included individuals having person weight greater than 0. The following table 3.2 provides detailed sample size from 2002-2017 under MEPS data categorized in weighted and unweighted sample size.

Table 3.2: MEPS-HC weighted Sample Sizes

Year	Sample Size			
	Total	With Positive Weights	With Nonpositive Weights	Total Weighted Frequency
2002	39,165	37,418	1,747	288,181,763
2003	34,215	32,681	1,534	290,604,436
2004	34,403	32,737	1,666	293,527,003

Year	Sample Size			
	Total	With Positive Weights	With Nonpositive Weights	Total Weighted Frequency
2005	33,961	32,320	1,641	296,185,002
2006	34,145	32,577	1,568	299,267,035
2007	30,964	29,370	1,594	301,309,149
2008	33,066	31,262	1,804	304,375,942
2009	36,855	34,920	1,935	306,660,588
2010	32,846	31,228	1,618	308,573,976
2011	35,313	33,622	1,691	311,125,758
2012	38,974	37,182	1,792	313,489,853
2013	36,940	35,068	1,872	315,721,982
2014	34,875	33,162	1,713	318,440,423
2015	35,427	33,893	1,534	321,423,251
2016	34,655	33,259	1396	323,141,687
2017	31,880	30,716	1164	324,779,909

3.2.1.3 Measurements

3.2.1.3.1 PPI use

The study population were classified into patients with and without esophageal disorders using PPIs. Clinical Classification Code 138 from MEPS data were used to identify patients as having any esophageal disorder.[153] For each year, the variable specifying the drug names, “RXNAME” labeled as MEDICATION NAME (IMPUTED)” were used to identify the major types of PPIs. In MEPS data, prescription name reported by the pharmacy is available through RXNAME variable in PRESCRIBED MEDICINES file. RXNAME variable contains the reported generic or brand name through the pharmacy. RXNAME variable specifying the drug names has been previously used to identify other drugs such as statin and classified them into the brand and generic.[248] We used the specific generic names and brand names (available in the U.S.) of the PPIs to identify the generic and brand PPIs through RXNAME variable. We

also used “RXNAME” variable to classify PPIs as Brand name or generic PPIs with the use of verbatim of PPIs names.

This study also expanded beyond the esophageal disorders diagnosis to identify the overall PPIs use among U.S population. Respondents in the MEPS data were categorized to PPI users and non-users, regardless of esophageal disorders diagnosis. Main analysis contained all the PPIs users regardless of having Esophageal disorders. Esophageal disorders were further used as a sub-analysis to identify the influence of esophageal disorders on PPIs use.

3.2.1.3.2 Health Expenditures

In the MEPS data, the exact dollar amount is reported for each PPI use event as well as the source of payment, including the out of pocket cost paid by self or family or by specific insurance coverages. This information on spending were used to calculate the prescription drug cost for PPIs for both self/family and specific insurance coverages and Consumer Price Index (CPI) (Table 3.2), which were used to adjust annual expenditures for all years to the constant 2016 U.S. dollars.

Table 3.3: Consumer Price Index (CPI)[249]

Year	Average CPI
2002	179.90
2003	184.00
2004	188.90
2005	195.30
2006	201.60
2007	207.30
2008	215.30
2009	214.53
2010	218.06
2011	224.94
2012	229.59
2013	232.96
2014	236.74

Year	Average CPI
2015	237.02
2016	240.01
2017	245.12

X's expenditure into 2016's dollar value= X's actual expenditures x (2016 CPI / X CPI)

[X=2002…..2015]

3.2.1.3.3 Covariates

The MEPS full-year population characteristics files contain demographic characteristics of the MEPS sampled population as well as employment, health status, quality of care, patient satisfaction, and health insurance coverage estimates. Age, sex, race/ethnicity, family income, GERD diagnosis (ICD9 code 530.81), Charlson comorbidity index (CCI), self-reported health status, marital status, education, alcohol use, smoking, and health insurance coverage were identified as potential factors affecting PPIs use. These factors were explored for overall PPIs use as well as for individual PPIs use and factors associated with the brand, and generic PPIs use were also explored in this study. Participants' age of the last day of the survey year were grouped into six categories: 0-4, 5-17, 18-25, 25-40, 40-64 and 65 and older. For race/ethnicity, the PPIs use were assessed among non-Hispanic white, non-Hispanic black, Hispanic, Asian, and other (American Indian, Alaska Native, and those who reported multiple races/ethnicities). There were 5 categories of family income level as a proportion of the federal poverty level (FPL): poor (<100% of FPL), near poor (100%-<125% of FPL), low income (125%-<200% of FPL), middle income (200%-<400% of FPL), and high income (≥400% of FPL). CCI were computed by using the ICD9 codes and patients' diagnosis information from the medical file of the MEPS. The following Table 3.4 details the covariates that were used to analyze the MEPS data.

Table 3.4: Covariates for MEPS analysis

MEPS Variable Name	Description	MEPS File	Categories
AGE15XAGE(Year)X		Household Component Full-Year files: Full-Year Consolidated Data files	1=0-4 2=5-17 3=18-24 4=25-44 5=45-64 6=65-85
SEX	Sex	Household Component Full-Year files: Full-Year Consolidated Data files	1= Male 2= Female
RACETHX	RACE/ETHNICITY	Household Component Full-Year files: Full-Year Consolidated Data files	1=Hispanic 2=Non-Hispanic White 3=Non-Hispanic Black 4=Non-Hispanic Asian 5=Other
POVCATX	Family income (as % of the poverty line)	Household Component Full-Year files: Full-Year Consolidated Data files	1=POOR 2=Near Poor 3=Low Income 4=Middle Income 5=High Income
REGIONX	Census Region	Household Component Full-Year files: Full-Year Consolidated Data files	1=NORTHEAST 2=MIDWEST 3=SOUTH 4=WEST
EDUCYR	Years of education when first entered MEPS	Household Component Full-Year files: Full-Year Consolidated Data files	1= No School/Kindergarten Only 2= Elementary Grades 1 – 8 3= High School Grades 9 – 11 4= Grade 12 5= Some College Education 6= 4-5 Years College Education
MARRY15X	Marital Status	Household Component Full-Year files: Full-Year Consolidated Data files	1=Married 2=Never Married 3=Widowed/Divorced/Separated
RTHLTH53	Perceived Health Status	Household Component Full-Year Files: Full-Year Consolidated Data Files	1=Excellent 2=Very Good 3=Good 4=Fair 5=Poor

MEPS Variable Name	Description	MEPS File	Categories
INSCOVX	HEALTH INSURANCE COVERAGE	Household Component Full-Year Files: Full-Year Consolidated Data Files	1=any private 2=Public3=Uninsured
BMINDX53 (for adults)	Body mass index	Household Component Full-Year files: Full-Year Consolidated Data files	1=Normal Weight = BMI is between 18.5 – 24.9 2=Overweight = BMI is between 25.0 – 29.9 inclusive, and 3=Obesity = BMI greater than or equal to 30.0 4= Child BMI
CHBMIX42 (for children)	Body mass index	Household Component Full-Year files: Full-Year Consolidated Data files	
CCCODEX	Esophageal disorders (Clinical Classification Codes 138 as esophageal disorders)	Medical Conditions File	0=Not esophageal disorders 1= esophageal disorders
CCI	Charlson Comorbidity Index (ICD-9-CM codes using ICD9CODX will be used to calculate Carlson comorbidity index)	Medical Conditions File	CCI will be used as continuous data

3.2.1.4 Statistical analysis

All analysis were conducted with the SAS 9.4 software. Total annual expenditure total out of pocket expenditure, and both private and public insurance paid expenditure of overall PPIs users, and individual PPIs users were calculated for each cycle. Trends for all PPI use as well as individual PPI use were measured and examined on 14 years period among all the adults as well as among different among different subgroups of the population. Descriptive analyses were used to identify the annual proportion of participants with any PPI use, overall and by patient subgroups, and simple linear regression models were used to examine the trends of PPIs by

identifying the P_{trend}. All the results were weighted to represent national estimates and $P<0.05$ was set for statistical significance.

Trends in use of overall PPIs, individual PPIs, brand and generic PPIs were evaluated across different subgroups of MEPS year, age, sex, family income, race/ethnicity, census region, education, marital status, perceived health status, health insurance coverage, smoking status, CCI and among all eligible MEPS respondents, and among respondents diagnosed esophageal disorders.

In addition, trends in total annual expenditures and total out-of-pocket (OOP) expenditures and the amount paid by private and public insurance on overall PPIs, brand, generic as well as individual PPIs for the non-institutionalized U.S. population were estimated. SAS procedure PROC SURVEYMEANS was used to generate average expenditure for both overall PPIs, and individual PPIs use. Trends for self-pay (OOP) expenditure were identified using the RXSLFxx (xx denotes the year: 02…….15) variable and RXXP0xx (xx denotes the year: 02…….15) variable was be used to identify the total expenditures associated with the use of overall PPIs and individual PPIs. We used RXPVxxX (xx denotes the year: 02…….15) and RXORxxX (xx denotes the year: 02…….15) variables to quantify the PPIs related expenditures through private insurance and for public insurance expenditures for PPIs, we used RXMDxxX (xx denotes the year: 02…….15), RXMR14X (xx denotes the year: 02…….15), RXOFxxX (xx denotes the year: 02…….15), and RXOUxxX (xx denotes the year: 02…….15) variables. The annual expenditures and total out-of-pocket (OOP) expenditures on brand and generic were also estimated by stratifying brand and generic PPIs use (using variable RXNAME to differentiate the brand and generic PPI

products). Simple linear regression models were used to examine the trends of PPIs by identifying the $P_{trend,}$ and we used the final person-weight and variance estimations (person sampling units and stratum) to estimate nationally representative totals, means (with 95% Confidence Interval), and rates for the noninstitutionalized population.

Multivariable generalized models with generalized estimating equation (GEE) using Proc Genmod procedure, binomial distribution, and logit-link function[250] were used to identify the factors influencing PPIs use among U.S. adults. Predictors of PPIs use were determined using multivariable model of PPIs use (yes vs. no) on possible predictor. Generalized models with GEE were performed on predictors including the MEPS year, age, sex, family income, race/ethnicity, census region, education, marital status, perceived health status, health insurance coverage, CCI. In all analyses, point estimates with 95% CIs were reported, and 2-sided $P < .05$ was considered statistically significant. Proc Genmod from SAS was used to fit a fit a generalized logit model to identify the influence of any predictors (unadjusted) on the use of PPs.

Multivariable generalized models with GEE were performed consisting of all the predictor variables to identify their influences on PPIs use. Odds ratio (OR) and 95% confidence interval were reported as a measure of the significance of the association. Adjusted models included all the predictor variables described in table 3.4 such as MEPS year, age, sex, family income, race/ethnicity, census region, education, marital status, perceived health status, health insurance coverage, CCI.

3.2.1.4.1 Model (Multiple predictors)

a. Overall PPIs use

logit $g(\mu_{ij})=\log(\mu_{ij}/(1-\mu_{ij}))= \beta 0 + \beta 1*x_{ij}1 + \ldots + \beta k*x_{ij}k$ [x_{ij} 1….. x_{ij} k= Set of predictor variables described in the table 3.4, μij is the probability of PPIs use at jth (j=1,2…k) time point for participant i (1,2…..n))]

3.2.1.5 Expected outcomes, potential problems and probable solutions

The expected outcomes of this aim were: 1) estimated trends in use and expenditure of PPIs among the different subgroups of population in the U.S.; 2) identified patient factors associated with PPIs use.

Results from aim1 should be interpreted cautiously due to its limited generalizability only to the noninstitutionalized U.S. population and not those living in nursing homes. However, results from MEPS data provided valuable information about the use of PPIs among the noninstitutionalized U.S. population, which represent the majority (79.12% in 2018)[251] of this population. Second, we cannot draw a causal effect relationship in our findings in factors associated with PPI use with the cross-sectional study design. Another limitation of this proposed study is that, the MEPS household components were completed by one household member who may be a proxy, which may result in inaccuracies in reporting of the demographic information, payment, drug use, health service use, and provider visit.[252,253] In addition, misreporting also can take place in MEPS data due to lack of technical knowledge among household respondents.[254] Inaccuracies in reporting of MEPS data can hinder the process of identifying PPIs users, patients suffering from esophageal disorders, and can overestimate or underestimate the associated expenditure with PPIs use.

Another limitation of this study is that using verbatim drug name with RXNAME variable might overestimate the use of generic PPIs. In this study, we used RXNAME as our preliminary analysis on MEPS data found RXNDC as not ascertained for several PPIs users in each MEPS calendar year, while pharmacy reported PPIs' name was available. In addition, several respondents had both RXNAME and RXNDC information, however their NDC codes were missing in the FDA orange book. Thus, using RXNDC code will consider these respondents as non-PPIs users and will underestimate the overall PPIs users. In MEPS data, the Pharmacy records of the prescription is collected with the written permission of household member with the prescription and for each medication listed, the date filled; national drug code (NDC); medication name; strength of medicine (amount and unit); quantity (package size/amount dispensed); and payments by source in requested from the pharmacies.[255] As RXNAME information is reported by pharmacy, using RXNAME could help identify overall PPIs users, brand and generic PPIs properly.

Another limitation is that, OTC use of PPIs cannot be verified through MEPS data. Due to this reason, the use of PPIs and associated expenditures can be underestimate than the actual value. Finally, this study is subject to limitations common to retrospective research designs such as selection bias, missing or incomplete information, recall bias, or misclassification stemming from coding errors, however MEPS database, presents accurate representations of the number of drug fills and total drug expenditures when compared with claims data.[256] While we cannot eliminate these inherent limitations of MEPS database, the limitations are balanced by strengths

which include that our analysis on 16 years MEPS data will give the robust number of sample size and cost data, thus the limitations were deemed to acceptable.[257]

We also implemented several steps to minimize the effects of these limitations. For instance, PPIs utilization were explored in various categories to review the consistency of the findings. We also examined PPIs use by brand, generic and expenditure associated with PPIs use were identified for self-pay, private and public insurance. For identifying different patient factors associated with PPIs use, multivariable models were conducted to have a complete overview of the influence of the MEPS year, age, sex, family income, race/ethnicity, census region, Years of education when first entered MEPS, marital Status, perceived health status, health insurance coverage, smoking status, and CCI. Working on overall PPIs, brand, and generic PPIs informed as a comprehensive scenario regarding the PPIs use and utilization in the US. This broad array of analyses among MEPS respondents informed us better regarding the utilization of PPIs among noninstitutionalized population of the U.S.

3.2.2 Specific Aim 2: To identify adverse outcomes associated with PPI Use: retrospective analyses of the U.S. FDA Adverse Events Reporting System (FAERS) and Medicare claims data

The FAERS data (2004-2019Q1Q2) were used to detect potential safety signals for PPIs, focusing on CKD, MI and GC. Influence of important research findings on AE reporting were tested before and after the availability of key publications using FAERS data. In the second part of aim 2, the 5% random sample of the 2013-2016 Medicare

administrative claims data were used to assess the associations of MI, CKD, and HF with the use of PPIs.

3.2.2.1 Identifying potential safety signals for PPI use using the FAERs data

3.2.2.1.1 Data source

The FDA MedWatch program is known as the historical foundation for post-marketing assessment of AEs in the U.S. The MedWatch program is a spontaneous reporting system designed to support the FDA's post-marketing safety surveillance program for drug, therapeutic biologic products, cosmetics, vaccines, and dietary supplements. AEs and medication error reports submitted to the FDA are reviewed and aggregated in the FDA Adverse Event Reporting System (FAERS) database. The public FAERS data include reports submitted to the FDA by patients, healthcare providers, and drug manufacturers. Information from FAERS contains seven files, including demographic information (DEMO), drug information (DRUG), the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) coded for the adverse event (REAC), patient outcomes (OUTC), source of the reports (RPSR), start dates and end dates of drug therapy (THER), and indications for use (INDI). By June 30, 2019, the FAERS includes a total of 16,470,9158 reports, of which 9,257,928 are serious reports. Table 3.5 details the total case numbers for omeprazole, esomeprazole, pantoprazole, rabeprazole, lansoprazole and dexlansoprazole from the first quarter 2004-2019 Q1Q2 public FAERS data.

Table 3.5: Cases identified for different PPIs from the FAERS database

Product	Total Cases	Serious Cases (Including Deaths)	Death Cases
Omeprazole	58,981	48,187	4,783
Esomeprazole	66,494	38,451	3,930
Pantoprazole	31,809	28,054	3,144
Rabeprazole	8,969	7,946	1,569
Lansoprazole	28,208	25,535	3,076
Dexlansoprazole	13,246	12,077	1,580

FAERS database has been previously used to assess the signals of several AEs on different drug products as well as compared the AE reporting rates among brand, generic, and authorized generic products of different therapeutic classes.[258-261] While the FAERS database predominantly used to assess the AE reporting of different drug products, it also has been used to assess specific AE due to targeted therapy among patients suffering from different disease conditions.[262,263] Existing published evidences on the use of FAERS database suggest that the FAERS is an important data source to assess the signals of several AEs on overall PPIs use, individual PPI use, and H2 blocker use.

3.2.2.1.2 Study design

Retrospective analyses of the FAERS data from 2004-2019Q1Q2 were conducted to identify the AE reports involving PPIs available in the U.S. market. Retrospective analysis of MI,CKD, and GC for all six available PPIs were conducted to comparatively assess AE reporting rates across all PPIs, individual PPIs. Known AEs associated with PPIs use that have been identified from existing literature are community-acquired pneumonia, hip fracture, colorectal cancer, acute kidney disease, chronic kidney disease, pneumonia, bone fractures, cardiovascular events, enteric

infections, bone fractures, Clostridium difficile infection, acute interstitial nephritis, cardiac infarction, dementia, and renal complications (Table 3.6). [24-29,34,157-162] The following table 3.7 details the top 20 case count by reaction for overall PPIs, Individual PPIs, and H2 blockers from the FAERS data.

Table 3.6 Known AEs associated with PPIs use

Name	ICD 9 code
Community-Acquired Pneumonia	486[264]
Hip Fracture	820.X[265]
Colorectal Cancer	153.X for colon cancer and 154.X for rectal cancer[266]
Acute Kidney Disease	584.X[267]
Chronic Kidney Disease	585.X[268]
Bone Fractures	800.X-829.X[269], E887[270]
Fall	E880-E886,E-088[271]
Cardiovascular Events	410X-414X, 427.5, 434X, 436X, 437.1, 437.3, 438X, 435X, 433X, 441X, 442X, 444X, 443.9, 44021-440.24, 360.X, 361.X, 362.X, 380.X, 381.X, 392.2-392.6, 392.8[272]
Cardiac Infarction	420.X, 421.X, 422.X[273,274]
Dementia	294.20[275]
Clostridium Difficile Infection	008.45[276]
Acute Interstitial Nephritis	583.89 [277]

Table 3.7: Top 20 case count by reaction for overall PPIs, Individual PPIs from the FAERS database ((2004-2019Q1Q2)

Overall PPIs (Count)	**Omeprazole (Count)**	**Esomeprazole (Count)**	**Pantoprazole (Count)**	**Rabeprazole (Count)**	**Lansoprazole (Count)**	**Dexlansoprazole (Count)**
Chronic Kidney Disease (77,785)	Chronic Kidney Disease (16,3437)	Chronic Kidney Disease (13,706)	Chronic Kidney Disease (16,368)	Chronic Kidney Disease (15,242)	Chronic Kidney Disease (18,560)	Chronic Kidney Disease (11,682)
Acute Kidney Injury (35,892)	Acute Kidney Injury (8,322)	Product dose omission (3,565)	Acute Kidney Injury (7,582)	Acute Kidney Injury (6,805)	Acute Kidney Injury (8,308)	Acute Kidney Injury (6,278)
Renal Failure (18,942)	Drug Ineffective (5,476)	Acute Kidney Injury (6,890)	Renal Failure (3,632)	Renal Failure (3.886)	Renal Failure (4,032)	Renal Failure (3,345)
End Stage Renal Disease (16,094)	Renal Failure (4277)	Drug Ineffective (5,855)	End Stage Renal Disease (2,445)	End Stage Renal Disease (2,995)	End Stage Renal Disease (2,995)	End Stage Renal Disease (2,016)
Drug Ineffective (12,675)	End Stage Renal Disease (2,794)	Malaise (4,233)	Tubulointerstitial Nephritis (1,977)	Tubulointerstitial Nephritis (2,305))	Tubulointerstitial Nephritis (2,370)	Tubulointerstitial Nephritis (1,651)
Tubulointerstitial Nephritis (10,415)	GERD (5,680)	Renal failure (4,214)	Drug Ineffective (1,344)	End Stage Renal Disease	Hyperchlorhydria (1,409)	Renal Haemangioma (977)

Overall PPIs (Count)	Omeprazole (Count)	Esomeprazole (Count)	Pantoprazole (Count)	Rabeprazole (Count)	Lansoprazole (Count)	Dexlansoprazole (Count)
Death (8129)	Product dose omission (2,285)	Dyspepsia (3,912)	Death (1,313)	Hyperchlorhydria (1,385)	Death (1,397)	Death (961)
Malaise (6,595)	Drug Interaction (2,152)	Intentional product misuse (3,778)	Drug Interaction (1,119)	Death (1.348)	Renal Haemangioma (978)	Hyperchlorhydria (890)
Nausea (6073)	Diarrhoea (2,130)	End Stage Renal Disease (2,849)	Nausea (1,074)	Renal Haemangioma (971)	Rebound Effect (969)	Rebound Effect (699)
Dyspepsia (5900)	Nausea (2,898)	Off label use (2,829)	Nausea	Rebound effect (947)	Diarrhoea (843)	Diarrhoea (9282)
GERD(5,783)	Dyspepsia (1,988)	Osteoporosis (2,472)	Diarrhoea ((1,088)	Diarrhoea (658)	Off Label Use (840)	Renal Injury (258)
Vomiting (5720)	Malaise (1,866)	Vomiting (2,322)	Renal Haemangioma (978)	Drug ineffective (648)	Incorrect Product Administration Duration (818)	Drug Ineffective (199)
Intentional product misuse (5,459)	Vomiting (1,825)	Abdominal Pain upper (2,310)	Hyperchlorhydria (923)	Nausea (523)	Drug Ineffective (796)	Nausea (154)
Abdominal pain (5445)	Dyspnoea (17,02)	Pain (2,188)	Dyspnoea (871)	Dialysis (495)	Drug Interaction (689)	Abdominal Pain Upper (127)

Overall PPIs (Count)	**Omeprazole (Count)**	**Esomeprazole (Count)**	**Pantoprazole (Count)**	**Rabeprazole (Count)**	**Lansoprazole (Count)**	**Dexlansoprazole (Count)**
Diarrhoea (5037)	Intentional product misuse (1,681)	Tubulointerstitial Nephritis (2,112)	Vomiting (787)	Dizziness (379)	Nausea (565)	Off Label Use (123)
Hyperchlorhydria (4607)	Abdominal Pain Upper (1,542)	Nausea (1,933)	Rebound Effect (721)	Abdominal pain (376)	Hyponatraemia (543)	Dizziness (110)
Drug interaction (4267)	Off label use (1,533)	Abdominal discomfort (1,915)	Fatigue (665)	Condition aggravated (352)	Dialysis (500)	Headache (100)
Renal Haemangioma (3880)	Dizziness (1,531)	Diarrhoea (1,772)	Dizziness (644)	Vomiting (341)	Malaise (496)	No Adverse Event (99)
Dizziness (2554)	Death (1,397)	Death (1,676)	Astthenia (594)	Renal injury (318)	Product Use In Unapproved Indication (475)	Dysponea (94)
Osteoporosis (2,472)	Headache (1,342)	Fall (1,519)	Headache (593)	Drug interaction (307)	Vomiting (445)	GERD (93)

3.2.2.1.3 Measurements

Data mining algorithm was used to identify Reporting Odds Ratios (ROR) by estimating expected reporting frequencies on the basis of information on all PPIs, all events in the database.[278-281]

For identifying AE reports, text string searches of brand names, generic names, and abbreviations were employed for the six available PPIs. To ensure the accuracy of identifying the PPIs, both drug names and shorted text strings were used. Although, abbreviations and shorter text string yielded a messy drug name list, it was further reviewed, cleaned and recoded manually to correct spelling mistakes and by removing the non-drugs of interest this list provided an all-inclusive list of PPIs.

The AEs in the FAERS are coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The Standardized MedDRA® Query (SMQ v17.0) for “MI” were used to identify a group of Preferred Terms (PTs) related to these events (Supplementary table 1). The SMQ-based MI was then used to match with the reported PTs in the FAERS reaction files. For records with PTs other than MI, we identified them as non-MI, and similar approach was employed for other two AEs (CKD and GC) (Supplementary table 1). Due to the potential influence of a few key publications for MI (Goodman, 2012), CKD (Lazarus 2016), and GC (Poulsen 2009) on spontaneous reporting for PPIs with these AEs, we identified AE reports with PPIs in the FEARS data during the entire study period, as well as before and after the availability of key publications.

3.2.2.1.4 Statistical analysis

Reporting Odds Ratios (ROR) were calculated to assess whether a PPI is disproportionately associated with an AE report or not.[282] Disproportionality analyses with RORs were used to evaluate the likelihood of specific known events to be reported with PPIs as opposed to all other drugs. ROR estimated the odds of reporting of a specific event (SMQ) in those exposed to PPIs, divided by the odds of the event occurring in those not exposed to the PPIs. A possible signal was defined as the lower bound of the 95% confidence interval (95% CI) exceeding 1.[283] This algorithm was performed for each drug-AE pair and product type (i.e., All PPIs, Specific PPI). Additionally, the Breslow-Day test was used to examine homogeneity of the RORs for overall PPIs compared to H2 blockers and P value of $P < 0.05$ was used to define statistical significance. The ROR can be expressed as (A/B) / (C/D), or AD/BC. The following table 3.8 details the A, B, C, and D in ROR calculation and tables 3.9, and 3.10express the strategy to calculate ROR for all PPIs, and individual PPI.

Table 3.8: Target drug vs. all other drugs

Number of Reports	Target Adverse Event	All Other Adverse Events
Target Drug	A	B
All Other Drugs	C	D

ROR=(A/B) / (C/D), or AD/BC

Table 3.9: All PPIs vs all other drugs

Number of Reports	Target Adverse Event	All Other Adverse Events
All PPIs	A	B
All Other Drugs	C	D

Table 3.10: Individual PPI vs all other drugs

Number of Reports	Target Adverse Event	All Other Adverse Events
Individual PPI	A	B
All other drugs	C	D

3.2.2.1.5 Expected outcomes, potential problems and probable solutions

The expected outcomes of this aim were: 1) potential safety signals for PPIs using the FAERS data, focusing on CKD, MI and GC, and 2) potential influence of a few key publications for MI, CKD, and GC on spontaneous reporting for PPIs with these AEs.

Potential FAERS data limitations include under-reporting and reporting biases.[282] The FAERS includes spontaneous reports to the FDA, so the reporting rates can be impacted by external factors such as mass media advertisements, labeling, physician preference of one drug over others, peer effect such as lawyer's perception well as close friend or family member's positive or negative experience with a drug product can shape patients perception and impact on the reporting rates. Although these limitations cannot be eliminated from this study, these issues were addressed in the context of under-reporting and reporting biases by using disproportionality analysis. We used disproportionality analysis as a means to consider the rate of reporting of specific events with a specific drug (all PPIs, specific PPI) as opposed to reporting of the same event with all other drugs and reporting odds ratios (ROR) were used to assess specific known adverse events. The ROR is similar to the commonly reported odds ratio in that it is an estimate of the incidence rate ratio. In other words, it estimates the odds of

reporting of a specific event in those exposed to a specific drug, divided by the odds of the event being reported in those not exposed to the drug. The ROR is not subject to biases of under-reporting for a specific drug or specific event, and has been suggested to be less biased than other disproportionality metric.

Another limitation is that there is a possibility of the presence of duplicate reports for the same event. This can cause the overestimation of reporting rates. This problem can be minimized by following FDA's recommendation, which is to delete duplicate reports and keep the most recent CASE number.[284] "Weber effect" can be another limitation for FAERS data, which suggests that AE reporting peaks at the end of the second year after approval.[285] However, more recent evidence has shown that modern FAERS data does not follow the pattern described by Weber, but we were cautious about Weber effect while evaluating the results from disproportionality study.[285] Sensitivity analyses was conducted by limiting to the FAERS reports came from healthcare providers (Physicians, Pharmacists, Other health-professional). These sensitivity analyses allows us to look more closely into the PPI related safety signals that generated in health care settings.

3.2.2.2 Aim 2.2: Use of Medicare data (2013-2016) to assess associations between PPI use with MI, CKD, and HF

3.2.2.2.1 Data source and study population

In the U.S., Medicare is a national health insurance program administered by the Centers for Medicaid and Medicare Services (CMS) of the U.S. federal government.[286] Medicare is designed to assist the nation's older adults with hospital, medical, and other health costs. Medicare is available to most individuals 65 years of age and older and

individuals under age 65 who are receiving disability benefits from Social Security or the Railroad Retirement Board, and those having End Stage Renal Disease (ESRD).[84]

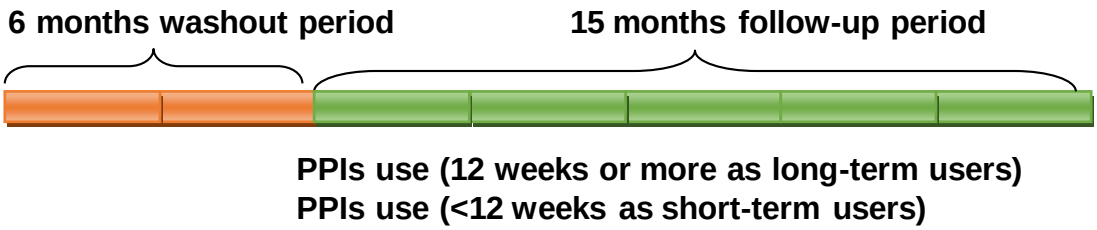
In this dissertation project, the random 5% sample of 2013-2016 Medicare administrative claims data was analyzed to support Aim 2.2. The Medicare claims data files include 1) Medicare enrollment files containing information on patient demographics, monthly eligibility and enrollment information (Master Beneficiary Summary File); 2) Carrier files (claims for physician services); 3) Outpatient files (claims for hospital outpatient visits); 4) Inpatient files (claims for hospital stays); 5) Home Health service files containing Medicare Advantage (MA) plan paid records for home health agency services ; 6) Skilled Nursing Facility (SNF) claim file contains information from paid bills submitted by SNF institutional facility providers 7) Part D files (prescription drug events); 8) The Medicare Part D Formulary file, containing information on how the plan covers the prescription drugs filled; 9) The Part D Pharmacy Characteristics file containing information about the pharmacy identified as the source of the drug for each Part D Event (PDE) prescription fill record; 10) Plan Characteristics File containing information about plan type, benefit design, premium, cost-sharing and service area of Part D plans; and 11) The Medicare Part D Prescriber Characteristics file containing descriptive information for the prescriber identified on a Part D Event file record.

3.2.2.2.2 Study design and study sample

This was a retrospective new user cohort study. The 5% random Medicare data from 2013-2016 was used to identify the comparative safety profile of different PPIs among different subgroup of Medicare population. We identified Medicare beneficiaries

who 1) had full coverage in Medicare Parts A (hospital care), B (physician and outpatient services), and D (prescription drugs) for continuously 21 months in 2013-2016; and 2) had no Medicare Advantage (Medicare Part C) coverage at any time during the 21 months continuous enrollment. Part C enrollees were excluded because their medical services are not fully captured in the Medicare claims data. New PPI users were identified using a 6-months washout period prior to index date (date of 1st observed PPI, or H2 blocker use for comparison group) and up to 15-months follow up period (Figure 3.2).

Figure 3.2: New user cohort of PPIs



3.2.2.2.2.1 Hypotheses

A. Examining the incidence of AEs between PPI users and H2 blocker users

H_{A0}: There is no difference in the incidence rate and ratio of AEs between PPI users and H2 locker users at any time point.

H_{A1}: The incidence rate and ratio of AEs of PPIs users is different from the incidence rate and ratio of AEs of H2 blocker users at any time point.

B**. Examining the AEs among long-term and short-term PPI users**

H_{C0}: There is no difference in the incidence of AEs between long-term and short-term PPI users.

H_{C1}: The incidence rate and ratio of AEs of long-term PPIs users is different from the incidence rate and ratio of AEs of short-term PPIs users at any time point.

C**. Examining the AEs among long-term PPI users and long-term H2 blocker users**

H_{C0}: There is no difference in the incidence of AEs between long-term PPI users and long-term H2 blocker users.

H_{C1}: The incidence rate and ratio of AEs of long-term PPIs users is different from the incidence rate and ratio of AEs of long-term H2 blocker users at any time point.

D**. Examining the AEs among different PPI users**

H_{D0}: There is no difference in the incidence of AEs between specific PPI users and all other PPI users at any time point.

H_{D1}: The incidence rate and ratio of AEs of specific PPIs users is different from the incidence rate and ratio of AEs of all other PPIs users at any time point.

3.2.2.2.3 Measurements

3.2.2.2.3.1 Exposure

The exposure of interest was defined as the use of any PPI or H2 blocker, and among PPI users, any individual PPI use among the Medicare population. Among PPI new users, long-term PPI use was defined as continuous use for at least 12 weeks.[236] The day after 12 weeks or 84 days usage of PPIs from the index date was considered as the starting point of the follow-up period, and enrollees was followed for 12 months to identify outcomes associated with the long-term use of PPIs. For those PPI users with short-term use (<12 weeks or 84 days), follow-up period started on the last day of PPI supply within the 12 weeks (or 84 days) after initiation. PPIs are widely used in the U.S. in the therapy of GERD and peptic ulcer diseases. By October 2020, six PPIs have

been approved in the U.S. in various formulations to treat the acid-related diseases.[125] Although all PPIs have the similar mechanism of action, three PPIs (omeprazole, esomeprazole, and lansoprazole) are available as over-the-counter (OTC), whereas other three PPIs (dexlansoprazole, pantoprazole, and rabeprazole) are not available as OTC. All six PPIs have available generics from different manufacturers except for dexlansoprazole (Table 3.11).[18] RXNDC variable containing NDC number from Medicare Part D prescription event data along with Orange book will be used to

Table 3.11: Approved PPIs in the U.S.[18,142-152]

PPI	Dosage form	Availability			Brand Name	Approval Date	
		Brand	Generic	OTC		First Brand	First Generic
Omeprazole	Oral	√	√	√	Prilosec	09/14/1989	11/012002
Lansoprazole	Oral, IV	√	√	√	Prevacid	05/10/1995	11/10/2009
Rabeprazole	Oral	√	√	×	Aciphex	08/19/1999	11/08/2013
Pantoprazole	Oral, IV	√	√	×	Protonix	02/02/2000	08/02/2007
Esomeprazole	Oral, IV	√	√	√	Nexium	2/20/2001	01/26/2015
Dexlansoprazole	Oral	√	×	×	Dexilant	01/30/2009	04/19/2017

IV= Intravenous, √= available, x=Not available

As the comparison group, H2 receptor blockers are a class of gastric acid-suppressing agents frequently used in a variety of gastric conditions. At present, four H2 blockers are available by prescription in both brand and generic form (Table 3.12).[84,287-294]

Table 3.12: Approved H2 Blockers in the U.S.

H2 Blockers	Dosage form	Availability			Brand Name	Approval Date	
		Brand	Generic	OTC		First Brand	First Generic
Cimetidine	Oral, IV	√	√	√	Tagamet	08/16/1977	08/31/1994
Ranitidine	Oral, IV	√	√	√	Zantac	10/19/1984	11/18/1997
Nizatidine	Oral	√	√	x	Axid	04/12/1988	07/08/2002
Famotidine	Oral, IV	√	√	√	Pepcid	10/15/1986	04/16/2001

3.2.2.2.3.2 Outcomes

In this study, the outcomes were the incidence of AEs. AEs including MI, CKD, and HF were selected as study outcomes to assess the associations with the use of PPIs (PPIs vs. H2 blockers, individual PPIs vs. all other PPIs, and long term PPIs use vs. short-term PPIs use). The International Classification of Diseases Version 9 codes (ICD9) and International Classification of Diseases Version 10 codes (ICD10) diagnosis codes were used to identify these AEs from Medicare claims data (Supplementary table 2). Carrier claim files, inpatient claims file, outpatient claim files, home health agency claim files, and skilled nurse facility claim files from 5% random sample of the 2013-2016 Medicare claims data were used to capture the diagnosis codes (ICD-9, ICD-10) for MI, CKD, and HF. Medicare carrier claim files contains the fee-for service (FFS) claims and diagnosis information submitted by professional providers. Similarly, inpatient claim file, outpatient claim file, home health agency (HHA) claim files, and skilled nursing facility (SNF) claim files contain diagnosis information and claims submitted by inpatient hospital providers, outpatient hospital providers, HHA providers, and submitted by SNF providers respectively. Cohorts of long term PPI users and long term H2 blocker users were followed for 12 months after the 12 weeks (84 days) of PPI/H2 blockers use from the index date. Enrollees were excluded if they developed the investigated AE prior to the 12 weeks of PPI/H2blocker use. In separate analyses, any PPI users were compared with any H2 blocker users and followed for 15 months from index date. Similar approach was employed when comparing individual PPIs with the first available PPI ‘omeprazole. Finally, long term PPI users were compared with short term PPI users and followed for 12 months where follow up period started for long term

PPI users form the last day of 12 weeks or 84 days of drug use (similar to the long term PPI vs Long term H2 blocker use) and follow up for short term PPI use started on last day of PPI supply.

3.2.2.2.3.3 Covariates

Different patient related and disease related factors were measured during the pre-index 6-month period to control for their influence on the association of AEs with the use of PPI. Beneficiary's age (>65, 65-74, 75-84, and 85 and above), sex, race/ethnicity, region (Northeast, Midwest, West, and South), residential area (urban vs. rural), low income subsidy (LIS), were considered as patient's related factors. Patients' health related condition at pre-index period such as a count of hospitalizations, count of ED visits, count of a physician office visit, Charlson comorbidity index (CCI) were also measured and controlled. Pharmacy type, benefit phase, Part D plan cost sharing, and Daily dosage of PPI were considered as prescription related factors. Daily dosage of PPI was calculated using Drug Strength, Quantity Dispensed, and Days Supply variables. The following table 3.14 details the covariates that were used to study the associated AEs with PPIs. Presence of different disease status (Obesity, Hypertension, Diabetes, High cholesterol, low HDL, and Metabolic disorder) and use of different drug (Azithromycin, Erythromycin, Betamethasone Fluconazole, Megestrol, and Metoclopramide) are known to be contributed factor in the development of MI[345,346]. In this study we explored different disease condition and drug use information in different sensitivity analyses to have a better understanding regarding the relation between PPI use and the risk of MI.

Table 3.13: Variables for Medicare data analysis

Variable	Description	Variable Name (From Claim)	File	Category
Age	Age will be calculated by using enrollee's date of birth (BENE_BIRTH_DT) and index date	NA	BENE_BIRTH_DT variable from Master Beneficiary Summary File	1= <65 2= 65-74 3= 75-84 4= 85 and older
Sex	The sex of a beneficiary	SEX_IDENT_CD	Master Beneficiary Summary File	1= Male 2= Female
Race	Race code from claim	BENE_RACE_CD	Master Beneficiary Summary File	1= White 2= Black 3= Asian 4= Hispanic 5=Other
Region	The social security administration (SSA) standard 2-digit state code (from (STATE_CODE) of a beneficiary's residence will be used to identify the region of each beneficiary.	NA	STATE_CODE from Master Beneficiary Summary File	1= Northeast 2= Midwest 3= West 4= South
Residential area	5-digit Zip codes will be used to match with 2010 Urban Area to ZCTA Relationship File to determine beneficiary's residence in an urban or rural area; if the zip code appear in the 2010 Urban Area to ZCTA Relationship File (variable ZCTA5), then the area will be urban, else area will be rural	NA	ZIP_CD variable from Master Beneficiary Summary File ZCTA5 from ZCTA relationship file	1= Urban 2= Rural
ESRD	End-stage Renal Disease (ESRD) will be identify using Original reason for Medicare entitlement.	ENTLMT_RSN_ORIG	Master Beneficiary Summary File (ENTLMT_RSN_ORIG = 2 or 3 then beneficiary has ESRD)	1= ESRD 2= No ESRD
Part D low income subsidy	Master file "mbsf_abcd_summary", variable CST_SHR_GRP_CD_<1-12>: if beneficiary has cost share in any month of the baseline 6 months period, LIS=1; else LIS=0	CST_SHR_GRP_CD_<1-12>	Master Beneficiary Summary File	1= LIS 0= No LIS
Count of hospitalizations, (at	Inpatient claims will be used to identify hospitalization information at pre-index	CLM_ADMSN_DT	inpatient_base_claims_k	NA

Variable	Description	Variable Name (From Claim)	File	Category
pre-index period)	period			
count of ED visits (at pre-index period)	Inpatient file or outpatient file will be used to identify ED visits. If Revenue Center Codes variable REV_CNTR = 0450-0459, 0981 then claims will be ED visit	REV_CNTR	inpatient_revenue_center_k outpatient_revenue_center_k	NA
count of physician office visit (at pre-index period)	Medicare Carrier files will be used to identify physician's office visit at pre-index period	CARR_LINE_PRV DR_TYPE_CD (1, 3, 5, 6 as office visit)	bcarrier_claims_k bcarrier_line_k	NA
count of unique prescription	Pde files will be used to identify unique prescriptions at pre-index period	PDE_ID	Pde file	
CCI (at pre-index period)	ICD9 codes will be used to calculate CCI at the pre-index period	ICD_DGNS_CD1-25	Carrier, inpatient, outpatient, home health, SNF files	NA
Average Dose	Pde files will be used to identify the daily dosage	Average daily dosage (Add) of PPI was calculated using Drug Strength, Quantity Dispensed, and Days Supply variables	Pde file	NA
Pharmacy Type	Pde files will be used to identify the type of pharmacies	PHRMCY_SRVC_ TYPE_CD	Pde file	1= Community/Retail 2= Institutional 3= mail order 4= Specialty 5= other

3.2.2.2.4 Propensity score methods

Since the use of PPI and H2 blockers were not randomly assigned, propensity score methods were used to balance for confounding variables between PPIs vs. H2 blockers users, as well as individual PPI vs. all other PPIs user subgroups. First, logistic regression models were used to estimate the propensity score of probabilities of initiating drug treatments of interest. Patient's baseline covariates: patient characteristics, including age, sex, race/ethnicity, residing region, urban-rural living area, ESRD diagnosis, low income subsidiary eligibility, CCI, Pharmacy type, benefit phase, and cost sharing in deductible phase covariates were used to calculate propensity score. Propensity score matching was used to create one to one matching between PPIs users and the comparison group using calipers of width equal to 0.2. However, matching can reduce the number of new users in each group by selecting patients having similar propensity scores. For this reason, propensity score weighting was used to retain all patients for outcome evaluation. Since matching on individual PPI yielded lower sample size, propensity score weighting was used for the analyses of individual PPIs, whereas propensity score matching was used for all other analyses. In this case, inverse probability of treatment weights (IPTWs) were created by estimating each patient's probability of receiving drug (PPIs, H2 blockers, or individual PPI) based on selected covariates (age, sex, race/ethnicity, residing region, urban-rural living area, ESRD diagnosis, low income subsidiary eligibility, CCI, Pharmacy type, benefit phase, and cost sharing in deductible phase covariates), and then weighted by the inverse estimate of the probability.[295] Under inverse probability of treatment weighting, observations that received the treatment were given the weight of 1/p and those that did

not receive the treatment are given the weight of 1/1−p, where p is the probability of getting the treatment.[258] Calculation of propensity score weighting can be described with the following equation:[296]

Weight, (T/P) + (1-T)/1-P, where,

T= a binary treatment, The treated t=1, and the controlled t=0

P= the obtained propensity score

In sum, weights are 1/p for the treated and 1/(1-p) for the controlled groups.

3.2.2.2.5 Statistical analysis

Descriptive statistics, Chi-square and t tests, were conducted to calculate and compare means and proportions of patients' baseline characteristics between any PPIs and H2 blockers users. To examine the associations between PPIs use and AEs (MI, CKD, HF), both logistic regression and cox proportional hazards models were conducted. Logistic regression was used to estimate the odds ratio (OR) and corresponding 95% confidence intervals (CI) which was a measure of association between exposed PPIs use and AEs during the follow-up period. Cox proportional hazards models were used to estimate the adjusted hazard ratios (HR) and corresponding 95% CI which was a measure of association between exposed PPIs use and time to AEs. Adjusted models included different covariate factors such as patient and disease related factors. Similarly, logistic regression and Cox proportional hazards models were conducted after employing propensity score matching and weighting approaches. In Cox proportional hazards models, treatment exposure was operationalized as a time-dependent variable by forming an interaction (product) term between the predictor and a function of time to assess the proportionality hazard

assumption for different covariates. Proportionality hazard assumption does not violate If the newly created time dependent variable is not statistically significant in the Cox model.

Model 1: Examining the risk of MI, CKD, and HF between PPIs users vs H2 blocker users for the cohorts with drug use 1 as PPI users and 0 as H2 blocker users (15 months follow up period)

Outcome: Specific AE (1 vs 0)

Study Sample: PPIs users as 1, H2 blocker users as 0

Covariates: Covariates stated in table 3.14

Logistic model was used to estimate the risk of MI, CKD, and HF between PPIs users and H2 blocker users:

logit $g(\mu_{ij})=\log(\mu_{ij} /(1- \mu_{ij}))= \beta 0 + \beta 1*x_{ij}1 + \ldots + \beta k*x_{ij}k$ [x_{ij} 1….. x_{ij} k= Set of predictor variables described in the table 3.14, µij is the probability of PPIs use at jth (j=1,2…k) time point for participant i (1,2…..n))]

Cox proportional hazard model were used to estimate the risk of MI, CKD, and HF between PPIs users and H2 blocker users:

h(t|X) = a conditional hazard of outcome (yes/no), h0(t)= an unspecified baseline hazards, and t=a patient's time of outcome with time measured in days.

h(t|X) = h0(t)exp (β1Xx1+β2Xx2+……+βkXk) [x1…..xk= Set of predictor variables described in the table 3.14)

Model 2: Examining the risk of MI between long-term PPI users vs long-term H2 blocker users for the cohorts with drug use 1 as long-term PPI users and 0 as long-term H2 blocker users (12 months follow-up)

Outcome: MI (1 vs 0)

Study Sample: Long-term PPIs users as 1, long-term H2 blocker users as 0

Covariates: Covariates stated in table 3.14

Logistic model was used to estimate the risk of MI between long-term PPI users and long-term H2 blocker users:

logit $g(\mu_{ij})=\log(\mu_{ij}/(1-\mu_{ij}))= \beta 0 + \beta 1*x_{ij}1 + \ldots + \beta k*x_{ij}k$ [x_{ij} 1….. x_{ij} k= Set of predictor variables described in the table 3.14, μij is the probability of long-term PPI use at jth (j=1,2…k) time point for participant i (1,2…..n))]

Cox proportional hazard model was used to estimate the risk of MI between long-term PPI users and long-term H2 blocker users:

h(t|X) = a conditional hazard of outcome (yes/no), h0(t)= an unspecified baseline hazards, and t=a patient's time of outcome with time measured in days.

$h(t|X) = h0(t)\exp(\beta 1Xx1+\beta 2Xx2+\ldots\ldots+\beta kXk)$ [x1…..xk= Set of predictor variables described in the table 3.14)

Model 3: Examining the risk of MI between long-term PPI users vs short-term PPI users for the cohorts with drug use 1 as long-term PPI users and 0 as short-term PPI users (12 months follow-up)

Outcome: MI (1 vs 0)

Study Sample: Long-term PPIs users as 1, short-term PPI users as 0

Covariates: Covariates stated in table 3.14

Logistic model was used to estimate the risk of MI between long-term PPI users and long-term H2 blocker users:

logit $g(\mu_{ij})=\log(\mu_{ij}/(1-\mu_{ij}))= \beta 0 + \beta 1*x_{ij}1 + \ldots + \beta k*x_{ij}k$ [x_{ij} 1….. x_{ij} k= Set of predictor variables described in the table 3.14, µij is the probability of long-term PPI use at jth (j=1,2…k) time point for participant i (1,2…..n))]

Cox proportional hazard model was used to estimate the risk of MI between long-term PPI users and short-term PPI users:

h(t|X) = a conditional hazard of outcome (yes/no), h0(t)= an unspecified baseline hazards, and t=a patient's time of outcome with time measured in days.

$h(t|X) = h0(t)\exp(\beta 1Xx1+\beta 2Xx2+\ldots\ldots+\beta kXk)$ [x1…..xk= Set of predictor variables described in the table 3.14)

Model 4: Examining the risk of MI between individual PPI (esomeprazole, pantoprazole, rabeprazole, lansoprazole, dexlansoprazole) users vs omeprazole users for the cohorts with Drug use 1 as individual PPI users and 0 as omeprazole users (15 months follow-up)

Outcome: MI (1 vs 0)

Study Sample: Individual PPI users as 1, omeprazole users as 0

Covariates: Covariates stated in table 3.14

Logistic model was used to estimate the risk of MI between individual PPI users and omeprazole users:

logit $g(\mu_{ij})=\log(\mu_{ij}/(1-\mu_{ij}))= \beta 0 + \beta 1*x_{ij}1 + \ldots + \beta k*x_{ij}k$ [x_{ij} 1….. x_{ij} k= Set of predictor variables described in the table 3.14, µij is the probability of long-term PPI use at jth (j=1,2…k) time point for participant i (1,2…..n))]

Cox proportional hazard model was used to estimate the risk of MI between Individual PPI users and omeprazole users:

h(t|X) = a conditional hazard of outcome (yes/no), h0(t)= an unspecified baseline hazards, and t=a patient's time of outcome with time measured in days.

h(t|X) = h0(t)exp (β1Xx1+β2Xx2+……+βkXk) [x1…..xk= Set of predictor variables described in the table 3.14)

3.2.2.2.6 Sensitivity analysis

Sensitivity analysis was conducted on indication-based cohort by identifying Medicare beneficiaries who had GERD diagnosis in the washout period. Findings from this sensitivity analysis provided prevented the estimation of adverse outcomes of PPI use among patients who use PPI/H2 blockers due to specific clinical manifestation. Both logistic regression and Cox proportional hazard model were used to calculate the AOR and AHR with corresponding 95% CI to evaluate the risk of MI. Additional sensitivity analyses were conducted to evaluate the risk of MI among PPI users comparing with the non-users of both PPI and H2 blockers. In separate sensitivity analyses, presence of different disease status (Obesity, Hypertension, Diabetes, High cholesterol, low HDL, and Metabolic disorder) and use of different drug (Azithromycin, Erythromycin, Betamethasone Fluconazole, Megestrol, and Metoclopramide) in the washout period along with different sociodemographic characteristics were also evaluated to understand their role in the risk of MI among PPI users. Presence of these disease condition and drug use are known to be contributed factor in the development of MI[345,346], thus further exploring them among PPI users can provide a better understanding in the relation between PPI use and the risk of MI.

3.2.2.2.7 Sample size and power

Based on the 5% of Medicare administrative claims data in 2013-2016, sample sizes for new users of different PPIs and H2 blockers are presented in table 3.15.

Table 3.14: New users of PPIs and H2 blockers

Drug	Number of New Users
Omeprazole	62,534
Rabeprazole	941
Pantoprazole	27742
Esomeprazole	8957
Lansoprazole	4469
Dexlansoprazole	2245
H2 blockers	25,955

Required sample size in each group of a cohort study (exposed and unexposed) have been identified with the use of the different value of expected incidence and risk ratio. Power was 80% for all the sample size calculation. The following table 3.16 details the necessary sample size (per group) for a range of incidence values and relative risks with power as 0.8.

Table 3.15: Estimated Sample size for exposed and unexposed cohort

Risk Ratio (RR)	I1	SS1	I2	SS2	I3	SS3	I4	SS4	I5	SS5	I6	SS6	I7	SS7
1.2	0.005	85859	0.01	42,691	0.02	21,106	0.03	13,911	0.04	10,314	0.05	8,155	0.1	3,839
1.5	0.005	15,596	0.01	7,747	0.02	3,823	0.03	2,515	0.04	1,861	0.05	1,468	0.1	683
2	0.005	4671	0.01	2316	0.02	1139	0.03	746	0.04	550	0.05	432	0.1	197
3	0.005	1551	0.01	766	0.02	373	0.03	243	0.04	177	0.05	138	0.1	59
4	0.005	858	0.01	422	0.02	204	0.03	131	0.04	95	0.05	73	0.1	29
5	0.005	576	0.01	282	0.02	135	0.03	86	0.04	61	0.05	47	0.1	17

I= Incidence value in the unexposed group; SS= Required sample in each group.

New users of H2 blockers and all PPIs except for rabeprazole have enough sample size to identify the anticipated risk ratio (RR) of 2 to 5 with the lowest incidence value. For RR=1.5, H2 blockers, omeprazole, pantoprazole, and esomeprazole have

enough sample size to identify the anticipated risk ratio with lowest incidence value, however, for other incidence values in the unexposed group, all the drugs except rabeprazole have enough sample size to identify the anticipated risk. Existing new users of rabeprazole also can identify the anticipated RR=4, 5, and other with least incidence in the unexposed group as well as RR=2 and 3 with lower incidence values (0.03, 0.04, 00.1 for RR 2 and 0.02, 0.03, 0.04, 00.1 for RR 3) in the unexposed group. For RR as 1.2, no drug has enough sample size to identify the anticipated risk for lowest incidence value. However, more drugs become usable to identify the anticipated risk as the incidence value increases (Table 3.16).

3.2.2. 2.8 Expected outcomes, potential problems, and alternative strategies

In this aim, the expected outcome is to generate comprehensive evidence about the association between PPI use and the risk of MI, CKD, and HF. However, this aim also possesses some challenges. There is a possibility that our result might be influenced by different confounding factors such as patient's medication adherence, patient's perception about PPIs related AEs as PPIs are considered safe class of drug. However, this study controlled possible the most complete series of factors (i.e., drug, product, patient, disease, and insurance related factors) to date that might impact study outcomes related to PPI use. Another potential limitation of this study is use of OTC PPIs are not covered by Medicare. This limitation can mislead us to identify OTC PPIs users as non-users. Although we cannot eliminate this limitation, our rigorous analysis on PPIs provided a comprehensive scenario regarding the AE profile of PPIs users. The sub aim 2.1 used the FAERS data, which contains the AEs reports for both prescription and OTC PPIs. Results from sub aim 2.2 could help us understand the signals identified

from sub aim 2.1. Finally, in specific aim 3, the comprehensive systematic review informed the existing evidence of any PPIs related AEs. This broad evidence, along with specific aim 2 provide a clear idea about AEs profile and help to compensate the absence of OTC PPIs use among Medicare population.

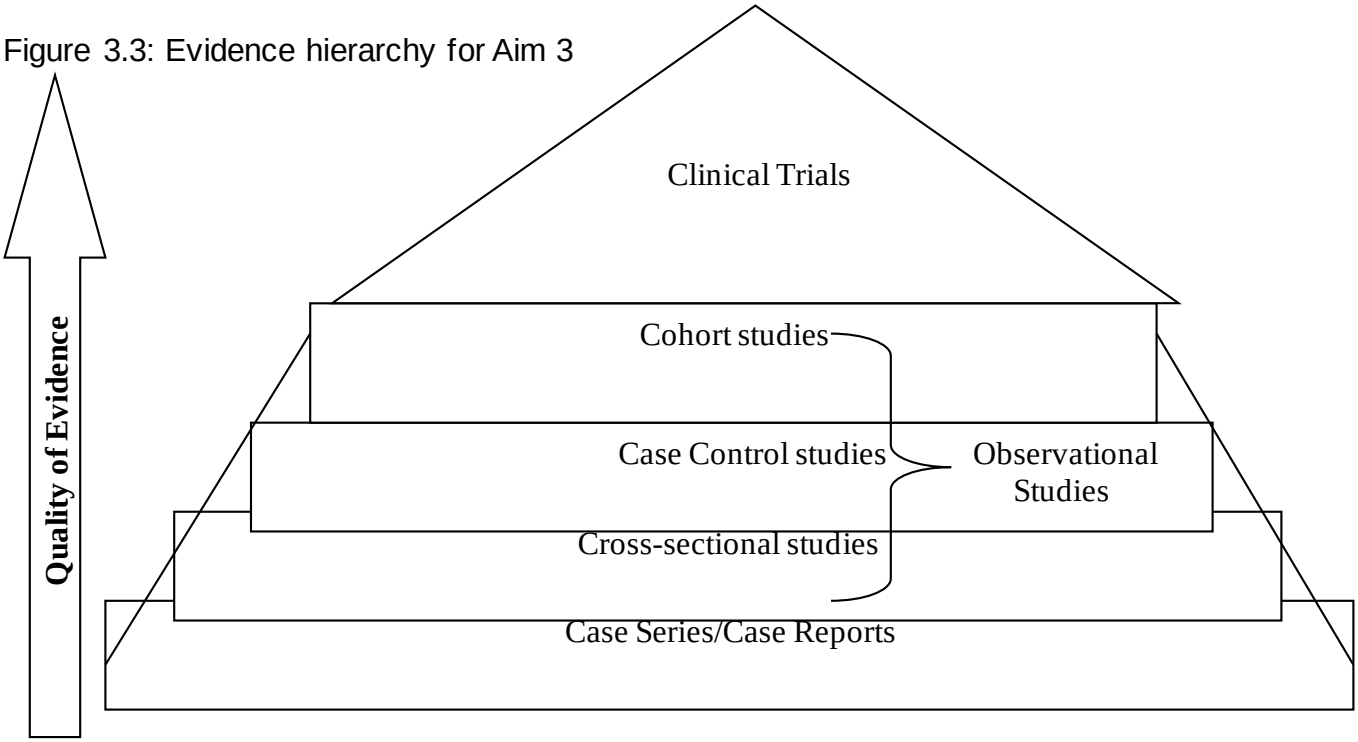
Another potential problem is that results from Aim 2.2 might not be generalized to non-Medicare enrollees. However, the Aim 2.1 FAERS analysis covered AE reports from the general U.S. population as well as patients outside of the U.S. Although findings from FAERS analysis can only support hypothesis generation instead of hypothesis testing, the broad range of AE reports related to PPI use provide rich insights in safety signals of PPI use across various patient populations.

In addition, the follow up period for Aim 2.2 might not be long enough to capture AEs that are likely to take place after treatment durations longer than the follow up period. Future follows up analysis using longer observation period should be conducted for those AE outcomes. Finally, due to the nature of observational study designs, our findings should still be interpreted as association rather than causality.

3.2.3 Aim 3. To assess the association between PPIs and MI and GC: a systematic review and meta-analysis.

A comprehensive systematic review was conducted focusing on the use of PPI and the risk of MI and GC. This systematic review and meta-analysis evaluated the most up-to-date evidence to assess the association between PPIs and MI and GC by including both clinical trials and observational studies.

Figure 3.3: Evidence hierarchy for Aim 3



3.2.3.1 Information sources

A systematic literature search was conducted in December 2019 to retrieve all potential studies using PubMed, PsycInfo, International Pharmaceutical Abstracts (IPA), Web of Science (WOS), and Clinicaltrials.gov. Literature search strategies and methods (i.e., keywords and Medical Subject Headings (MeSH) terms) were guided by a health sciences librarian with considerations of different features among search engines. This systematic search initially identified any published studies describing any AE related to PPI, which was further limited to specific AE, including GC and MI.

3.2.3.2 Methods

In this aim, a comprehensive systematic review was conducted focusing on MI and GC associated with the use of PPIs. RCTs and observational studies were included

to synthesize and compare the different evidence level with each other. Identification and reporting of the literature were conducted according to the PRISMA method and report the findings of each cluster (RCT, and observational studies) separately.

The identified titles and abstracts were assessed by two reviewers independently. Records were included in this study if: a) published in English, b) study design was clinical trials, observational studies, case series or case reports, c) PPI use was the exposure of interest, and d) study outcome was the incidence of GC or MI. Abstracts that were not written in English, did not have PPI as exposure, and other outcomes were excluded. If the title and abstract provided insufficient information to assess the inclusion criteria, a full-text review was conducted. Records retrieved from the Clinicaltrials.gov database were reviewed completely by both reviewers to identify their relevance to this study.

Two reviewers independently identified studies and extract study-level data into standardized evidence tables. The information included in the evidence table contained the author's last name, publication year, study design, number of PPI users, number of PPI nonusers, number of individuals affected with MI and/or GC, and their corresponding Odds Ratio (OR)/ Relative Risk (RR)/ Hazard Ratio (HR) with 95% Confidence Interval (CI). Identified articles without a comparison group were be included in the meta-analysis. Qualitative information was extracted on from these articles to identify the risk of MI/GC related to PPU use.

Meta-analysis on clinical trials and observational clusters by combining their effects was conducted based on the availability of the studies as the number of studies having quantitative information determines the feasibility of meta-analysis. All Meta-

analysis were conducted using the software R studio. At least 3 studies was required for meta-analysis on the same AE outcome and 10 studies were required for test for asymmetry.[297,298] Summary effect was determined through either fixed effect or random effect model depending upon the characteristics of included studies.[299] Fixed effect model assumes the population in the studies are uniform and studies are sufficient to draw a conclusion, whereas in random effect model, we can relax the assumption of population being uniform.[299] Forest plot was constructed to visually inspect the effect estimate of individual studies and how they are distributed around a null value as well as around the overall effect.[290,300] Heterogeneity of each meta-analysis was tested by using the I^2 statistic.[301] An I^2 value of 0% indicates "no heterogeneity," whereas 25% is "low," 50% is "moderate," and 75% is "high" heterogeneity.[302] Funnel plots was used to estimate possible publication bias caused by the tendency of published studies to be negative.

Quality Assessment: Two different tools were to assess the quality of the studies since included studies were either clinical trials or different observational studies such as case-control and cohort studies, etc. The Newcastle-Ottawa scale, recommended by Cochrane Handbook for Systematic Reviews of Interventions, was used for case-control and cohort studies to assess the study quality by two reviewers.[303] Quality of studies was rated as good, fair, and poor judged through three categories: a) selection of the study groups, b) comparability of the groups, and c) ascertainment of the exposure for case-control studies or outcome of interest for cohort studies. Study receiving 3 or 4 stars in selection, 1 or 2 stars in comparability, and 2 or 3 stars in outcomes is considered as good quality. Study receiving 2 stars in selection, 1 or 2 stars in

comparability, and 2 or 3 stars in outcomes is considered to have fair quality whereas 0 or 1 star(s) in selection, or 0 stars in comparability, or 0 or 1 star(s) in outcomes reflects the poor quality of the study. In addition, the “Quality Assessment Tool for Quantitative Studies” developed by the Effective Public Health Practice Project (EPHPP) was used to critically assess the quality of all identified RCTs. Studies were ranked “strong”, “moderate”, and “weak” after assessing eight different categories of a particular study, including a) Selection bias, b) Study design, c) Confounders, d) Blinding, e) Data collection methods, f) Withdrawals and drop-outs, g) Intervention integrity, and h) Analysis.[304]

3.2.3.3 Expected outcomes, potential problems and alternative strategies

In this aim, a comprehensive evidence about the safety of PPI was provided through the comparison and contrast of existing evidence. All published RCTs and observational studies, providing some evidence of AEs (MI, GC) associated with PPI use, were identified systematically and evidence levels were compared with each other. This aim allows the comparison in how well one evidence level corroborates the result of another evidence level. Another outcome of this aim was to compare the systematic review result with the results identified in Aim 2. We clustered each evidence level by study design and compared with other clusters. This approach provides valuable information in explaining the differences in AE risks by different types of studies. This historical analysis of different types of evidence may help inform the current post-marketing pharmacovigilance system and process.

One potential problem is that some potential literature might be missed. This could happen because of not choosing potential data base, using inappropriate search terms or simply due to the unavailability of literatures. It can be handled to working with experienced librarian to determine search strategies and collaborating with other institutions which will have access to multiple data sources. Second, at least 3 studies containing quantitative information was required to conduct a meta-analysis and at least 10 studies to conduct a publication bias asymmetry test. If number of studies was less than these pre-defined numbers for any evidence level/any specific AEs, then it was not be possible to conduct meta-analysis. However, qualitative systematic review can be conducted to draw conclusions among different levels of evidence regarding the safety of PPI among the U.S. population.

Chapter 4

Results

Aim 1 Paper: Trends in PPIs use and associated healthcare spending among the U.S. population.

Abstract

Background: In the U.S., proton pump inhibitors (PPIs) are one of the most commonly prescribed classes of drugs, but contemporary data on national-level utilization patterns for PPI use are limited.

Objective: This study examined the trends in prescription PPI use and expenditures, overall and by patient subgroups, and identified predictors of PPI use.

Methods: Prescription PPI use was identified from the 2002-2017 Medical Expenditure Panel Survey (MEPS) data by using the brand and generic names. Trends in PPI use were examined overall and by patient's socio-demographic characteristics and disease status. Trends in brand and generic PPI users, total and average PPI expenditures were also examined. Multivariable model was used to identify patient factors associated with PPI use.

Results: The overall proportion of PPI users increased from 5.70% in 2002-2003 to 6.73% in 2016-2017 (P-value=0.011). Increased trends in PPI use were observed among U.S. adults aged 65 and above, both males and females, non-Hispanic Whites, non-Hispanic Blacks, Hispanics, Asians, in all four geographic regions, with public health insurance and those who were obese (all P-value<0.05). While PPI use increased significantly, the average PPI expenditure per patient decreased significantly.

Multivariable results found that participants aged 25 years or older, female, non-Hispanic Whites, residing in the Northeast, with higher income, having public or private health insurance, obese, and married had a higher likelihood of using PPI.

Conclusion: Increased PPI use was observed among the majority of patient subgroups. Understanding utilization patterns of PPIs could help practitioners identify potential treatment disparities and monitor the safety of PPI use.

Keywords: MEPS, Trends, Utilization, Expenditure, Proton Pump Inhibitor

1.0 Introduction:

Gastroesophageal reflux disease (GERD) is one of the most common digestive disorders contributing to serious harm, burden, and economic consequences for patients.[6] In western countries, GERD is the most common upper gastrointestinal (GIT) disease, where 10-20% of the total population experience GERD symptoms weekly.[2,305] GERD is one of the most common GIT diagnoses in the U.S., with annual direct cost of $12 billion in 2004,[75,76] which increased to $18.1 billion in 2015.[306] In addition to the economic burden, GERD also impacts patient's health-related quality of life (HRQoL) in the dimensions of vitality, eating/drinking, and emotional well-being.[7,8,307]

Proton Pump Inhibitors (PPIs) are the most common and potent acid-suppressive medications that inhibit the final step of acid secretion.[308] According to the American Gastroenterological Association, PPIs should be prescribed to patients with GERD, erosive esophagitis, and peptic stricture for short and long-term management.[309] As of October 2019, six PPIs have been approved in the U.S. in various formulations.[18] At present, three PPIs (omeprazole, esomeprazole, and lansoprazole) are available as over-the-counter (OTC) and other three (dexlansoprazole, pantoprazole, and rabeprazole) are available as prescription only.[18] Although all PPIs have a similar mechanism of action[310], expenditure for high cost PPI use was about four times compared to the expenditure of low cost PPIs.[311]

PPIs are widely prescribed drugs in the U.S.,[160] with an estimated spending of $10 billion per year including both prescriptions and OTCs.[61] However, contemporary data on national-level utilization patterns for PPI use are limited. Kantor et al. found the use of prescription PPIs doubled in 1999-2012,[312] but PPI use and expenditures among

patient subgroups are unknown. In addition, although PPIs have generally been considered safe and short-term use of PPIs is usually well-tolerated, emerging evidence has raised concerns over the safety of PPI use. For example, a case-control study in the U.K. identified the association of community-acquired *C difficile* with the use of PPIs.[313] Other adverse events (AEs) such as community-acquired pneumonia,[314,315] acute kidney disease, chronic kidney disease, pneumonia, bone fractures, cardiovascular events, and enteric infections were also reported with PPI use.[28,238,316] Therefore, understanding how patients use PPIs and individual factors associated with PPI use will help practitioners and policymakers to identify potential high use subgroups of patients, monitor patient symptom control, and prevent adverse outcomes. In this study, we examined the trends in prescription PPI use and expenditures, overall and by different patient subgroups, and identified patient factors associated with PPI use among a nationally representative U.S. population. We hypothesized that trends in PPI use and expenditure increased over time, and trends were different among patient subgroups.

2.0 Study Design and Study Sample

This study used a serial cross-sectional analysis of U.S. individuals using the 2002-2017 Medical Expenditure Panel Survey (MEPS). The MEPS is a multi-stage probability survey, which collects data on the health services that Americans use, frequency and cost of use, costs associated and payment of the services, as well as data on the private health insurance available to the U.S. civilian non-institutionalized population.[317] The probability sampling of MEPS provides national level estimations. MEPS respondents of all ages that completed the survey were included in this study. In

MEPS, person weight is used to compensate for oversampling and non-response. Individuals having person weight ≤0 (indicating not in scope for the survey)[247] were excluded.

MEPS Household Components' full-year consolidated, medical conditions, and prescribed medicines files from 2002 to 2017 were used to identify participant's sociodemographic characteristics, medical conditions, medication use, and expenditures. This study was approved by the Auburn University Institutional Review Board.

2.1 PPI Use and Expenditure

In the MEPS, interviewers contacted pharmacies with written permission from patients to obtain information such as filled date, national drug code, medication name, the strength of medicine, quantity, amount paid, and source of payments.[248] MEPS data does not include any OTC medication use information, so this study only focused on prescription PPI use and related expenditures. Both brand and generic names of the available individual PPIs in the U.S. were used to determine their usage in each MEPS cycle. MEPS participants having at least one prescription for any PPI were considered as PPI users and further categorized as the brand or generic users based on the reported drug name, and PPI users who reported with both brand and generic PPIs were categorized as users of both brand and generic PPIs.

In the MEPS, expenditure and source of payment (out of pocket (OOP) cost paid by self or family or by specific insurance coverages (private and public)) were reported in each MEPS cycle for each PPI prescription. Total PPI-related expenditures were calculated by the sum of OOP and health insurance expenses and the averaged

expenditure was calculated for each PPI user in each MEPS cycle. Additionally, total OOP expenditure, total expenditure by private and public insurance for PPIs were calculated. Consumer Price Index (CPI-U) was used to adjust all PPI-related expenditure to constant 2017 U.S. dollars value.[318]

2.2 Covariates

In this study, respondent's age (<25, 25 to <40, 40 to <65, and 65 and older), sex, race/ethnicity (Non-Hispanic Blacks, Hispanics, Asians, Non-Hispanic Whites, and others), geographic regions (Northeast, Midwest, West, and South), family annual income, self-perceived health status (unknown, fair/poor, good/very good, and, excellent), body mass index (BMI), marital status (never married, married, divorced, widowed, and other), health insurance coverage (uninsured, privately and publicly insured), and number of comorbidities were identified from the MEPS full-year population characteristics files and included as potential factors affecting PPI use. Participants' family income level as a proportion of the federal poverty level (FPL) was classified as poor (<100% of FPL)/near poor (100%-<125% of FPL), low income (125%-<200% of FPL), middle income (200%-<400% of FPL), and high income (≥400% of FPL). BMI for adults were computed using the MEPS respondent's height and weight and classified into: underweight (<18.5), normal weight (18.5-24.9), overweight (25.0-29.9), and obese (>30). For younger participants, age percentile chart[319] adjusted with gender were used to calculate BMI. Charlson comorbidity index (CCI) was computed by using patients' diagnosis information[320] from the medical file and further categorized into 0, 1, 2, and 3 or above. In addition, Clinical Classification Code 138 was used from the

MEPS medical files to estimate the proportion of PPI users among patients with any esophageal disorder.[321]

2.3 Statistical Analyses

Trends in proportions of participants with any PPI use were examined during the 16 years (8 MEPS cycles) among all of the MEPS respondents and different subgroups. The proportion of PPI use was calculated as the percentage of PPI users (numerator) among the total population (denominator). Generalized linear models were used to examine the trends in PPI use, overall and by patient subgroups (i.e. covariates), and the proportions of brand and generic PPI users were also examined. All results were weighted using the MEPS person-level weights to represent national estimates.

Trends in total expenditures and average expenditure, as well as total OOP, and expenditures by private and public insurance were examined. CPI-U was used to adjust all identified PPI related expenditures to constant 2017 U.S. dollar value[318] .

Pooling all 8 cycles' data, multivariable logistic regression models were performed with generalized estimating equation (GEE) using the proc genmod procedure, binomial distribution, and logit-link function to identify the factors influencing PPI use. GEE was used due to the presence of time repeated measurements for 8 cycles. The adjusted odds ratio (AOR) and 95% confidence intervals (CIs) of any PPI use was reported with 2-sided $P < 0.05$ for statistical significance. Sensitivity analyses were conducted to re-run the GEE multivariable models in participants with and without esophageal disorder. All analyses were weighted and conducted using the SAS 9.4 software.

3.0 Results:

3.1 Study Sample

A total of 520,100 individual MEPS participants were included in this study in 2002-2017 (cumulative weighted n=4,808,164,180 in 16 years, and average annual weighted n=300,510,261). Overall, about 6.59% of the study sample were PPI users, and the majority of them were female (58.10%), 40 years and older (86.01%), non-Hispanic Whites (77.81%), residing in the South region (39.08%), overweight/obese (73.83%), married (57.03%), and had private health insurance (67.38%) (Table 1).

3.2 Trends in PPI Use, Overall and by Patient Subgroups

PPI use among the U.S. population increased from 5.70% in 2002-2003 to 6.73% in 2016-2017 (P-value=0.011, Figure 1), representing an 18.07% overall increase of PPI use. Increased trends in PPI use were observed among U.S. adults aged 65 and above, both males and females, non-Hispanic Whites, non-Hispanic Blacks, Hispanics, Asians, and all four geographic regions (all P-value <0.05, Supplemental Figure 1).

PPI use trends significantly increased among individuals with poor/near poor and low-income (P-value <0.05) but remained stable among middle and high-income participants (Supplemental Figure 2). Trends in PPI use increased among individuals having public health insurance (P-value <0.001), among participants who were obese (P-value <0.05). Trends in PPI use were significantly increased among those who were divorced (P-value <0.001), never married (P-value <0.001), and married (P-value <0.05) while the trend was stable among participants who were widowed.

3.3 Trends in PPI Use by Patient's Disease and Comorbidity Status

Trends in PPI use were stable among patients with esophageal disorders during study period (75.25% in 2002-2003 and 66.33% in 2016-2017, P-value=0.70, Supplemental Figure 3). In addition, PPI use trend increased significantly among patients with CCI of 3 or more (P-value <0.001, Supplemental Figure 3); however, throughout the study duration, participants with CCI=0 had the higher proportion of PPI use compared to other CCI subgroups.

3.4 Trends in Proportions of Brand Name and Generic PPI Users

In 2002-2003, 88.92 % of all PPI users used brand PPI while brand PPI users reduced to 10.76% in 2016-2017. Correspondingly, proportions of generic PPI users significantly increased over time (Supplemental Figure 4). The proportion of brand PPI users was lower compared to the proportion of generic PPI users after 2008-2009 when 3 out of 6 individual PPIs had generic versions available in the U.S. market.

3.5 Trends in PPI Expenditures

Total expenditure (Figure 2) for PPIs was $28.43 billion in 2002-2003 and peaked at $36.71 billion in 2008-2009. PPI expenditure decreased gradually after 2008-2009 and reduced to $19.99 billion in 2016-2017. Although total PPI expenditure decreased by 45.56% from 2002-2003 to 2016-2017, the trend was not statistically significant (P-value=0.22). However, the average PPI expenditure per patient reduced by 39.01% ($174.69 in 2002-2003 to $106.54 in 2016-2017) and the decreased trend in average PPI expenditure was significant (P-value=0.005).

In addition, trends in PPI expenditures from OOP, private, and public insurance payment sources were also examined (Supplemental Figure 5). A decreased trend in

PPI expenditures was observed for OOP (P-value <0.001) payment source, but the trend increased for public insurance expenditure (P-value <0.001).

3.6 Factors Associated with PPI use

Table 1 details factors associated with PPI use among the U.S. population. Bivariate results showed that all investigated patient factors were associated with PPI use, including sex, age, race/ethnicity, region, health insurance, income, BMI, marital status, self-perceived health condition, and CCI (all P<0.05).

Multivariable results showed that patients who were females (AOR for male vs. female=0.78 (95% CI, 0.77-0.81)) and aged more than 25 years old (25 to <40, 40 to <65, and 65 and above vs. <25 years with AOR=2.32 (95% CI, 2.05-2.62), AOR=5.60 (95% CI, 4.99-6.32), and AOR=8.40 (95% CI, 7.42-9.52), respectively) were more likely to use PPIs. In addition, non-Hispanic Whites were more likely to use PPIs compared to other racial/ethnical subgroups (AORs: 0.69 (95% CI, 0.65-0.73), 0.59 (95% CI, 0.55-0.62), 0.55 (95% CI, 0.50-0.60), and 0.77 (95% CI, 0.69-0.86) for Hispanics, non-Hispanic Blacks, Asians, and others compared to non-Hispanic Whites, respectively).

Compared to patients in the Northeast region, Western residents were less likely to use PPIs (AOR=0.81, (95% CI, 0.76-0.86). Health insurance status was strongly associated with PPI use. Specifically, compared to the uninsured population, patients with public only (AOR=2.75 (95% CI, 2.53-2.99)) and any private (AOR=3.08 (95% CI, 2.82-3.36)) coverages were more likely to use PPIs. Compared to the poor/near poor subgroup, low, middle- and high-income population were less likely to use PPIs (AORs: 0.88 (95% CI, 0.84-0.94), 0.86 (95% CI, 0.81-0.90), and 0.96 (95% CI, 0.89-0.99), respectively). Multivariable results also found that the obese (AOR=1.55 (95% CI, 1.47-

1.63)) and overweight (AOR=1.33 (95% CI, 1.26-1.39)) subgroups were more likely to use PPIs compared to those with normal weight. Moreover, those with good/very good (AOR=0.53 (95% CI, 0.51-0.55)) and excellent (AOR=0.28 (95% CI, 0.26-0.30)) perceived health were less likely to use PPI compared to those with fair/poor health condition. Finally, number of comorbidities was significantly associated with PPI use (AOR=1.26 (95% CI, 1.24-1.29)), meaning that patients with 1 increase in CCI count had a 26% increased likelihood of PPI use. Patient's marital status was not associated with PPI use in multivariable results.

Multivariable results from sensitivity analyses among participants with and without esophageal disorder confirmed main findings that participants' age (>40), race/ethnicity (non-Hispanic Whites), geographic region (Northeast vs. West), health insurance (public or private), and obesity status were independently associated with the likelihood of using PPI (Supplemental Table 1).

4.0 Discussion

This study provided national estimates for the U.S. population about trends in overall prescription PPI use, PPI use among different sociodemographic subgroups, PPI use by patient's disease and comorbidity status, brand and generic PPI use, and expenditures associated with prescription PPI use in 2002-2017. Overall, the proportion of any prescription PPI use in the U.S. increased significantly from 5.70% in 2002-2003 to 6.73% in 2016-2017, which is an 18.07% increase. Our findings are consistent with previous studies that found the increase in PPI prescriptions in inpatient setting and emergency department in the U.S.[322,323] Findings of this study are also in accord with

the existing evidence of increased PPI use worldwide, such as in Australia[324] and Taiwan.[325]

This study found an increased trend in PPI use among U.S. adults aged 65 and above, in both males and females, in the majority of racial/ethical subgroups, and in all four geographic regions. Findings of PPI use in patient subgroups provide national estimates in PPI use patterns in the U.S. Mazer-Amirshahi et al. found increased PPI prescribing among males, Whites, aged 65 years and older, and residing in all U.S. regions at emergency department settings.[323] The slight differences in PPI use among patient's sex and race subgroups between Mazer-Amirshahi et al. and the current study might be due to the different study settings since our study included the non-institutionalized U.S. population.

In this study, about 66-75% of the study population with esophageal disorder used PPIs from 2002-2017. About 75% of patients with esophageal disorder used PPIs in 2002-2003, indicating the high use of PPIs in treating this disease. However, the proportion of PPI use reduced to 66% in 2016-2017 among this patient population. Previous research has found that patients receiving prescription PPI from a gastroenterologist are more likely to be optimal users with better symptom control.[326] Although the current study could not ascertain provider specialty for PPI prescriptions, findings of reduced PPI use among patients with esophageal disorder needs additional investigation to explain potential reasons.

Although PPI use increased significantly over 2002-2017, the average spending for PPIs per patient decreased significantly. The availability and increased use of generic PPIs might explain the reduction in OOP expenditure for PPI use, given that in

2002-2017, 5 out of 6 PPIs had generics available. While this study found the reduction in OOP expenditure for PPIs, PPI expenditure paid by public insurance sources increased. The overall increased use of PPIs and non-availability of generic version of some PPIs can influence public insurance expenditure on PPIs.

Finally, our multivariable results identified that participants aged >25, female, non-Hispanic Whites, residing in the Northeast, with low income, having public or private health insurance, obese or overweight, having poor health status, and having more comorbidities had higher likelihoods of using PPIs. Our findings are consistent with some previous studies. For example, previous study identified the association of low income and low educational level with chronic PPI use among Netherland population.[327] Higher likelihood in PPI use among females found in our study might be explained by physician's practice, where physicians are more likely to prescribe drugs to females than males while the health problem is similar.[328] In addition, women experience slightly higher severity of GERD symptoms,[329], and females also more likely to seek healthcare.[330] These factors may result in differential disease recognition with increased PPI prescriptions.[327] Health conditions such as obesity have been recognized as an important risk factor for GERD development,[331] which can explain the higher likelihood of PPI use among obese or overweight populations. Understanding these utilization patterns of PPIs can help practitioners identify potential treatment disparities and proactively monitor treatment safety among high use patient subgroups.

In addition, existing evidence has identified the associations between several adverse events (AEs) with the use of PPIs. Particularly, PPI users aged 65 and over might be highly vulnerable to potential drug-drug interactions, and AEs such as

osteoporosis, pneumonia, enteric infections, and electrolyte abnormalities.[323] Our findings also indicated the significantly higher (8 folds) likelihood of PPI use among older adults aged 65 and above compared to those younger than 25 years. In 2010, a safety announcement was issued by the U.S. Food and Drug Administration (FDA) regarding the increased risk of fracture associated with long-term use of PPIs, followed by another safety announcement for the increased risk of infection due to PPI use.[332,333] Pharmacists' role in deprescribing long-term PPI therapy has been tested and proved successful in family medicine clinic settings when implementing a clinical pharmacist-managed program that includes detailed tapering instructions, patient education, and follow-up.[334] The increased use of PPIs calls for attention of practitioners to properly prescribe PPIs and monitor PPI use among high-risk populations. Our study identified patient factors associated with PPI use, which could help the identification of potential high-risk patients. Regardless, more research of post-marketing surveillance in real world use of PPIs is warranted.

5.0 Limitations:

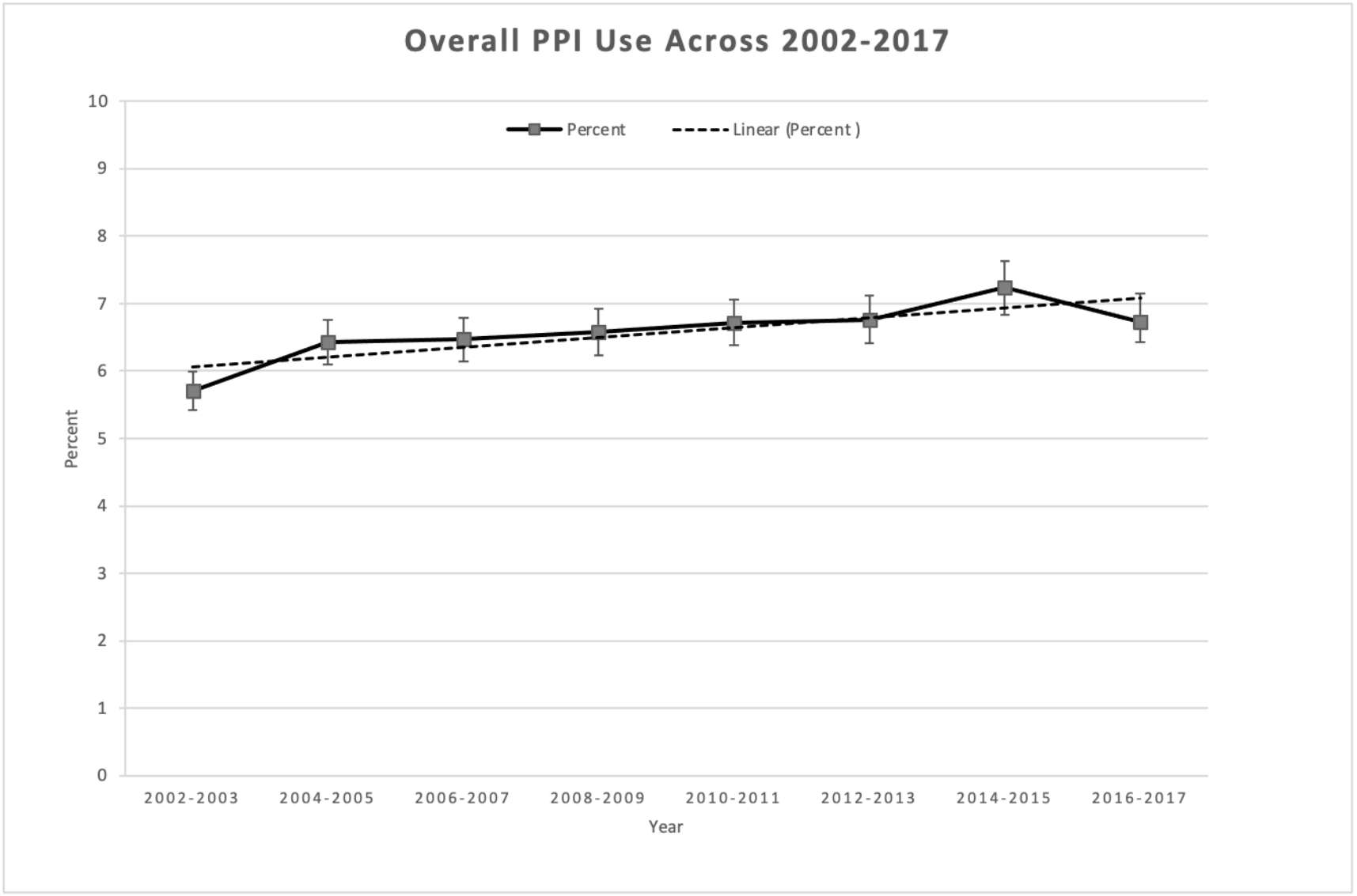
This study has several limitations. First, findings are limited to be generalizable to the noninstitutionalized U.S. population. However, results from MEPS data provide valuable information about PPI use among the noninstitutionalized U.S. population. In 2018, 79.12%[335] of the U.S. population were noninstitutionalized, representing the largest U.S. population. Second, we cannot draw a causal relationship in factors associated with PPI use with the cross-sectional study design. In addition, MEPS household components were completed by one household member who may be a proxy, which may result in inaccuracies in reporting of survey queries. Moreover, OTC

use of PPIs are not included in the MEPS prescribed medicine, which can lead to underestimation of the use and expenditure of PPIs. Future research may also focus on patients with certain diagnosis such as GERD or peptic ulcer disease (PUD) that requires PPI use and examine potential treatment disparities among subgroups of patient populations. Finally, this study is subject to limitations common to retrospective research designs such as selection bias, missing or incomplete information, recall bias, or misclassification stemming from coding errors; however, the MEPS data present accurate representations of the number of drug fills and total drug expenditures when compared with claims data.[336]

6.0 Conclusions:

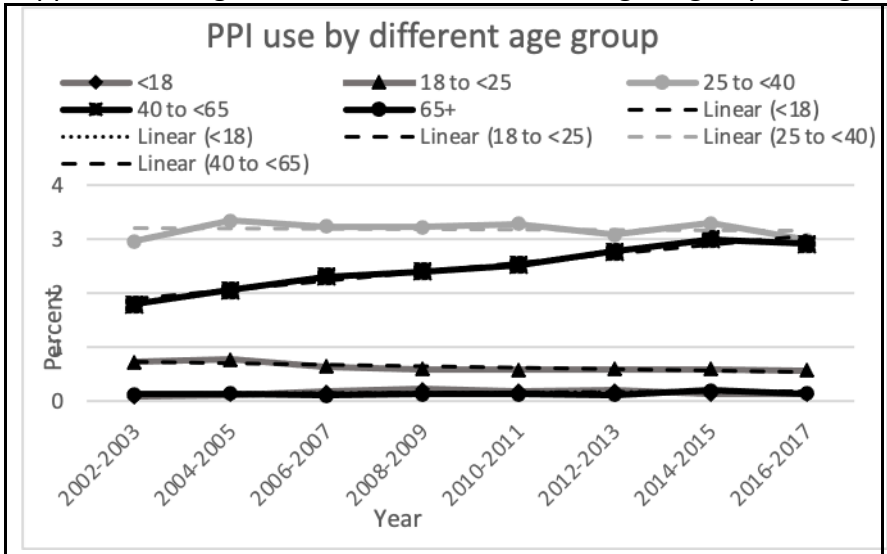
The proportion of the U.S. population who used any PPI increased by 18.07% from 2002-2003 to 2016-2017. Increased use of PPI was also observed among the majority of patient subgroups. Understanding utilization patterns of PPIs could help practitioners identify potential treatment disparities and monitor the safety of PPI use.

Figure 1: Trend in Any PPI Use among Nationally Representative U.S. Population: 2002-2017

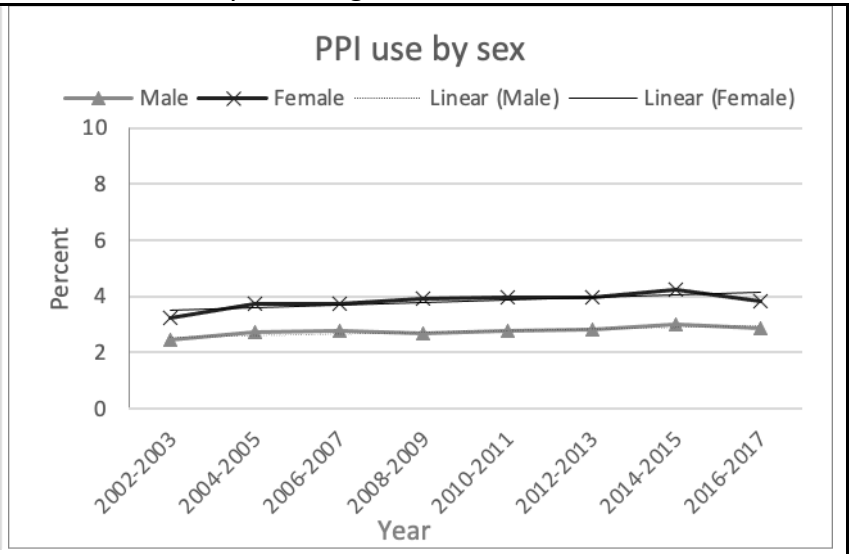


P-value=0.011

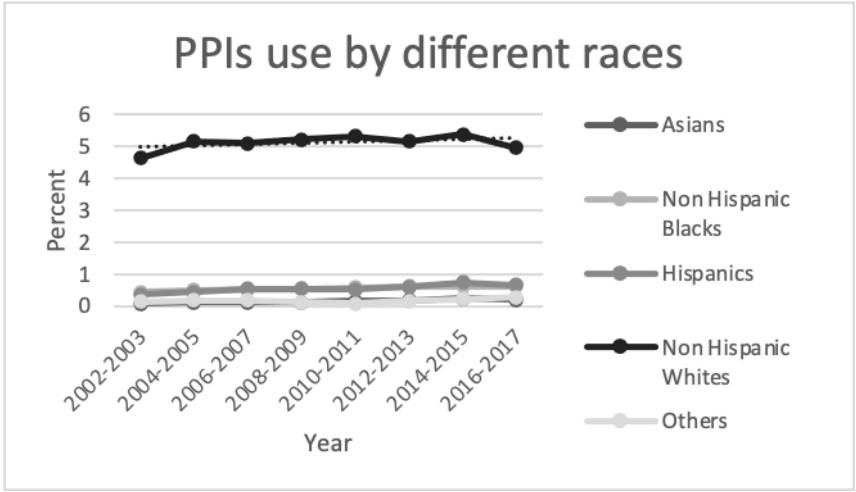
Supplemental Figure 1: Trends in PPI Use among Subgroups of Age, Sex, Race/Ethnicity, and Region



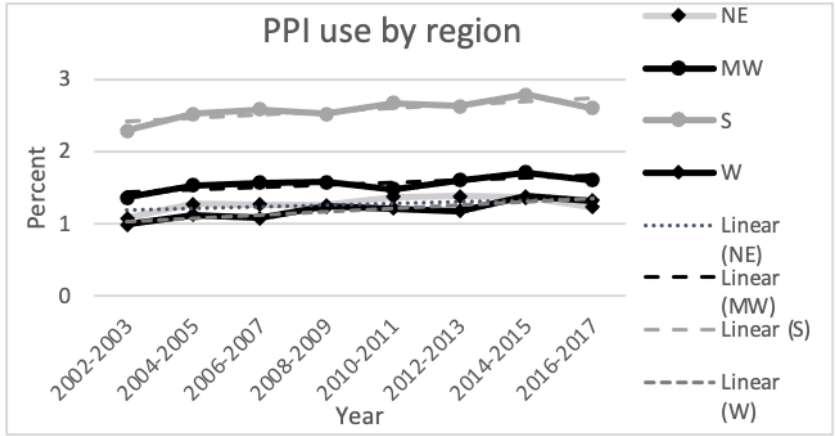
P-value: <18=0.31, 18 to <25=0.31, 25 to <40=0.024, 40 to <65=0.51, 65+=<0.001



P-value: Male=0.010, Female=0.004

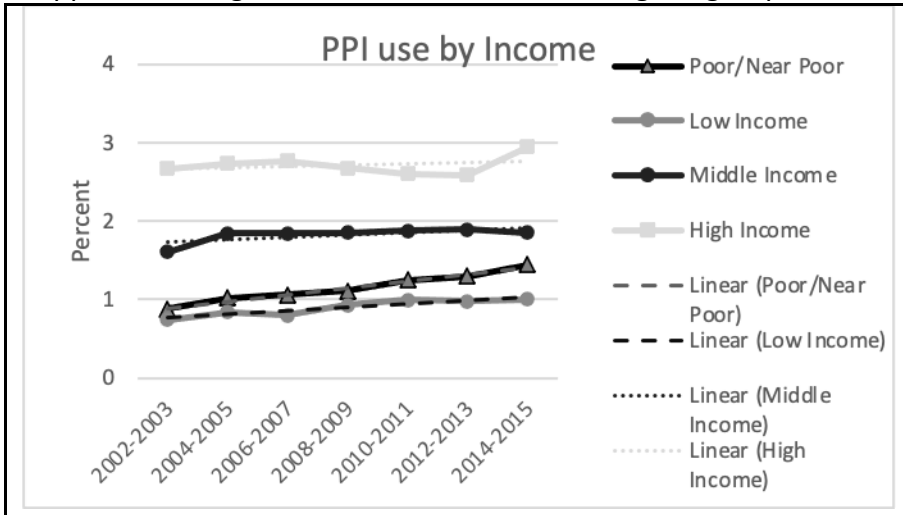


P-value: Asian= 0.0008, Non-Hispanic Black=0.0004, Hispanic = 0.002, Non-Hispanic White=0.041, Other=0.68

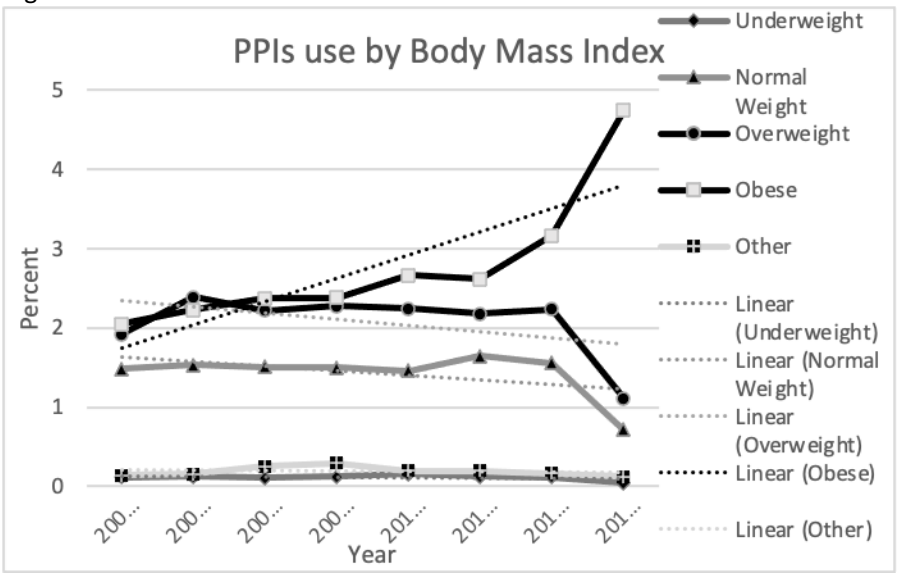


P-value: NE (Northeast)= 0.013, ME (Midwest)= 0.04, S (South)= 0.007, W (West)= 0.011

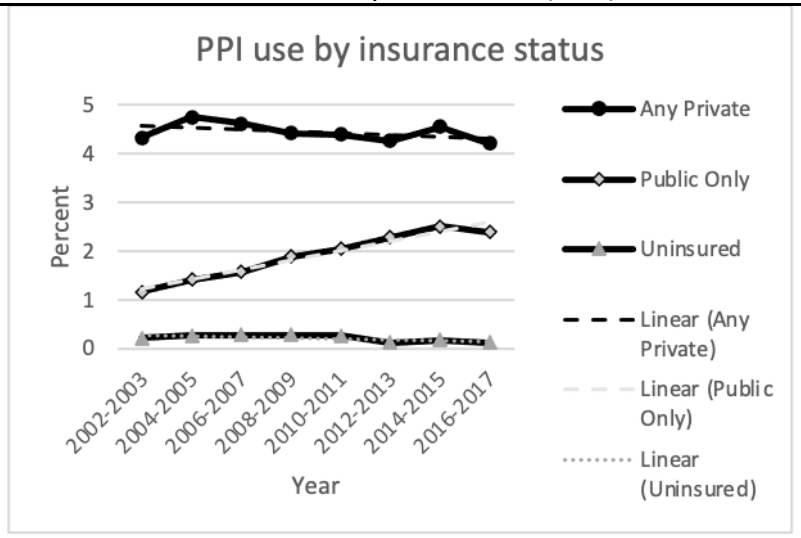
Supplemental Figure 2: Trends in PPI Use among Subgroups of Income, Health insurance status, Body Mass Index (BMI), and Marital Status



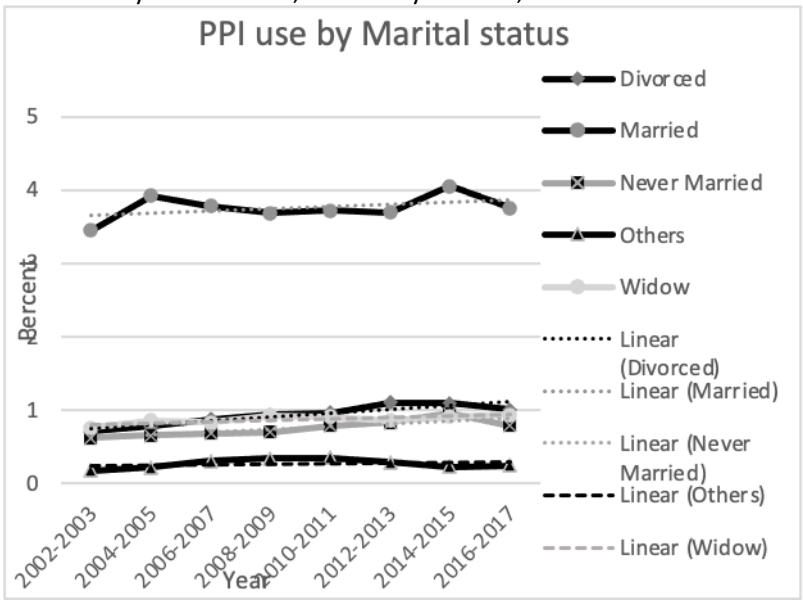
P-value: Poor/Near Poor= <0.001, Low Income= < 0.05, Middle Income= 0.085, High Income= 0.60



P-value: IA=0.80, Underweight Weight=0.62, Normal Weight= 0.27, Overweight= 0.50, Obese= 0.0017

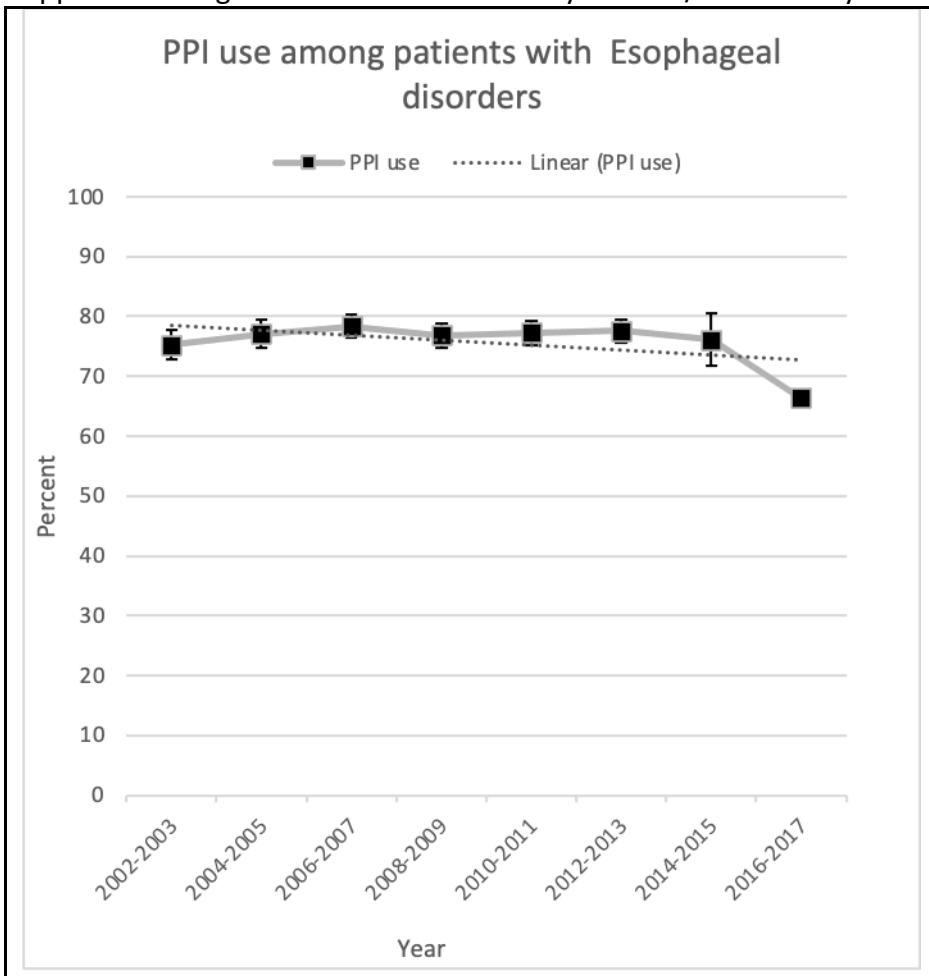


P-value: Any Private= 0.59, Public only =<0.001, Uninsured=0.42

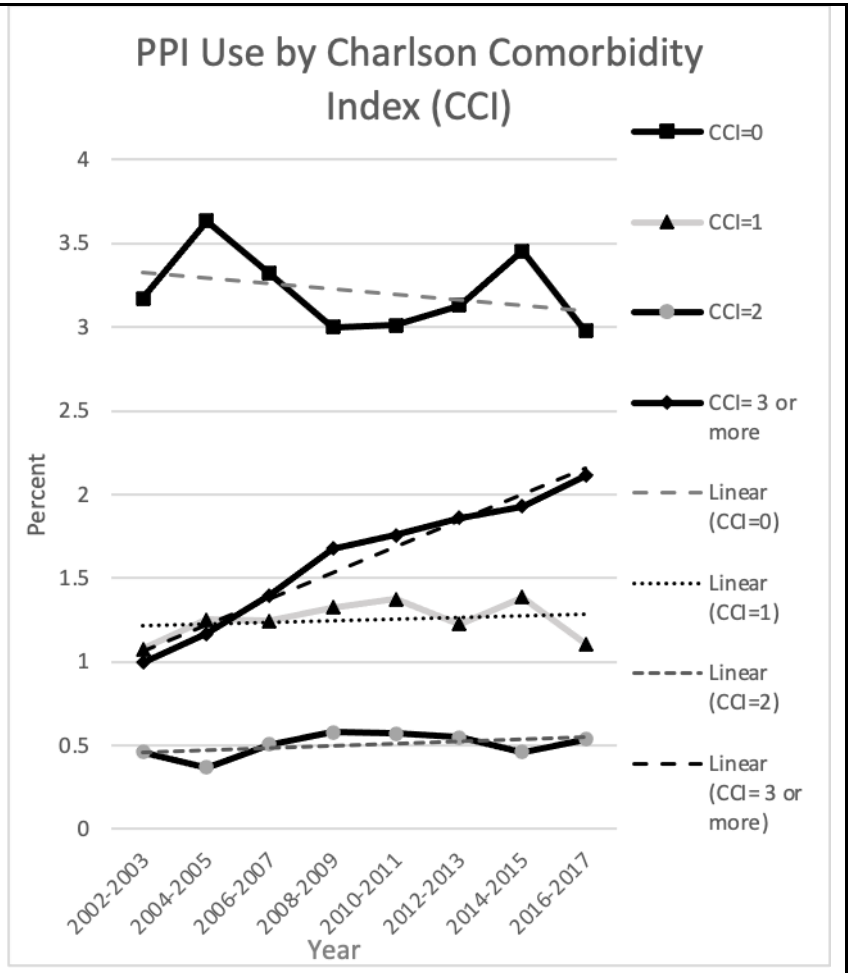


P-value: Divorced=<0.001, Married=0.034, Never Married= 0.0007, Others=0.37, Widow=0.067

Supplemental Figure 3: Trends in PPI Use by Disease/Comorbidity

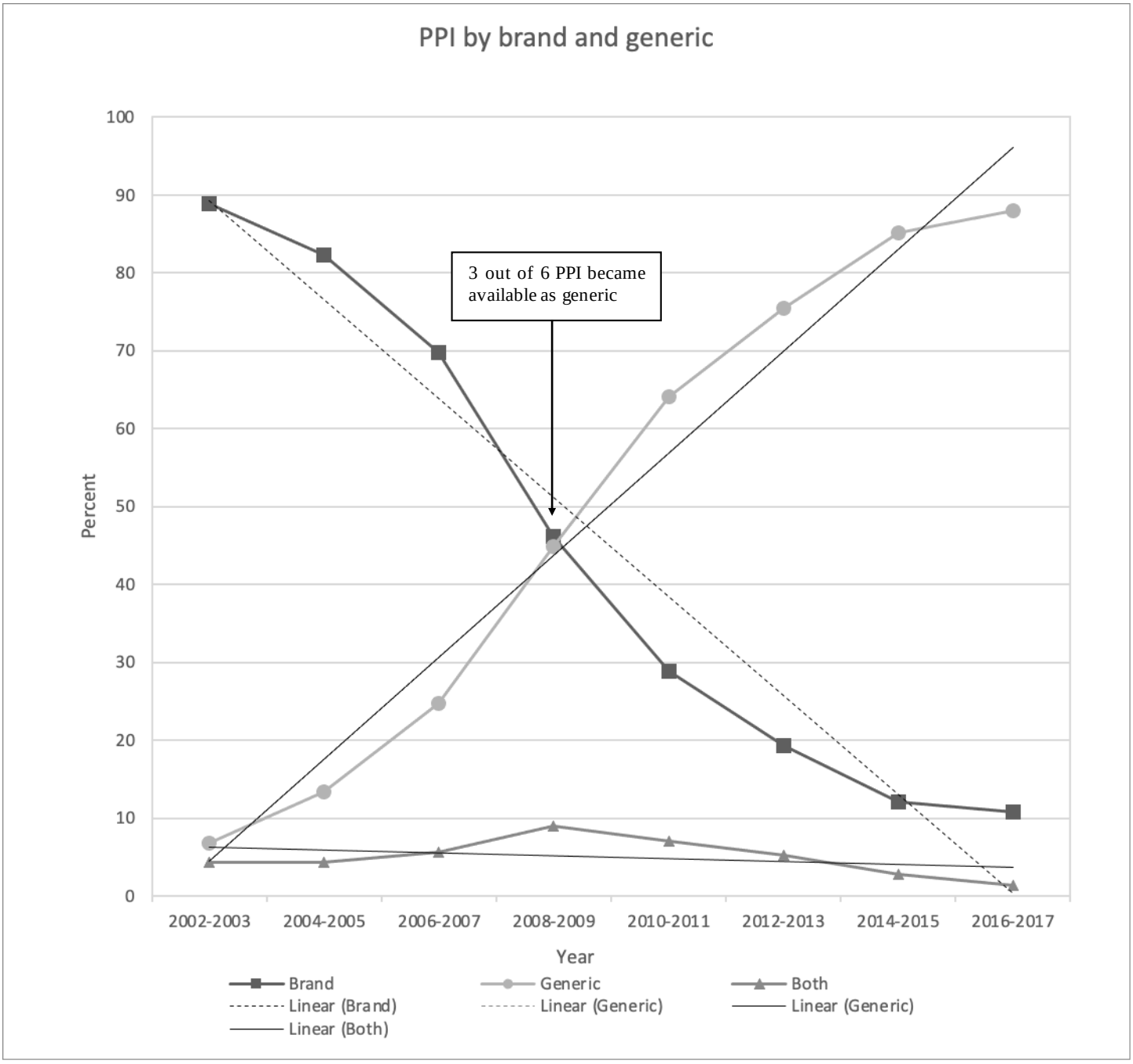


P-value= 0.70



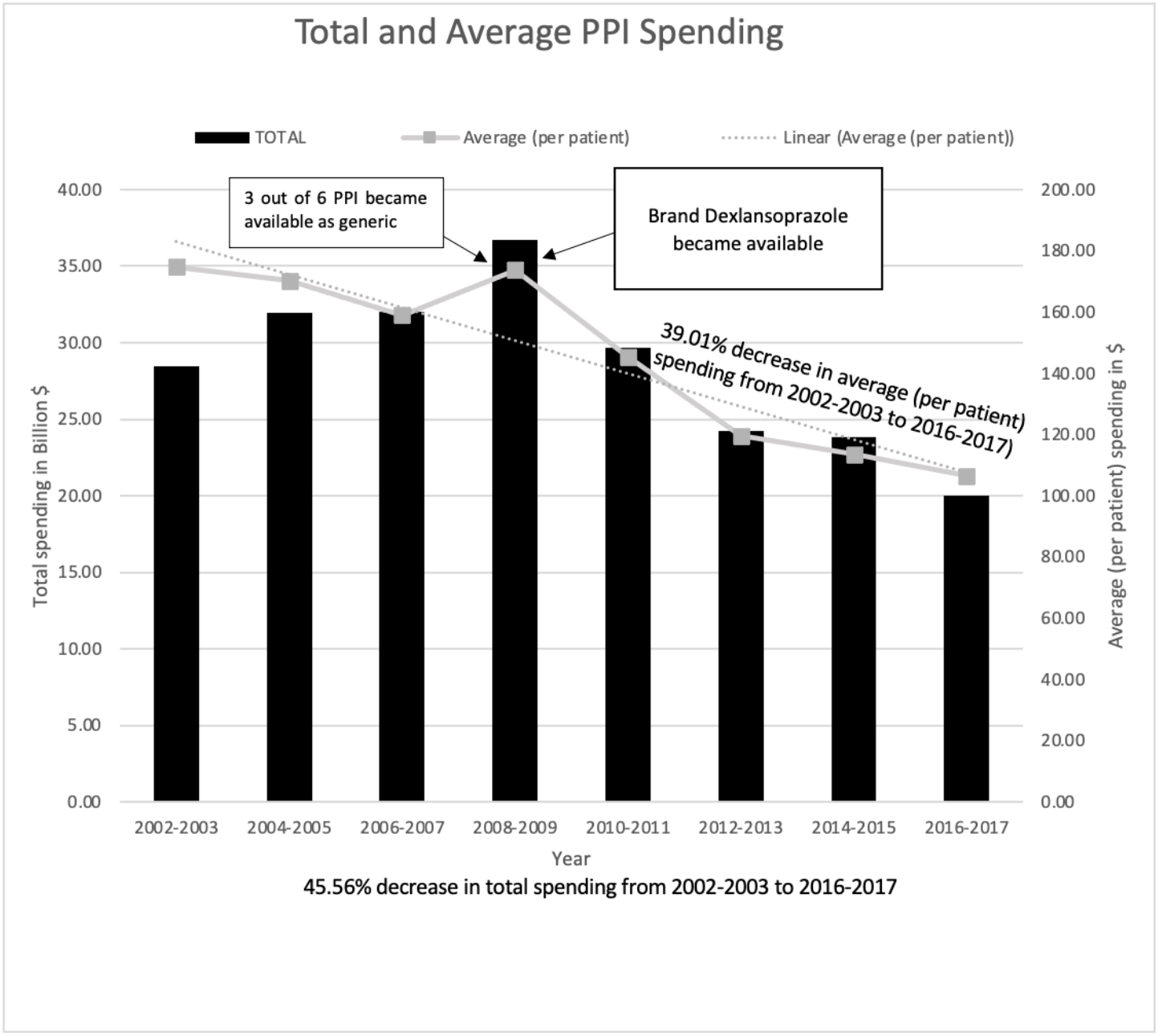
P-value: CCI 0= 0.78, CCI 1=0.061, CCI 2=0.33, CCI 3 or more=<0.001

Supplemental Figure 4: Proportions of Brand and Generic PPI Users



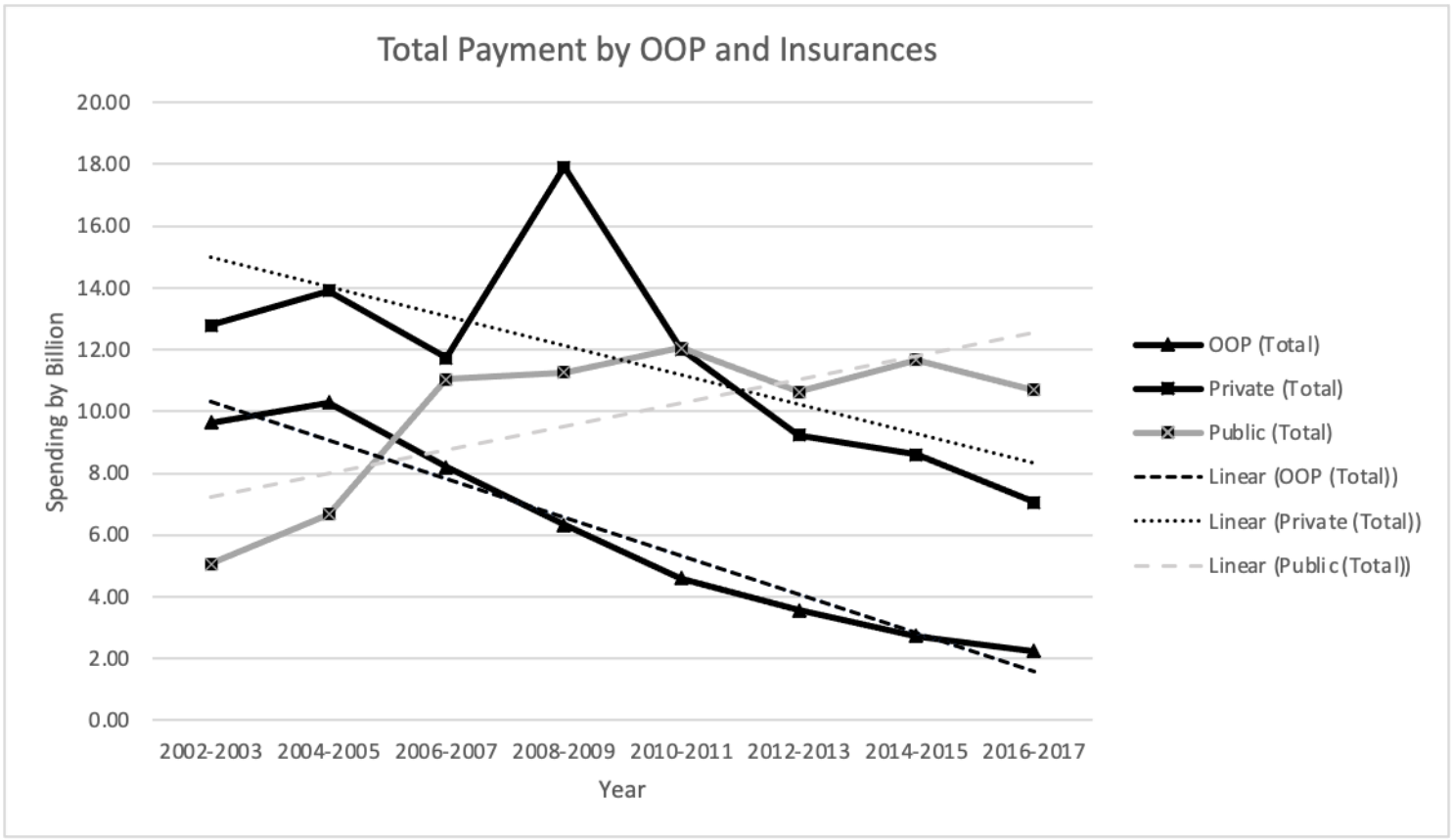
P-value: Brand=<.0.001, Generic=<0.001, Both= 0.91

Figure 2: Trends in Total and Average (per patient) PPI Expenditures among Nationally Representative U.S. Population: 2002-2017



*Total spending in Billion USD ($) and Average (per patient) spending in USD ($)
P-value: Total= 0.22, Average (per patient) = 0.0051

Supplemental Figure 5: Trends in PPI Expenditures among nationally Representative U.S. Population by Payment Sources: 2002-2017



P-value: Out-of-pocket (OOP) (Total)= <0.001, Private (Total)= 0.38, Public (Total)= 0.0068

Table 1: Study Sample Characteristics and Factors Associated with PPI use among U.S. population (n*=520,100 weighted n**=4,808,164,180)

Characteristics		PPI Use: Weighted % (95% CI)		P-value^	Adjusted Odds Ratio (AOR) for PPI^^ Use		
		Users= 316,841,496 (Weighted)	Nonusers= 4,491,322,684 (Weighted)		AOR	95% CI	
Overall		6.59 (6.43-6.75)	93.41 (93.25-93.57)	<.0001			
Sex	Male	41.90 (41.07-42.72)	49.37 (49.17-49.58)	<.0001	0.78	0.77	0.81
	Female (ref.)	58.10 (57.28-58.93)	50.63 (50.42-50.83)		Ref		
Age	<18	2.34 (2.11-2.63)	25.35 (24.83-25.79)	<.0001	Ref (<25)		
	18 to <25	2.08 (1.76-2.34)	9.82 (9.74-10.12)				
	25 to <40	9.57 (9.00-10.13)	21.09 (20.72-21.46)		2.32	2.05	2.62
	40 to <65	48.23 (47.30-49.15)	31.90 (31.58-32.23)		5.60	4.99	6.32
	65+	37.78 (36.77-38.79)	11.84 (11.49-12.19)		8.40	7.42	9.52
Race/Ethnicity [1]	Hispanics	8.51 (7.73-9.30)	15.62 (14.45-16.78)	<.0001	0.69	0.65	0.73
	Non Hispanic Blacks	8.55 (7.86-9.25)	12.38 (11.52-13.24)		0.59	0.55	0.62
	Asians	2.43 (2.10-2.75)	4.98 (4.49-5.47)		0.55	0.50	0.60
	Others	2.70 (2.30-3.09)	3.91 (3.55-4.27)		0.77	0.69	0.86
	Non Hispanic Whites (ref.)	77.81 (76.63-78.99)	63.11 (61.78-64.43)		Ref		
Region	Midwest	23.54 (22.11-24.97)	21.55 (20.60-22.49)	<.0001	0.99	0.93	1.05
	South	39.08 (37.53-40.62)	36.74 (35.57-37.91)		1.05	0.99	1.11
	West	18.05 (16.83-19.27)	23.79 (22.80-24.77)		0.81	0.76	0.86
	Northeast (ref.)	19.33 (18.14-20.53)	17.93 (17.10-18.76)		Ref		
Health Insurance Status	Any Private	67.38 (66.35-68.41)	67.59 (66.75-68.43)	<.0001	3.08	2.82	3.36
	Public Only	29.18 (28.17-30.20)	20.45 (19.83-21.07)		2.75	2.53	2.99
	Uninsured (ref.)	3.43 (3.16-3.71)	11.96 (11.53-12.38)		Ref		
Income Level [2]	Low	13.82 (13.22-14.42)	13.77 (13.48-14.06)	<.0001	0.88	0.84	0.94
	Middle	27.80 (26.99-28.61)	30.53 (30.09-30.96)		0.86	0.81	0.90
	High	40.72 (39.48-41.96)	37.87 (37.08-38.66)		0.96	0.89	0.99
	Poor/Near Poor (ref.)	17.66 (16.93-18.39)	17.83 (17.23-18.43)		Ref		

Body Weight Index (BMI)	Unknown	2.91 (2.62-3.19)	13.09 (12.80-13.39)	<.0001	0.88	0.78	0.98
	Under Weight	1.71 (1.52-1.91)	6.53 (6.34-6.67)		0.83	0.76	1.01
	Over Weight	31.34 (30.56-32.12)	24.93 (24.68-25.18)		1.33	1.26	1.39
	Obese	42.49 (41.59-43.38)	25.29 (24.96-25.63)		1.55	1.47	1.63
	Normal Weight (ref.)	21.56 (20.83-22.28)	30.15 (29.82-30.48)		Ref		
Marital Status	Divorce	14.20 (13.58-14.82)	8.33 (8.11-8.56)	<.0001	1.00	0.95	1.06
	Never Married	11.44 (10.87-12.02)	24.13 (23.78-24.48)		0.94	0.88	1.01
	Others[3]	4.07 (3.76-4.39)	23.39 (23.06-23.73)		0.95	0.89	1.02
	Widow	13.25 (12.56-13.93)	4.24 (4.09-4.37)		1.01	0.95	1.08
	Married (ref.)	57.03 (55.93-58.13)	39.90 (39.47-40.34)		Ref		
Self-perceived Health Condition	Unknown	0.38 (0.30-0.47)	0.15 (0.13-0.16)	<.0001	0.82	0.63	1.06
	Good / Very Good	59.80 (58.99-60.62)	57.58 (57.19-57.98)		0.53	0.51	0.55
	Excellent	29.12 (28.30-29.94)	9.02 (8.82-9.22)		0.28	0.26	0.30
	Fair/Poor (ref.)	10.70 (10.18-11.21)	33.25 (32.79-33.71)		Ref		
CCI	0	48.71 (47.74-49.68)	81.52 (81.22-81.81)	<.0001	CCI as a continuous covariate		
	1	18.96 (18.35-19.58)	9.56 (9.36-9.76)				
	2	7.67 (7.23-8.08)	2.00 (1.93-2.06)				
	3+	24.66 (23.83-25.49)	6.93 (6.76-7.09)		1.26	1.24	1.29
Year	2002-2003 (ref.)	10.13 (9.54-10.71)	11.81 (11.37-12.26)	<.0001	Ref		
	2004-2005	11.60 (10.93-142.27)	11.91 (11.44-12.39)		1.15	1.08	1.23
	2006-2007	12.15 (11.52-12.78)	12.41 (12.01-12.79)		1.16	1.08	1.23
	2008-2009	12.57 (11.90-13.24)	12.59 (12.21-12.97)		1.13	1.05	1.21
	2010-2011	12.77 (12.20-13.24)	12.52 (12.16-12.88)		1.13	1.05	1.21
	2012-2013	13.08 (12.42-13.74)	12.72 (12.37-13.07)		1.13	1.05	1.21
	2014-2015	14.22 (13.48-14.96)	12.87 (12.47-13.27)		1.20	1.12	1.28
	2016-2017	13.48 (12.85-14.11)	13.17 (12.83-13.52)		0.98	0.91	1.05

[1]Race/Ethnicity: Others=American Indian/Alaska Native, Native Hawaiian/Pacific Islander, Multiple races
[2]Income Level: Poor= <100% Federal Poverty Level (FPL), Near Poor=100%-124% of FPL), Low Income= (125%-199% of FPL), Middle Income= (200%-399%) of FPL, High Income= ≥400% of FPL
[3]Marital Status: Other= Not ascertained, Do not know, Refused, Inapplicable (under 16)

^Chi-square tests

^^Adjusted Odds ratio was calculated with General Estimating Equation (GEE) by using Proc Genmod in SAS

* Individual MEPS participants from 2002-2017

** Cumulative weighted sample from 2002-20

Supplementary Table 1: Factors Associated with PPI use among U.S. population with and without esophageal disorder

Factors Associated with PPI use among U.S. population with esophageal disorder				
Characteristics		Adjusted Odds Ratio (AOR) for PPI Use		
		AOR	95% CI	
Sex	Male	0.96	0.86	1.06
	Female	Ref		
Age	<25	Ref		
	25 to <40	1.11	0.86	1.43
	40 to <65	1.86	1.46	2.37
	65+	2.34	1.80	3.04
Race/Ethnicity1	Hispanic	0.66	0.56	0.75
	Non Hispanic Black	0.70	0.61	0.79
	Asian	0.64	0.48	0.87
	Others	0.77	0.58	0.86
	Non Hispanic White (ref.)	Ref		
Region	Midwest	0.8156	0.6885	0.9662
	South	0.9415	0.8128	1.0905
	West	0.9263	0.7888	1.0877
	Northeast (ref.)	Ref		
Health Insurance Status	Any Private	1.79	1.47	2.19
	Public Only	2.03	1.67	2.45
	Uninsured (ref.)	Ref		
Self-perceived Health Condition	Unknown	1.36	0.47	3.91
	Good / Very Good	0.89	0.79	1.00
	Excellent	0.73	0.61	0.87
	Fair/Poor	Ref		
Income Level2	Middle	1.04	0.89	1.21
	High	1.19	1.02	1.40

	Low/Poor/Near Poor	Ref		
Characteristics		Adjusted Odds Ratio (AOR) for PPI Use		
		AOR	95% CI	
Body Mass Index (BMI)	Unknown	0.82	0.63	1.06
	Under Weight	0.94	0.66	1.34
	Over Weight	1.16	1.02	1.32
	Obese	1.32	1.16	1.50
	Normal Weight	Ref		
Marital Status	Divorce	1.03	0.88	1.20
	Never Married	0.87	0.74	1.02
	Others3	0.79	0.62	1.01
	Widow	0.9	0.76	1.10
	Married	Ref		
CCI as a continuous covariate		1.09	1.04	1.14
Year	2002-2003	Ref		
	2004-2005	1.28	1.04	1.57
	2006-2007	1.21	0.99	1.49
	2008-2009	0.33	0.28	0.40
	2010-2011	0.34	0.28	0.41
	2012-2013	0.34	0.28	0.40
	2014-2015	0.34	0.26	0.44
	2016-2017	0.20	0.16	0.25
Factors Associated with PPI use among U.S. population without esophageal disorder				
Characteristics		Adjusted Odds Ratio (AOR) for PPI Use		
		AOR	95% CI	
Sex	Male	0.77	0.73	0.81

	Female	Ref		
Age	<25	Ref		
	25 to <40	2.06	1.77	2.42
	40 to <65	4.52	3.89	5.26
	65+	7.30	6.24	8.54
Characteristics		Adjusted Odds Ratio (AOR) for PPI Use		
		AOR	95% CI	
Race/Ethnicity1	Hispanics	0.94	0.88	1.01
	Non Hispanic Blacks	0.61	0.57	0.66
	Asians	0.75	0.67	0.84
	Others	0.89	0.79	1.01
	Non Hispanic White	Ref		
Region	Midwest	1.01	0.94	1.09
	South	0.98	0.91	1.05
	West	0.83	0.77	0.90
	Northeast	Ref		
Health Insurance Status	Any Private	2.92	2.62	3.25
	Public Only	2.49	2.24	2.76
	Uninsured	Ref		
Self-perceived Health Condition	Unknown	1.23	0.92	1.65
	Good / Very Good	0.48	0.46	0.51
	Excellent	0.24	0.22	0.26
	Fair/Poor	Ref		
Income Level[2]	Middle	0.95	0.89	1.02
	High	0.94	0.87	1.01
	Low/Poor/Near Poor	Ref		
Body Mass Index (BMI)	Unknown	0.70	0.60	0.81
	Under Weight	0.93	0.79	1.09

	Over Weight	1.21	1.14	1.30
	Obese	1.33	1.25	1.42
	Normal Weight	Ref		
Marital Status	Divorce	1.04	0.97	1.12
	Never Married	0.96	0.89	1.04
	Others[3]	0.73	0.63	0.84
	Widow	1.04	0.96	1.13
	Married	Ref		
Characteristics		Adjusted Odds Ratio (AOR) for PPI Use		
		AOR	95% CI	
CCI as a continuous covariate		1.30	1.27	1.32
Year	2002-2003	Ref		
	2004-2005	2.07	1.90	2.25
	2006-2007	2.43	2.24	2.65
	2008-2009	1.03	0.94	1.14
	2010-2011	0.99	0.90	1.10
	2012-2013	1.06	0.96	1.16
	2014-2015	0.97	0.88	1.07
	2016-2017	0.96	0.89	1.06

[1]Race/Ethnicity: Other=American Indian/Alaska Native, Native Hawaiian/Pacific Islander, Multiple races

[2]Income Level: Poor= <100% Federal Poverty Level (FPL), Near Poor=100%-124% of FPL), Low Income= (125%-199% of FPL), Middle Income= (200%-399%) of FPL, High Income= ⩾400% of FPL

[3]Marital Status: Other= Not ascertained, Do not know, Refused, Inapplicable (under 16)

Aim 2 Paper: Adverse Outcomes Associated with Proton Pump Inhibitor Use: Retrospective Analyses of the FAERS and Medicare Claims Data

Abstract

Introduction: Proton Pump Inhibitors (PPIs) are widely used among the U.S. population and generally considered safe, however recent evidence indicate otherwise. Existing evidence provide mixed findings regarding the risk of myocardial infarction (MI), chronic kidney disease (CKD), gastric cancer (GC), and heart failure (HF).

Objectives: The objectives of this study are 1) to identify potential safety signals for PPIs using the FDA Adverse Event Reporting System (FAERS) data, focusing on CKD, MI and GC; 2) to assess the association of MI, CKD, HF with PPI use using Medicare claims data.

Methods: The 2004-2019 (first and second quarter) U.S. FDA Adverse Event Report System (FAERS) data were analyzed. Individual PPI's brand and generic names were used to identify AE reports. The Medical Dictionary for Regulatory Activities was used to identify MI, CKD, and GC. The year of key publications for MI (Goodman 2012), CKD (Lazarus 2016), and GC (Poulsen 2009) were used as the cut-off time points to analyze the relative reporting rates (disproportionality analyses using the reporting odds ratio (ROR) with 95% confidence interval (CI)) of these AEs with before and after these publications, as well as the entire study duration in 2004-2019 (first and second quarter). Then, the 5% random sample of the 2013-2016 Medicare administrative claims data was used to assess the associations of MI and CKD, and HF with the use of PPIs. New users of PPI and H2 blockers were identified and safety profile was evaluated for long term (>=84days) PPI use, short term PPI use, any PPI use, and individual PPI use.

Both logistic regression and cox proportional hazards models were conducted examine the associations between PPIs use and AEs (MI, CKD, HF)

Results: Overall, no risk signals in MI were detected for all PPIs (ROR=0.87, 95% CI: 0.86-0.88) or individual PPIs from FAERS analyses. No drastic elevations in RORs for MI were observed when we consider the report before and after publication of key research in 2012. For individual PPIs, RORs were consistent as in the entire study period except for lansoprazole (ROR=1.10, 95% CI: 1.05-1.16). Risk signals in GC were detected for all PPIs (ROR=1.65, 95% CI: 1.55-1.75) or individual PPIs except for dexlansoprazole (ROR=1.26, 95% CI: 0.81-1.85). Similar RORs for GC were observed before and after publication of key research in 2009. Potential influences of publication bias on AE reporting with PPIs found no impact on MI and GC AE reporting. The ROR for CKD for all PPIs was 2.40 (95% CI: 2.39-2.41) indicating a potential safety signal. However, CKD AE reporting related to PPIs increased dramatically after the key publication of Lazarus et al in 2016, indicating a strong impact of publication bias. From the Medicare claims data analyses, long-term PPI users did not show increased risk of MI compared with long-term H2 blocker users. Individual PPI users were compared with omeprazole users, and only pantoprazole users showed an increase in the risk of MI than omeprazole users while all other PPIs did not show any statistically significant results. Furthermore, no association was observed in risk of CKD and HF when PPI users were compared with H2 blocker users.

Conclusions: Findings from this study suggest the PPI use does not contribute to the risk of MI, CKD, and HF among Medicare enrollees while FAERS analyses indicates the

risk of GC with PPI use. Future high-quality, longitudinal studies are warranted to investigate the causal relationship between PPI use the risk of GC.

1.0 **Introduction**

Acid-related diseases such as gastroduodenal ulcers, gastroesophageal reflux disease (GERD), Barrett's esophagus, and functional dyspepsia can affect people of all ages.[124] Several gastric acid secretion inhibitors and neutralizing agents such as Histamine 2 receptor antagonists (H2RAs, referred as H2 blockers) and proton pump inhibitors (PPIs) are widely used to treat different acid related disorders. However, they are not effective enough to heal the esophagitis, and their use cannot prevent relapse among the patients suffering from GERD.[14,15] At present, PPIs are the most common and most potent acid-suppressive medications which work by inhibiting the final step of acid secretion.[16] PPIs were first introduced in the 1980"s and demonstrated better efficacy than H2 blockers.[17] Currently, six PPIs are commercially available in the U.S. (omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, and rabeprazole) in various doses and dosage forms.[18] Although not all PPIs are the same and have some variations in their pharmacokinetic properties, they share a similar mechanism of action.[19,20]

PPIs are generally considered safe, and short-term use of PPIs are usually well tolerated. However, there is evidence indicating that long-term use of PPIs among older adults is associated with some adverse events (AEs) such as bone fractures, Clostridium difficile infection and acute interstitial nephritis.[31,32] PPIs played a revolutionary role in the medical approach to treat gastrointestinal disorders,[21] however, the rate of inappropriate use of PPIs are increasing alarmingly.[22]

Several clinical trials and observational studies were conducted to identify the probable association between PPI use and adverse cardiovascular outcomes such as

Myocardial Infarction (MI). Although existing evidence on animal model and ex-vivo human tissue experiments indicates the AEs on coronary vessels with PPI use,[33] findings from existing observational studies provide mixed evidence.[34,35] In addition, concerns with the use of acid-suppressive drugs and kidney diseases have been raised, and several population-based studies have been conducted to explore the potential relationship. Risk of acute kidney injury (AKI) was evaluated in several studies. However, evidence was mixed regarding its association with PPI use.[217-219] Risk of chronic kidney disease (CKD) with PPI therapy was also explored and presented mixed results. While some studies identified no association,[53,218,219] Arora et al identified a positive association between PPI use and CKD.[220]

In this study, we first identified potential safety signals for PPIs using the FDA Adverse Event Reporting System (FAERS) data, focusing on MI, CKD, and Gastric Cancer (GC). Then we used the 5% random sample of the 2013-2016 Medicare administrative claims data to assess the associations of MI, CKD, and heart failure (HF) with the use of PPIs. Findings from this study help build real-world evidence in safety of PPI use, thus guide clinical practice in optimizing PPI treatment. This study was reviewed and approved by the Auburn University Institutional Review Board for research involving human subjects.

2. 0 Methods

2.1 Identifying potential safety signals for PPI use using the FAERs data

2.1.1 Data source

The U.S. Food and Drug Administration (FDA) MedWatch program is known as the historical foundation for post-marketing assessment of AEs in the U.S.[337] The

MedWatch program is a spontaneous reporting system designed to support the FDA's post-marketing safety surveillance program for drug, therapeutic biologic products, cosmetics, vaccines, and dietary supplements. AEs and medication error reports submitted to the FDA are reviewed and aggregated in the FDA Adverse Event Reporting System (FAERS) database. The FAERS database has been predominantly used to assess the AE reporting of different drug products, as well as specific AEs due to targeted therapy among patients suffering from different disease conditions.[262,263] The FAERS data files contain case-related medication, reaction, outcome, source of report, and the patient's demographic information. For this study, we used the publicly available FAERS data and combined data files from January 1, 2004 to June 30, 2019. Duplicated cases were identified and eliminated from the data by adopting the most recent case number according to the FDA's recommendation.[338]

2.1.2 Measurements

For identifying AE reports related to PPIs, text string searches of brand names, generic names, and abbreviations were employed for the six available PPIs that were considered as primary suspect. To ensure the accuracy of identifying the PPIs, both drugnames and shortened text strings were used. Although, abbreviations and shorter text string yeileded an extensive drug name list, it was further reviewed, cleaned, and recoded manually to correct spelling mistakes. By removing the non-drugs of interest, this list provided an all-inclusive list of PPIs.

The AEs in the FAERS are coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The Standardized MedDRA® Query (SMQ v17.0) for MI, CKD, and GC were used to identify a group of Preferred Terms (PTs) related to these events

(Supplementary Table 1). The SMQ-based MI was then used to match with the reported PTs in the FAERS reaction files. For records with PTs other than MI, CKD, and GC we identified them as non-MI, CKD, and GC respectively (Supplementary Table 1). Due to the potential influence of a few key publications for MI (Goodman, 2012), CKD (Lazarus 2016), and GC (Poulsen 2009) on spontaneous reporting for PPIs with these AEs, we identified AE reports with PPIs in the FEARS data during the entire study period, as well as before and after the availability of key publications.

2.1.3 Statistical analysis

Disproportionality analyses with reporting odds ratios (RORs) were used to evaluate the likelihood of specific known events to be reported with PPIs as opposed to all other drugs. ROR estimated the odds of reporting of a specific event (SMQ) in those exposed to PPIs, divided by the odds of the event occurring in those not exposed to the PPIs. A possible signal was defined as the lower bound of the 95% confidence interval (95% CI) exceeding 1.[283] Statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC). Sensitivity analyses was conducted by limiting to the FAERS reports came from healthcare providers (Physicians, Pharmacists, Other health-professional). Similar to the primary analyses sensetivity analyses, disproportionality analyses with reporting odds ratios (RORs) were used to evaluate the likelihood of specific known events to be reported with PPIs as opposed to all other drugs.

2.2 The associations between PPI use with MI, CKD, and HF

2.2.1 Data source and study design

Medicare is a national health insurance program administered by the Centers for Medicaid and Medicare Services (CMS) of the U.S. Medicare is designed to assist the

nation's older adults with hospital, medical, and other health costs. Medicare is available to individuals 65 years of age and older and individuals under age 65 who are receiving disability benefits from Social Security or the Railroad Retirement Board, and those having End Stage Renal Disease (ESRD).

This retrospective new user cohort analysis used the 5% random sample of the 2013-2016 Medicare claims data. Medicare beneficiaries who 1) had full coverage in Medicare Parts A (hospital care), B (physician and outpatient services), and D (prescription drugs) for continuously 21 months in 2013-2016; and 2) had no Medicare Advantage (Medicare Part C) coverage at any time were included in this study. Part C enrollees were excluded because their medical services are not fully captured in the Medicare claims data. New PPI users and H2 blocker users were identified using a 6-months washout period prior to index date (date of 1st observed PPI, or H2 blocker use for comparison group) and up to 15-months follow up period (Figure 1).

2.2.2 Exposures

The exposure of interest was defined as the use of any PPI or H2 blocker, and among PPI users, any individual PPI use among the Medicare population. The RXNDC variable containing National Drug Code (NDC) from Medicare Part D prescription event data along with Orange book were used to identify the fills of all PPI and H2 blocker prescriptions. Among PPI new users, long-term PPI use was defined as continuous use for at least 12 weeks.[236] The day after 12 weeks or 84 days usage of PPIs from the index date was considered as the starting point of the follow-up period, and enrollees was followed for 12 months to identify outcomes associated with the long-term use of

PPIs. For those PPI users with short-term use (<12 weeks or 84 days), follow-up period started on the last day of PPI supply within the 12 weeks (or 84 days) after initiation.

2.2.3 Outcomes

We selected AEs including MI, CKD, and HF as study outcomes to assess the associations with the use of PPIs (PPIs vs. H2 blockers, individual PPIs vs. all other PPIs, and long-term PPIs use vs. short-term PPIs use). International Classification of Diseases Version 9 codes (ICD9) and International Classification of Diseases Version 10 codes (ICD10) diagnosis codes were used to identify these AEs from Medicare claims data (Supplementary Table 2).[339-342] Carrier claim files, inpatient claims file, outpatient claim files, home health agency claim files, and skilled nurse facility claim files from the 5% random sample of the 2013-2016 Medicare claims data were used to capture the diagnosis codes (ICD-9, ICD-10) for MI, CKD, and HF from primary diagnosis as well as all other diagnosis. In order to capture the diagnosis properly, a total of 25 diagnosis code variables were used from Medicare carrier claim files, inpatient claims file, outpatient claim files, home health agency claim files, and skilled nurse facility claim files. Study outcomes were captured in a 15 months follow up period after index date any PPI or H2 blocker users, and 12 months for long-term PPI or H2 blocker users.

2.2.4 Covariates

Different patient related and disease related factors were measured during the pre-index 6-month period to control for their influence on the association of AEs with the use of PPI. Beneficiary's age (<65, 65-74, 75-84, 85 and above), sex, race/ethnicity, region (Northeast, Midwest, West, and South), residential area (urban vs. rural), and low

income subsidy (LIS) were considered as patient's related factors. Patients' health related condition at pre-index period such as a count of hospitalizations, count of ED visits, count of a physician office visit, Charlson comorbidity index (CCI) were also measured and controlled. Pharmacy type, benefit phase, Part D plan cost sharing, and daily dosage of PPI were considered as prescription related factors. Average daily dosage of PPI was calculated using Drug Strength, Quantity Dispensed, and Days Supply variables. For long-term use average daily dosage was calculated by considering the use of PPIs for 84 days, For short-term use, average daily dosage was calculated by using the total number of days of PPI use which is less than 84 days, and for any use, average daily dosage was calculated using the last prescription fill date adding the days of supply on the last prescription.

2.2.5 Statistical analysis

Descriptive and bivariable statistics, Chi-square and t tests, were conducted to calculate and compare means and proportions of patients' baseline characteristics between any PPIs and H2 blockers users.

To examine the associations between PPIs use and AEs (MI, CKD, HF), both logistic regression and cox proportional hazards models were conducted. Logistic regression was used to estimate the odds ratio (OR) and corresponding 95% confidence intervals (CI) which was a measure of association between exposed PPIs use and AEs during the follow-up period. Cox proportional hazards models was used to estimate the adjusted hazard ratios (HR) and corresponding 95% CI which was a measure of association between exposed PPIs use and time to AEs. Adjusted models included different covariate factors such as patient and disease related factors.

Since the use of PPI and H2 blockers were not randomly assigned, propensity score methods were used to balance for confounding variables between PPIs vs. H2 blockers users, as well as individual PPI vs. all other PPIs user subgroups. First, logistic regression models were used to estimate the propensity score of probabilities of initiating drug treatments of interest. Patient related, disease related, and prescription related factors described in section 2.2.4 except for daily dosage were used to calculate propensity score. Propensity score matching was used to create one to one matching between PPIs users and the comparison group using calipers of width equal to 0.2. However, matching can reduce the number of new users in each group by selecting patients having similar propensity scores. For this reason, propensity score weighting was used to retain all patients for outcome evaluation for analyses of individual PPIs. In this case, inverse probability of treatment weights (IPTWs) were created by estimating each patient's probability of receiving drug (individual PPIs) based on selected covariates (age, sex, race/ethnicity, residing region, urban-rural living area, ESRD diagnosis, low income subsidiary eligibility, CCI, Pharmacy type, benefit phase, and cost sharing in deductible phase covariates), and then weighted by the inverse estimate of the probability.

Similarly, logistic regression and Cox proportional hazards models were conducted after employing propensity score matching and weighting approaches. In Cox proportional hazards models, treatment exposure was operationalized as a time-dependent variable by forming an interaction (product) term between the predictor and a function of time. Proportionality hazard assumptions were tested and not violated before conducting the propensity score matching/weighting. Similarly, proportionality hazard

assumptions were tested after propensity score matching using independent variable and proportionality hazard assumptions were tested and not violated after conducting the propensity score matching

Sensitivity analysis was conducted on indication-based cohort by limiting to Medicare beneficiaries who had GERD diagnosis (Supplementary Table 3)[343,344] in the washout period. Findings from this sensitivity analysis provide additional information related to adverse outcomes of PPI use among patients who use PPI/H2 blockers due to specific clinical manifestation. Sensitivity analyses were also conducted by identifying the nonusers of PPI and H2 blockers to evaluate the risk of MI among PPI users comparing with the non-users of both PPI and H2 blockers. In separate sensitivity analyses, presence of different disease status (Obesity, Hypertension, Diabetes, High cholesterol, low HDL, and Metabolic disorder) and use of different drug (Azithromycin, Erythromycin, Betamethasone Fluconazole, Megestrol, and Metoclopramide) in the washout period along with different sociodemographic characteristics were also evaluated to understand their role in the risk of MI among PPI users. Presence of these disease condition and drug use are known to be contributed factor in the development of MI[345,346], thus further exploring them among PPI users can provide a better understanding in the relation between PPI use and the risk of MI. Both logistic regression and Cox proportional hazard model were used to calculate the AOR and AHR with corresponding 95% CI to evaluate the risk of MI.

3.0 Results

3.1 Risks Reporting in MI, CKD, and GC of PPI Use: the FAERS analysis

3.1.1 RORs for PPI and MI

In 2004-2019 (Q1Q2), no risk signals in MI were detected for all PPIs (ROR=0.87, 95% CI: 0.86-0.88) or individual PPIs (Table 1). No drastic elevations in RORs for MI were observed when we consider the report before and after publication of key research in 2012. In 2004-2011, RORs were consistent as in the entire study period except for lansoprazole (ROR=1.10, 95% CI: 1.05-1.16), which showed increased risk by 10% (Table 1). Similarly, findings were similar in 2012-2019 (Q1Q2) compared to the entire study duration.

3.1.2 RORs for PPI and CKD

Table 1 details the RORs for PPIs by all PPIs and across individual PPIs. For the entire study duration in 2004-2019 (Q1Q2), statistically significant RORs were observed for all PPIs and individual PPIs. The ROR for CKD for all PPIs was 2.40 (95% CI: 2.39-2.41), which indicated a safety signal for PPI use and the risk of CKD events. Similar statistically significant safety signals were observed for all individual PPIs during this study duration. However, after applying the cut-off time point of year 2016, changes of RORs were observed regarding CKD signal detection. In 2004-2015, the ROR for all PPIs was 1.01 (95% CI: 1.00-1.02), similarly for omeprazole (ROR=1.01, 95% CI: 0.99-1.02), esomeprazole (ROR=0.78, 95% CI: 0.76-0.80), and dexlansoprazole (ROR=0.29, 95% CI: 0.24-0.34). However, in 2016-2019 (Q1Q2), significant increases in the RORs for all PPIs (ROR=9.69, 95% CI: 9.64-9.73) and all individual PPIs were observed.

3.1.3 RORs for PPI and GC

Risk signals for GC were detected for all PPIs (ROR=1.65, 95% CI: 1.55-1.75), as well as omeprazole (ROR=1.32, 95% CI: 1.18-1.48), pantoprazole (ROR=1.18, 95% CI: 1.02-1.36), esomeprazole (ROR=2.00, 95% CI: 1.78-2.26), rabeprazole (ROR=3.17, 95% CI: 2.55-3.94), and lansoprazole (ROR=2.17, 95% CI: 1.89-2.50) with the analyses of FAERS data from 2004-2019 (Q1Q2) (Table 1). Findings were similar when we considered the cut-off time point based on important research publication in 2009.

3.1.4 Sensitivity Analyses

Sensitivity analyses was conducted by limiting to the FAERS reports came from healthcare providers (Physicians, Pharmacists, Other health-professional) and results were similar as main results. For PPI use and MI, RORs were not statistically significant for entire study period (ROR=1.02, 95% CI: 0.99-1.04), nor before (ROR=1.02, 95% CI: 1.00-1.06) or after (ROR=1.00, 95% CI: 0.97-1.30) publication of key research in 2012 (Supplementary table 4). Risk signal for CKD was observed for entire study period (ROR=1.30, 95% CI: 1.28-1.31), however protective ROR (ROR=0.94, 95% CI: 0.92-0.95) was observed prior the publication of Lazarus 2016 and potential safety signal (ROR=1.77, 95% CI: 1.74-1.79) was observed after the publication in 2016 (Supplementary table 4). For PPI use and GC, risk signal (ROR=1.24, 95% CI: 1.13-1.34) was observed for entire study period and findings were stable before (ROR=1.38, 95% CI: 1.10-1.73) and after (ROR=1.21, 95% CI: 1.09-1.35) the publication of Poulsen 2009 (Supplementary table 4), showing no impact from publication bias.

3.2 Safety of PPI Use among the Medicare population

3.2.1 PPI and H2 blocker use among the Medicare population

A total of 108,775 new users of PPI and 25,955 new users of H2 blockers were identified from Medicare enrollees in 2013-2016 (Figure 1). Among new users of PPI, 63,429 (58.31%) were long-term PPI users and the rest were short-term PPI users (Figure 1). For new users of H2 blockers, 11,703 (45.09%) were long term users of H2 blockers (Figure 1). Bivariate analysis between PPI and H2 blocker new users found that PPI users were more likely in the age group of 65-74, being female and white, and residing in the South region of the U.S. (all $P<0.05$) (Table 2).

3.2.2 PPI use and risk of MI

After controlling for baseline covariates, results from both logistic regression (AOR=0.64, 95%CI=0.58-0.71) (Table 3) and Cox proportional hazard models (AHR=0.68, 95%CI=0.61-0.75) (Table 3) found decreased risk of MI between PPI uses and H2 blocker users during the 15 months follow-up period. After propensity score matching, results were similar for logistic (AOR=0.60, 95%CI=0.53-0.67) and Cox proportional hazard models (AHR=0.62, 95%CI=0.55-0.70) (Table 3) as before matching.

Then we limited to beneficiaries with long-term PPI and H2 blocker use and compared with their association with MI in 12 months. After controlling for covariates, results in logistic regression showed non-significant association (AOR=0.95, 95%CI=0.79-1.14) between long-term PPI use and the risk of MI; however, results from Cox proportional hazard model found that PPI use was associated with a decreased risk of MI (AHR=0.98, 95%CI=0.79-1.22) compared to H2 blocker users (Table 3). Findings

were similar when analyses were conducted by applying the propensity score matching approach.

Individual PPI molecules were also compared with the oldest PPI molecule "omeprazole" to assess their comparative safety profile for risk of MI. Except for pantoprazole, all other PPIs did not show any statistically significant risk of MI when compared with omeprazole. Pantoprazole users showed an increased risk of MI in both logistic (AOR=1.14, 95%CI=1.03-1.25) and Cox model (AHR=1.15, 95%CI=1.05-1.26) (Table 3).

3.2.3 PPI use and risk of CKD and HF

In the assessment of PPI use and the risk of CKD, PPI users and H2 blocker users were followed for 15 months from their index date of drug use. After controlling for covariates, PPI user were not associated with risk of CKD in both logistic regression (AOR=1.01, 95%CI=0.97-1.05) and Cox proportional hazard model (AHR=1.00, 95%CI=0.99-1.08) (Table 4). Findings were similar when analyses were conducted by applying the propensity score matching approach in logistic regression (AOR=1.04, 95%CI=0.97-1.04) and Cox model (AHR=1.04, 95%CI=0.99-1.09). Similar approaches were taken to evaluate the risk of HF with the use of PPIs comparing with H2 blocker users. PPI use was not associated with risk of HF compared to H2 blocker use in covariates controlled and propensity score matched models (Table 5).

3.2.4 Sensitivity Analyses

In the sensitivity analysis limiting to beneficiaries with GERD in the washout period after controlling for all the covariates, results from neither logistic regression (AOR=0.74, 95%CI=0.49-1.10) nor Cox proportional hazard model (AHR=0.77,

95%CI=0.52-1.12) showed any significant association between PPI use and the risk of MI compared to users of H2 blockers (Table 3).

Sensitivity analyses were also conducted to evaluate the risk of MI among PPI users comparing with the non-users of both PPI and H2 blockers. Findings from logistic regression (AOR=0.39, 95%CI=0.36-0.41) found a decrease risk of MI among nonusers whereas findings from Cox proportional hazard models (AHR=0.96, 95%CI=0.90-1.02) were not statistically significant (Supplementary table 5). After propensity score matching findings from both logistic regression (AOR=0.38, 95%CI=0.36-0.41) and cox proportional hazard model (AHR=0.87, 95%CI=0.80-0.94) found a decrease risk of MI among PPI nonusers (Supplementary table 5).

In separate sensitivity analyses, presence of different disease status (Obesity, Hypertension, Diabetes, High cholesterol, low HDL, and Metabolic disorder) and use of different drug (Azithromycin, Erythromycin, Betamethasone Fluconazole, Megestrol, and Metoclopramide) in the washout period along with different sociodemographic characteristics. Similar to the main analyses, PPI use was not associated with the increased risk of MI (Supplementary table 6). Both logistic regression and cox proportional hazard model fond the risk of MI is associated with increased age, among males, among enrollees who have ESRD, who are obese, have hypertension, diabetes, and high cholesterol and use megestrol and metoclopramide (Supplementary table 7).

4.0 Discussion

To evaluate the adverse outcomes associated with PPI use, we analyzed the FAERS and Medicare claims data to detect risk signals and examine associations between PPI exposure and adverse outcomes. In the first approach of using the FAERS

data, we evaluated the safety signals of MI, CKD, and GC for all and individual PPIs. In the second approach, the risk of MI with PPI use was studied rigorously along with CKD and HF using the Medicare claims data from 2013-2016.

4.1 Safety signal detection for PPI use with MI, CKD, and GC

We did not observe risk signals between PPI and MI, nor did we find the influence of publication bias on the stimulated reporting in the FAERS. Findings were similar when FAERS analyses were conducted limiting the AE reports reported by health care providers only. While some existing observational studies indicated the risk of MI with PPI use, our findings from the FAERS data are consistent with a previous meta-analysis which did not observe the increased CV risk of among patients with and without PPI use in RCTs.[347] In observational studies of PPI use and risk of MI, protopathic bias is a concern since early MI symptoms such as chest pain and heartburn could be misdiagnosed as GERD. [36] This misdiagnosis can initiate the use of PPIs which can be misclassified as a risk factor of MI later.

Findings from FAERS analyses showed significantly higher RORs for CKD and GC compared to all other drugs from 2004-2019 (Q1Q2). However, we believed that publication bias impacted the results in CKD AE reporting and PPI. Specifically, the first research article indicating a potential risk of CKD associated with PPIs was published in JAMA Internal Medicine in 2016.[348] Shortly after the availability of this study, the number of AE reports of CKD involving PPIs increased dramatically in the FAERS. A few observational studies also found increased risk of CKD with PPI use, but the causal link was not established.[236,349]

Several observational studies indicated the association between PPI use and risk of GC[350-353], which is in agreement with our FAERS results. However, RCTs conducted on this topic showed no association between PPI use and the risk of GC.[354-356] This disagreement between observational studies and RCTs could be explained in the view of protopathic bias.[357] In addition, early symptoms of stomach cancer are similar to peptic ulcer, GERD, or other gastrointestinal diseases.[357] These early symptoms could also lead to the use of PPIs, which later could be considered as risk factors for GC. Therefore, future studies with long observational duration should be conducted to investigate any potential causal link between PPI use and GC.

4.2 Safety of PPI use among the Medicare population

In the second part of this study, we applied a new user cohort design using the Medicare claims data to compare risk of MI, CKD, and HF between PPI and H2 blocker users. Consistent with the FAERS results, we observed decreased risk of MI in a 15-month follow-up period among PPI users compared to H2 blocker users. When limiting to long-term users with at least 84 days of use, findings indicated no statistically significant risk of MI between PPI and H2 blocker users. Additionally, individual PPIs were also compared and only pantoprazole users showed an increase in the risk of MI compared with omeprazole users. In the sensitivity analyses, individual disease state and drug use were also evaluated along with different socio-demographic information to understand their role in the developing MI. This study found that MI is associated with increased age, among males, among enrollees who have ESRD, who are obese, have hypertension, diabetes, and high cholesterol and use megestrol and metoclopramide when comparing PPI users with H2 blocker users. These findings for different

covariates are in consistent with existing literature where authors identify that increased age, being males, presence of ESRD, obesity, hypertension, diabetes, and high cholesterol and along with the use megestrol and metoclopramide are contributing factor in the development of MI among general population. [345,346]

While PPI use did not show any increase in the risk of MI when comparing with H2 blocker use, further analyses on PPI use comparing no use of PPI/H2 blocker showed the association of PPI use with the increased risk of MI. Findings of this study also indicated no association between PPI use and the risk of CKD and HF among the Medicare population.

Findings of the relationship between PPI use and MI risk among Medicare fee-for-service beneficiaries were consistent with another observational study among Medicare beneficiaries with supplementary coverages.[231] The authors found decreased risk of MI among PPI users compared with H2 blocker users at 3 months post initiation and the early onset association disappeared after 12 months of treatment initiation.[231] Our findings are also consistent with Qian et al., which found the MI risk among PPI users were close to null whereas MI risk was elevated among H2 blocker users.[358] Additionally, elevated risk of MI related to PPI use in previous observational studies could be due to the unmeasured baseline confouding.[359] Observational studies using retrospective administrative claims data usually lack information on known MI risk factors such as smoking, alcohol use, lipid levels, body mass index, diet and exercise habits.[33,360,361] Our findings using two real-world datasets (the FDA FAERS and Medicare claims) and different observational study approaches (cross-sectional and

new user cohort) did not observe a significant association between PPI use and risk of MI.

In addition, our Medicare claim results did not find any association between PPI use and the risk of CKD with a 15 months follow-up period. A few observational studies found an association between PPI use the risk of chronic renal illness.[362-364] However, confounding and biases might have hindered the assessment of PPI use and risk of CKD in observational studies. For example, PPI users have been found more likely to be obese, smoking, having multiple comorbid chronic diseases, and having a history of hospitalization.[362] PPI users are also more likely to use different drugs, such as calcineurin inhibitors, antibiotics, antivirals, NSAIDS, diuretics, ACE inhibitors and ARBS, lithium, chemotherapy, warfarin, and allopurinol, for comorbidities which can cause the kidney damage, or renal injury.[362] Our FAERS results indicated publication bias on CKD AE reporting for PPIs. The Medicare administrative claims analysis conducted in this study provided head-to-head comparative effectiveness evidence in risk of CKD between PPI and H2 blocker new users, and we found no difference in risk between the two treatment groups.

Finally, risk of HF was examined among PPI and H2 blocker users and we did not find association between PPI use and the risk of HF. Findings of this observational cohort study are similar to the previous meta-analysis examining the correlation between elevated CV risk and simultaneous clopidogrel and PPI therapy.[347] This meta-analysis did not observe the increased CV risk among patients on clopidogrel treatment between PPI users and nonusers in RCTs. In contrast to our findings, Lazaro et al. found an association with PPI use and increased incidence of HF and death in patients

with coronary artery disease (CAD).[365] However, Lazaro et al. was inherently different from our study since they only included patients aged 85 years or more who had CAD. Furthermore, another study assessed the outcomes of PPI use among patients with HF and did not find any association with harm and exhibited a relative reduction in mortality rate compared to the nonusers in the ambulatory settings.[366] Additionally, the FDA's safety review in 2007 did not find any evidence of increased risk of cardiac events among omeprazole and esomeprazole users, which is consistent with our findings.[367] In summary, our study including a new user cohort of Medicare beneficiaries did not observe any difference in risk of HF between PPI and h2 blocker users.

5.0 Limitations

In this study, multiple data source and different methodological and statistical approaches were applied to build a comprehensive and comparative safety profile of PPIs. However, our findings should be interpreted with consideration of the following limitations. First, the FAERS data are prone to under-reporting and over-reporting biases. The FAERS includes spontaneous reports to the FDA, so the reporting rates can be impacted by external factors such as mass media advertisements, labeling, and peer effect. We did observe publication bias on MI and CKD AE reporting, but not for GC. Similarly, our Medicare data analyses can be influenced by different confounding factors such as patient's medication adherence and patient's perception. By limiting to long-term users, we observed the association between relatively stable and long-term treatment exposure of PPIs with future risk events. And our findings indicated no risk of MI, CKD or HF related to PPI use. In addition, our results from the Medicare claims data might not be generalizable to non-Medicare enrollees. Finally, due to the nature of

observational study designs, our findings should still be interpreted as association rather than causality.

6.0 Conclusions

Our findings indicated that PPI use is not associated with increased risk of CKD, MI, or HF. However, future research is needed to further investigate the relationship between PPI use and GC.

Table 1. Reporting Odd Ratios for PPI use and MI, CKD, and GC in the FAERS

	2004-2019 (Q1Q2)				**2004-2011**			**2012-2019 (Q1Q2)**			
Drug	AE	ROR	95% CI		ROR	95% CI		ROR	95% CI		
All PPI	MI	0.87	0.86	0.88	0.98	0.96	0.99	0.85	0.83	0.86	Goodman 2012
Omeprazole		0.82	0.80	0.83	0.92	0.89	0.96	0.81	0.78	0.83	
Pantoprazole		0.99	0.97	1.02	1.00	0.96	1.05	1.07	1.04	1.10	
Esomeprazole		0.86	0.83	0.88	0.93	0.89	0.97	0.83	0.8	0.87	
Rabeprazole		1.05	0.99	1.11	1.04	0.96	1.13	0.93	0.85	1.02	
Lansoprazole		0.90	0.87	0.94	1.10	1.05	1.16	0.7	0.66	0.74	
Dexlansoprazole		0.30	0.26	0.34	0.40	0.24	0.68	0.36	0.31	0.42	
	CKD	**2004-2019 (Q1Q2)**			**2004-2015**			**2016-2019 (Q1Q2)**			Lazarus 2016
Drug		ROR	95% CI	ROR	ROR	95% CI	ROR	ROR	95% CI	ROR	
All PPI		2.40	2.39	2.40	1.01	1.00	1.01	9.69	9.64	9.69	
Omeprazole		1.96	1.94	1.96	1.01	0.99	1.01	6.12	6.07	6.12	
Pantoprazole		1.90	1.88	1.90	1.25	1.22	1.25	4.25	4.20	4.25	
Esomeprazole		2.40	2.38	2.40	0.78	0.76	0.78	11.49	11.39	11.49	
Rabeprazole		2.58	2.52	2.58	1.14	1.09	1.14	8.52	8.33	8.52	
Lansoprazole		3.35	3.32	3.35	1.07	1.05	1.07	15.30	15.16	15.30	
Dexlansoprazole		5.29	5.17	5.29	0.29	0.24	0.29	18.19	17.90	18.19	
	2004-2019 (Q1Q2)				**2004-2008**			**2009-2019 (Q1Q2)**			
Drug	AE	ROR	95% CI		ROR	95% CI		ROR	95% CI		
All PPI	GC	1.65	1.55	1.75	1.54	1.28	1.84	1.67	1.56	1.78	Poulsen 2009
Omeprazole		1.32	1.18	1.48	1.41	1.01	1.97	1.31	1.16	1.48	
Pantoprazole		1.18	1.02	1.36	1.22	0.78	1.89	1.17	1.01	1.38	
Esomeprazole		2.00	1.78	2.26	1.60	1.10	2.35	2.06	1.82	2.34	
Rabeprazole		3.17	2.55	3.94	1.99	1.11	3.61	3.45	2.75	4.38	
Lansoprazole		2.17	1.89	2.50	1.75	1.22	2.53	2.26	1.94	2.64	
Dexlansoprazole		1.26	0.81	1.95	NA	NA	NA	1.27	0.82	1.97	

CKD=Chronic Kidney Disease, MI= Myocardial Infarction, GC= Gastric Cancer, FAERS= FDA Adverse Event Reporting System

Figure 1: Sample flow chart for PPI new user cohort, H2RA new user cohort

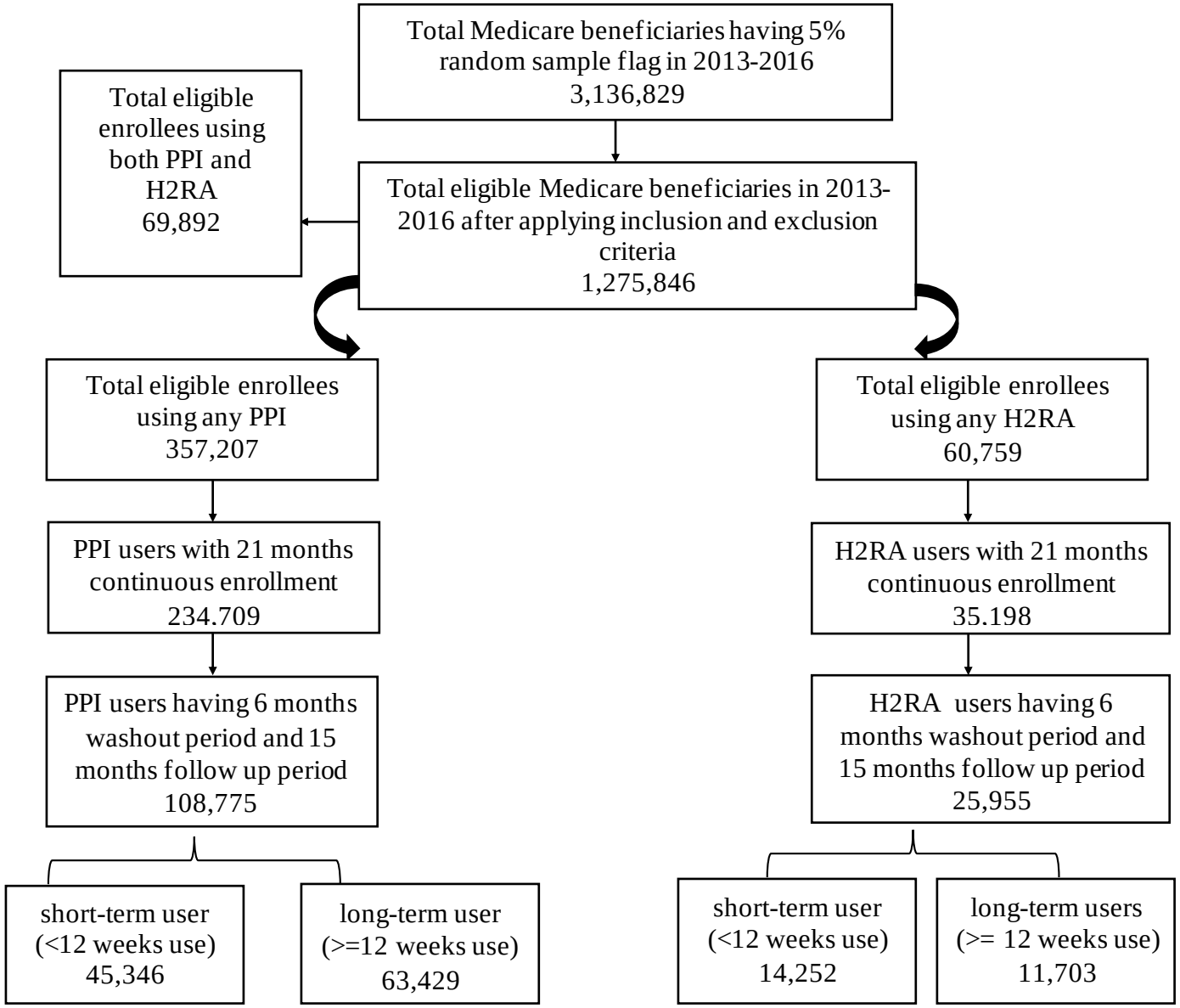


Table 2. Sample characteristics for PPI and H2 blocker users in the Medicare claims data

Factors	PPI* Users		H2 Blocker** Users		P[e]	P[ee]
	N	%	N	%		
Sample size	108775	80.74	25955	19.26		
Patient characteristics						
Age					<.0001	0.83
<65	9736	8.95	2940	11.33		
65-74	48661	44.74	9905	38.16		
75-84	32890	30.24	8365	32.23		
85 and older	17488	16.08	4745	18.28		
Sex					<.0001	0.60
Male	43397	39.90	9621	37.07		
Female	65378	60.10	16334	62.93		
Race/ethnicity					<.0001	0.30
White	96361	88.59	22369	86.18		
Black	7286	6.70	2275	8.77		
Asian	890	0.82	265	1.02		
Hispanic	964	0.89	310	1.19		
Other [a]	3274	3.01	736	2.84		
Region					<.0001	0.99
Northeast	21200	19.49	4922	18.96		
Midwest	26876	24.71	6672	25.71		
South	43998	40.45	10650	41.03		
West	16701	15.35	3711	14.30		
Residential area					0.0090	0.71
Urban	94015	86.43	22272	85.81		
Rural	14760	13.57	3683	14.19		
ESRD [b]					<.0001	0.87
Yes	775	0.71	283	1.09		
No	108000	99.29	22122	85.23		
LIS [c] eligible					<.0001	0.98
Yes	10840	9.97	3833	14.77		
No	97935	90.03	22122	85.23		
Patient health service utilization factors at pre-index period						
Count of unique prescriptions						
0	10042	9.23	1498	5.77	<.0001	
1-2	9967	9.16	1764	6.80		
3-5	14362	13.20	3033	11.69		
6-10	22292	20.49	5164	19.90		

11 or more	52112	47.91	14496	55.85		
Count of hospitalizations					<.0001	
0	85604	78.70	19331	74.48		
1	15360	14.12	4083	15.73		
2 or more	7811	7.18	2541	9.79		
Count of ED [d] visits					<.0001	
0	78396	72.07	16976	65.41		
1	19069	17.53	5380	20.73		
2	6540	6.01	1993	7.68		
3	2549	2.34	842	3.24		
4 or more	2221	2.04	764	2.94		
Count of physician office visits					<.0001	
1 or less	14324	13.17	2855	11.00		
2-5	23106	21.24	5009	19.30		
6-10	22994	21.14	5292	20.39		
11-20	24943	22.93	6217	23.95		
21-30	11266	10.36	2988	11.51		
31 or more	12142	11.16	3594	13.85		
Charlson comorbidity index					<.0001	0.64
0	29671	27.28	5771	22.23		
1	20636	18.97	4619	17.80		
2	15549	14.29	3861	14.88		
3	12202	11.22	3051	11.75		
4 or more	30717	28.24	8653	33.34		
Prescription-level factors						
Daily dosage: MG (mean, SD)	Mean: 36.15	Sd: 22.35	Mean: 198.07	Sd: 225.92	<.0001	
Short term/Long term use					<.0001	
Short term	45346	41.69	14252	54.91		
Long term use	63429	58.31	11703	45.09		
Pharmacy Type						0.34
Community/retail pharmacy	89833	82.59	21536	82.97	<.0001	
Institutional pharmacy	3896	3.58	1789	6.89		
Mail-order pharmacy	8051	7.40	1141	4.40		
Specialty pharmacy	8	0.01	7	0.03		
Others [e]	6987	6.42	1482	5.71		
Part D plan benefit phase					<.0001	0.48

Deductible	17272	15.88	3251	12.53		
Coverage	56238	51.70	13957	53.77		
Gap	5782	5.32	2351	9.06		
Catastrophic	1971	1.81	878	3.38		
Others [f]	27512	25.29	5518	21.26		
Cost sharing in deductible phase					<.0001	0.27
Yes	11784	10.83	2718	10.47		
No	69395	63.80	17691	68.16		
Unknown	27596	25.37	5546	21.37		

* PPI = Proton Pump Inhibitor, ** H2 Blocker= H2RA/Histamine Type-2 Receptor Antagonists

P^{e}= P-value before propensity score matching, P^{ee}= P-value after propensity score matching

[a] Race/Ethnicity: Others = North american native, Other, Unknown,

[b] ESRD = End-Stage Renal Disease

[c] LIS = Low-Income Subsidy

[d] ED = Emergency department

[e] Pharmacy Type: Others= Compounding pharmacy, Home infusion therapy provider, Long-term care pharmacy, Managed care organization (MCO) pharmacy, Other, all the rest are missing

[f] Part D plan benefit phase: Others = Beneficiary enrolled in PACE or employer-sponsored plan, all the rest and missing

Table 3. Adjusted associations between PPI use and risk of MI

Exposure	PPI Users	H2 Blocker Users	Statistical Modeling	Measures of Association	AOR/AHR (95% CL)
PPI vs. H2 blocker users (reference)					
Any use (15 months follow-up)	106,884	25,447	Logistic Regression	AOR	0.64 (0.58-0.71)
			Cox Model	AHR	0.68 (0.61-0.75)
Any use (15 months follow-up ,propensity score matched)	24,882	24,882	Logistic Regression	AOR	0.60 (0.53-0.67)
			Cox Model	AHR	0.62 (0.55-0.70)
Long-term use (12 months follow-up)	62,415	11,449	Logistic Regression	AOR	0.95 (0.79-1.14)
			Cox Model	AHR	0.98(0.79-1.22)
Long-term use (12 months follow-up, propensity score matched)	11,236	11,236	Logistic Regression	AOR	0.87 (0.70-1.08)
			Cox Model	AHR	0.88 (0.71-1.21)
Long-term vs. short-term PPI users (reference)					
Long-term vs. short-term	Long-term PPI users; 62415 vs. short-term PPI users; 44,469	NA	Logistic Regression	AOR	0.92 (0.84-1.00)
			Cox Model	AHR	0.89 (0.82-0.97)
Long-term vs. short-term (propensity score matched)	Long term PPI users; 44,106. Short term PPI users; 44,106.	NA	Logistic Regression	AOR	0.93 (0.85-1.02)
			Cox Model	AHR	0.89 (0.81-0.98)
Individual PPI comparison					

Pantoprazole users vs Omeprazole users (Propensity Score Weighted Sample. 15 months follow up period from Index date)		NA	Logistic Regression	AOR	1.14 (1.03-1.25)
			Cox Model	AHR	1.15 (1.05-1.26)
Sensitivity analysis					
PPI users vs. H2 blocker users (among patients with GERD)	10,213	10,213	Logistic Regression	AOR	0.74 (0.49-1.10)
			Cox Model	AHR	0.77 (0.52-1.12)

PPI= Proton Pump Inhibitors, GERD= Gastro Esophageal Reflux Disease, AOR= Adjusted Odds Ratio, AHR= Adjusted Hazard ratio
Table 4. Adjusted associations between PPI use and risk of CKD

Study Approach	PPI users	H2 blocker users	Statistical approach	Measures of Association	AOR/AHR (95% CL)
PPI users vs. H2 blocker users (15 months follow-up)	106,868	254,36	Logistic Regression	AOR	1.01 (0.96-1.05)
			Cox Model	AHR	1.00 (0.97-1.04)
PPI users vs. H2 blocker users (propensity score matched)	24,871	24,871	Logistic Regression	AOR	1.04 (0.99-1.09)
			Cox Model	AHR	1.03 (0.98-1.08)

PPI= Proton Pump Inhibitors, AOR= Adjusted Odds Ratio, AHR= Adjusted Hazard ratio

Table 5. Adjusted associations between PPI use and risk of HF

Study Approach	PPI users	H2 blocker users	Statistical approach	Measures of Association	AOR/AHR (95% CL)
PPI users vs. H2 blocker users (15 months follow-up)	106,368	25,227	Logistic Regression	AOR	1.02 (0.98-1.07)
			Cox Model	AHR	1.01 (0.95-1.07)
PPI users vs. H2 blocker users (propensity score matched)	24,812	24,812	Logistic Regression	AOR	1.00 (0.96-1.06)
			Cox Model	AHR	1.03 (0.96-1.05)

PPI= Proton Pump Inhibitors, AOR= Adjusted Odds Ratio, AHR= Adjusted Hazard ratio

Supplementary Table 1: Preferred terms (PTs) related to MI, CKD, and GC

Adverse Event (AE)	Preferred Term (PT)
Myocardial Infarction (MI)	Myocardial Infarction
	Acute Coronary Syndrome
	Acute Myocardial Infarction
	Angina Unstable
	Blood Creatine Phosphokinase Mb Abnormal
	Blood Creatine Phosphokinase Mb Increased
	Coronary Artery Embolism
	Coronary Artery Occlusion
	Coronary Artery Reocclusion
	Coronary Artery Thrombosis
	Coronary Bypass Thrombosis
	Kounis Syndrome
	Myocardial Infarction
	Myocardial Necrosis
	Myocardial Reperfusion Injury
	Myocardial Stunning
	Papillary Muscle Infarction
	Post Procedural Myocardial Infarction
	Postinfarction Angina
	Silent Myocardial Infarction
	Troponin I Increased
	Troponin Increased
	Troponin T Increased
	Blood Creatine Phosphokinase Abnormal
	Blood Creatine Phosphokinase Increased
	Cardiac Enzymes Increased
	Ecg Electrically Inactive Area
	Electrocardiogram Q Wave Abnormal
	Electrocardiogram St Segment Abnormal
	Electrocardiogram St Segment Elevation
	Electrocardiogram St-T Segment Elevation
	Infarction
	Scan Myocardial Perfusion Abnormal
	Vascular Graft Occlusion
Chronic Kidney Disease (CKD)	Chronic Kidney Disease
	Artificial Kidney Device User
	Azotaemia
	Coma Uraemic
	Diabetic End Stage Renal Disease

	Dialysis
	Dialysis Device Insertion
	Glomerulonephritis Chronic
	Haemodialysis
	Haemofiltration
	Hepatorenal Failure
	High Turnover Osteopathy
	Hyperparathyroidism Secondary
	Kidney Fibrosis
	Low Turnover Osteopathy
	Nephrogenic Anaemia
	Nephrogenic Systemic Fibrosis
	Nephrosclerosis
	Oedema Due To Renal Disease
	Pericarditis Uraemic
	Peritoneal Dialysis
	Renal And Liver Transplant
	Renal And Pancreas Transplant
	Renal Failure
	Renal Failure Chronic
	Renal Osteodystrophy
	Renal Replacement Therapy
	Renal Rickets
	Renal Transplant
	Uraemia Odour
	Uraemic Acidosis
	Uraemic Encephalopathy
	Uraemic Gastropathy
	Uraemic Neuropathy
	Uraemic Pruritus
	Uridrosis
	Acquired Cystic Kidney Disease
	Acute Phosphate Nephropathy
	Albumin Urine Present
	Albuminuria
	Aluminium Overload
	Biopsy Kidney Abnormal
	Blood 1,25-Dihydroxycholecalciferol Decreased
	Blood Bicarbonate Abnormal
	Blood Bicarbonate Decreased
	Blood Calcium Abnormal

	Blood Calcium Decreased
	Blood Creatinine Abnormal
	Blood Creatinine Increased
	Blood Erythropoietin Abnormal
	Blood Erythropoietin Decreased
	Blood Parathyroid Hormone Abnormal
	Blood Parathyroid Hormone Increased
	Blood Phosphorus Abnormal
	Blood Phosphorus Increased
	Blood Potassium Abnormal
	Blood Potassium Increased
	Blood Sodium Abnormal
	Blood Sodium Decreased
	Blood Urea Abnormal
	Blood Urea Increased
	Bloody Peritoneal Effluent
	Bone Cyst
	Calcification Of Muscle
	Calciphylaxis
	Chronic Allograft Nephropathy
	Creatinine Renal Clearance Abnormal
	Creatinine Renal Clearance Decreased
	Diabetic Nephropathy
	Dialysis Amyloidosis
	Dialysis Disequilibrium Syndrome
	Dialysis Related Complication
	Diffuse Mesangial Sclerosis
	Effective Peritoneal Surface Area Increased
	Encephalopathy
	Eosinophils Urine Present
	Epidemic Nephropathy
	Extensive Interdialytic Weight Gain
	Fibrillary Glomerulonephritis
	First Use Syndrome
	Focal Segmental Glomerulosclerosis
	Glomerular Filtration Rate Abnormal
	Glomerular Filtration Rate Decreased
	Glomerulonephritis
	Glomerulonephritis Membranoproliferative
	Glomerulonephritis Membranous
	Glomerulonephritis Minimal Lesion
	Glomerulonephritis Proliferative

	Glomerulonephritis Rapidly Progressive
	Glomerulonephropathy
	Glomerulosclerosis
	Goodpasture's Syndrome
	Haemodialysis Complication
	Haemodialysis-Induced Symptom
	Haemolytic Uraemic Syndrome
	Haemorrhagic Diathesis
	Hiv Associated Nephropathy
	Hypercalcaemic Nephropathy
	Hypercreatininaemia
	Hyperkalaemia
	Hyperparathyroidism
	Hyperphosphataemia
	Hypertensive Nephropathy
	Hypervolaemia
	Hypoalbuminaemia
	Hypocalcaemia
	Hyponatraemia
	Iga Nephropathy
	Immunotactoid Glomerulonephritis
	Intercapillary Glomerulosclerosis
	Intradialytic Parenteral Nutrition
	Inulin Renal Clearance Decreased
	Ischaemic Nephropathy
	Kidney Small
	Leukocyturia
	Lupus Nephritis
	Mesangioproliferative Glomerulonephritis
	Metabolic Acidosis
	Microalbuminuria
	Nephritic Syndrome
	Nephropathy
	Nephropathy Toxic
	Nephrotic Syndrome
	Normochromic Normocytic Anaemia
	Osteomalacia
	Parathyroid Gland Enlargement
	Pericarditis
	Peritoneal Cloudy Effluent
	Peritoneal Dialysis Complication
	Peritoneal Effluent Abnormal

	Peritoneal Effluent Erythrocyte Count Increased
	Peritoneal Effluent Leukocyte Count Increased
	Peritoneal Equilibration Test Abnormal
	Peritoneal Fluid Analysis Abnormal
	Peritoneal Fluid Protein Abnormal
	Peritoneal Fluid Protein Increased
	Peritoneal Permeability Increased
	Pigment Nephropathy
	Peritoneal Dialysis Complication
	Polyomavirus-Associated Nephropathy
	Protein Urine Present
	Proteinuria
	Red Blood Cells Urine Positive
	Reflux Nephropathy
	Renal Amyloidosis
	Renal Atrophy
	Renal Papillary Necrosis
	Renal Tubular Atrophy
	Secondary Hypertension
	Tubulointerstitial Nephritis
	Ultrafiltration Failure
	Ultrasound Kidney Abnormal
	Urate Nephropathy
	Urea Renal Clearance Decreased
	Urinary Casts Present
	Urine Albumin/Creatinine Ratio Abnormal
	Urine Albumin/Creatinine Ratio Increased
	Urine Output Decreased
	Urine Protein/Creatinine Ratio Abnormal
	Urine Protein/Creatinine Ratio Increased
	Vascular Calcification
	White Blood Cells Urine Positive
Gastric Cancer (GC)	Gastric Cancer
	Gastric Cancer Recurrent
	Gastric Cancer Stage 0
	Gastric Cancer Stage I
	Gastric Cancer Stage Ii
	Gastric Cancer Stage Iii
	Gastric Cancer Stage Iv
	Gastric Sarcoma

	Gastrinoma Malignant
	Gastrointestinal Cancer Metastatic
	Gastrointestinal Carcinoma
	Gastrointestinal Carcinoma In Situ
	Gastrointestinal Stromal Cancer
	Gastrooesophageal Cancer
	Her-2 Positive Gastric Cancer
	Metastatic Gastric Cancer

Supplementary Table 2: International Classification of Diseases Version 9 and 10 codes for MI, CKD, and HF

Diagnosis	ICD-9 codes	ICD-10 codes
Myocardial Infarction (MI)	410	I21
	41001	I210
	41002	I211
	4101	I212
	41011	I213
	41012	I214
	4102	I219
	41021	I22
	41022	I220
	4103	I221
	41031	I228
	41032	I229
	4104	
	41041	
	41042	
	4105	
	41051	
	41052	
	4106	
	41061	
	41062	
	4107	
	41071	
	41072	
	4108	
	4108	
	41081	
	41082	
	4109	
	41091	
	41092	
Chronic Kidney Disease (CKD)	5851	N181
	5852	N182
	5853	N183
	5854	N184
	5855	N185
	5856	N186
	5859	N189

Diagnosis	ICD-9 codes	ICD-10 codes
Heart Failure (HF)	428	I50
	4281	I501
	4282	I502
	42820	I503
	42821	I504
	42822	I509
	42823	
	42830	
	42831	
	42832	
	42833	
	42840	
	42841	
	42842	
	42843	
	4289	

Supplementary Table 3: International Classification of Diseases Version 9 and 10 codes for GERD

Diagnosis	ICD-9 codes	ICD-10 codes
Gastro-esophageal reflux disease (GERD)	5300	K210
	5301	K219
	5304	K2270
	5308	
	53011	
	53019	
	5302	
	5303	
	5305	
	53081	
	53089	
	5309	
	5363	
	5648	
	7871	
	7872	
	78906	

Supplementary table 4. Reporting Odd Ratios for PPI use and MI, CKD, and GC in the FAERS (Limited to reports came from healthcare providers)

Drug	AE	2004-2019 (Q1Q2)			2004-2011			2012-2019 (Q1Q2)			Important Publication
		ROR	95% CI		ROR	95% CI		ROR	95% CI		Goodman 2012
All PPI	MI	1.02	0.99	1.04	1.02	1.00	1.06	1.00	0.97	1.03	
	CKD	**2004-2019 (Q1Q2)**			**2004-2015**			**2016-2019 (Q1Q2)**			Lazarus 2016
		ROR	95% CI		ROR	95% CI		ROR	95% CI		
		1.30	1.28	1.31	0.94	0.92	0.95	1.77	1.74	1.79	
	GC	**2004-2019 (Q1Q2)**			**2004-2008**			**2009-2019 (Q1Q2)**			Poulsen 2009
		ROR	95% CI		ROR	95% CI		ROR	95% CI		
		1.24	1.13	1.34	1.38	1.10	1.73	1.21	1.09	1.35	

Supplementary table 5. Risk of MI among PPI/H2 blocker nonusers vs PPI users

Exposure	**PPI Users**	**PP/H2 blocker non user**	**Statistical Modeling**	**Measures of Association**	**AOR/AHR (95% CL)**
PP/H2 blocker nonuser vs PPI user					
Any use (15 months follow-up)	106,884	475,460	Logistic Regression	AOR	0.39 (0.36-0.41)
			Cox Model	AHR	0.96 (0.90-1.02)
Any use (15 months follow-up ,propensity score matched)	106,884	106,884	Logistic Regression	AOR	0.38 (0.36-0.41)
			Cox Model	AHR	0.87 (0.80-0.94)

Supplementary table 6. Role of different disease and drug use and risk of MI among PPI users (Statistical Approach; Logistic Regression).

Characteristics	**AOR**	**95% Confidence Limits**	
PPI use vs H2 blocker use	0.63	0.56	0.69
Age 75-84 vs <65	1.51	1.28	1.77
Age 85 and older vs <65	2.24	1.89	2.65
Gender Female vs Male	0.64	0.60	0.69
ESRD 0 vs 1	0.37	0.28	0.49
LIS 0 vs 1	0.79	0.70	0.90
Obesity (Presence vs Absence)	1.28	1.15	1.42
Hypertension (Presence vs Absence)	1.79	1.63	1.97
Diabetes (Presence vs Absence)	1.60	1.48	1.73
High cholesterol Yes vs No	1.34	1.18	1.52
Low HDL (Presence vs Absence)	1.25	0.30	5.14
Metabolic disorder (Presence vs Absence)	1.45	0.71	2.95
Azithromycin (Use vs No use)	0.95	0.88	1.03
Erythromycin (Use vs No use)	0.72	0.59	0.89
Betamethasone (Use vs No use)	0.95	0.82	1.09
Fluconazole (Use vs No use)	1.03	0.91	1.17
Megestrol (Use vs No use)	1.78	1.44	2.19
Metoclopramide Yes vs No	1.38	1.17	1.63

Supplementary table 7. Role of different disease and drug use and risk of MI among PPI users (Statistical Approach; Cox Model).

Characteristics	**AHR**	**95% Confidence Limits**	
PPI use vs H2 blocker use	0.66	0.59	0.73
Age 65-74 and older vs <65	1.09	0.93	1.28
Age 75-84 vs <65	1.52	1.29	1.78
Age 85 and older vs <65	2.27	1.91	2.68
Gender Female vs Male	0.61	0.63	0.73
ESRD (Absence vs Presence)	2.62	2.03	3.38
LIS (Not eligible vs eligible)	0.79	0.70	0.90
Obesity (Presence vs Absence)	1.27	1.15	1.42
Hypertension (Presence vs Absence)	1.79	1.63	1.97
Diabetes (Presence vs Absence)	1.60	1.47	1.78
High cholesterol Yes vs No	1.34	1.18	1.51
Low HDL (Presence vs Absence)	1.20	0.30	4.78
Metabolic disorder (Presence vs Absence)	1.43	0.71	2.90
Azithromycin (Use vs No use)	0.93	0.86	1.01
Erythromycin (Use vs No use)	0.72	0.58	0.88
Betamethasone (Use vs No use)	0.93	0.81	1.07
Fluconazole (Use vs No use)	1.02	0.90	1.16
Megestrol (Use vs No use)	1.84	1.49	2.26
Metoclopramide Yes vs No	1.37	1.17	1.61

Aim 3 Paper: Association between PPIs and MI and GC: A Systematic Review and Meta-analysis.

Abstract

Introduction: Proton Pump Inhibitors (PPIs) are the most common and potent acid-suppressive medications and used widely in the U.S. PPIs have generally been considered safe and short-term use of PPIs is usually well-tolerated, however, emerging number of case reports and observational studies have raised concerns over the safety of long-term PPI use.

Objectives: This systematic review and meta-analysis assessed the association between PPIs and risk of myocardial infarction (MI) and gastric cancer (GC) including both clinical trials and observational studies.

Methods: The Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines were used to identify potential studies and report findings. A systematic search was performed in December 2019 to retrieve all potential studies using PubMed, PsycInfo, International Pharmaceutical Abstracts, Web of Science, and Clinicaltrials.gov. This systematic search initially identified any published studies describing any adverse event (AE) or outcomes related to PPI. Records were included in this study if 1) studies were published in English, 2) study design was clinical trials, observational studies, case series or case reports, 3) PPI use was the exposure or treatment, and 4) study outcome was the incidence of MI or GC. If the title and abstract provided insufficient information to assess the inclusion criteria, a full-text review was conducted. Two researchers independently reviewed all identified records, performed full article review, extracted data into structured evidence table, and conducted quality assessment using Newcastle–Ottawa Scale and Quality Assessment Tool for Quantitative Studies. Meta-analysis was performed using the RStudio software to assess the association between PPIs and risk of MI and GC.

Results: A total of 4,507 abstracts meeting the inclusion criteria were identified, and 20 full articles were included in this study, among which 10 were cohort, 3 were case-

control, 3 were RCT post-hoc analysis, and 4 were RCT studies. The pooled Odds Ratio (OR)=1.40 with 95% CI=1.20-1.63 for all studies indicated the presence of an association between PPI use and increased risk of MI compared to PPI non-users. Meta-analysis found a similar association between PPI use and increased risk of MI in observational studies (OR=1.40; 95% CI=1.20, 1.64) but no association (OR=0.90; 95% CI=0.47, 1.73) in RCT-studies. Heterogeneity was high (I^2 > 75%) for all analyses except for RCTs (I2=0%). For GC, there were 3 cohort, 2 case-control, 8 RCT, and 2 clinical trial studies. 5 out of the 8 RCTs had the same intervention PPI as a comparator group with a different dose, and 2 clinical trials did not have any comparator drugs or placebo, hence they were not included in meta-analysis. The pooled statistic (OR 1.90; 95% CI 1.48, 2.45) for all studies indicated the presence of an association between PPI use and increased risk of GC with high heterogeneity (I^2 = 75%). Meta-analysis of observational studies indicates the association PPI use and GC (OR 1.88; 95% CI 1.45, 2.45). However, meta-analysis found no association between PPI use and risk of GC when limiting to RCTs (OR 3.09; 95% CI 0.57, 16.73, I^2 = 0%).

Conclusions: Meta-analysis findings for PPI use and the risk of MI and GC are not consistent between RCT and observational study designs. This disagreement between RCTs and observational studies indicates the need for more rigorous, well-designed studies to evaluate any potential causal relationship between PPI use the risk of MI and GC.

1. Introduction

Gastroesophageal reflux disease (GERD) is one of the most common and highly prevalent digestive disorders across the world.[368] Acid suppressive agents (antacids, alginates) are used as GERD treatments to relieve and prevent the recurrence of symptoms.[11,369,370] Proton Pump Inhibitors (PPIs) are the most common and potent acid-suppressive medications which work by inhibiting the final step of acid secretion.[127] Currently, six PPIs are commercially available in the United States (U.S.), including omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, and rabeprazole in various dosage forms.[32] Although not all PPIs are the same in pharmacokinetic properties, they share a similar mechanism of action.[32]

Although PPIs have generally been considered safe and short-term use of PPIs is usually well-tolerated, recent evidence on long-term use suggests otherwise. The emerging number of case reports and observational studies have raised concerns over the safety of long-term PPI use. For example, a case-control study in the U.K. identified the association of community-acquired *C difficile* with the use of PPIs.[313] Several other adverse events (AEs) such as community-acquired pneumonia (CAP) have been found to be associated with the use of PPIs.[314,315] Studies among non-U.S. populations also identified the associations of PPI use and potential AEs such as acute kidney disease, chronic kidney disease, pneumonia, bone fractures, cardiovascular events, and enteric infections.[28,238,316] In 2010, a safety announcement was issued by the U.S. Food and Drug Administration (FDA) regarding the increased risk of fracture associated with long-term use of PPIs, followed by another safety announcement for the increased risk of infection due to PPI use.[332,333]

The bulk of existing studies have focused on the risk of long-term PPI use with bone fractures, enteric infection, pneumonia, and vitamin B12 deficiency.[371] For example, clinical trials and observational studies have examined the increased risk of any fracture, hip fracture, spine fracture, femur fracture, and vertebral fracture with PPI use, but findings from these studies were inconsistent.[372] In 2018, a systematic review and meta-analysis reported an increased risk of fracture with the use of PPIs. For enteric infection, findings from an updated meta-analysis supported an increased risk of salmonella and campylobacter infection among PPI users.[373] Another analysis of ten randomized controlled trials (RCTs) and 48 observational studies explored the risk of pneumonia with PPI use and found mixed results. While a recent meta-analysis based on observational studies found a risk of pneumonia with PPI use, the opposite results were found in RCTs.[223] Findings from available studies are also inconsistent for the association between PPI use and vitamin B12 deficiency.[374] For instance, experimental evidence showed a reduction in the absorption of protein-bound vitamin B12 with PPI use, but PPI use did not completely inhibit vitamin B12 absorption.[375,376] Observational studies such as case-control studies found no association between PPI use and vitamin B12 deficiency whereas longitudinal and cross-sectional studies found low serum vitamin B12 levels among PPI users.[377-380]

Regarding the association between PPI use and the risk of MI, earlier studies on animal models and ex vivo human tissue experiments found that the increases in plasma asymmetrical dimethylarginine (ADMA) are associated with PPI use.[33] The elevation of plasma ADMA caused by the use of PPI could exert AEs on coronary vessels, thus increasing the risk of MI. Several clinical trials and observational studies

also explored the risk of MI with the use of PPIs and presented mixed results.[34,35] Findings from both clinical trials and observational studies should be evaluated comprehensively to understand the discrepancies in the risk of MI with PPI use by different types of studies to facilitate post-marketing surveillance of drug products.

Limited existing evidence also suggested the association between PPI use and gastric cancer (GC). It is suspected that hypergastrinemia caused by profound acid suppression caused by PPIs could be a responsible factor for the increased risk of GC among PPI users.[221] At present, one meta-analysis evaluated the association between PPI use and the risk of GC, but it only synthesized the findings from observational studies.[222] This meta-analysis identified one cohort and three case-control studies and found that PPI use might increase the risk of GC by 43% (OR: 1.43; 95% CI: 1.23 - 1.66).[222] While this meta-analysis provided valuable information on the risk of GC and PPI use, the included observational studies are susceptible to several biases, such as protopathic bias.[223] A significant proportion of patients with early GC experience typical dyspeptic symptoms and use PPI to control these dyspeptic symptoms.[224] Thus, protopathic bias may lead to the erroneous conclusion that PPIs are responsible for GC.[224,225] Therefore, including newer studies and further synthesizing findings from both observational studies and clinical trials will provide a more comprehensive evaluation regarding the risk of GC with PPI use.

This systematic review and meta-analysis evaluated the most up-to-date evidence to assess the association between PPIs and MI and GC by including both clinical trials and observational studies. Subgroup analyses based on the study design and comparator group further help to understand potential associations.

2.0 Methods

2.1 Literature Search

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were used to identify potential studies and report findings.[381] A systematic literature search was conducted in December 2019 and search was updated in November 2020 to retrieve all potential studies using PubMed, PsycInfo, International Pharmaceutical Abstracts (IPA), Web of Science (WOS), and Clinicaltrials.gov. Literature search strategies and methods (i.e., keywords and Medical Subject Headings (MeSH) terms) were guided by a health sciences librarian with considerations of different features among search engines. This systematic search initially identified any published studies describing any AE related to PPI, which was further limited to specific AE, including GC and MI. The complete search strategy is provided in table 1.

2.2 Inclusion and Exclusion Criteria

The identified titles and abstracts were assessed by two reviewers (AM and SMF) independently. Records were included in this study if: a) published in English, b) study design was clinical trials, observational studiesc) PPI use was the exposure of interest, and d) study outcome was the incidence of GC or MI. Abstracts that were duplicates, not written in English, did not have PPI as exposure, and other outcomes were excluded. If the title and abstract provided insufficient information to assess the inclusion criteria, a full-text review was conducted. Records retrieved from the clinicaltrial.gov database were reviewed completely by both reviewers to identify their relevance to this study.

2.3 Data Extraction

Two reviewers (AM and SMF) independently identified studies and extracted study-level data into standardized evidence tables. The information included in the evidence table contained the author's last name, publication year, study design, number of PPI users, number of PPI nonusers, number of individuals affected with MI and/or GC, and their corresponding Odds Ratio (OR)/ Relative Risk (RR)/ Hazard Ratio (HR) with 95% Confidence Interval (CI). Identified articles without a comparison group were not included in the meta-analysis. Qualitative information was extracted on from these articles and presented in the evidence table.

2.4 Quality Assessment

Two different tools were used to assess the quality of the studies since included studies were either clinical trials or different observational studies such as case-control and cohort studies, etc. The Newcastle-Ottawa scale, recommended by the Cochrane Handbook for Systematic Reviews of Interventions, was used for case-control and cohort studies to assess the study quality by two reviewers.[303] Quality of studies was rated as good, fair, and poor judged by three categories: a) selection of the study groups, b) comparability of the groups, and c) ascertainment of the exposure for case-control studies or outcome of interest for cohort studies.[382] Study receiving 3 or 4 stars in selection, 1 or 2 stars in comparability, and 2 or 3 stars in outcomes were considered as good quality. Study receiving 2 stars in selection, 1 or 2 stars in comparability, and 2 or 3 stars in outcomes is considered to have fair quality, whereas 0 or 1 star(s) in selection, or 0 stars in comparability, or 0 or 1 star(s) in outcomes reflects the poor quality of the study. In addition, the "Quality Assessment Tool for Quantitative Studies"

developed by the Effective Public Health Practice Project (EPHPP) was used to critically assess the quality of all identified RCTs.[304] Studies were ranked “strong”, “moderate”, and “weak” after assessing eight different categories of a particular study, including a) Selection bias, b) Study design, c) Confounders, d) Blinding, e) Data collection methods, f) Withdrawals and drop-outs, g) Intervention integrity, and h) Analysis.[304]

2.5 Statistical Analyses

This study used the meta package in RStudio software version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) to conduct meta-analysis. ORs were used as a common measure of association between PPI use and AEs. The ORs, along with a 95% CIs for the association PPI use and AEs, were calculated from all the identified studies for MI and GC regardless of their study design and then categorized by study design types (RCT, observational studies, cohort alone, and case-control alone). Because studies included in the meta-analysis were heterogeneous study samples and settings, we specified all meta-analyses as random-effects instead of fixed-effects models.[383] The heterogeneity of each meta-analysis was tested by using the I^2 statistic.[301] An I^2 value of 0% indicates “no heterogeneity,” whereas 25% is “low,” 50% is “moderate,” and 75% is “high” heterogeneity.[384] Sensitivity analyses were conducted to test the robustness of main findings, limiting to studies with good QA ratings.

3.0 Results

3.1 Systematic search

Through the systematic search, a total of 4,507 abstracts meeting the essential inclusion criteria were identified, and 3,432 abstracts remained after removing

duplicates. After two independent reviewers reviewed the abstracts, 102 articles met the inclusion criteria for full-text review. Further, a total of 67 articles were excluded, resulting in 35 full articles included in our systematic review (Figure 1). These 67 articles were excluded from the full-text review as they did not report MI or GC as PPI related AEs. Among the 34 included studies, 20 studies identified MI, and 15 studies identified GC as PPI related AEs.[34,35,350-356,358,360,385-408] Included studies were further classified based on study design. For MI, 10 studies were identified as cohort, 3 studies as case-control, 3 were RCT post-hoc analysis, and 4 were RCT studies.[34,35,358,360,385-400] Among these 20 identified studies for MI, PPI users and PPI non users in 7 cohort studies and 3 RCTs received clopidogrel treatment.[385,386,390,394-400]

For GC, there were 3 cohort, 2 case-control, 8 RCT, and 2 clinical trial studies.[350-356,401-408] However, 5 out of the 8 RCTs had same intervention PPI as a comparator group with a different dose, and 2 clinical trials did not have any comparator drugs or placebo.[401,403-408] Due to the unavailability of sufficient quantitative information, these 5 RCTs, and 2 clinical trials were excluded from the meta-analysis of PPI use and GC.[401,403-408] Among these 7 studies, rabeprazole was the drug of interest in 3 studies, lansoprazole was the drug of interest in 2 studies, and esomeprazole was the drug of interest in 2 studies.[401,403-408] All of these studies showed at least one GC event among the study participants with the maximum number of events (n=4) identified for the use of rabeprazole and lansoprazole.[59,61] Finally, 20 studies for PPI related MI[34,35,358,360,385-393] and 8 studies for PPI related GC[350-356,402] were included in the meta-analysis. Table 2 details the characteristics of each identified study included in the meta-analysis.

3.2 Quality Assessment (QA)

For the 13 observational studies with MI outcomes, 7 cohort studies had good quality, whereas 2 case-control and 2 cohort studies had fair quality, and the remaining 1 case-control and 1 cohort study had poor quality. For the 4 RCTs with MI outcomes, 1 had strong quality, 2 had moderate quality, and the other 1 were weak in quality and all the 3 RCT post-hoc design studies were fair in quality (Table 3).

QA on studies identifying the risk of GC with PPI use showed that 1 case-control study had fair quality, whereas the remaining 1 case-control and 3 cohort studies had good quality. All 3 RCTs with GC had moderate quality (Table 3).

3.3 PPI use and risk of MI

At first, all of the studies, regardless of study design, were included in the meta-analysis. Among these 20 studies, Rodriguez et al., 2014, Landi et al., 2018, and Goodman et al., 2012 each reported PPI related MI in 2 different cohorts, totaling 6 different cohorts for these 3 studies. Therefore, the number of PPI users and nonusers for different cohorts under the same study were merged to represent the total sample for the study. The pooled results (OR 1.40; 95% CI: 1.20-1.63) for all 20 identified studies indicated the presence of an association between PPI use and increased risk of MI (Figure 2). Meta-analysis was further conducted based on study design and found the association between PPI use and increased risk of MI in observational studies (OR 1.40; 95% CI 1.20, 1.64) (Figure 3), but no association (OR=0.90; 95% CI=0.47, 1.73) in RCT studies (Figure 4). Furthermore, meta-analysis on specific observational study designs found an association between PPI use and risk of MI in cohort studies (OR

1.35; 95% CI 1.13, 1.60), and RCT post hoc analysis (OR 1.35; 95% CI 1.12, 1.62) but not in and case-control studies (OR 1.52; 95% CI 0.77, 2.99) (Figure 5). Heterogeneity was examined in all quantitative analysis for PPI use and MI. Heterogeneity was high (I^2 > 75%) for all analyses except for RCTs (I^2=0%) and RCT post hoc analysis (I^2=20%), which indicates a high variation in MI outcomes between the identified studies. Due to the high variation of heterogeneity, pooled estimates should be interpreted cautiously.

Meta-analysis limiting to the PPI users and PPI nonusers who received clopidogrel treatment (7 cohort studies and 1 RCT, 2 RCT post-hoc) found an association between PPI use and risk of MI (OR 1.50; 95% CI 1.21, 1.86; Figure 6). Further analysis based on study design found no association between PPI use and increased risk of MI in RCT post hoc analysis (OR 1.39; 95% CI: 0.92, 2.10; Figure 7) who used clopidogrel. However, meta-analysis found an association between PPI use and risk of MI among clopidogrel users in cohort studies (OR 1.59; 95% CI 1.22, 2.07; Figure 8). Heterogeneity was moderate in the analysis of all studies, cohort studies, and RCT post-hoc studies where patients received clopidogrel treatment.

Similar analyses were conducted between PPI users and PPI nonusers who did not receive clopidogrel treatment. Meta-analysis found an increased risk of MI with PPI use (OR 1.24; 95% CI 1.05, 1.47; Figure 9) when considering all studies. Furthermore, subgroup analyses of cohort studies found no association between PPI use and MI (OR 1.15; 95% 0.97 1.37 Figure 10)

3.4 PPI use and risk of GC

Among the 5 observational studies, Tamim et al., 2008, and Rodriguez et al., 2006 each reported PPI related GC in 2 different cohorts, totaling 4 different cohorts for

these 4 studies. In both Tamim et al., 2008, and Rodriguez et al., 2006 PPI users were compared with PPI nonusers and users of H2 Blockers. Therefore, these 2 studies contributed 2 samples to the meta-analysis for all studies. The pooled statistic (OR 1.90; 95% CI 1.48, 2.45) for all the 8 studies indicated the presence of an association between PPI use and increased risk of GC (Figure 11) with high heterogeneity (I^2 = 75%). Meta-analysis was further conducted based on study design and found no association between PPI use and risk of GC limiting to RCTs (OR 3.09; 95% CI 0.57, 16.73; Figure 12). The pooled results (OR 1.88; 95% CI 1.45, 2.45) for all observational studies indicated the association between PPI use and increased risk of GC (Figure 13), although heterogeneity was high (I^2=83%). Similar findings were observed when limiting to cohort studies (OR 2.90; 95% CI 1.89, 4.46) (moderate heterogeneity (I^2=63%), Figure 14) and case-control studies (OR 1.48; 95% CI 1.20, 1.83) (moderate heterogeneity (I^2=71%), Figure 14).

Meta-analyses were further conducted based on the comparator groups regardless of study design. For all studies, the pooled statistic (OR 1.90; 95% CI 1.15, 3.13) with high heterogeneity (I^2=90%) indicated an association between PPI use and increased risk of GC when the comparator group was H2 blocker (Figure 15). The pooled results (OR 1.86; 95% CI 1.52, 2.28) with low heterogeneity (I^2=21%) indicated an association between PPI use and risk of GC among PPI users when compared with the nonusers of acid suppressant drugs (Figure 16). Furthermore, when limited to observational studies with non-users of any acid suppressant drugs as a comparator group, a positive association (OR 1.90; 95% CI 1.47, 2.45) was observed between PPI use and GC with moderate heterogeneity (I^2=59%) (Figure 17).

3.5 Publication bias.

The number of studies included in our meta-analysis was low (< 10) for specific study design except for cohort study design exploring MI among PPI users. Hence, it was feasible to use the tests for funnel plot asymmetry for cohort study design exploring MI among PPI users.[409] For cohort studies exploring the risk of MI among PPI users, ORs of reported articles were not distributed symmetrically (Figure 18) around the pooled effect size, indicating the presence of publication bias. Although the total number of studies, including different study designs, was more than 10 for each AE, the interpretation regarding the publication bias may not be valid since clinical trials are inherently different compared with observational studies. Because of this constraint, valid interpretation regarding the potential for publication bias cannot be derived through funnel plot asymmetry test.[410]

4. Sensitivity Analysis

Sensitivity analyses were further conducted based on study quality for each AE. Observational studies with good quality ratings found an association between PPI use and risk of MI (OR 1.43; 95% CI 1.12, 1.83; I^2=90%) (Figure 19). A similar sensitivity analysis was also conducted on studies exploring the risk of GC. Observational studies with good quality ratings found an association on the risk of GC (OR 2.23; 95% CI 1.54, 3.25) with PPI use (Figure 20).

5.0 Discussion

This systematic review and meta-analysis examined the most up-to-date evidence and assessed the risk of MI and GC with PPI use, including both observational

studies and RCT studies. Findings will strengthen the current body of evidence regarding the risk of PPI use.

5.1 PPI use and MI

Meta-analysis results from all included studies showed that the use of PPI was associated with an increased risk of MI; however, the results from RTCs only found no association between PPI use and risk of MI. Mixed results were similar with subgroup analysis limiting to studies including patients receiving clopidogrel treatment.

However, heterogeneity from these meta-analyses was high, especially among observational studies, indicating substantial within-study sampling and measurement variability across included studies.[411] Although findings from observational studies indicate an association between PPI use and MI, the summary estimates and measures of such an association from the majority of the studies were weak in nature. Grimes and Schulz suggested that findings from observational studies should be interpreted cautiously unless ORs for case-control studies exceed 3 to 4 and RRs exceed 2 to 3 for cohort studies.[412] All of our meta-analysis findings in PPI use and risk of MI fell within this range of potential bias.

A novel mechanism of PPI use and increased risk of MI follows the hypothesis that PPI use increases levels of asymmetrical dimethylarginine (ADMA) by inhibiting dimethylarginine dimethylaminohydrolase (DDAH), causing the blockade of vascular nitric oxide synthase activity, and enhanced contractility with loss of normal relaxation.[226,227] Several studies support this hypothesis of PPI use and this MI mechanism.[228,229] For example, Ghebremariam et al., found that cellular ADMA levels increased with the use of PPI in animal and ex vivo human models.[228] In another study,

baseline ADMA levels predicted cardiovascular death among patients with coronary diseases.[229] Similarly, ADMA concentrations were associated with increased risk of cardiovascular death among patients who were free from cardiovascular disease at baseline.[230] These studies indicated a theoretical plausibility of PPI induced CV, but this mechanism has not been validated in human coronary diseases.

While observational studies showed statistical significance in PPI use and the risk of MI, meta-analysis results of RCTs disagreed. Findings from our meta-analysis limiting to RCT studies are similar to the previous meta-analysis examining the correlation between elevated CV risk and simultaneous clopidogrel and PPI therapy, which did not observe the increased risk of CV risk among patients on clopidogrel treatment between PPI users and nonusers in RCTs.[413] One reason for increased MI risk based on the majority of observational studies could be attributed to protopathic bias.[357] Protopathic bias arises when the initiation of a drug occurs in response to a symptom of the undiagnosed disease.[357] In observational studies of PPI use and risk of MI, protopathic bias is a concern since early MI symptoms such as chest pain and heartburn could be misdiagnosed as GERD.[36] This misdiagnosis can initiate the use of PPIs which can be misclassified as a risk factor of MI later. In our meta-analysis, all the observational studies except Qian et al.,[358] were prone to protopathic bias. In a sensitivity analysis, Qian et al., excluded PPI exposure in the short period before the diagnosis of MI by shifting the index date of MI by 30 days and 60 days. After minimizing the effect of protopathic bias, the risk of MI among current PPI users was close to null, whereas MI risk was elevated among H2 blocker users.[358] Another reason to explain the elevated risk of MI among observational studies could be unmeasured or

under-measured baseline comorbidities or risk factors.[359] Observational studies using retrospective administrative claims data lack information on known MI risk factors such as smoking, alcohol use, lipid levels, body mass index, diet, exercise, and food habits.[33,360,361] These unmeasured confounders could elevate MI risk in individual studies, which could be reflected in our meta-analysis results.

5.2 PPI Use and GC

Our meta-analysis results of 8 studies[222,350-356,402] (5 observational studies and 3 RCTs) showed that the use of PPIs might increase the risk of GC by 80% compared with PPI non-users. Similarly, the pooled result showed no association between PPI use and GC when limiting to RCTs, and the increased risk of GC with PPI users mainly came from observational studies. Furthermore, we observed an association between PPI use and increased risk of GC when comparing to H2 blocker users.

Our finding is in agreement with a previous meta-analysis.[222] Tran-duy et al., also found an increased risk of GC with the use of PPIs,[222] including 3 observational studies, which were also included in our analysis.[350,353,402] Our study expanded the scope to include both observational and RCT studies and further conducted subgroup analysis based on study design and comparator group, which provided a more comprehensive evaluation on the risk of GC.

PPI induced hypergastrinemia due to the reduced secretion of gastric acid has been considered as the most plausible hypothesis regarding PPI use and the development of GC.[414] Long-term PPI and other antacids use inhibits the gastrin release on antral G-cells gastric hypochlorhydria leading to hypergastrinemia and hyperplasia of gastric mucosa.[415] Although this hypothesis theoretically establishes the

relationship between PPI use and GC, Parsons et al., showed that use of PPIs does not significantly contribute to the development of GC.[416]

Although our findings, including observational studies, indicated an increased risk of GC with PPI use, results from RCT studies showed no significance. This disagreement between observational studies and RCTs could be explained in the view of protopathic bias.[357] Early symptoms of stomach cancer are similar to peptic ulcer, GERD, or other gastrointestinal diseases.[357] These early symptoms could lead to the use of PPIs, which later could be considered as risk factors for GC. In this meta-analysis, no studies except Rodriguez et al., controlled for peptic ulcer diseases to reduce the potential bias.[353] Similarly, other potential confounders such as diet, genetic predisposition, and family history were not controlled in any of the included studies. Another major confounder is the history of H pylori eradication since H pylori infection is associated with both GC and PPI use.[222] Among the 5 included observational studies, only Poulsen et al., adjusted for the status of H pylori infection.[402]

6. Limitations:

This study has some limitations. First, we may have missed articles that could be relevant, including in the gray literature, although our systematic review and meta-analysis included published studies extracted from 5 individual search engines. Second, heterogeneity was high for all analyses of observational studies for meta-analysis of PPI use with the risk of MI and GC. Although we specified all meta-analyses as random-effects instead of fixed-effects models, the unexplained heterogeneity may limit our meta-analytic results. Third, since the numbers of studies were small when limiting to individual study design, we were not able to conduct the test for forest plot asymmetry

for publication bias. Therefore, results yielded from this meta-analysis may be biased by the characteristics of the studies we analyzed and further affect the generalizability of findings. Finally, for PPI use and GC, the status of H pylori infection was only partially controlled for in 1 study, and we could not distinguish between an isolated PPI effect and a synergistic PPI–H pylori effect.

7. Conclusions:

Although our meta-analysis identified the associations between PPI use and increased risk of MI and GC, results from RCTs did not agree with observational studies. Since PPIs are used widely among the general population to treat various gastrointestinal disorders, well-designed RCTs and observational studies are needed to assess any potential causal link between PPI use and risk of MI and GC. Due to the mixed findings by study designs and high variation of heterogeneity among included studies, the post-marketing pharmacovigilance system should evaluate different levels of evidence to support decision making in the safety of drug products, but this study does not provide sufficient evidence to alter current prescribing patterns.

Figure 1: PRISMA flow diagram

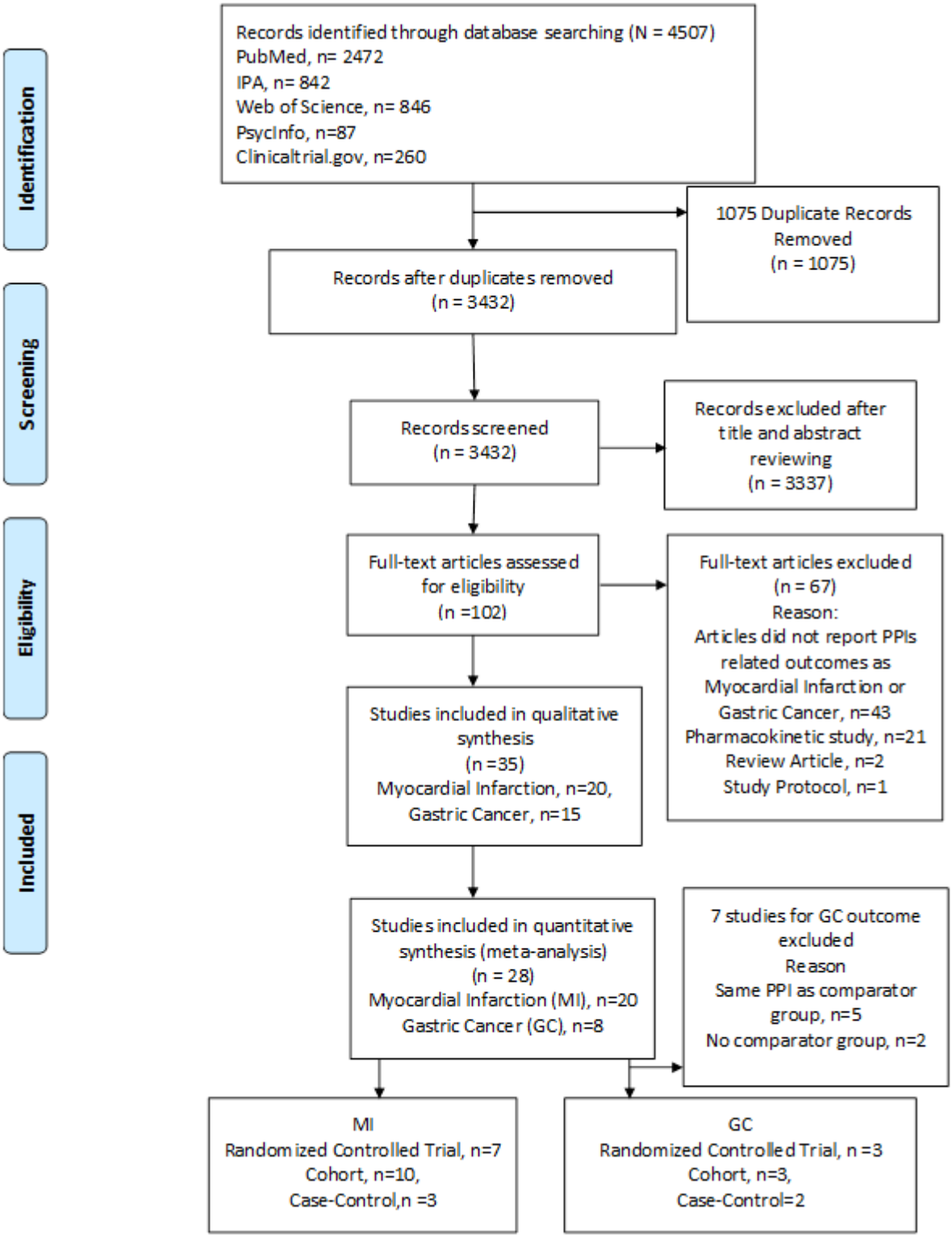


Table 1: Search strategy in different search engines

Search Engines	Search Term	
Pubmed	Drug	((("Proton Pump Inhibitors"[Pharmacological Action] OR "Proton Pump Inhibitors"[Mesh] OR "Proton Pumps/antagonists and inhibitors"[Mesh] OR "Proton-Translocating ATPases"[Mesh] OR (proton[tiab] AND pump[tiab] AND inhibit*[tiab]))))
	Adverse event	((((Adverse[tiab] OR Negative[tiab]) AND (event*[tiab] OR effects*[tiab] OR reaction*[tiab])) OR (side[tiab] AND effect*[tiab]) OR complication*[tiab] OR harm*[tiab] OR Risk*[tiab]))
Psycinfo	Drug	(Proton Pump Inhibitors OR Proton-Translocating ATPases OR (proton AND pump AND inhibit*))
	Adverse event	(((Adverse OR Negative) AND (event* OR effects* OR reaction*)) OR (side AND effect*) OR complication* OR harm* OR Risk*)
IPA	Drug	(Proton Pump Inhibitors OR Proton-Translocating ATPases OR (proton AND pump AND inhibit*))
	Adverse event	(((Adverse OR Negative) AND (event* OR effects* OR reaction*)) OR (side AND effect*) OR complication* OR harm* OR Risk*)
Web of Science	Drug	TI= (Proton Pump Inhibitors OR Proton-Translocating ATPases OR (proton AND pump AND inhibit*))
	Adverse event	TI= (((Adverse OR Negative) AND (event* OR effects* OR reaction*)) OR (side AND effect*) OR complication* OR harm* OR Risk*)
Clinicaltrials.gov	Drug	Proton Pump Inhibitors

Table 2: Study Characteristics

Study	Adverse Event	Study Design	Age (Mean/Range)	PPI User	Adverse events in PPI User	PPI Nonuser	Adverse events in PPI Nonuser	Summary Result
Rassen et al 2009	MI	Cohort	Aged ≥ 65	3996	238	14569	751	Slight increase of MI among older patiets.
Van Boxel et al 2010	MI	Cohort	Aged 18 years or older	5734	84	12405	78	Increased risk of MI among PPI users who received clopidogrel treatment
Hudzik et al 2010	MI	Cohort	Mean Age Omepranole user- 62.8 ± 9.4, Omepranole nonuser-	18	6	20	1	The incidence of myocardial infarction was higher in group Omeprazole users
Bhatt et al 2010	MI	RCT	Aged 21 years of age or older	1876	14	1885	15	No significant association between PPI use and MI compafred to placebo
Burkard et al 2011	MI	RCT (Post-Hoc)	Mean Age PPI user: 66.5±10.5, PPI Non user: 63.3±11.3	109	25	692	94	PPI use identified as an independent risk factor of MI
Hsu et al 2011 2011	MI	RCT	Mean Age Esomerazole user: 70.6±11.5 Esomerazole nonuser: 73.3±10.7	83	2	82	2	Both PPI users and non users had same number (2) of MI event.
Valkhoff et al 2011	MI	Case Control	Mean Age PPI user: 68.1, PPI Non user: 66.3	44423	458	110768	766	Current PPI use was associated with an increased risk of recurrent

Study	Adverse Event	Study Design	Age (Mean/Range)	PPI User	Adverse events in PPI User	PPI Nonuser	Adverse events in PPI Nonuser	Summary Result
								MI compared with no PPI use
Chitose et al 2012	MI	Cohort	Mean Age PPI user: 70.3±11.0, PPI Non user: 68.9±10.9	331	3	939	1	No significant differences in nonfatal myocardial infarction (3 vs. 5) between PPI and non-PPI groups
Goodman et al 2012	MI	RCT (Post-Hoc)	Mean Age PPI user: 54 to 71 PPI Non user: 54-70	6539	456	12062	646	No significant association between PPI use (also treated with clopidogrel/ticagerol) and MI.
Sugano et al 2013	MI	RCT	Aged ≥20 years	214.5	0	213	2	PPI users did not have any MI.
Juurlink et al 2013	MI	Case Control	Aged ≥66 years	5550	2595	5550	1439	Initiation of a PPI was associated with a higher risk of acute myocardial infarction
Rodriguez et al 2014	MI	Cohort	Aged ≥60 years	2795	583	7048	1243	PPI use was not associated with increased risk of non-fatal MI.
Zou et al 2014	MI	Cohort	Mean Age PPI user: 66.2±10.2 PPI Non user: 65.7± 10.6	6188	132	1465	15	PPI use might be associated with an increased risk for developing major adverse cardiovascular events such as MI

Study	Adverse Event	Study Design	Age (Mean/Range)	PPI User	Adverse events in PPI User	PPI Nonuser	Adverse events in PPI Nonuser	Summary Result
Shih et al 2014	MI	Cohort	Mean Age PPI user: 49.3 PPI Non user: 49.3	5430	114	5430	78	PPI use was associated with an increased risk of MI
NCT00251927	MI	RCT	Aged 18 Years to 70 Years	266.5	5.5	40.5	0.5	PPI non users had no MI, 5 users of PPI had MI.
Weisz et al 2015	MI	Cohort	Mean Age PPI user: 64.4±10.5 PPI Non user: 63.2±11.0	2162	100	6419	235	PPI use was independently associated with increased risk for postdischarge major adverse cardiac events such as cardiac death, myocardial infarction.
Gargiulo et al 2016	MI	RCT (Post-Hoc)	PPI user: Aged 63.2 to77.3 PPI Non user: Aged 59.0 to75.4	738	32	1232	48	No difference in adverse event btween PPI user and Ppi not user.
Sehested et al 2017	MI	Cohort	Aged 30 to 100	116986	267	96720	175	High-dose PPI was associated with increased rates of ischemic MI
Landi et al 2018	MI	Cohort	18 years or older	4569941	36714	1022048	8513	No evidence of increse in MI risk for PPI users.
Qian et al 2019	MI	Case Control	Mean Age: 55	66125	13130	238	19663	No evidence of increse in MI risk for PPI users.
Rodriguez et al 2006	GC	Case-control	40-84 years old	613	58	11052	594	Long term use of PPI use has relation with incresed risk of GC
Tamim et al 2008	GC	Case-control	>65 years of age	1402	248	10500	1176	Minor increase in the risk of GC among PPI users
Poulsen et al	GC	Cohort	40 years or above	15065	109	16176	52	Increased incidence of

Study	Adverse Event	Study Design	Age (Mean/Range)	PPI User	Adverse events in PPI User	PPI Nonuser	Adverse events in PPI Nonuser	Summary Result
2009								gastric cancer associated with PPI use was observed
Cheung et al 2017	GC	Cohort	18 years or above	3271	19	60126	134	Long term PPI used is associated with increased risk of GC
Brusselaers et al 2017	GC	Cohort	18 years or above	797067	2219	20210	12	Long term PPI use identified as an independent risk factor of GC
NCT00542789	GC	RCT	20 Years and older	173	1	168	1	Similar GC as adverse event between 2 groups
NCT00787254	GC	RCT	20 Years and older	183	3	181	0	GC event in control group.
NCT00401752	GC	RCT	18 Years to 70 Years	107	2	110	0	GC event in control group.

*MI=Myocardial Infarction
*GC=Gastric Cancer
*RCT=Randomized controlled trial

Table 3: Quality assessment of studies included in systematic review and meta-analysis

Study	AE	Study Design	Scale/Tool	Rating	Quality
Rassen et al 2009	MI	Cohort	NEWCASTLE - OTTAWA	8 star	Good
Boxel et al 2010	MI	Cohort	NEWCASTLE - OTTAWA	7 star	Good
Hudzik et al 2010	MI	Cohort	NEWCASTLE - OTTAWA	6 star	Fair
Bhatt et al 2010	MI	RCT	EPHPP	Strong	Strong
Valkhoff et al 2011	MI	Case Control	NEWCASTLE - OTTAWA	6 star	Fair
Hsu et al 2011	MI	RCT	EPHPP	Moderate	Moderate
Burkard et al 2011	MI	RCT (Post-Hoc)	NEWCASTLE - OTTAWA	5 star	Fair
Goodman et al 2012	MI	RCT (Post-Hoc)	NEWCASTLE - OTTAWA	5 star	Fair
Chitose et al 2012	MI	Cohort	NEWCASTLE - OTTAWA	7 star	Good
Juurlink et al 2013	MI	Case Control	NEWCASTLE - OTTAWA	3 star	Poor
Sugano et al 2013	MI	RCT	EPHPP	Moderate	Moderate
Rodriguez et al 2014	MI	Cohort	NEWCASTLE - OTTAWA	4 star	Poor
Shih et al 2014	MI	Cohort	NEWCASTLE - OTTAWA	8 star	Good
Study	**AE**	**Study Design**	**Scale/Tool**	**Rating**	**Quality**
Zou et al 2014	MI	Cohort	NEWCASTLE - OTTAWA	8 star	Good
Weisz et al 2015	MI	Cohort	NEWCASTLE - OTTAWA	6 star	Fair

Gargiulo et al 2016	MI	RCT (Post-Hoc)	NEWCASTLE - OTTAWA	5 star	Fair
Sehested et al 2017	MI	Cohort	NEWCASTLE - OTTAWA	9 star	Good
Landi et al 2018	MI	Cohort	NEWCASTLE - OTTAWA	9 star	Good
Qian et al 2019	MI	Case Control	NEWCASTLE - OTTAWA	6 star	Fair
NCT00251927	MI	RCT	EPHPP	Weak	Weak
Rodriguez et al 2006	GC	Case-control	NEWCASTLE - OTTAWA	8 star	Good
Tamim et al 2008	GC	Case-control	NEWCASTLE - OTTAWA	5 star	Fair
Poulsen et al 2009	GC	Cohort	NEWCASTLE - OTTAWA	8 star	Good
Cheung et al 2017	GC	Cohort	NEWCASTLE - OTTAWA	7 star	Good
Brusselaers et al 2017	GC	Cohort	NEWCASTLE - OTTAWA	7 star	Good
NCT00787254	GC	RCT	EPHPP	Moderate	Moderate
NCT00401752	GC	RCT	EPHPP	Moderate	Moderate
NCT00542789	GC	RCT	EPHPP	Moderate	Moderate

EPHPP= Effective Public Health Practice Project; AE=Adverse Event; MI=Myocardial Infarction; GC=Gastric Cancer
Table 2: Quality Assessment of the included studies in the meta-analysis

Figure 2: Forest plots of odds ratios for Myocardial Infarction in patients receiving proton pump Inhibitors with all studies included

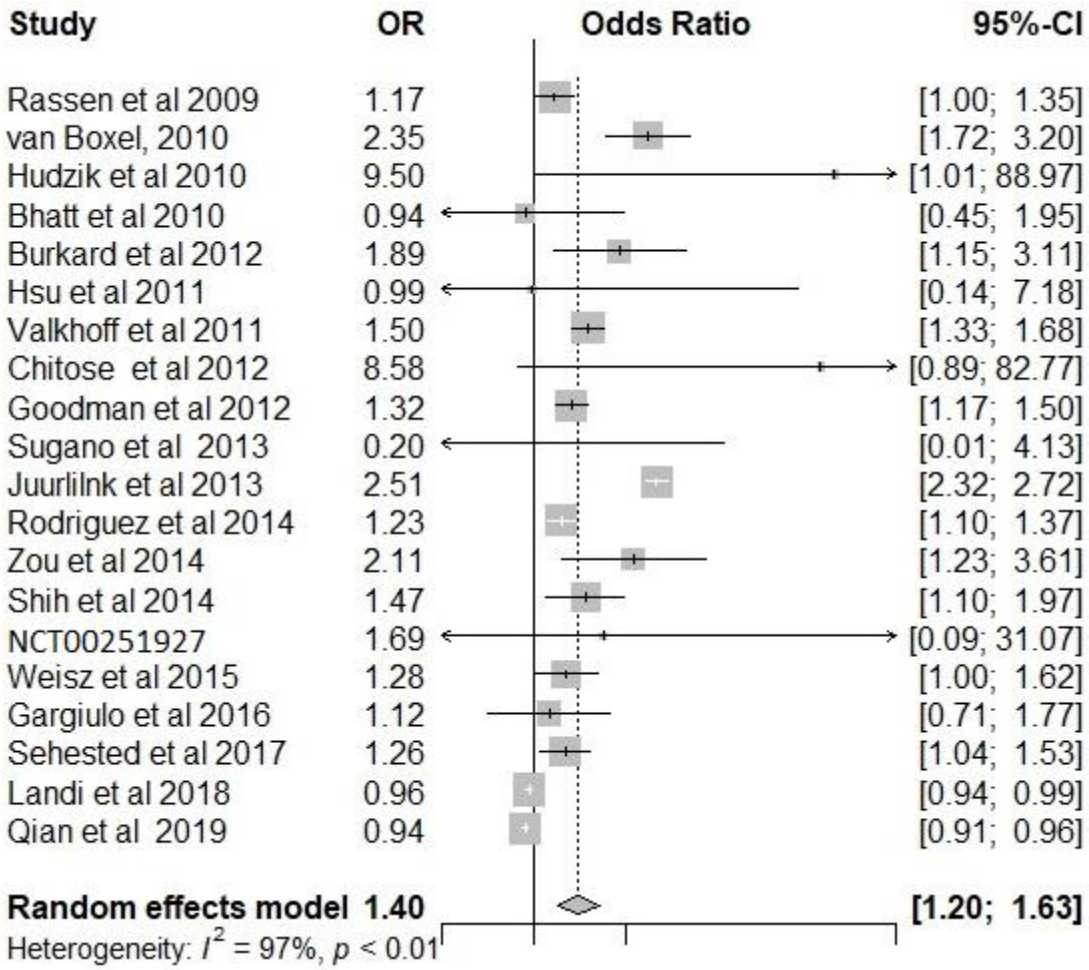


Figure 3: Forest plots of odds ratios for Myocardial Infarction in patients receiving proton pump Inhibitors among observational Studies

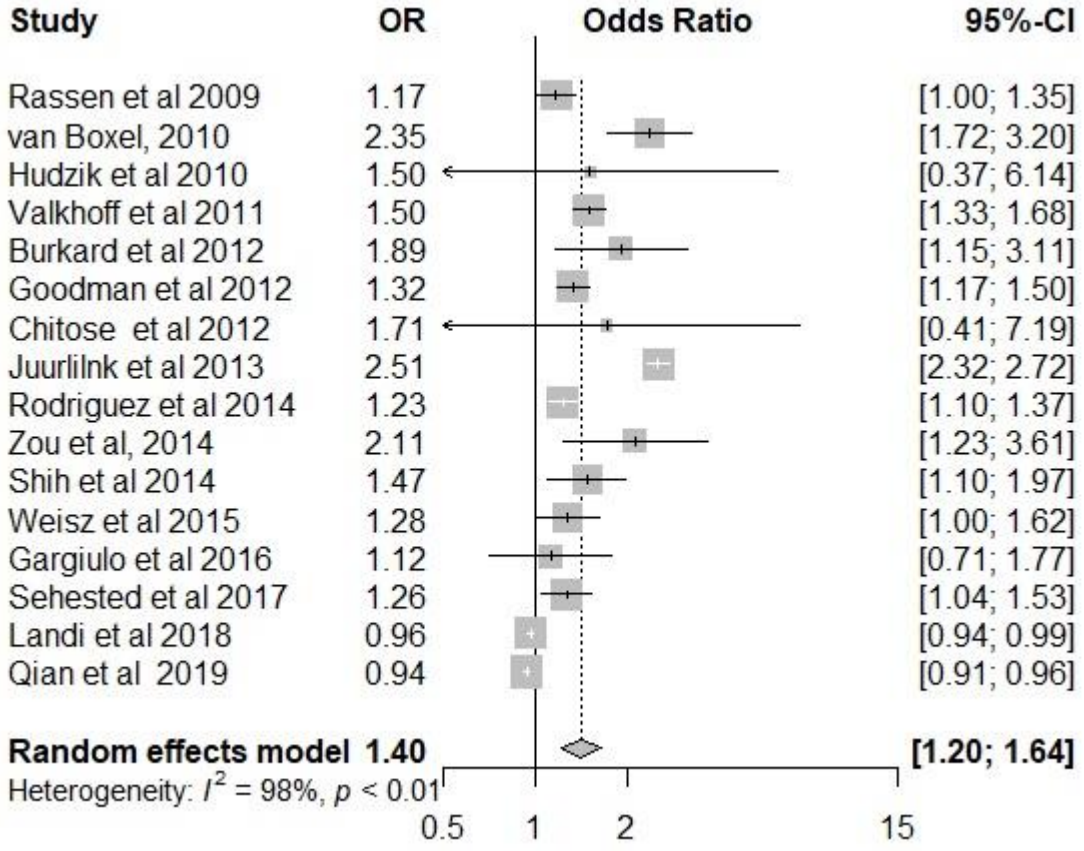


Figure 4: Forest plots of odds ratios for Myocardial Infarction in patients receiving proton pump Inhibitors among studies with a RCT design

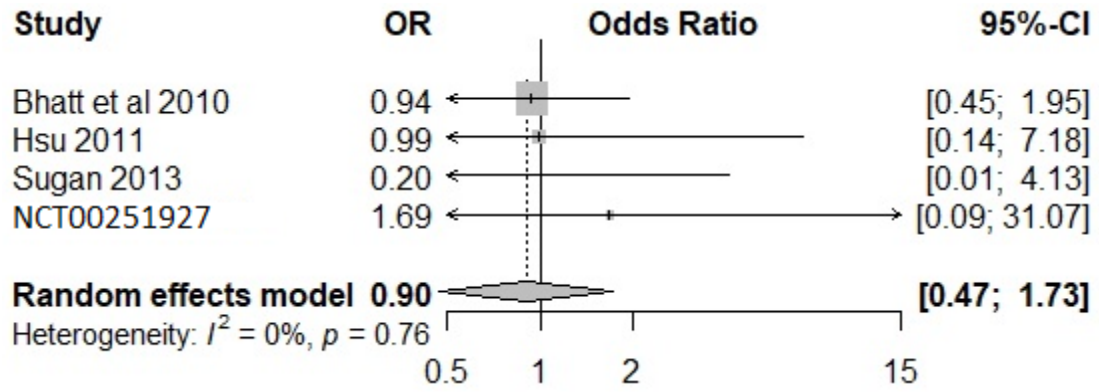
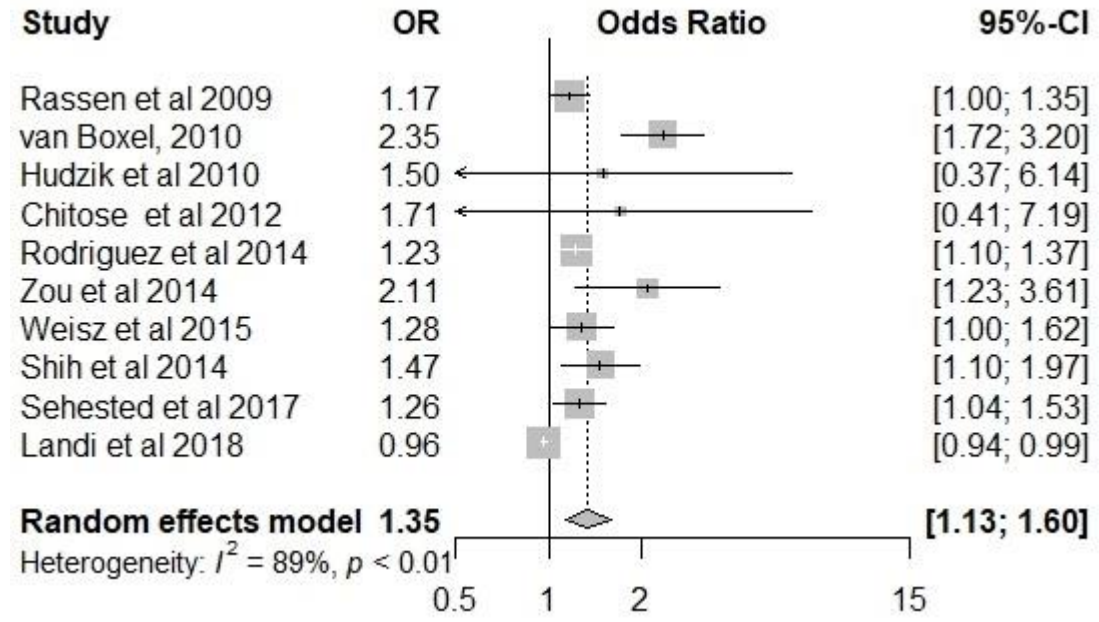
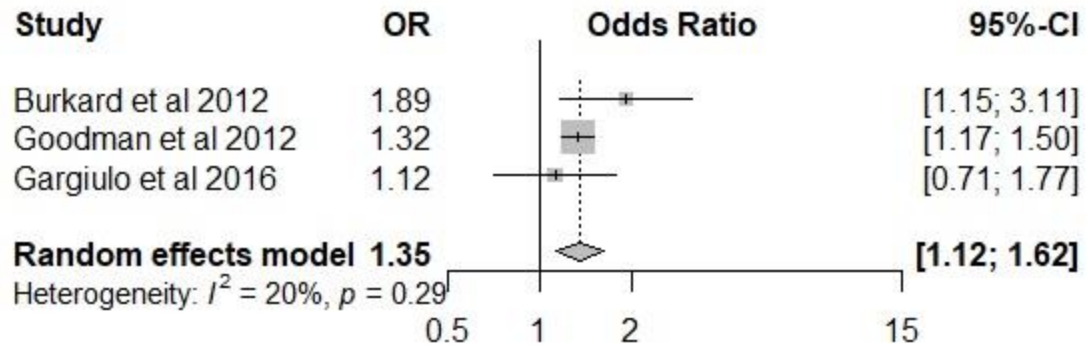


Figure 5: Forest plots of odds ratios for Myocardial Infarction in patients receiving proton pump Inhibitors (Cohort Studies (A), RCT-Posthoc analysis (B) and case-control studies (C))

A)



B)



C)

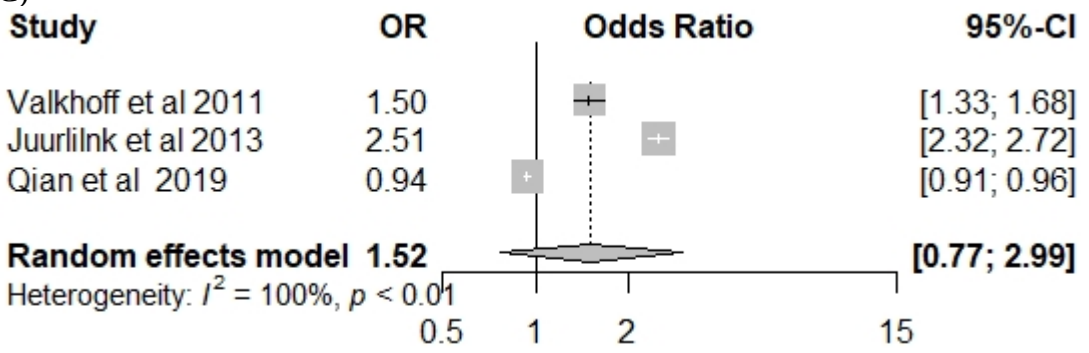


Figure 6: Forest plots of odds ratios for Myocardial Infarction in patients receiving proton pump Inhibitors with all studies included (Clopidogrel users)

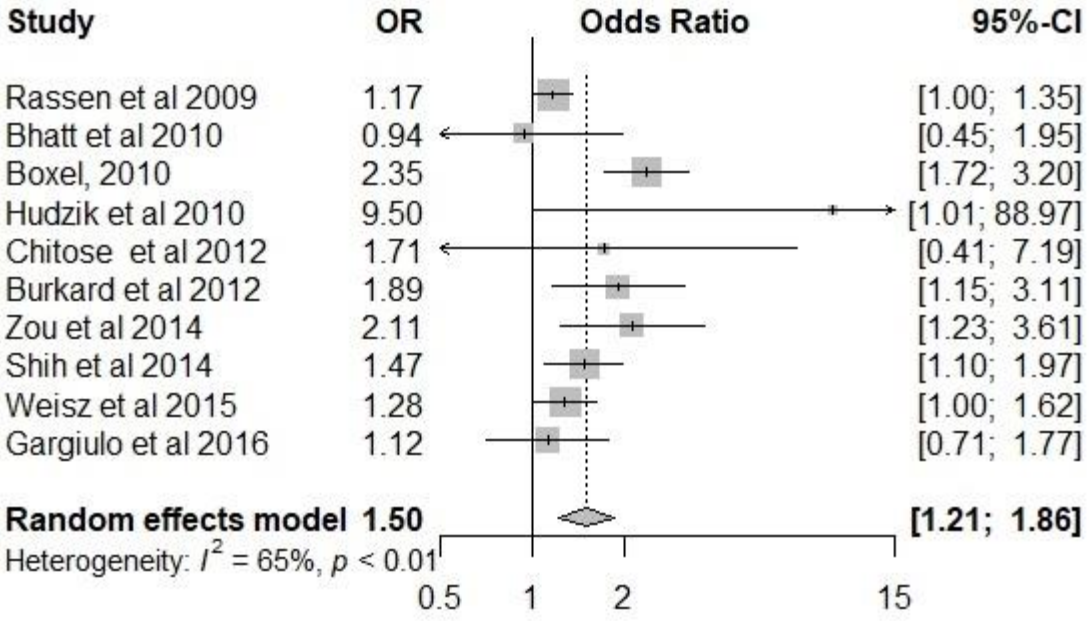


Figure 7: Forest plots of odds ratios for Myocardial Infarction in patients receiving proton pump Inhibitors among studies with RCT posthoc analysis design (Clopidogrel users)

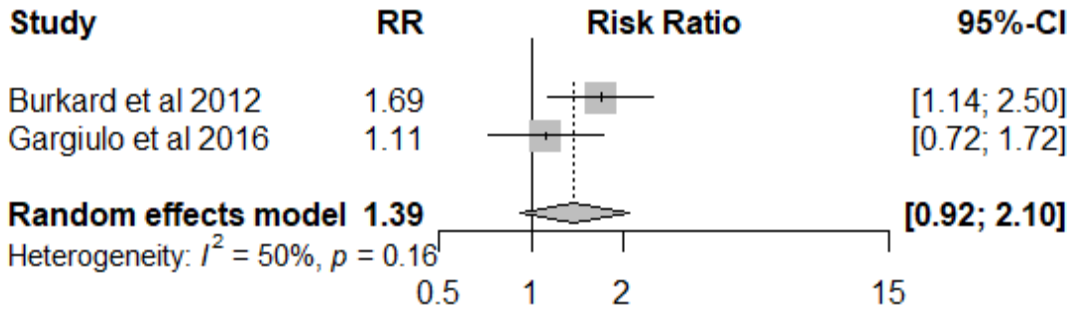


Figure 8: Forest plots of odds ratios for Myocardial Infarction in patients receiving proton pump Inhibitors among studies with cohort design (Clopidogrel users)

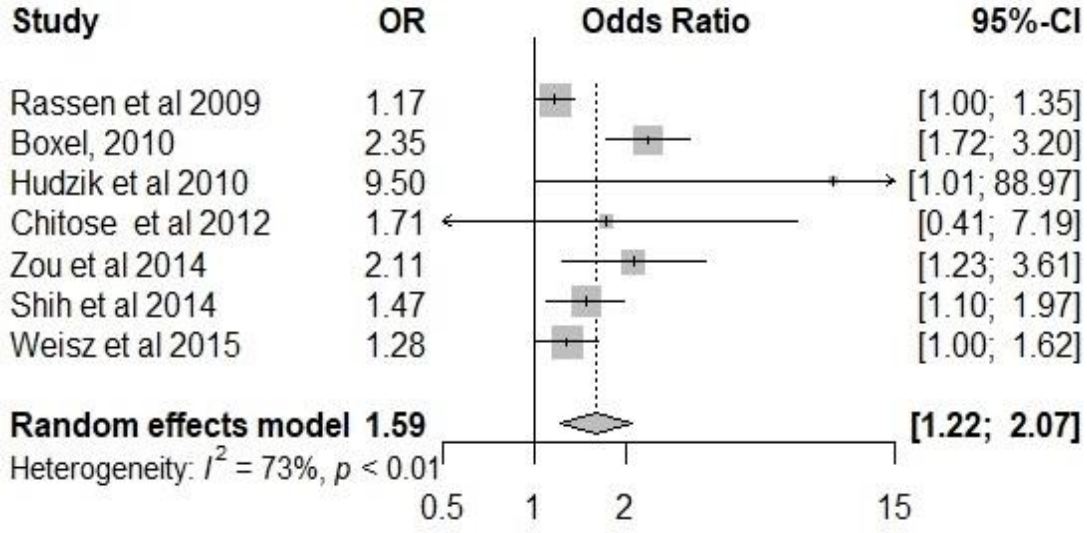


Figure 9: Forest plots of odds ratios for Myocardial Infarction in patients receiving proton pump Inhibitors with all studies included (Did not receive clopidogrel)

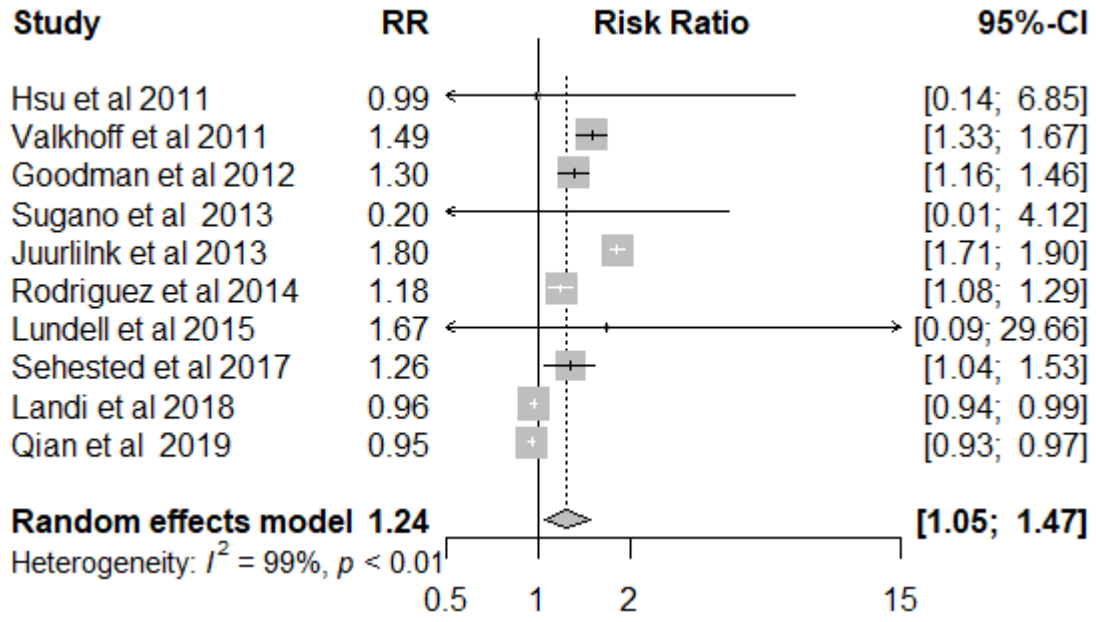


Figure 10: Forest plots of odds ratios for Myocardial Infarction in patients receiving proton pump Inhibitors among studies with cohort design (Did not receive clopidogrel)

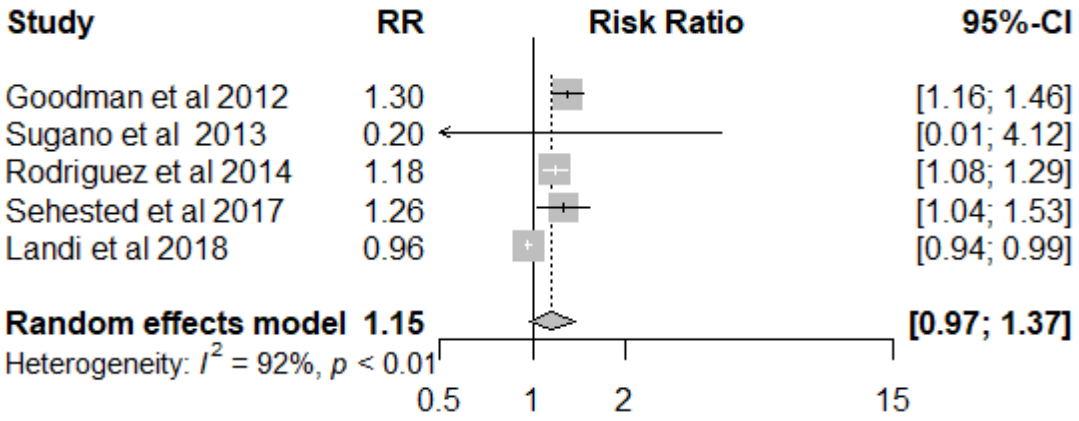


Figure 11: Forest plots of odds ratios for Gastric Cancer in patients receiving proton pump Inhibitors with all studies included

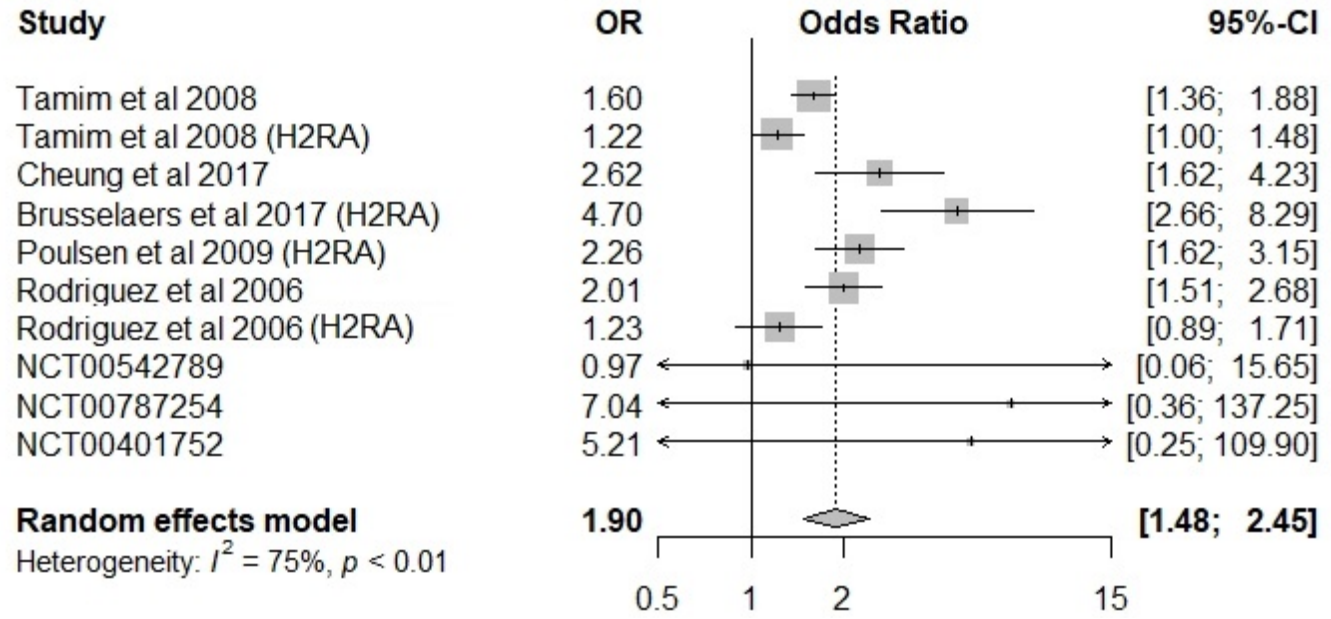


Figure 12: Forest plots of odds ratios for Gastric Cancer in patients receiving proton pump Inhibitors among studies with a RCT design

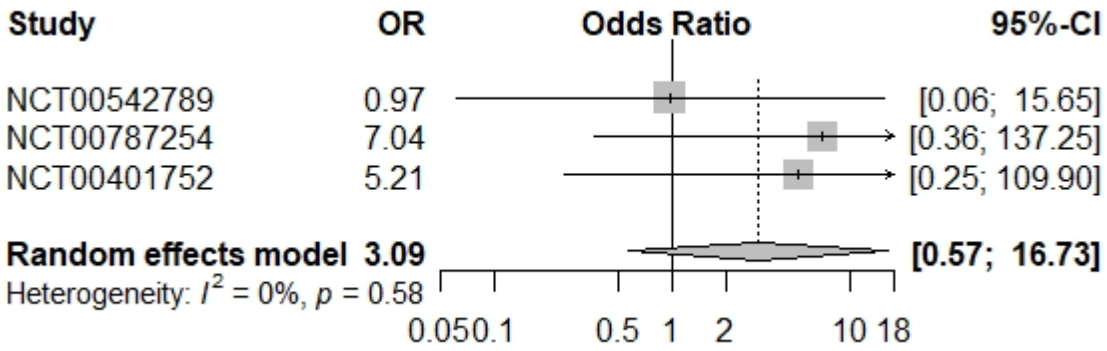


Figure 13: Forest plots of odds ratios for Gastric Cancer in patients receiving proton pump Inhibitors among observational Studies

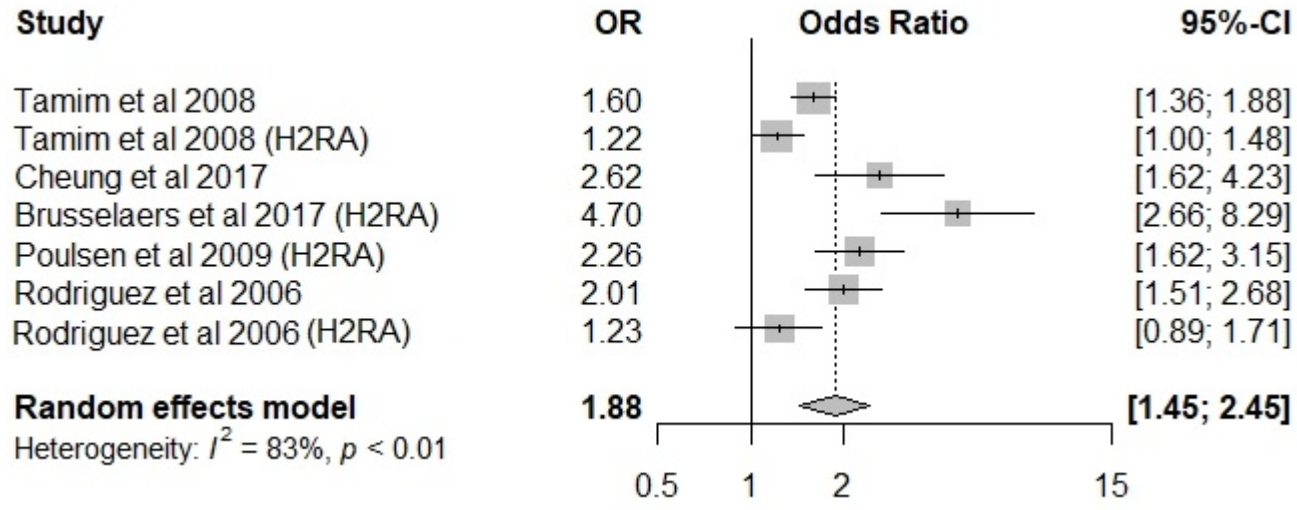
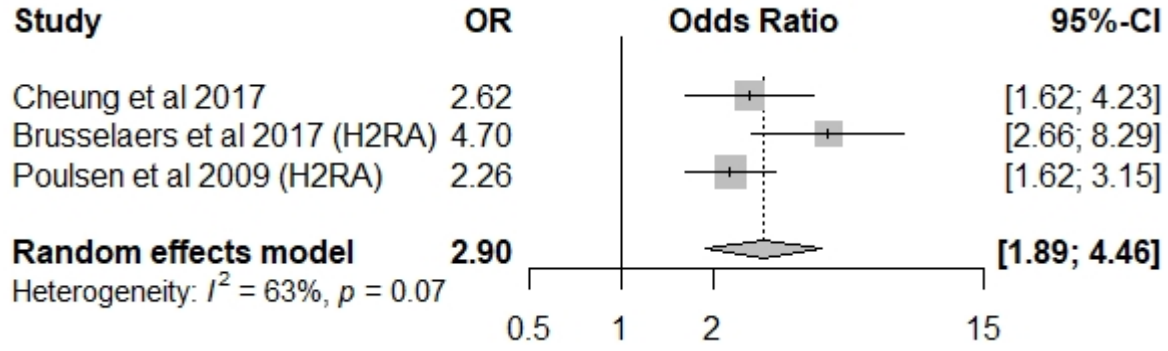


Figure 14: Forest plots of odds ratios for Myocardial Infarction in patients receiving proton pump Inhibitors (Cohort Studies (A) and case-control studies (B))

A)



B)

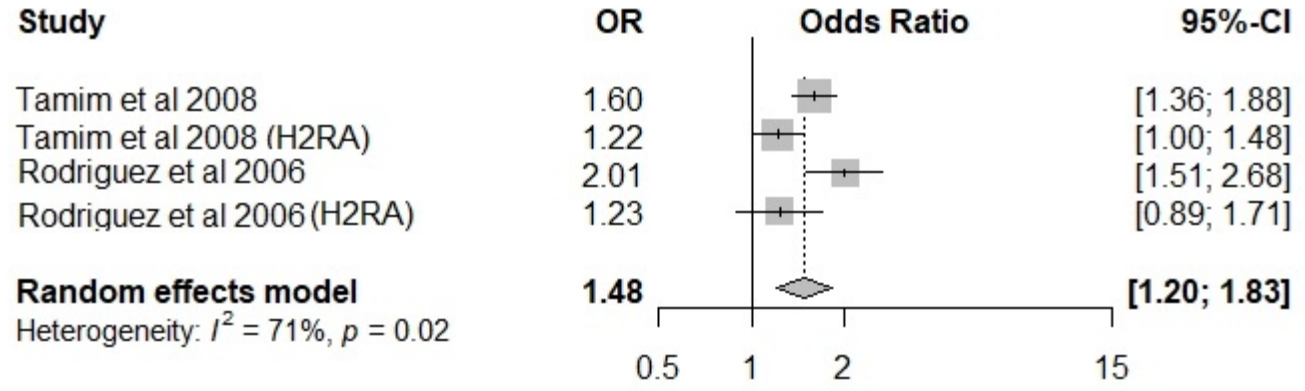


Figure 15: Forest plots of odds ratios for Gastric Cancer patients receiving proton pump inhibitors (PPI users compared with H2RA users)

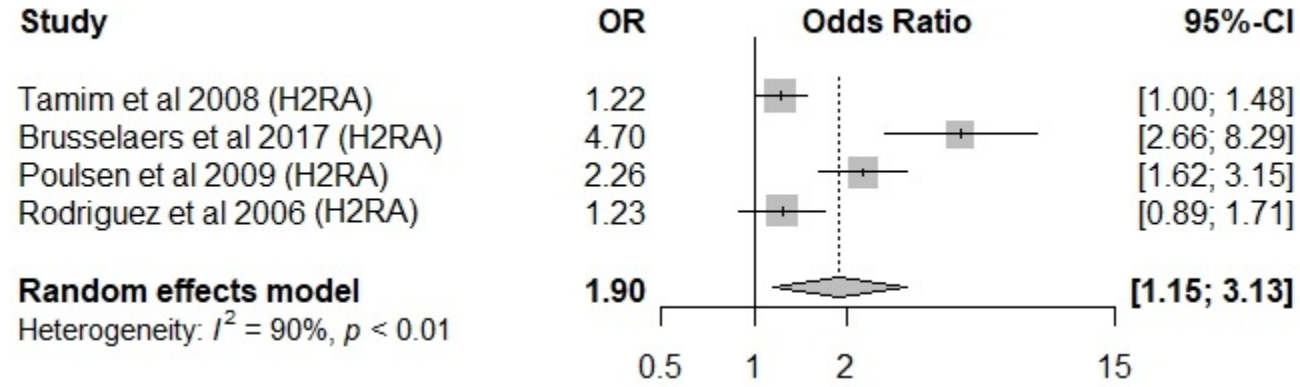


Figure 16: Forest plots of odds ratios for Gastric Cancer patients receiving proton pump inhibitors (PPI users compared with nonusers PPI/H2RA)

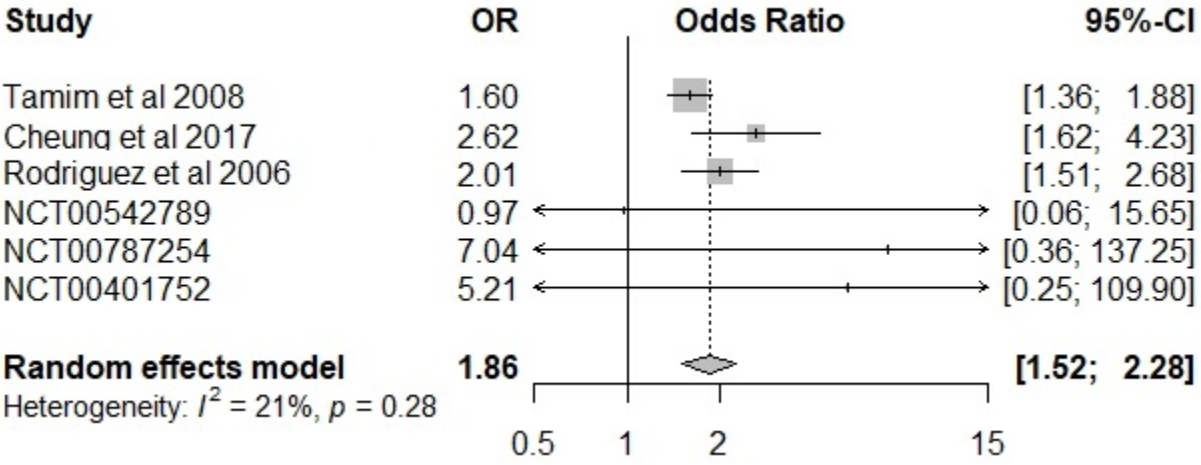


Figure 17: Forest plots of odds ratios for Gastric Cancer patients receiving proton pump Inhibitors (Observational studies; PPI users compared with non users PPI/H2RA)

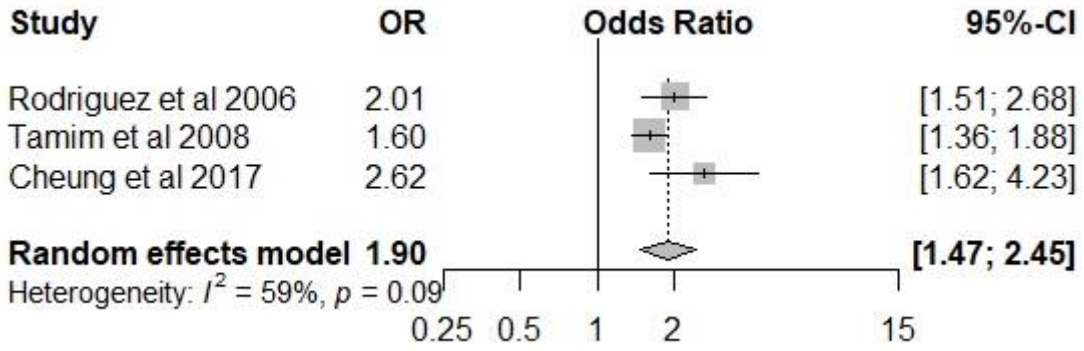


Figure 18: Funnel plots for cohort studies in PP use and the risk of MI

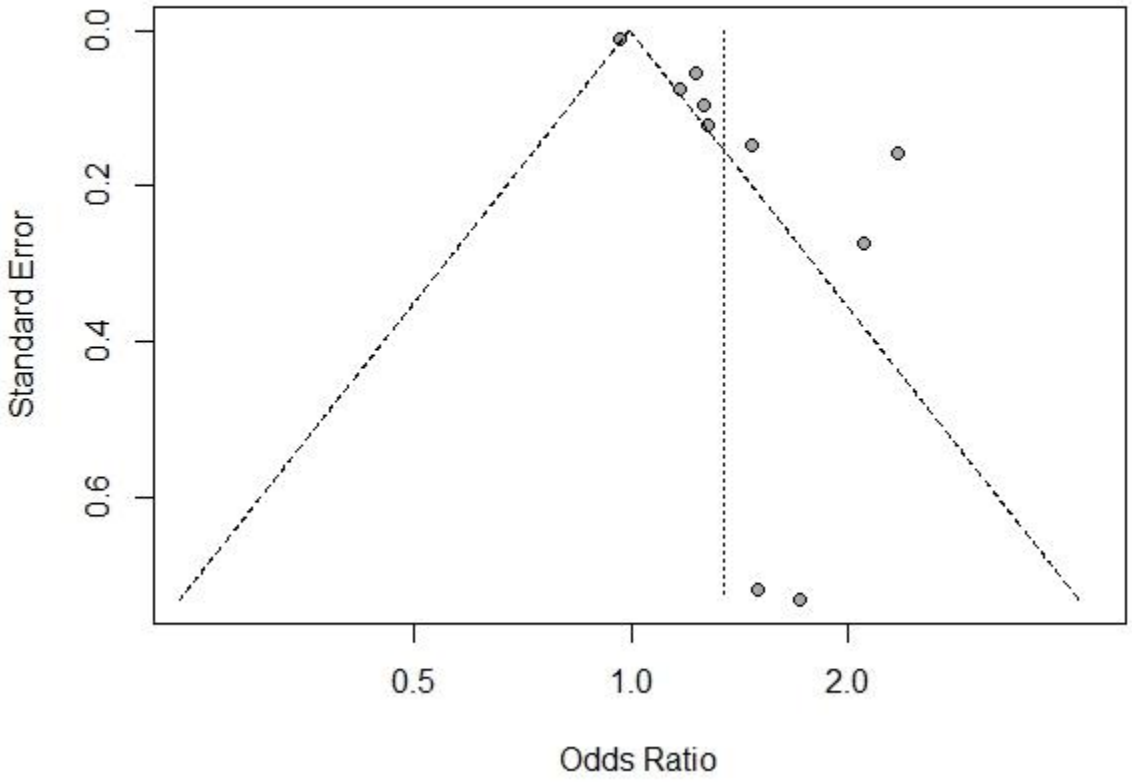


Figure 19: Forest plots of odds ratios for Myocardial Infarction in patients receiving proton pump Inhibitors (Observational studies with good quality ratings)

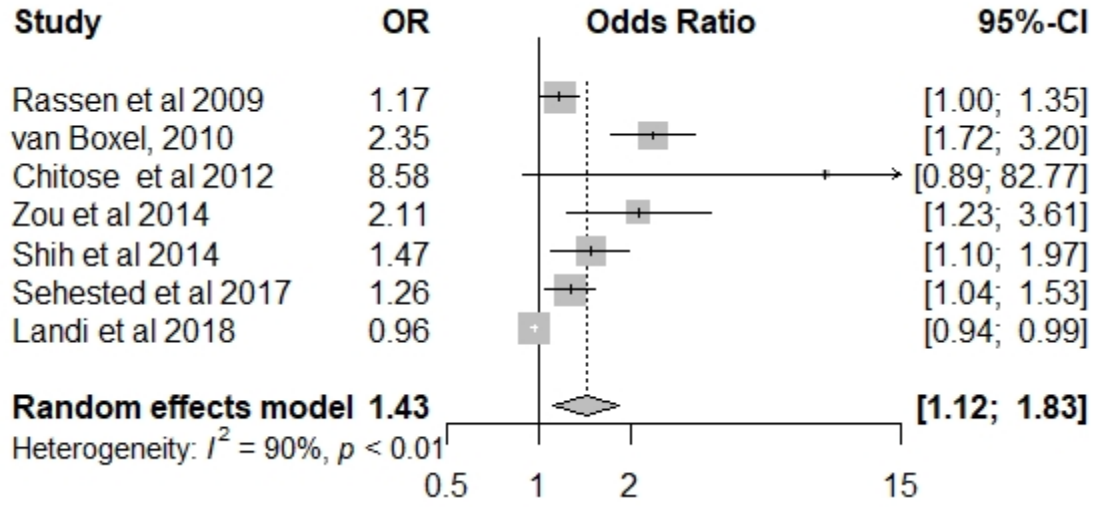
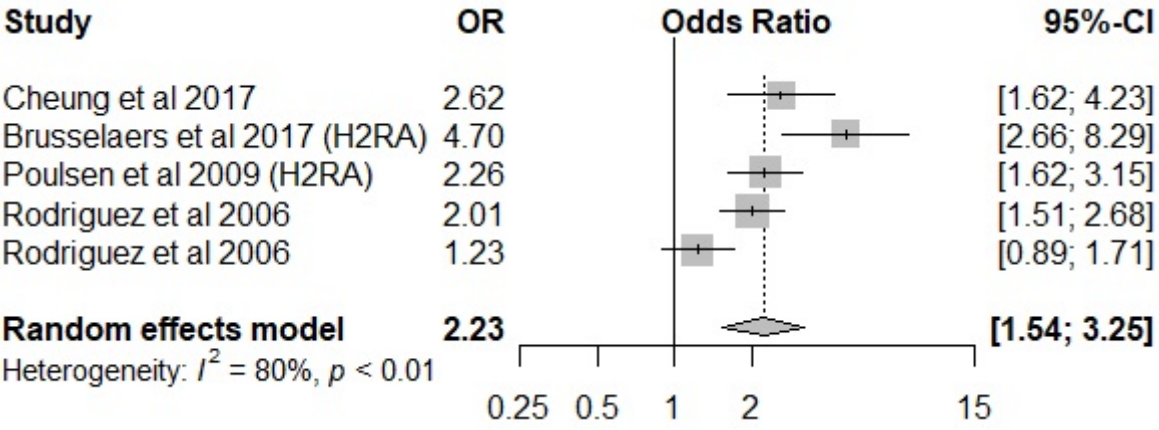


Figure 20: Forest plots of odds ratios for Gastric Cancer in patients receiving proton pump Inhibitors (Observational studies with good quality ratings)



Chapter 5

Discussion and Conclusions

Proton pump inhibitors (PPI) are widely used to treat acid-related diseases such as gastroduodenal ulcers, gastroesophageal reflux disease (GERD), Barrett's esophagus, and functional dyspepsia.[417] Existing evidence on the safety of PPI indicate that long-term use of PPIs among older adults is associated with some adverse events (AEs) such as bone fractures, Clostridium difficile infection, and acute interstitial nephritis.[31,32] While existing evidence provides a strong argument for the association between several AEs and PPI use, for some AEs such as Myocardial infarction (MI), Chronic kidney disease (CKD), Heart failure (HF) and gastric cancer (GC), more information is required to confirm any causal relation.

In this study, we assessed the utilization of PPIs among the U.S. population, and evaluated the safety profile of overall PPI use. In aim1, we examined the trends in prescription PPI use and expenditures, overall and by patient subgroups, and identified predictors of PPI use. In aim 2 we first identified potential safety signals for PPIs using the FDA Adverse Event Reporting System (FAERS) data, focusing on CKD, MI, and GC. Then we used the 5% random sample of the 2013-2016 Medicare administrative claims data to assess the associations of MI CKD, and HF with PPI use. Finally, in aim 3, we conducted a systematic review and meta-analysis by evaluating the most up-to-date evidence in the association between PPIs with MI and GC by including clinical trials and observational studies.

In this chapter, we summarized the overall findings and the implications of the findings, as well as provides recommendations for future research.

5.1 Overall findings for aim 1

The findings from aim 1 suggest that the overall prescription PPI use increased significantly from 2002 to 2017. The trends in PPI use significantly increased among U.S. adults aged 65 and above, in both males and females, in the majority of racial/ethical subgroups and in all four geographic regions. Furthermore, trends in the use of brand PPI decreased significantly, while trends in generic PPI use increased correspondingly. While PPI use increased significantly from 2002-2017, the average spending and out of pocket expenditure on PPIs per patient decreased significantly. Finally, we identified that individuals who were aged >25, female, non-Hispanic Whites, residing in the Northeast, with low income, having public or private health insurance, obese or overweight, having poor health status, and having more comorbidities had higher likelihoods of using PPIs.

5.1.1 Implications of the findings for aim 1

Findings from aim 1 provide national estimates in proportion and trends in prescription PPI use and expenditures among the U.S. population, which provides a number of clinical and policy implications. First, PPI utilization patterns may help policymakers develop and implement new policies that can reduce prescription costs related to PPI use, including the promotion of generic PPI use given that most PPIs have generics available. Second, the utilization patterns of PPI among different subgroups can inform potential existing treatment disparities. Future research may investigate these disparities in the use of PPIs and how they could impact the optimal

prescribing and intake of PPIs. Finally, understanding how patients use PPIs and individual factors associated with PPI use will help practitioners and policymakers identify potential high use subgroups of patients, monitor patient symptom control, and prevent adverse outcomes.

5.2 Overall findings for aim 2

In aim 2, both the spontaneous FAERS and Medicare administrative claims data were analyzed to evaluate the safety profile of PPIs. The findings from FAERS analyses indicated no disproportionate reporting signals for MI AEs with PPI use, but disproportionate reporting signals of CKD and GC AEs were identified. We further evaluated potential influences of publication bias on AE reporting with PPIs and found no impact on MI and GC AE reporting. However, CKD AE reporting related to PPIs increased dramatically after the key publication of Lazarus et al, indicating a strong impact of publication bias on CKD AE reporting with PPIs.

Results from the Medicare claims data analyses found a decreased risk of MI incidence for PPI users compared to H2 blocker users, while no associations in risk of CKD and HF with PPI use were observed. Furthermore, we did not observe the association between MI risk and long-term (84 days of use) PPI use compared with long-term H2 blocker user either. Finally, individual PPI users were compared with omeprazole users, and only pantoprazole users showed an increase in the risk of MI compared with omeprazole users, while other PPI users did not differ.

5.2.1 Implications of the findings for aim2

Findings from aim 2 provide a number of clinical and policy implications on the safety profile of PPIs. First, although animal models show the probable relation between

PPI use and cardiovascular events, we found that PPI use does not increase the risk of MI. Second, while some existing observational studies found the risk of CKD and PPI use, the association might not exist or has been affected by unobservable bias such as publication or perception bias. Due to the limited follow up period of this study, we could not observe CKD events beyond 15 months of the initiation of PPI use (and 12 months of long-term PPI use). Future high-quality, longitudinal studies are warranted to investigate the causal relationship between PPI use and the risk of GC. Finally, findings from this aim regarding the safety of individual PPIs can guide practitioners and policymakers to monitor and improve the safe use of PPIs.

5.3 Overall findings for aim 3

Aim 3 evaluated the most up-to-date evidence to assess the associations between PPIs with MI and GC by including both clinical trials and observational studies. Findings from our meta-analysis found no association between PPI use and risk of MI or GC among RCTs; however, adding evidence from observational studies elevated the risk and demonstrated significant associations between PPI use with MI and GC. In all of these analyses, the magnitudes of the associations were weak in nature.

5.3.1 Implications of the findings for aim 3

Findings from aim 3 have a number of clinical and policy implications in ensuring the safe use of PPIs. First, the findings for PPI use and the risk of MI and GC are not consistent between RCT and observational study designs. This discrepancy indicates the need for a more rigorous, well-designed studies to evaluate the causal relationship between PPI use the risk of MI and GC. Second, since the findings are mixed for risk of MI and GC with PPI use, the post-marketing pharmacovigilance system should evaluate

different levels and hierarchy of evidence to support decision making in the safety of drug products.

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