INVESTIGATING THE RISK OF ADVERSE CARDIOVASCULAR EVENTS ASSOCIATED WITH CONCOMITANT TREATMENT OF CLOPIDOGREL AND PROTON PUMP INHIBITORS

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ABSTRACT

Proton pump inhibitors (PPIs) are commonly coadministered with clopidogrel, an antiplatelet agent, to patients with acute coronary syndrome (ACS). Mechanistic studies suggest that PPIs have the potential to competitively inhibit the bioactivation of clopidogrel and may attenuate its antiplatelet action in the body. The clinical implications of this drug-drug interaction have been extensively studied; however reported findings are inconsistent. More recently, several studies have questioned whether PPIs are associated with adverse cardiovascular events independent of clopidogrel. Given that PPIs and clopidogrel are widely used, it is critical to better understand the clinical impact of the concomitant treatment with both drugs.

This thesis includes four studies that investigate the clinical effects of the drug-drug interaction between clopidogrel and PPIs. Chapter 2, a systematic review and meta-analysis, summarizes findings from 118 studies. Findings do not provide strong evidence for an association between adverse cardiovascular events and the use of PPIs when used alone, in combination with clopidogrel, or in combination with other antiplatelets. Chapters 3, 4, and 5 present analyses of real-world data comprised of electronic medical records. Results of these analyses demonstrate 1) that the concomitant use of clopidogrel and PPIs among inpatients was consistent with clinical guidelines suggested by the FDA (Chapter 3); 2) a lack of association between PPI use vs nonuse and four adverse cardiovascular outcomes among clopidogrel users (Chapter 4); and 3) a lack of association between PPI use vs nonuse and adverse cardiovascular outcomes among prasugrel users or ticagrelor users (Chapter 5).

Collectively, our findings do not provide evidence of an elevated risk of adverse cardiovascular outcomes with the combined use of PPIs and clopidogrel. Although pharmacodynamic and pharmacokinetic studies have demonstrated an interaction between these two drugs, our findings support the opinion that the biological interaction does not translate into adverse clinical events among patients with acute coronary syndrome.

To the memory of my mother-in-law…

To the life she lived with courage, resilience, and positivity…

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TABLE OF CONTENTS

LIST OF TABLES

CHAPTER 2

SUPPLEMENTAL MATERIAL

CHAPTER 3

SUPPLEMENTAL MATERIAL

CHAPTER 4

SUPPLEMENTAL MATERIAL

CHAPTER 5

SUPPLEMENTAL MATERIAL

LIST OF FIGURES

CHAPTER 2

SUPPLEMENTAL MATERIAL

CHAPTER 3

SUPPLEMENTAL MATERIAL

LIST OF ABBREVIATIONS

ACE	ANGIOTENSIN CONVERTING ENZYME
ACS	ACUTE CORONARY SYNDROME
ADMA	ASYMMETRICAL DIMETHYARGININE
AOR	ADJUSTED ODDS RATIO
CABG	CORONARY ARTERY BYPASS GRAFTING
CAD	CORONARY ARTERY DISEASE
CCB	CALCIUM CHANNEL BLOCKER
CI	CONFIDENCE INTERVAL
COGENT	CLOPIDOGREL AND THE OPTIMIZATION OF GASTROINTESTINAL EVENTS TRIAL
COPD	CHRONIC OBSTRUCTIVE PULMONARY DISEASE
CTN I	CARDIAC TROPONIN I
CTN T	CARDIAC TROPONIN T
CVD	CARDIOVASCULAR DISEASE
CYP	HEPATIC CYTOCHROME
DDAH	DIMETHYLARGININE DIMETHYLAMINOHYDROLASE
DDI	DRUG-DRUG INTERACTION
ECM	ELIXHAUSER COMORBIDITY MEASURES
EMR	ELECTRONIC MEDICAL RECORDS
ESRD	END STAGE RENAL DISEASE
FDA	FOOD AND DRUG ADMINISTRATION
GERD	GASTROESOPHAGEAL REFLUX DISEASE
GI	GASTROINTESTINAL
GPR	GLYCOPROTEIN IIB/IIIA RECEPTOR
H2RA	HISTAMINE-2 RECEPTOR ANTAGONIST
HR	HAZARDS RATIO
ICD	INTERNATIONAL CLASSIFICATION OF DISEASES
IRR	INCIDENCE RATE RATIO
MACE	MAJOR ADVERSE CARDIOVASCULAR EVENTS
MI	MYOCARDIAL INFARCTION
NO	NITRIC OXIDE
NOS	NEWCASTLE-OTTAWA SCALE
NSTEMI	NON-ST-ELEVATION MYOCARDIAL INFARCTION
OR	ODDS RATIO
PCI	PERCUTANEOUS CORONARY INTERVENTION
PLATO	PLATELET INHIBITION AND PATIENT OUTCOMES
PPI	PROTON PUMP INHIBITOR
PS	PROPENSITY SCORES
RCT	RANDOMIZED CONTROLLED TRIAL
REM	RANDOM EFFECTS MODEL
RR	RISK RATIO
RWD	REAL WORLD DATA

SD	STANDARD DEVIATION
STEMI	ST-ELEVATION MYOCARDIAL INFARCTION
UGIB	UPPER GASTROINTESTINAL BLEEDING
US	UNITED STATES

CHAPTER 1

INTRODUCTION

1.1 INTRODUCTION

Recent estimates suggest that 195,000 hospitalizations and 74,000 emergency room visits are a result of drug-drug interactions (DDIs) in the United States (US) every year (Percha and Altman 2013). DDIs are expected to become a greater concern to public health with the increasing prevalence of polypharmacy. In fact, the percent of Americans receiving more than two prescription drugs increased from 12% in 1988-1994 to 21% in 2007-2010, while those receiving more than four drugs increased from 4% to 10 % over the same time period (National Center for Health Statistics 2012 in Percha and Altman 2013). These statistics highlight the importance of understanding DDIs and their concomitant health impacts. Detecting adverse effects of DDIs and assessing their clinical significance, however, can be challenging, particularly if the resulting effects are long term or occur at a very low rate (Chan et al. 2015).

In 2006, findings of a potential DDI between two commonly coprescribed medications, clopidogrel and proton pump inhibitors (PPIs), suggested patients receiving these two drugs may be at increased risk of adverse cardiovascular outcomes (Gilard et al. 2006). Clopidogrel, an antiplatelet agent, is prescribed to patients with cardiovascular conditions, including acute coronary syndrome (ACS), a recent myocardial infarction (MI), or stroke (Gerson 2013). It was first approved by the US FDA in 1997 (US FDA 1997). It remains one of the most prescribed P2Y12 receptor antagonists (Pelliccia et al. 2015) despite the availability of newer and more potent antiplatelets such as prasugrel and ticagrelor. Since clopidogrel can increase the risk of gastrointestinal complications, particularly GI bleeding, current guidelines recommend the co-prescription of PPIs for gastric protection (Bhatt et al. 2008; Bhatt et al. 2010). The interaction reported between clopidogrel and PPIs is biologically plausible since the two drugs may compete for the same hepatic enzyme. Clopidogrel is a pro-drug that is metabolised in the human body into its active form by the CYP2C19 enzyme. However, CYP2C19 is also involved in the metabolism of PPIs (Ishizaki and Horai 1999). Through the mechanism of competitive inhibition, PPIs may hinder the activation of clopidogrel and thereby attenuate clopidogrel's antiplatelet activity.

The potential for an increased risk of clinical events among patients receiving both drugs prompted the US FDA and other regulatory bodies to issue warnings discouraging concomitant use (FDA 2009; Health Canada 2009; EMA 2010) and sparked in intense debate regarding the safety of combined treatment. Since 2009, numerous observational studies have investigated the clinical significance of the underlying DDI. Many studies have reported a lack of association between concomitant treatment and adverse cardiovascular events, while others have reported an elevated risk. Further, a number of recent studies reporting positive findings attributed their results to limitations inherent observational studies, including selection bias and bias from unmeasured confounders. Several studies have noted that PPI-users are typically at a higher baseline risk for adverse events, as they are typically older, receiving more medications and have more comorbidities relative to nonusers of PPIs (Goodman et al. 2012; Focks et al. 2013; Cardoso et al. 2015).

More recently, preliminary findings reported in the literature suggest that PPIs may have an adverse effect on cardiovascular health independent of clopidogrel, such as reduced cardiac contractility (Schillinger et al. 2007) and direct cardiotoxic effects (Ghebremariam et al. 2013).

A substantial number of patients are coprescribed clopidogrel and PPIs; consequently, even small increases in the risk of adverse events associated with their concomitant use would represent a public health concern. As the question whether the DDI translates into a meaningful clinical impact remains unanswered, this thesis further investigates the association between concomitant use and major adverse cardiovascular events.

1.2 OBJECTIVES

The overall objective of the research project was to investigate the association between the concomitant use of clopidogrel and PPIs and major adverse cardiovascular events. Specifically, I completed four original studies to address the following five objectives:

1- Perform a systematic review and meta-analysis of published epidemiological studies examining the potential risk of cardiovascular events associated with PPIs.
2- Examine the trends of concomitant use of clopidogrel and PPIs in response to the US FDA safety warnings.
3- Assess the risk of adverse cardiovascular events associated with concomitant treatment of PPIs and clopidogrel among patients with ACS.
4- Assess the risk of adverse cardiovascular events associated with concomitant treatment of PPIs and other antiplatelets (that have not been reported to interact with PPIs).

5- Explore the potential for confounding in the findings.

1.3 USE OF LARGE DATABASES IN PHARMACOEPIDEMIOLOGIC RESEARCH

Large health care databases contain data that is routinely collected by hospitals and health insurance companies in the course of providing and administering health services. The clinical information stored in these databases represents real-world data (RWD) and reflects clinical practice in large populations, in contrast to the far fewer and healthier patients typically included in clinical trials (Schneeweiss 2006). In recent years, there has been a significant increase in the use of health care databases for health research, particularly in the field of pharmacoepidemiology (Arana et al. 2004). Such applications have resulted in a better understanding of the safety and effectiveness of many drugs.

The two main types of large databases useful in pharmacoepidemiology are claims data and electronic medical records (EMRs). EMRs have the advantage of containing more detailed clinical information than claims data, including diagnostic test results, medical history and lifestyle information on factors such as smoking and obesity (Schneeweiss and Avorn 2005). Clinical research based on large databases has additional advantages such as representativeness of the data collected from real-world settings and the coverage of large populations that allows the investigation of rare events. Their use in research is further characterized by relatively low cost, quick access to data, and the possibility to complement missing data by linking to external sources (Spasoff 1999; Schneeweiss and Avorn 2005).

At the same time, the use of EMRs in clinical research is accompanied by several challenges, considering that the databases are not designed nor intended for research purposes. Dealing with lower data quality, possibly incomplete data, the absence of information on important confounders, and the extent of generalizability of findings can pose significant challenges to researchers, all of which have the potential to bias study findings (Strom et al. 2013). Many of the challenges can be often addressed by careful planning at the research design stage and the use of methods that allow adjusting for potential biases that could compromise the study validity. With proper management of challenges and cautious interpretation the findings, evidence from database studies can complement findings from clinical trials to improve our understanding of the safety and effectiveness of drugs under real-world conditions of use (Schneeweiss et al. 2016).

1.3.1 HEALTH FACTS® DATABASE

The analytical studies presented in this thesis are based on the analysis of electronic medical records from the Health Facts® database provided by Cerner Corporation in the United States. Health Facts® consists of patient-level electronic medical records collected from more than 500 contributing US health facilities. Records include over 300 data elements with time-stamped information on admissions, discharges, diagnoses, hospital procedures, drug prescriptions and laboratory tests.

The dataset I had access to for this thesis covered the period from January 1, 2000 to December 31, 2016. It included 460 million distinct encounters corresponding to over 69 million unique patients. Health Facts® is a longitudinal database that allows researchers to follow patients over time if they receive health care within the same health system. It also complies with the Health Insurance Portability and Accountability Act and contains only de-identified information to protect the identity of patients and contributing organizations.

1.4 ORGANIZATION OF THE THESIS

This thesis is manuscript-based and contains four original studies presented in Chapters 2-5 (Figure 1-1). Chapter 2 is a comprehensive systematic review and meta-analysis that summarizes findings from epidemiological studies that reported on the association between PPI exposure (taken alone or with other drugs) and major adverse cardiovascular events (MI, stroke, cardiovascular mortality, all-cause mortality). This chapter directly addresses Objective 1.

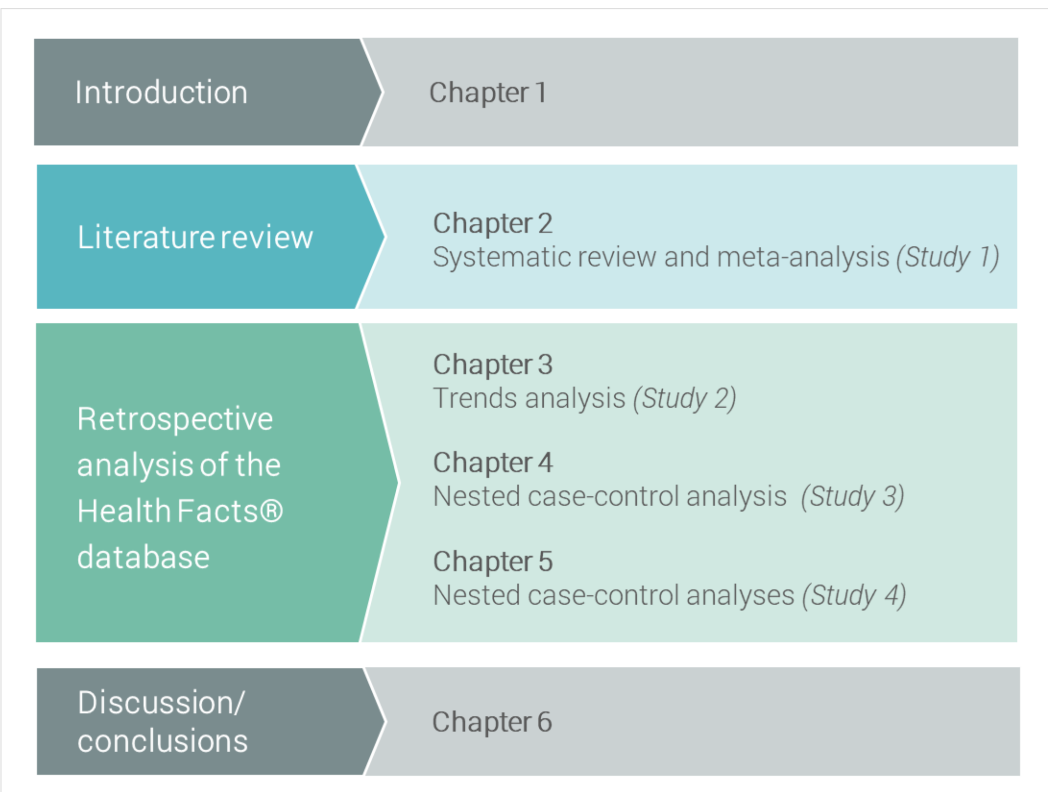

FIGURE 1-1. ORGANIZATION OF THE THESIS.

The remaining three studies are based on the analysis of electronic medical records derived from Health Facts®. Chapter 3 presents a study describing the trends of clopidogrel and PPI use in US inpatient settings from 2000 to 2016. In addressing the second objective of the thesis, this study examines the changes in trends in relation to the FDA safety warnings. Chapter 4 is a nested case-control study that assesses the main association of interest of this thesis: the risk of adverse cardiovascular events associated with concomitant clopidogrel and PPI treatment. The fourth study, presented in Chapter 5, represents two case-control analyses similar in design to that of Chapter 4; however, the potential risks are assessed in a cohort of prasugrel users and a cohort of ticagrelor users (Objective 4).

I have presented each study in Chapters 2-5 in a manuscript format. The supplemental material relevant to each chapter is found at the end of each respective chapter. Finally, in the general discussion of this thesis, Chapter 6, I summarize the findings from the four studies and discuss how they meet the thesis objectives. I further discuss how findings from the case-control analyses in Chapters 4 and 5 can be used to examine the potential for confounding in the effect estimates of the association between concomitant clopidogrel and PPI treatment and cardiovascular events (Objective 5).

CHAPTER 2

SYSTEMATIC REVIEW AND META-ANALYSIS OF ADVERSE CARDIOVASCULAR EVENTS ASSOCIATED WITH PROTON PUMP INHIBITORS USED ALONE OR IN COMBINATION WITH ANTIPLATELET AGENTS

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PREFACE

This chapter comprises the first manuscript from this thesis that addresses Objective 1. The purpose of this study was to systematically summarize the findings available in the literature from studies that have examined the associations between PPI use (alone and in combination with clopidogrel or other drugs) and four adverse cardiovascular events, as well as to use meta-analytic methods to generate pooled effect estimates when possible.

Supplemental material referenced throughout the manuscript is presented at the end of this chapter: detailed search strategies (I), screening and extraction forms (II and III), detailed characteristics of studies (IV), reasons for exclusion of studies from the meta-analyses (V), and additional findings not presented in the manuscript (VI, VII, VIII and IX).

Ethical approval for this study was obtained from the Ottawa Health Science Network Research Ethics Board at the Ottawa Hospital, Ottawa, Canada (Appendix A).

The manuscript was submitted to Critical Reviews in Toxicology; it was recently accepted for publication pending minor revisions (Appendix B).

Contributions statement

The authors had sole responsibility for preparation of this paper, including determining the strategy for reviewing the scientific literature summarized in this article, synthesizing the findings, and drawing conclusions. NF developed the initial study protocol and wrote the first draft of the manuscript. NF, YF and NH screened references for inclusion and abstracted key data elements from included references. NF performed the quantitative analyses and generated the tables and graphs. All authors contributed to the development of the final study protocol, provided detailed comments on drafts of this article and participated in the formulation of the study conclusions.

Declaration of interests

The authors, whose affiliations are shown on the title page, had sole responsibility for preparation of this paper, including determining the strategy for reviewing the scientific literature summarized in this article, synthesizing the findings, and drawing conclusions. NF developed the initial study protocol and wrote the first draft of the manuscript. NF, YF, and NH screened references for inclusion in the systematic review, and abstracted key data elements from included references. All authors contributed to the development of the final study protocol, provided detailed comments on drafts of this article and participated in the formulation of the study conclusions.

NF was supported by Doctoral Research Awards from the Canadian Institutes of Health Research and the McLaughlin Center for Population Health Risk Assessment (www.mclaughlincentre.ca), and by an admission scholarship from the University of Ottawa (www.uottawa.ca). YF was supported by doctoral training awards from the Fonds de recherche du Québec en santé (http://www.frqs.gouv.qc.ca), the University of Ottawa admission scholarship, the McLaughlin Centre for Population Health Risk Assessment and the Ontario Ministry of Advanced Education and Skills Development (https://osap.gov.on.ca). NH was supported by the University of Ottawa admission scholarship and the McLaughlin Centre for Population Health Risk Assessment. DK and NB are cosupervisors of NF's doctoral thesis, with FM, DM and SW serving as members of NF's thesis advisory committee.

DK is the Natural Sciences and Engineering Research Council of Canada Chair in Risk Science at the University of Ottawa, a peer reviewed university-industry research partnership program. DK and DM respectively serve as Chief Risk Scientist and Chief Medical Officer for Risk Sciences International (RSI) (www.risksciences.com), a Canadian company established in 2006 in partnership with the University of Ottawa, to provide consulting services in risk science to both public and private sector clients. To date, RSI has not conducted work on PPIs or antiplatelet agents that are the subject of the present paper. NF has served as a consultant to RSI and to international clients on issues unrelated to those discussed in the present paper. NH is a senior epidemiologist with the Public Health Agency of Canada working on matters unrelated to the subject of the present paper.

Within the last ten years, none of the authors have served as consultants either for a fee or pro bono to public or private sector clients regarding the pharmaceutical products reviewed in this paper, nor have any of the authors participated in legal proceedings related to these products. FM has consulted with Novartis in 2003, prior to their marketing of Prevacid in 2009, on matters unrelated to the subject of the present paper.

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SYSTEMATIC REVIEW AND META-ANALYSIS OF ADVERSE CARDIOVASCULAR EVENTS ASSOCIATED WITH PROTON PUMP INHIBITORS USED ALONE OR IN COMBINATION WITH ANTIPLATELET AGENTS

ABSTRACT

Background The potential association between major adverse cardiovascular events (MACE) and concomitant treatment with proton pump inhibitors (PPIs) and clopidogrel has been debated since 2009. Recent reports, however, suggest that PPIs may increase the risk of MACE independently of clopidogrel.

Purpose This review evaluates epidemiological findings relevant to the association between PPIs, taken alone or concomitantly with antiplatelets, and the risk of MACE.

Methods A systematic review and meta-analysis were conducted. Relevant studies were identified from MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials and then screened. Included studies were categorized into three groups: Group A: PPIs vs no PPIs; Group B: combined PPIs and clopidogrel vs clopidogrel alone; Group C: combined PPIs and other drugs vs other drugs. Pooled risk ratios (RRs) were calculated for each outcome of interest in each comparison group.

Results Of the 1,667 studies identified, 118 were included in the systematic review, of which 66 were included in the meta-analyses. Among Group A observational studies, RRs for MACE outcomes were statistically significant for some patient populations but not others. Pooled RRs from Group A RCTs were not statistically significant for any outcome. Pooled RRs for Group B observational studies were statistically significant for all-cause mortality and MI, but were diminished in magnitude when pooling was restricted to propensity score matched studies or post-hoc analyses of RCTs. Group C studies did not demonstrate an association with MACE.

Conclusions Findings do not consistently support an association between MACE and PPIs when taken alone, or concomitantly with antiplatelets.

Keywords: Systematic review, meta-analysis, proton pump inhibitors, clopidogrel, platelet aggregation inhibitors, cardiovascular diseases, myocardial infarction, drug interactions.

Word count: 11,933

2.1 INTRODUCTION

Proton pump inhibitors (PPIs) are among the most widely used medications worldwide (Asim Syed and Abbas Naqvi 2016). They are commonly prescribed for gastric acid-related disorders, as well as for the prevention of gastrointestinal (GI) bleeding in patients with acute coronary syndrome (ACS) receiving antiplatelet treatment (Ogawa and Echizen 2010). Compared to H2 receptor antagonists (H2RAs), PPIs provide more effective relief of symptoms and a longer duration of action (Owen et al. 2014). Though PPIs are considered to have an excellent safety profile, recent studies suggest that their use by ACS patients receiving clopidogrel, a commonly prescribed antiplatelet agent, may put them at an increased risk for adverse cardiovascular events. In 2006, an observational study by Gilard et al. raised concern about a possible interaction between omeprazole (a PPI) and clopidogrel that may attenuate clopidogrel's antiplatelet effect. The biological plausibility of this interaction is based on competitive inhibition, as both drugs depend on the activity of the cytochrome P450 system, specifically the CYP2C19 enzyme. Gilard et al. (2008) also reported findings of an RCT that showed patients who received omeprazole and clopidogrel had a higher platelet reactivity index compared to patients that received clopidogrel and a placebo. Potential increases in major adverse cardiovascular events (MACE) among clopidogrel users have been investigated and debated extensively, particularly after warnings were first issued in 2009 by regulatory agencies regarding potential risks of concomitant therapy (European Medicines Agency 2009; FDA 2009; Health Canada 2009). Despite the warnings issued, the use of PPIs is still on the rise (Asim Syed and Abbas Naqvi 2016) and the question of whether the PPI-antiplatelet interaction has a meaningful impact on clinical care remains unanswered. Moreover, an alternative hypothesis has recently emerged, suggesting that patients receiving PPIs may be at an increased risk of cardiovascular events regardless of concomitant clopidogrel treatment (Charlot et al. 2010; Ghebremariam et al. 2013).

PPIs have been available for over thirty years. In 1980, the first PPI, omeprazole, was introduced to the market and was followed by five additional PPIs in subsequent years (Asim Syed and Abbas Naqvi 2016). Although PPIs are believed to have a good safety profile, a growing number of studies identified in the literature suggest various adverse effects associated with their long-term. These include hypomagnesaemia, bone fractures, vitamin B12 and iron deficiency, enteric infections, and pneumonia (Reimer 2013).

A better understanding of PPIs' potential to increase the risk of adverse cardiovascular events is critical, as they are one of the most widely prescribed drugs worldwide. Given the large number of patients receiving these drugs, particularly patients with cardiovascular conditions requiring concomitant treatment of PPIs with antiplatelet agents, even a minor increase in risk would translate to a considerable number of potentially preventable adverse events. Although numerous studies have focused on the combined treatment of clopidogrel-PPI among ACS patients, relatively fewer studies have looked at the potential adverse cardiovascular effects of PPIs when taken alone or in combination with other drugs.

The purpose of this review was to evaluate the potential increased risk of adverse cardiovascular events and all-cause mortality (ACM) from PPI use. To accomplish this objective, we performed a systematic review and meta-analysis of epidemiological studies that assessed the potential effect of PPIs, either alone or in combination with other drugs including clopidogrel, on major adverse cardiovascular events and ACM.

2.2 METHODS

The protocol for this systematic review was approved by the Ottawa Health Science Network Research Ethics Board at the Ottawa Hospital, Ottawa, Canada.

2.2.1 ELIGIBILITY CRITERIA

We included original epidemiological studies that assessed the association with at least one of the outcomes of interest among patients receiving PPIs compared to patients not receiving PPIs or to those receiving a placebo. Study participants were 18 years of age or older. Outcomes of interest were: 1) ACM; 2) myocardial infarction (MI); 3) cardiovascular mortality; and 4) stroke/cerebrovascular accident. Studies that assessed composite outcomes of individual outcomes were excluded unless they reported findings on at least one of the outcomes of interest. We included studies that were either non-randomised observational studies, randomised controlled trials (RCTs) or post-hoc analyses of RCTs. Cross-sectional studies and those published in languages other than English were excluded. There were no restrictions on the date of publication.

2.2.2 SEARCH STRATEGY

We searched EMBASE, MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) for potentially relevant studies published up to October 2018. Specific search strategies were developed for each database in consultation with a research librarian at the University of Ottawa. The search strategies included a combination of medical subject headings (MESH) and keywords defining the exposure and outcomes of interest (Supplemental Material I). We applied search filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) to exclude irrelevant study designs. The reference lists of recent systematic reviews and the references of the included articles were manually reviewed to identify additional relevant articles.

2.2.3 STUDY SELECTION

Two reviewers independently screened all studies identified in the bibliographic database searches using a two-stage selection process. Customized screening forms were used to guide the selection process (Supplemental Material II). Titles and abstracts were screened in the first stage. Full-text articles of potentially relevant studies were then retrieved and screened in the second stage. Disagreements between the reviewers were resolved through discussion following the second stage screening.

Abstracts were included in the systematic review (but were not eligible for inclusion in the meta-analysis) only when a corresponding full-text publication was not identified and if they had reported quantitative findings relevant to the research question; otherwise they were excluded.

2.2.4 DATA EXTRACTION

One reviewer extracted data from the included studies using a customized form. Detailed information was collected on the study design, patient characteristics, data source, methods, exposure and outcome ascertainment, results, and strengths and limitations (Supplemental Material III).

During data extraction, the following statistical outcome measures were retrieved in order of priority: 1) propensity score (PS) matched adjusted effect estimates, 2) maximally adjusted effect estimates (if results of different models were reported with varying numbers confounders being adjusted for), 3) unadjusted effect estimates, or 4) counts of events or event rates. The effect estimates extracted included relative risks, odds ratios (ORs), or hazard ratios (HRs). Duplicate extraction was performed on a 10% random sample of all included studies by the second reviewer. Data extracted by both reviewers was cross-checked for inconsistencies. In instances where additional data was needed beyond what was reported in the articles, the corresponding authors were contacted once by email to obtain the information. For RCTs that did not report a funding source, the clinicaltrials.gov database or other clinical trial registries reported in the study were searched for this information. Distiller SR software (Evidence Partners) was used for reference screening, data extraction and data management.

2.2.5 DATA SYNTHESIS

Included studies were categorized into three groups based on the exposure being assessed (PPIs taken alone or in combination with other drugs) in order to allow comparability across findings. Characteristics of included studies (location, setting, sample size and characteristics, exposure and outcomes) as well as detailed findings (adjusted effects or counts/rates of events) were summarized in tabular format classified by exposure and by outcome of interest.

Observational studies that reported adjusted effect estimates were considered for inclusion in the meta-analyses. Observational studies that reported counts or proportions/rates of events were included in the systematic review but not in the meta-analyses; findings from these studies, which mainly consisted of raw counts/percentages of events, were summarized in tables. RCTs that reported counts of events, however, were considered for inclusion in the meta-analysis. Studies for which only an abstract was available were not eligible for inclusion in the meta-analysis.

2.2.6 QUALITY ASSESSMENT/ RISK OF BIAS

The quality of non-randomised studies included in the meta-analyses was assessed using the Newcastle-Ottawa Scale (NOS) (Wells et al. 2008), as recommended in the Cochrane Handbook (Higgins and Green 2011). The NOS attributes a maximum of nine stars to studies based on methodological design and formal reporting. These include the selection of participants, the comparability of treatment groups, exposure ascertainment (for case-control studies), and outcome ascertainment (for cohort studies). Post-hoc analyses of RCTs were also assessed for quality using the NOS because PPI exposure is not randomized in such studies (Cardoso et al.

2015). Like prior meta-analysis, we considered a NOS score of six or higher to represent a high quality score for each study (Cardoso et al. 2015). RCTs were assessed for bias using the Cochrane risk-of-bias tool (Higgins and Green 2011). This is a domain-based tool that assesses the likelihood of bias from six potential sources (selection bias, performance bias, detection bias, attrition bias, reporting bias and "other" sources of bias) by attributing to each domain a score of "low risk, "high risk" or "unclear risk". Based on findings reported in recent Cochrane reviews (Lundh et al. 2012; Lundh et al. 2017), sources of other bias were assessed as "high risk" if the study reported funding from industry or if the authors reported conflict of interest and financial ties to industry. Publication bias was assessed by examining funnel plots generated by Review Manager corresponding to meta-analyses comprised of ten or more studies based on guidelines presented in the Cochrane Handbook (Higgins and Green 2011).

2.2.7 STATISTICAL ANALYSES

Findings for each outcome of interest within each exposure group were analysed separately. Within each outcome, effects were pooled across patient populations with similar characteristics or pre-existing conditions. Findings for a particular outcome that could not be combined with other findings due to incomparable patient populations were excluded from the meta-analysis. Adjusted effects estimates from observational studies were input directly in Review Manager (The Cochrane Collaboration 2014). Relative risks, hazard rate ratios and odds ratios were assumed approximately equal because of the rare endpoints assessed (Symons and Moore 2002). Summary effects (pooled risk ratios (RRs)) for each group were derived from individual studies by a random effects model using the inverse variance method with 95% confidence intervals (DerSimonian and Laird 1986). For RCTs, counts of events in each exposure group of RCTs with similar patient population for each outcome were pooled using fixed effects models. In this case, counts of each outcome were input directly into Review Manager to calculate the pooled effect estimate. In the case of observational studies, studies that that only reported counts of events in each exposure group instead of adjusted effects were not eligible for inclusion in the meta-analysis as this is not recommended in meta-analysis of non-randomized studies (CIOMS 2016).

Subgroup analyses were conducted across observational studies by grouping post-hoc analyses of RCTs and cohort studies that used PS matching versus the remaining cohort and case-control studies, as previously performed in two recent systematic reviews (Kwok and Loke 2010; Cardoso et al. 2015). Subgroup analyses were also conducted by PPI type when possible across studies that stratified their findings by PPI type.

The I^2 statistic, a measure of the variability in effect estimates due to heterogeneity rather than chance, was used to assess statistical differences amongst the pooled studies. I^2 values greater than 75% represented considerable heterogeneity (Higgins and Green 2011). Forest plots were also visually examined to identify overlaps between individual effect estimates and to assess heterogeneity. All meta-analyses were performed in Review Manager, version 5.3.

2.2.7.1 SENSITIVITY ANALYSES

Sensitivity analyses were conducted to assess the impact of funding source on the overall pooled estimates. The funding source of each study was categorized as *industry, public, non-profit or no* *funding, and not reported.* Sensitivity analyses were also performed to assess the impact of the potential risk of bias among RCTs when possible.

2.3 RESULTS

2.3.1 ELECTRONIC SEARCHES AND STUDY SELECTION

The electronic database searches identified 2,300 candidate references. After removing duplicates, 1,677 proceeded to the title and abstract screening stage. Fourteen additional references were identified by manually searching the reference lists of recent systematic reviews identified in the first screening stage. After the two-stage screening process, 118 references remained relevant for data extraction (Figure 2-1). Of these, 71 were either observational studies that reported adjusted effect estimates or RCTs and were eligible for inclusion in the meta-analysis. Exclusion at the second stage of screening was primarily due to either failure to meet the inclusion criteria (87%), or duplicates of articles that were not previously identified (9%).

Reference screening was performed independently by two reviewers. The level of agreement between both reviewers was measured by Cohen's kappa, which is automatically calculated in Distiller SR. Cohen's kappa for *whether or not to exclude a reference from Stage 1 to Stage 2 screening* was 0.57, representing moderate agreement. At the end of Stage 2 screening, the Cohen's kappa for *whether or not to exclude a study* was 0.77, indicating substantial agreement. Disagreements about study inclusion were resolved by discussion. Three authors were contacted by email requesting important information that was not reported in the articles. Only one author replied and no further attempts were made to contact the remaining authors.

Included studies were categorized into three comparison groups based on the exposure being assessed:

- Group A: Studies comparing PPI use vs non-use (61 studies);
- Group B: Studies comparing concomitant PPI and clopidogrel use vs clopidogrel alone (many of these studies included patients on dual antiplatelet therapy (DAPT) that were taking aspirin in addition to clopidogrel) (50 studies);
- Group C: Studies comparing the concomitant use of PPIs and other antiplatelet agents (other than clopidogrel) vs other antiplatelet agents alone (13 studies).

Studies could be included in more than one comparison group if they reported findings for multiple relevant comparisons.

2.3.2 GROUP A (PPI USE VS NON-USE)

2.3.2.1 STUDY CHARACTERISTICS

Sixty one studies (40 observational studies and 21 RCTs) assessed the effect of PPI use versus non-use and reported on at least one of the outcomes of interest. Characteristics of included studies that reported on the effects of PPI use vs non-use are summarized in Table 2-1 (detailed characteristics are presented in the Supplemental Material IV).

Twenty one RCTs reported on the association between PPI use and at least one outcome of interest. Seventeen studies were published after 1999, with the remaining studies published in the 1990s. Sample sizes varied between 90 and 3,298 participants recruited from a range of one to 91 hospitals/health care centers. Omeprazole was the most common drug studied followed by pantoprazole and esomeprazole. Only one study assessed the effect of lansoprazole. All studies evaluated ACM as an outcome and four reported on MI and stroke. Study follow-up periods ranged from two weeks to three months after exposure. The study population in fifteen of these RCTs were patients with a history of upper gastrointestinal bleeding (UGIB) requiring endoscopy. Generally, these patients were randomized to receive either PPI treatment or a placebo administered at regular intervals before undergoing endoscopic treatment. After successful endoscopy, participants were generally prescribed PPIs. Thus, the aim of the majority of these studies was to study the effect of pre-endoscopic PPI treatment on rebleeding events and other events, such as mortality or MI. In terms of study funding, six of the RCTs did not report their funding source, five studies were funded by industry, and the remaining ten studies reported receiving funding from non-profit or public sources.

Included observational studies were generally recently published. The majority of these studies (n=36) were published after 2009 and the remaining four studies were published between 2000 and 2009. Thirty of the observational studies were retrospective cohort studies based on analyses of large databases. The designs of the remaining studies were either prospective cohort (n=7), nested case-control (n=3), or self-controlled case-series design (n=2). The patient populations in Group A observational studies varied, with patients having conditions such as ACS, end stage renal disease (ESRD), cirrhosis, gastrointestinal disorders, clostridium difficile infection (CDI), pneumonia, or chronic obstructive pulmonary disease (COPD). In addition, some of the studies focused on elderly and frail patients requiring daily assistance or critically ill patients admitted to the intensive care unit. Sample sizes also varied substantially, ranging from 200 to over 250,000 patients. The mean age of the participants in most of Group A studies was above 60 years and ethnicity was generally not reported. Information on PPI exposure in the observational studies of Group A were, in general, extracted from large databases including electronic medical records (EMRs), prescription databases, insurance claims databases, hospital records, registries and medical charts. Five studies collected the data at the time of hospital admission by means of an interview or administration of questionnaires during and/or after hospitalization. In most studies, the exposure was reported as PPIs in general, without mentioning the specific type of PPI. Each included study assessed at least one of the four outcomes of interest, with follow-up periods ranging from one month up to 16 years. Information on outcomes of interest was collected retrospectively from large databases including electronic medical records, prescription records, claims databases and national death registers in 16 of the studies. More than half of the observational studies (53%, n=21) reported funding from public/non-profit sources, while five reported funding from industry, seven did not report the funding source and the remaining seven studies reported that their study was not funded.

2.3.2.2 STUDY FINDINGS

2.3.2.2.1 OBSERVATIONAL STUDIES

Quantitative findings extracted from Group A observational studies are summarized in Table 2-2. Reported effect estimates were adjusted for a wide variety of variables including age, sex, comorbidities, comorbidity indices, co-medications, as well as prior medical procedures. Several studies further adjusted for geographical region and levels of certain blood markers. Findings from the meta-analysis for each outcome are presented below. Reasons for not including certain studies in the meta-analysis are detailed for each study in Supplemental Material V.

ALL-CAUSE MORTALITY

Reported findings for ACM were pooled across four different patient populations. Pooled risk ratios (RR) were 1.36 (95% CI: 1.02-1.82) among frail patients requiring assisted living, 1.74 (95% CI: 1.05-2.90) among cirrhotic patients, 1.25 (95% CI: 0.77-2.03) for patients with MI or heart failure, and 1.31 (95% CI: 1.13-1.51) among patients with ESRD (Figure 2-2). There was a considerable amount of heterogeneity in the subgroup of studies among cirrhotic patients (I^2=79%), possibly a result of the variation in the variables adjusted and in the length of follow-up. The follow-up durations varied between 1 month (Kwon et al. 2013) and up to five years (Mandorfer et al. 2014). A high degree of heterogeneity was also observed in the subgroup of four studies among MI or heart failure patients (I^2=99%). Although these studies all had a follow-up period of one year and adjusted for numerous potential cofounders, the study by Charlot et al (2010), which reported a HR of 1.95 (95% CI: 1.82–2.09), was the major contributor to the heterogeneity observed. A meta-analysis restricted to the remaining three studies in this subgroup resulted in a lower pooled RR of 0.97 (95% CI: 0.89 - 1.06) and a substantially lower I^2 (16%).

Eight studies were abstracts where a corresponding full-text publication could not be identified (Taha et al. 2013; Antunes et al. 2016; Caffrey et al. 2016; Kwon et al. 2016; Bell et al. 2017; Bang and Bendtsen 2018; Gardezi et al. 2018; Sehested et al. 2018) and were therefore excluded from the meta-analyses. An additional seven studies reporting adjusted effect estimates (Myles et al.

2009; Maggio et al. 2013; Chen et al. 2014; Im et al. 2014; Shih et al. 2014; Lee et al. 2015; Bettinger et al. 2018) could not be included in the meta-analysis due to variations in the baseline characteristics of the study populations (COPD, percutaneous endoscopic gastrostomy, elderly, UGIB, pneumonia, and pyogenic liver disease). See Supplemental Material V for a list of the studies excluded from the meta-analyses. Assuming these patient populations have substantially different baseline event rates, it is not recommended to pool these studies (CIOMS, 2016). Individual findings of these studies that were not included in the meta-analyses suggest a higher risk of mortality with PPI use among COPD patients (Lee et al. 2015), elderly patients discharged from acute care hospitals (Maggio et al. 2013), patients with pyogenic liver disease (Bettinger et al. 2018) and PPI users in general (Shih et al. 2014). However, no significant associations were reported with PPI use and ACM among patients with pneumonia (Myles et al. 2009) or patients with UGIB (Taha et al. 2013). A possible association was concluded with PPI use among patients with percutaneous endoscopic gastrostomy (Im et al. 2014).

MYOCARDIAL INFARCTION

A pooled risk ratio of 1.37 (95% CI: 1.05-1.80) was obtained based on five studies among ACS patients (Figure 2-3), with considerably high heterogeneity between the studies (I^2=93%). The pooled RR is suggestive of a significant association between PPI use and MI. In two of these studies, however, the authors attribute the positive findings to unmeasured confounding (Charlot et al. 2010; Juurlink et al. 2013).

A meta-analysis of four studies among GERD patients (Figure 2-3) suggested a lack of association between PPI use and MI (RR 1.16, 95% CI: 0.84-1.59).

STROKE

Five studies reporting on the stroke outcome among the general population and among ACS patients were included in a meta-analysis (Figure 2-4). The RR for PPI use vs non-use among the general population pooled across two studies was RR=1.21 (95% CI: 0.97-1.52), suggestive of an increased risk. A study by Bell et al. (2017), in which only the abstract was identified and was therefore not included in the meta-analysis, also reported a positive and significant association between PPI use and stroke among the general population, with a follow up period up to 12 years (aHR 1.49; 95% CI: 1.35-1.65).

On the other hand, a statistically significant and positive pooled RR of 1.36 (95% CI: 1.19-1.56) was obtained among patients with ACS after pooling two studies. However, one of these studies was a large cohort study Charlot et al. (2010) contributing to 99.7% to the pooled RR relative to the second included study by Simon et al. (2011).

The remaining that assessed the stroke outcome but were not included in the meta-analyses reported positive associations between PPI use and stroke among patients with ESRD (Chen et al. 2014) and with UGIB (Sehested et al. 2018).

CARDIOVASCULAR MORTALITY

Four studies reported adjusted effect estimates but could not be pooled due to different patient populations (Charlot et al. 2010; Arana et al. 2015; Shah et al. 2015; de Francisco et al. 2018). Quantitative findings from these studies, which are all suggestive of a positive association between PPI use and cardiovascular mortality are summarized in Table 2-2.

2.3.2.3 RCTS

Fifteen of the 21 RCTs that reported findings on ACM as an adverse effect of PPI treatment (compared to placebo) in patients with upper gastrointestinal bleeding (UGIB) were pooled in a meta-analysis. The pooled RR was 0.94 (95% CI: 0.72-1.22), suggesting no increased risk in mortality among UGIB patients treated with PPIs compared to patients that received a placebo (Figure 2-5). Heterogeneity among these studies was low (I^2= 7%). Mortality was evaluated as in-hospital mortality with follow-up periods up to 40 days. Further, findings from two studies among critically ill patients with a 3-month follow-up period were pooled; the RR was 1.04 (95% CI: 0.93-1.14). One of the studies in this meta-analysis, which had no apparent sources of bias in the ROB scoring, contributed 94.5% to the pooled RR (Krag et al. 2018). The ROB ratings for the RCTs reporting on ACM in Group A are displayed in Figure 2-5.

Four studies that reported on ACM could not be pooled due differences in patient population (Gao et al. 2009; Liu et al. 2013; Leung et al. 2018) or the presence of the abstract only (Nikcevic et al. 2011). Quantitative findings from these studies are summarized in Table 2-3.

Three studies were included in a meta-analysis for the MI outcome among patients with UGIB (Figure 2-6). I^2 for heterogeneity was 0%, and the pooled RR was 0.88 (95% CI: 0.49-1.58). One RCT evaluated the number of stroke events among UGIB patients that had received omeprazole compared to placebo and reported no difference between the two groups (Hasselgren et al. 1997).

SENSITIVITY ANALYSES

A sensitivity analyses was performed on the funding source of Group A RCTs that assessed the risk of ACM among patients with UGIB. Although the RRs stratified by funding source were not statistically significant, the RR among the industry-sponsored (RR 1.10; 95% CI: 0.75-1.60) was higher than the RR among studies that were funded from public or non-profit sources (RR 0.73; 95% CI: 0.44-1.23) and studies that did not report their source of funding (RR 0.78; 95% CI: 0.37-1.66).

A sensitivity analysis was also carried out to assess the impact of risk of bias among RCTs. Comparing the pooled RR from studies that had no domains with "high risk" of bias (RR 0.88; 95% CI: 0.50-1.54) to the RR from studies that had one or more domains with "high risk" of bias (RR 0.94; 95% CI: 0.68-1.31), the overlap in the confidence intervals do not suggest funding has an effect on the study outcome. Forest plots for these sensitivity analyses are presented in Supplemental Material VI.

2.3.3 GROUP B (PPIS/CLOPIDOGREL VS CLOPIDOGREL)

2.3.3.1 STUDY CHARACTERISTICS

Fifty studies were identified that compared the outcomes of interest among patients co-prescribed clopidogrel and PPIs to users prescribed only clopidogrel (Table 2-4). Ninety four percent of these studies were observational studies (n=47), of which 32 were retrospective cohort studies. All studies in this group were published after 2009. Since these studies included clopidogrel users, all participants had some form of ACS at entry; this included conditions such as prior MI or stroke, percutaneous coronary intervention (PCI), or a prior stent placement. Thirty percent of these studies collected exposure information from prescription databases (either claims or national registries), followed by 16% that used hospital discharge databases. The remaining studies reported using pharmacy records, EMRs, medical chart abstraction, or prospective data collection through telephone or personal interviews. The retrospective cohort studies included a wide range of cohort sizes that varied between 300 patients and over 56,000 patients. The mean age of participants was over 60 years in all the studies that reported age distribution. Approximately half of the observational studies reported public or non-profit sources of funding, while a third did not report on their funding source. Five studies reported funding from industry and five studies reported not receiving any financial support.

The three RCTs in this group reported on the risk of one of the targeted outcomes with concomitant clopidogrel/PPI treatment compared to treatment with clopidogrel (Table 2-4). The study by Bhatt et al. (2010), conducted in 15 countries, is commonly cited as the only double-blind RCT that was designed to assess MACE endpoints as primary outcomes among clopidogrel users randomized to PPI (omeprazole) or placebo. The authors reported their findings on the 3,761 participants that were recruited before the study was terminated due to loss of funding from the sponsor (Bhatt et al. 2010). The sample included elderly males and females, with Caucasians predominating the sample (94%). The follow-up period for the MACE endpoints was six months. The second RCT was a six-month open label trial conducted in Taiwan and assessed the effect of esomeprazole among clopidogrel users with atherosclerosis and a history of peptic ulcers (Hsu et al. 2011). The study included 165 elderly men and women. Although the primary endpoint was the occurrence of ulcers, cardiovascular events confirmed by an independent committee were included as secondary endpoints. The third RCT in this group was carried out at three cardiology centers among ACS patients with a high risk for UGIB that were receiving clopidogrel (Wu et al. 2011). This study consisted of 665 participants randomized to receive either pantoprazole or placebo. The primary endpoint was gastrointestinal bleeding, but ACM was also evaluated after a follow-up period of one month. Information on 30-day mortality was collected from medical records or from the patient's family. Study participants were mostly above 75 years of age and predominantly male (70%).

2.3.3.2 STUDY FINDINGS

2.3.3.2.1 OBSERVATIONAL STUDIES

Thirty-eight of the included Group B observational studies reported adjusted effect estimates comparing the concomitant clopidogrel/PPI use vs clopidogrel use; these studies were eligible for inclusion in the meta-analyses. Many of the studies reported on more than one outcome of interest. In general, the majority of these studies reported on ACM (n=27 or 71%) while 23 studies (6%) reported on MI as an individual outcome. All studies included patients that had ACS including a prior MI or a stent placement or PCI procedure (Table 2-5).

ALL-CAUSE MORTALITY

Figure 2-7 presents the meta-analysis for ACM among Group B observational studies. Within this meta-analysis, the pooled RR for the subgroup of studies that are case-control or cohort studies was 1.26 (95% CI: 1.11-1.42), suggestive an increased risk of ACM with PPI use among clopidogrel users. However, the pooled RR for the subgroup of studies that are post-hoc analyses of RCTs or PS matched studies was slightly lower (RR 1.17, 95% CI: 0.82-1.67). There was substantial amount of heterogeneity among studies in both subgroups.

MYOCARDIAL INFARCTION

The RR for the subgroup of case-control or cohort studies was 1.23 (1.04-1.47), whereas the RR for PS matched studies and post-hoc analyses of RCTs was lower (RR 1.15, 95% CI: 1.00-1.32) (Figure 2-8). While substantive heterogeneity was found among the cohort and case-control studies (I^2=82%), the subgroup of PS matched studies and post-hoc analyses of RCTs showed less heterogeneity (I^2=37%).

Subgroup analyses were performed for specific types of PPIs for the MI outcome in Group B for esomeprazole (n=2), pantoprazole (n=3) and omeprazole (n=3) (Supplemental Material VI). The pooled RR for omeprazole (RR 0.97, 95% CI: 0.76-1.22) was lower than the pooled RR for esomeprazole (RR 1.18, 95% CI: 0.83-1.68) and pantoprazole (RR 1.18, 95% CI: 0.72-1.95); however, there was substantial overlap in the confidence intervals of the three pooled estimates suggesting they are similar.

CARDIOVASCULAR MORTALITY

A similar trend was observed for this outcome, with a significant and positive RR among case-control and cohort studies (RR 1.21; 95% CI: 1.09-1.34), and a slightly lower RR among studies that had PS matched design or post-hoc analyses of RCTs (RR 1.17; 95% CI: 0.80-1.71) (Figure 2-9). The cohort and case-control studies did not show any heterogeneity (I^2=0%), while the latter subgroup studies had substantial heterogeneity (I^2=85%).

STROKE

Seven Group B studies that reported on the association between concomitant treatment and the risk of stroke were pooled together (Figure 2-10). The pooled risk ratio for the subgroup of case-control or cohort studies was 1.05 (95% CI: 0.85-1.29), whereas the higher RR for the subgroup of two PS matched cohort studies was suggestive of an association with stroke (RR 1.75, 95% CI: 1.45-2.11). The latter subgroup analyses included the study by Charlot et al (2010), in which the authors reported positive associations for MACE endpoints but attributed their findings to the presence of confounding.

SENSITIVITY ANALYSES

Sensitivity analyses were feasible among observational studies of Group B for source of study funding. Among the studies that assessed MI and ACM outcomes, the point estimates of the RR for industry sponsored studies were generally higher than those corresponding to non-profit or public funding sources or studies that did not report their funding sources (Supplemental Material VI). This trend was not observed among studies that assessed cardiovascular mortality and stroke, which involved considerably fewer studies compared to the remaining endpoints of interest.

Sensitivity analysis exploring the effect of NOS quality on the pooled estimates was planned. However, all the observational studies included in the meta-analysis were classified to have good quality (NOS ≥6), and further exploration of the effect of quality was not feasible. Quality scores of observational studies included in the meta-analyses are presented in Supplemental Material VII.

2.3.3.3 RCTS

Findings from the three RCTs in Group B could not be pooled due to differences among patients' indications for PPI treatment. The Clopidogrel and the Optimization of Gastrointestinal Events

Trial (COGENT) by Bhatt et al (2010) assessed all four outcomes of interest among ACS patients and concluded that there was no association between concomitant clopidogrel/omeprazole treatment and MACE. The difference in event rates across the comparison groups was not statistically significant for either outcome. The remaining two studies also concluded that there was no association between pantoprazole and ACM (Wu et al. 2011) and esomeprazole and MACE (Hsu et al. 2011). Detailed quantitative findings from these studies are summarized in Table 2-6.

2.3.4 GROUP C (PPI/OTHER ANTIPLATELET VS ANTIPLATELET)

2.3.4.1 STUDY CHARACTERISTICS

Five observational studies and eight RCTs assessed the MACE risk of PPIs in combination with antiplatelet agents other than clopidogrel (Table 2-7). The study populations in the observational studies consisted of ACS patients, with mean ages over 60 years, and sample sizes greater than 9,000 individuals. Exposure to PPIs was assessed differently in the studies, such as self-reports at study entry, the use of prescription claims or hospital pharmacy data. Each observational study in this group reported on at least two outcomes of interest, with follow-up periods ranging from one to three years.

The RCTs in this group assessed the effect of esomeprazole, omeprazole or lansoprazole with at least one of the outcomes of interest among users of various drugs including naproxen, celecoxib, aspirin or ethanol injections (Table 2-7). These studies were published from 2000 and onwards. Participating hospitals/centers in the studies varied between one and 240 centers, with sample sizes ranging between 123 and 2,426 patients. Participants included male and female patients with mean ages over 60 years, treated for either peptic ulcers or GI bleeding. Follow up periods for the reported outcomes varied between 1 month and over one year. Five of the eight RCTs reported receiving funding from pharmaceutical companies.

2.3.4.2 STUDY FINDINGS

2.3.4.2.1 OBSERVATIONAL STUDIES

Five Group C observational studies evaluated the effect of concomitant PPI use with other antiplatelet agent (ticagrelor, prasugrel or aspirin) compared to the antiplatelet agent alone. A meta-analysis was only feasible for the ACM outcome, which included two studies among ticagrelor users (Figure 2-11). The pooled RR was 1.11 (95% CI: 0.89-1.39), a result dominated by the much larger study of Goodman et al. (2012) as compared to Yan et al. (2016). The study by Goodman et al (2012), a post-hoc analysis of the PLATO trial (Platelet Inhibition and Patient Outcomes trial), also reported a lack of association between PPI use and both MI and cardiovascular mortality in ticagrelor users (Table 2-8). In an additional analysis in this study, the authors compared the effect of PPIs among clopidogrel users; PPI use was reported to be associated with a higher rate of the composite outcome of cardiovascular death, MI or stroke. The authors suggest that the association may be due to confounding because similar associations were obtained when examining the effect of other gastric protection treatment among ticagrelor users. The authors concluded that PPI can be seen as a marker for, rather than a cause of, cardiovascular events. Charlot et al (2011) looked at PPI use among aspirin users and reported positive and statistically significant results for cardiovascular mortality, ACM, and MI using PS matching statistical methods. The authors concluded that the observed association requires further investigation.

O'Donoghue et al. (2009) evaluated the endpoints among ACS patients on PPIs and prasugrel compared to users of prasugrel alone. Findings suggest a lack of association with MI, ACM and cardiovascular mortality. This study also assessed the effect of PPIs among clopidogrel users and reported no association with cardiovascular outcomes. For the MI outcome, results were reported by specific types of PPIs, suggesting a lack of an association (Table 2-8).

2.3.4.2.2 RCTS

RCTs in this group evaluated the effect of PPIs among patients receiving naproxen, aspirin, and celecoxib; all studies reported no statistically significant difference between PPIs users and nonusers across the four outcomes assessed (Table 2-9) (Sofia et al. 2000; Lai et al. 2002; Chan et al. 2007; Yeomans et al. 2008; Scheiman et al. 2011; Angiolillo et al. 2014; Sugano et al. 2014; Whellan et al. 2014).

Meta-analyses were feasible for studies assessing the outcomes among aspirin users. Pooled RRs suggested no increase in risk with PPI use compared to non-use. The pooled RR for ACM associated with PPI use vs non-use among aspirin users was 1.09 (95% CI: 0.06-19.90) (Figure 2-12), while the pooled RR for MI was 0.69 (95% CI: 0.07-6.45) (Figure 2-13).

2.3.5 OBSERVATIONAL STUDIES ONLY REPORTING COUNTS/RATES OF EVENTS

Findings were extracted from observational studies that did not report adjusted effects estimates but included counts/rates of events for outcomes of interest. These studies were not eligible for inclusion in the meta-analysis but were included in the systematic review since they could contribute information -although limited- that is relevant to the research question of this review. Findings are summarized below qualitatively and extracted quantitative findings are presented in Supplemental Material VIII.

Six Group A studies reported counts of ACM among PPI users and nonusers. Higher mortality rates were reported among CDI patients within 90 days follow up (Freedberg et al. 2013) and elderly women (mean follow-up of 6.6 years). Haider et al. (2012) reported higher in-hospital mortality among CDI patients that received PPIs, but not when considering a longer follow up of 90 days. Among UGIB patients, two studies reported no difference in ACM between PPI users and nonusers (Keyvani et al. 2006; Win et al. 2010; Gardezi et al. 2018).

One Group A study assessed other outcomes of interest among PCI patients and reported no increased risk of cardiovascular events when comparing PPI users vs nonusers (Chitose et al. 2012).

Findings of Group B studies that reported counts of events were generally inconsistent. Four studies among patients with cardiovascular disease reported that there was no difference ACM between the comparison groups (Hudzik et al. 2010; Burkard et al. 2012; Galante et al. 2012; Depta et al. 2015). On the other hand, three studies reported that there was an association between the concomitant use of clopidogrel and PPIs with ACM (Chan et al. 2007; Gaglia et al. 2010; Munoz-Torrero et al. 2011). As for cardiovascular mortality, it was not found to be associated with concomitant PPI/clopidogrel treatment in three studies (Hokimoto and Ogawa 2010; Chitose et al. 2012; Yi et al. 2018).

Eight Group B studies reported on the number of MI events among concomitant PPI/clopidogrel users and clopidogrel users. An increased risk of MI was reported in two studies (Munoz-Torrero et al. 2011; Bhurke et al. 2012), while four studies reported no statistical difference between the two groups (Gaglia et al. 2010; Hokimoto and Ogawa 2010; Chitose et al. 2012; Yi et al. 2018). Further, a possible association between concomitant treatment and MI was reported by Ulhaq et al. (2011) and Hudzik et al. (2010).

Five Group B studies that examined the effect of PPI use on the rate of stroke events among clopidogrel users reported differences that were not statistically different between the groups (Hokimoto and Ogawa 2010; Hudzik et al. 2010; Chitose et al. 2012; Depta et al. 2015; Yi et al. 2018). Only one study concluded that there was an association between concomitant use of PPIs and clopidogrel with MI among patients with established arterial disease (Munoz-Torrero et al. 2011).

Kimura et al. (2011) reported on all four outcomes of interest among PCI patients that were receiving ticlopidine and aspirin (Group C). A possible association between PPIs and MACE was reported by the authors based on statistically significant differences between PPI users and nonusers for cardiovascular mortality, ACM, and MI. The difference in stroke events between the comparison groups, however, was not statistically significant.

2.4 DISCUSSION

The aim of this paper was to systematically review and summarize published findings from the literature that examine the effect of PPIs on adverse cardiovascular events. The quantity and weight of the evidence examined varied substantially across the three comparison groups evaluated. There were numerous studies looking at the effect of PPIs vs no PPIs among specific patient populations (Group A) as well as the effect of concomitant PPI/clopidogrel treatment vs clopidogrel treatment among ACS patients (Group B). On the other hand, studies examining the effect of PPI treatment combined with other drugs, mainly antiplatelet agents other than clopidogrel, were fewer in number (Group C). Findings for each outcome of interest from studies in Group A and Group B studies were pooled from two or more studies among similar patient populations. Group B studies consisted of ACS patients and findings were divided into subgroups based on study design characteristics when possible, to allow comparisons with previously published meta-analyses on this topic.

2.4.1 GROUP A (PPI VS NO PPI)

The suggestion that PPIs are associated with an increased risk of cardiovascular events is relatively recent, originally proposed as an alternative explanation to the modest positive associations reported with concomitant PPI/clopidogrel treatment. Findings from this review show that evidence in the literature on the association between PPIs and MACE is inconsistent. Although the number of Group A studies combined for each outcome and patient population was generally low (≤5 studies per subgroup), pooled RRs from observational studies were mainly positive for some individual outcomes among certain patient populations: 1) ACM: among frail patients, cirrhotic patients and patients with ESRD; 2) MI: among patients with ACS; and 3) stroke: among the general population. Statistical significance in the pooled RRs was not observed among other patient populations, such as heart failure patients (for ACM outcome), GERD patients (for MI outcome), and patients with ACS (for stroke outcome). Prior observational studies that reported positive associations sometimes attributed their findings to the presence of residual confounding, as in the positive associations reported among elderly frail patients who are more vulnerable to infections and vascular complications (Teramura-Gronblad et al. 2012). Juurlink et al. (2013) noted that an association of similar magnitude between MACE endpoints and PPI use was also observed with H2RA use, which have similar indications to PPIs but are not suspected of causing adverse cardiac events; the authors suggested that the association with PPIs is either spurious or due to bias. On the other hand, Charlot et al. (2010) reported positive associations for PPI use and MACE regardless of clopidogrel use; however, they dismissed causality noting that their use of administrative registry data did not allow adjusting for important risk factors such as BMI and smoking, which may introduced bias to their results. Charlot et al. (2010) estimated that unmeasured confounders would have to increase the risk by 2.5 to 3 fold in order to explain their observed association between PPIs and cardiovascular events. Nevertheless, they suspect that the observed increased risk for cardiovascular events in patients that received PPIs compared to those that did not receive PPIs in their study is due to differences in baseline characteristics that could not be accounted for in their analysis.

Among Group A RCTs included in this review, the meta-analyses suggest lack of associations between PPI use and the risk of MI or ACM among UGIB patients and critically ill patients. Sensitivity analyses among the studies assessing ACM showed that industry-sponsored studies generally reported lower effects compared to studies that did not report their funding source or those that received funding from public or non-profit sources.

Heterogeneity was substantial among observational studies, likely due to variations in patient characteristics, exposure assessment, outcome ascertainment and statistical analyses. Heterogeneity among RCTs, however, was relatively low ($I^2 \leq 7\%$). The visual evaluation of the funnel plots of the meta-analyses for ACM did not suggest the presence of publication bias (Supplementary Material IX).

Among the observational studies that did not report adjusted effect estimates (Supplemental Material VIII), five of seven studies reported no statistical differences in the proportion of events for MACE endpoints among PPI users and nonusers. Comparisons were based on raw counts of events without any adjustment for potential confounders. Findings from these studies should be looked at with caution, since the objectives of many of these reports were not directly relevant to this review, and counts of adverse cardiovascular events or mortality were incidentally reported. Therefore, in addition to the potential for confounding in these studies, they may also be underpowered to detect significant differences in these outcomes.

A lack of association between PPIs and mortality is supported in two systematic reviews. Leontiadis et al. (2007) reported no significant effect of PPIs on mortality in a review that looked at the effectiveness of PPIs for UGIB. Yu et al. (2016) examined the association between PPI use and spontaneous bacterial peritonitis (SBP) incidence in a systematic review and also reported no association with in-hospital mortality. However, two recent systematic reviews, each based on five observational studies, reported an increased risk of cardiovascular events (Al-Shammari et al. 2017; Shiraev and Bullen 2018) and of ACM (Shiraev and Bullen 2018) with PPI use. Both of these reviews did not include data from RCTs and recommended further studies are needed on this topic.

2.4.2 GROUP B (PPI/CLOPIDOGREL VS CLOPIDOGREL)

The potential for PPIs to increase the risk of MACE among clopidogrel users with ACS has been widely debated since 2009. Aside from the one high quality RCT examining this association, and which reported no association (Bhatt et al. 2010), findings have come from observational studies, with a wide range of designs, sample sizes and statistical methods. Findings presented in this review show that the evidence in the literature is inconclusive.

In the present review, pooled estimates for ACM and for MI were positive and statistically significant when pooled across all included observational studies for each outcome. A positive pooled RR was also obtained for the cardiovascular mortality endpoint, although it did not reach statistical significance. However, when the findings were grouped by separating the post-hoc analyses of RCTs and studies that used PS matching from the remaining observational studies, point estimates were reduced for these three endpoints and were no longer statistically significant in the case of ACM and cardiovascular mortality (Figures 2-7, 2-8 and 2-9). There was also no suggestion of publication bias based on the visual examination of the funnel plots of the meta-analyses that included ten or more studies (Supplementary Material IX).

Similar patterns to those reported in this review were noted in two prior systematic reviews that had employed comparable subgroup analyses. Kwok and Like (2010) reported that pooling across PS matched or post-hoc analysis of RCTs showed no association in cardiovascular risk with

PPIs compared to the significant association seen across other observational studies. Using a slightly different subgrouping approach, Cardoso et al (2015) reported positive and statistically significant effects for ACM, MI and stroke, across all studies. However, when they restricted their analyses to studies that used PS matching and one RCT, which they referred to as studies “less prone to selection bias”, the effect estimates were notably reduced (by as much as one third) and were no longer statistically significant. Similarly, Siller-Matula et al (2010) reported reductions in pooled effect estimates when the meta-analysis was restricted to RCTs and post-hoc analyses of RCTs.

Possible reasons for these observations may be related to the data collection process in RCTs, where adverse events are commonly adjudicated by independent committees; consequently, outcome ascertainment may be more reliable in the data available for post-hoc analyses of RCTs (Kwok and Loke 2010). Further, using propensity score matching in observational studies results in better balance between treatment groups in the variables included to calculate the propensity score for each patient (Joffe and Rosenbaum 1999; Seeger et al. 2007; Pattanayak et al. 2011). Although PS matching can only lead to balance on known and measured confounders and thus findings may still be subject to bias from unmeasured confounding, this method is powerful in reducing selection bias (Morgan 2018). If pooling across findings from study designs that better control for confounding and less prone to selection bias yielded non-significant effects, this may indicate that the modest increases in risk from cohort and case-control studies are due to residual confounding and not a result of a true association between concomitant PPI/clopidogrel treatment and MACE. Such an argument would support the absence of a clinical impact of the drug-drug interaction between PPIs and clopidogrel, despite findings from laboratory studies which support a biological interaction.

Conversely, for the stroke endpoint, the pooled estimate was statistically significant among two PS matched studies, but not among the remaining five observational studies.

Some reviews have examined composite cardiovascular outcomes rather than individual cardiovascular endpoints. Kwok et al (2013) reported that pooled effect estimates for individual PPIs were significantly associated with MACE with ORs in the range of 1.24 to 1.41. The authors also reported a significant association between PPIs and MACE independent of clopidogrel (OR 1.28; 95% CI: 1.14-1.44). When analyses were restricted to two RCTs that assessed the composite MACE outcome, pooled estimates were non-significant. The authors reported their results to support a lack of association with concomitant clopidogrel and PPI treatment, and considered the inconsistent evidence as suggestive of the presence of bias and confounding leading to positive findings. On the other hand, a recent systematic review of 21 studies (Niu et al. 2016) reported an increased risk of MACE with concomitant treatment relative to clopidogrel alone (OR 1.42, 95% CI: 1.30-1.55) among patients with coronary artery disease. The authors defined MACE as a composite outcome consisting of cardiovascular death, nonfatal MI, stroke, stent thrombosis and revascularization. An increased risk was detected among all types of individual PPIs except rabeprazole. Further, no statistical difference was reported between subgroup analyses of randomized studies and observational studies. Reported limitations of the review by Niu et al. (2016) include: 1) variation in the definition of MACE among studies; 2) the substantial degree of heterogeneity among studies indicating there may be confounding among findings; and 3) the number of studies in some subgroup analyses was small. Moreover, findings for MACE between prospective and retrospective studies were compared in a recent meta-analysis (Focks et al. 2013). A lower OR was reported for the association between combined clopidogrel/PPI treatment and risk of MACE in prospective studies (OR 1.13, 95% CI 0.98-1.3) relative to retrospective studies (OR 1.63, 95% CI: 1.45-1.83). The authors concluded that observational studies are prone to prescription bias as well as residual confounding due to imbalances in baseline characteristics of the treatment groups.

Moreover, in a systematic review of 25 studies, Siller-Matula et al. (2010) concluded that there is no increased risk of mortality, although there may be an increased risk of MACE (RR 1.29, 95% CI: 1.15-1.45) and MI (RR 1.31, 95% CI: 1.12-1.53) with concomitant clopidogrel/PPI treatment. The authors suggest that significant heterogeneity found among studies may indicate confounding. Further, the authors pointed out that PPI users were generally older, had more comorbidities, and were more likely to have had an MI or heart failure prior to hospitalization, all of which are factors associated with less favorable clinical outcomes. Their findings were unchanged when stratified by different publication types, study quality and sample sizes.

In summary, systematic reviews assessing this potential association have arrived at inconsistent conclusions. Findings suggest that pooling of observational studies sometimes yields positive associations that are reduced when certain subgroup analysis are carried out. Many authors have used this finding as support that modest positive associations are a result of confounding inherent in observational research.

2.4.2.1 SENSITIVITY ANALYSES

There was no impact of the source of funding on pooled RRs. In this sensitivity analysis, studies were grouped for each outcome depending on whether they reported funding by 1) industry, 2) public or non-profit organisations, or 3) whether the source was not reported. This sensitivity analysis was motivated by the recent reviews reporting that drug trials financed by pharmaceutical companies are more likely to report conclusions that are favorable for the drug manufacturer compared to when trials are financed from other sources (Schott et al. 2010; Lundh et al. 2012; Lundh et al. 2017).

2.4.3 GROUP C (PPI/OTHER ANTIPLATELET VS ANTIPLATELET)

Group C studies were less represented in our meta-analyses than were Group A and B studies because of the smaller number of such studies and the requirement for adjusted effect estimates for meta-analyses. Among studies in this group, the risk of adverse cardiovascular events with PPI use was assessed in patients receiving antiplatelet agents other than clopidogrel, namely aspirin, ticagrelor and prasugrel. Pooling of two studies, a post-hoc analysis of the PLATO trial (Goodman et al. 2012) and a retrospective analysis of the BleeMACS registry (Bleeding complications in a Multicenter registry of patients discharged after an Acute Coronary Syndrome) (Yan et al. 2016), did not suggest an association between PPI use and ACM among patients receiving ticagrelor (Figure 2-11). Among prasugrel users, a post-hoc analyses of the PRINCIPLE-TIMI 38 trial (O'Donoghue et al. 2009) also suggested that PPI use was not associated with MACE.

The association between PPI use and MACE among aspirin users was examined in several studies. A retrospective PS matched analysis of administrative data in Denmark found an increased risk across all four outcomes of interest associated with PPI use among aspirin users that have had a first time MI (Charlot et al. 2011). The authors speculated about a biological mechanism, involving the potential for reduced gastric absorption of aspirin as a result of a change in gastric pH in the presence of PPIs. The authors also reported that no increase in risk was detected with the use of H2RAs and aspirin and recommended further investigation of their observation. Three RCTs also examined this association among patients receiving aspirin, where pooling of findings suggested a lack of association between PPIs and ACM (Yeomans et al. 2008; Scheiman et al. 2011) and between PPIs and MI (Yeomans et al. 2008; Whellan et al. 2014).

2.4.4 LIMITATIONS OF INDIVIDUAL STUDIES

Several limitations were common to individual studies included in the review. For example, studies did not take into account patient adherence to the drug exposure being evaluated. Exposure ascertainment was assessed in many of the retrospective studies based on database information that included prescribed medications or pharmacy records that includes only dispensed medications. Siller-Matula et al (2010) report that low compliance is more common in observational studies compared to RCTs that are characterised by close monitoring of exposure. They also suggest that strict adherence to antiplatelet treatments is less likely among patients with gastric symptoms. An additional concern is that several PPIs (such as omeprazole and lansoprazole) can be purchased without a prescription; as such, observational studies that do not assess over the counter use of PPIs may be subject to exposure misclassification. Although some prior studies, have reported that this is not likely to introduce bias; patients would have had to pay to obtain it over the counter, whereas it would be less expensive through their insurance. The likelihood of bias would vary from study to study depending on the database and corresponding insurance policies.

The majority of studies assessing the association between concomitant PPI and clopidogrel treatment in this review were observational studies, which are inherently prone to certain biases. The main limitation reported in several of these observational studies was the potential bias from residual confounding (Daskalopoulou et al. 2008; Myles et al. 2009; Oudit et al. 2011; Kwon et al. 2013; Maggio et al. 2013; Chen et al. 2014; Mandorfer et al. 2014; Shih et al. 2014; Dultz et al. 2015; Lee et al. 2015). Indeed, the issue of unmeasured confounders is important, as many of the observational studies included in this review were based on analyses of large databases of medical records; consequently, important information on MACE risk factors such as smoking, obesity, alcohol consumption, family history of cardiovascular disease and other variables was not available to the investigators.

Confounding by indication has been cited as a possible concern (Charlot et al. 2010; Valkhoff et al. 2011; Kwok et al. 2013). Strom et al. (2006) describe confounding by indication as a form of selection bias in observational studies, where “patients taking a particular medication are selected in a fashion that makes them at unequal risk of the outcome under study”. In observational studies, PPIs are not randomized to patients but are prescribed at the discretion of the treating physician. Thus, patients receiving PPIs may have particular characteristics that increase their baseline risk of experiencing a cardiovascular, leading to an imbalance in the baseline risk between PPI users and nonusers. For example, Dultz et al. (2015) indicated that advanced liver disease was more common among PPI users, putting them at a higher risk for death compared to nonusers. Similarly, Oudit et al. (2011) reported a higher prevalence of anemia among PPI users which is associated with adverse effects in patients with heart failure. Moreover, Focks et al. (2013) speculate whether doctors may be more likely to prescribe PPI to patients with comorbidities compared to the healthier patients. The issue of protopathic bias was noted by Juurlink et al. (2013), as a possible reasons for their observed increased risk of cardiac events among PPI users. Protopathic bias occurs "when the drug is initiated in response to the first symptoms of the diseases which is, at this point, undiagnosed" (Faillie 2015). For example, patients presenting with abdominal pain, which may be a sign of MI, may be more likely to receive a PPI prescription. These considerations have led several authors to suggest that PPI use should be viewed as a marker for an increased risk of MACE rather than a cause (Goodman et al. 2012; Focks et al. 2013; Cardoso et al. 2015).

2.4.5 BIOLOGICAL PLAUSIBILITY LINKING PPIS TO MACE

Investigating the biological mechanisms by which PPIs may be linked to cardiovascular events is relatively recent. Ghebremariam et al. (2013) suggested that PPIs have the potential to impair vascular homeostasis. They proposed a biological mechanism where PPIs may inhibit the activity of the enzyme dimethylarginine dimethylaminohydrolase (DDAH) that degrades asymmetrical dimethyarginine (ADMA). As a result, higher levels of ADMA may lead to lower levels of nitric oxide (NO), since ADMA is an inhibitor of nitric oxide (NO) synthase. Through a series experiments in animals and ex-vivo human models, Ghebremariam et al. showed that PPIs can increase intracellular ADMA levels. The concern is that lower levels of NO have been suggested to be associated with an increased risk for MACE (Rochette et al. 2013). The authors acknowledge that their findings are to be used for hypothesis generation, and the potential for PPIs to lead to adverse clinical effects should be further investigated. Other publications have also suggested that increased ADMA levels may be associated with cardiovascular disease risk factors, such as hypertension and hypercholesterolemia (Cooke 2004; Rochette et al. 2013). The use of ADMA levels as a cardiovascular risk factor has also been suggested for prediction of future MACE events and mortality in ESRD patients (Böger & Zoccali 2003). Future investigations may provide a clearer understanding on the association between PPIs and ADMA.

The potential impact of ADMA levels has also been the subject of epidemiological studies. In a cohort of healthy women, Leong et al. (2008) reported positive associations between ADMA concentrations and cardiovascular mortality as well as MI events, but not with ACM. Conversely, in another prospective study among non-diabetics, associations between higher ADMA levels and ACM were reported, but no associations were found with adverse cardiovascular events (Böger et al. 2009). Further, Schillinger et al. (2007) reported a dose dependent effect of pantoprazole in reducing cardiac contractility in vitro, although this finding was not found to have any clinical relevance in a randomized cross-over trial among 18 healthy adults (Schillinger et al. 2009).

Findings linking an interaction between clopidogrel and PPIs that could potentially lead to adverse cardiovascular events are more common in the literature. Clopidogrel is a second-generation thienopyridine taken as a prodrug. It is transformed into an active metabolite in the liver in a two-step process that is regulated by the cytochrome P450 (CYP) enzymatic pathway, where the CYP2C19 enzyme has the major role (Mackenzie et al. 2010). Enzymes that are active in both steps of clopidogrel activation are also important in the metabolism of many drugs including PPIs, possibly facilitating a drug-drug interaction by means of competitive inhibition. The effectiveness of antiplatelet treatment is commonly assessed using platelet function tests (Harrison and Mahaffey 2012). Earlier ex-vivo platelet aggregation studies using a variety of platelet function tests have showed that clopidogrel's antiplatelet effect is attenuated when it is combined with PPIs. Moreover, the reduction in clopidogrel's antiplatelet effect as a result of combining with PPIs does not seem to apply to all the class of PPIs. For example, pharmacodynamic studies have shown that omeprazole interacts with clopidogrel, whereas pantoprazole does not affect platelet activity (Harrison and Mahaffey 2012). From a biological perspective, this can be explained by the degree of dependency on the CYP2C19 metabolic pathways for different types of PPIs. Again, how this difference translates into clinical effects is not clear based on epidemiological studies.

The relevance of ex-vivo findings as a surrogate for endpoints in the case combined treatment with clopidogrel and PPIs was questioned in a recent systematic review. Focks et al (2013) report that meta-analysis findings from laboratory studies support the presence of a pharmacological interaction between clopidogrel and PPIs in healthy volunteers, but that the findings are less uniform among studies involving patients.

Biological interactions between PPIs and other antiplatelet agents have also been examined in the literature. In the case of aspirin, one hypothesis is that PPIs lead to an increase in the gastric pH which affects the solubility of aspirin and reduces its bioavailability (Hollander et al. 1981). The effect of PPIs on gastric absorption has been demonstrated in rats, where omeprazole resulted in reduced absorption and reduced bioavailability of aspirin (Giraud et al. 1997). Würtz et al. (2010) also reported that platelet aggregation was higher in aspirin treated patients taking PPIs compared to those not on PPIs. Despite this plausible biological pathway, several cross-over studies have reported no differences in ex-vivo experiments measuring platelet aggregation or aspirin plasma levels among patients on aspirin/PPI treatment compared to those on aspirin alone (Iñarrea et al. 2000; Chan et al. 2007; Adamopoulos et al. 2009; Andersson et al. 2012). Although the number of epidemiological studies on aspirin is considerably less than those done on clopidogrel, conflicting data exists between the presence of biological plausibility of an interaction and the inconsistent findings in epidemiological studies.

Newer antiplatelet agents, prasugrel and ticagrelor, have different biological pathways that lead to their antiplatelet action. Ticagrelor does not require biotransformation (Kalantzi et al. 2012) and therefore does not have the potential for direct interaction with PPIs through CYP450 enzymatic pathways. Prasugrel, on the other hand is a prodrug, and like clopidogrel, belongs to the thienopyridine class. It must be activated in the body by CYP450 enzymes for its antiplatelet benefits. However, its conversion to its active form is not substantially diminished by CYP enzymes (Fayer Rehmel et al. 2006; Small et al. 2008; Norgard and DiNicolantonio 2013). In the case of ticagrelor, there is no known biological plausibility that suggests a possible interaction between PPIs and ticagrelor. Since the role of CYP450 enzymes varies from the action of one antiplatelet agent to another, it is important to compare the potential clinical impacts of concomitant PPIs and clopidogrel, prasugrel and ticagrelor. Such analyses would allow making comparisons between concomitant treatments taking into account the biological plausibility related to each drug. This may clarify the nature of the reported associations with clopidogrel since pharmacodynamics and pharmacokinetic studies have suggested an interaction between clopidogrel and PPIs.

2.4.6 STRENGTHS AND LIMITATIONS OF THE REVIEW

This comprehensive review sought to identify and summarize published evidence assessing the potential cardiovascular and mortality risks associated with PPIs. Adjusted effects estimates reported in epidemiological studies were included in the meta-analysis. Findings were analysed and presented for individual cardiovascular endpoints, but not for the composite MACE outcome. MACE is commonly used in cardiovascular research as an important measure of the overall impact of an intervention. Its use may also add statistical power to a study and reduce the sample size required by ensuring that the outcome will have a large number of events (Kip et al. 2008). However, there are some concerns with its use in systematic reviews. First, there is no standard definition for MACE; individual outcomes combined to make this endpoint were found to vary by study (Kip et al. 2008). For example, mortality was included in the MACE outcome in some studies, but not in others, making it difficult to pool together MACE endpoints that had been defined differently in individual studies. Second, conclusions arrived at by only considering MACE endpoint may be misleading if the size of effect varies significantly across individual endpoints and the number of events of the more important outcome is small. For example, Ferreira-González et al. (2007) argue that if a particular intervention was found to reduce MACE consisting of cardiovascular deaths, MI and revascularization procedures, then it may be misleading to readers if the majority of the events during the study were revascularization procedures compared to deaths or MIs. Based on their systematic review, the authors concluded that reporting individual endpoints is important for better interpretation of the effects.

Moreover, studies that did not report adjusted effects were excluded from the meta-analysis, but findings were included in the systematic review. While counts of events - compared to adjusted measures of association - provide limited evidence by, findings have been compiled and tabulated for interested readers to review.

The main limitation of the pooled results presented in this review is that findings are largely based on observational studies. Observational studies generally have a higher chance of confounding when compared to RCTs, particularly due to the non-random assignment of PPIs to patients. Although only adjusted effect estimates were pooled in the meta-analyses and all studies were found to be of high quality, findings from observational studies still have the potential for residual confounding. It is difficult to confirm that all of potential biases have been accounted for in observational studies. Nonetheless, findings from such studies represent “real world” data from participants on the medications. This is in contrast with RCTs, which typically recruit patients that are generally healthier than patients that end up taking the study medications in the real world. This is critical in the case of PPIs, which have been reported to be taken by elderly patients usually having multiple comorbidities and being prescribed multiple medications. Although many methods are used to account for confounding, Strom et al (2006) suggests that when confounding by indication is likely present, it is difficult to control unless the severity of the underlying illness is reliably measured. Instead, studies that randomize exposure may be necessary to arrive at a valid estimate of the true association (Strom et al. 2006).

Another limitation is the considerable heterogeneity among the observational studies. This is not unusual in observational studies which include more variation in the methodology of study design and execution studies compared to RCTs (CIOMS 2016). Much of the heterogeneity can be attributed to differences between the studies, which include differences in patient populations, variables adjusted for, follow-up periods, statistical analyses, and exposure and outcome ascertainment. Further, including a relatively large number of individual studies in the meta-analysis increases the power of the chi-squared statistical test to detect small amounts of heterogeneity, which may be, in some cases, clinically insignificant (Higgins and Green 2011). In order to incorporate heterogeneity in the meta-analyses of observational studies, random effect modelling methods were used as recommended in the Cochrane Handbook (Higgins and Green 2011).

Group C included fewer studies compared to Group A and Group B, which limited the number of meta-analyses performed.

Despite the review's limitations, the findings summarized here provide a comprehensive and up-to-date synthesis of the potential cardiovascular risks of PPIs alone and in combination with other drugs. The present review also identifies the need for further well-designed studies investigating the potential effects, particularly of PPIs alone and with antiplatelet agents other than clopidogrel, while controlling for potential biases.

2.5 CONCLUSIONS

Although findings from platelet aggregation studies support the presence of an interaction between clopidogrel and PPIs at the cellular level, evidence of a clinical impact presented in this review is not sufficiently strong to support a causal relationship. It is possible that the interaction at the cellular level does not result in significant clinical effects. Rather, it may be that patients who are prescribed PPIs have a higher burden of comorbidities and are consequently at increased risk for adverse cardiovascular events. It is important to keep in mind that PPIs have many benefits and are effective in reducing GI bleeding among patients taking clopidogrel. Further investigation is needed to determine whether reported associations are indeed causal, and whether modest associations - if present - may be outweighed by the benefits that combined treatment brings.

Findings from epidemiological and laboratory studies examining the harms associated with PPIs independent of concomitant clopidogrel are still in the early stages. Experts in the field suggest that the evidence is insufficient to warrant major changes in management of patients requiring PPIs except for the careful assessment of the need for the medication (Schnoll-Sussman and Katz 2017). PPIs have many benefits, as they are clearly highly effective in managing gastric acid-related disorders, even more effective than H2RAs. Although PPIs have been linked to certain conditions such as pneumonia, interstitial nephritis, bone fractures and Clostridium difficile infections (Würtz and Grove 2016), the studies examining their potential adverse effects on cardiovascular endpoints are limited and reported findings warrant further research for a better understanding of the potential association and to support risk-benefit analyses.

Many authors have pointed to the need for a well-designed RCT on this topic to address the issue of selection bias and unmeasured confounding which cannot be completely eliminated in observational studies. The COGENT (Bhatt et al. 2010) provides randomized evidence of the potential effects of combined PPI/clopidogrel treatment among ACS patients; subjects were randomized to receive either clopidogrel alone or clopidogrel in combination with omeprazole. The trial, however, was stopped before recruitment of the planned sample size due to lack of funding and was therefore underpowered for adverse cardiovascular outcomes. An analysis on the 3,873 patients included suggests that there was no evidence of an increased risk of cardiovascular events or mortality with the combination treatment. Further, PPIs were found to significantly reduce upper GI adverse events and bleeding (Bhatt et al. 2010). Juurlink (2011) noted that the drugs given to the patients in this study had a unique formulation that allows for the separate release of omeprazole and clopidogrel. This differs from the commercially available omeprazole used in clinical settings and may have a role in attenuating the potential interaction between the two drugs. The authors of COGENT argue that although the formulation was different, the significant reduction in clinical GI events indicates that omeprazole was adequately absorbed (Bhatt et al. 2011). Nevertheless, the investigators did not dismiss the possibility of an interaction, but reported that a clinically significant interaction is unlikely.

In conclusion, findings from this comprehensive systematic review and meta-analysis suggest that currently available scientific evidence does not consistently support an increased risk of cardiovascular events or mortality with the use of PPIs, whether taken alone and concomitantly with clopidogrel or other antiplatelets. Some of the outcomes evaluated showed modest positive associations in the meta-analyses of observational studies; however, these associations were reduced when limiting analysis to studies that were based on designs that may be more efficient in controlling confounding. Further, pooled findings from RCTs comparing the effect of PPI use compared to a placebo, among patients with UGIB, do not suggest an increased risk in MACE outcomes. Although there is evidence for a pharmacodynamic and pharmacokinetic drug-drug interaction, the clinical importance of this effect remains unclear. It is recommended that well designed RCTs be developed to investigate the potential of PPIs -alone or in combination with other drugs- to lead to adverse events.

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FIGURES

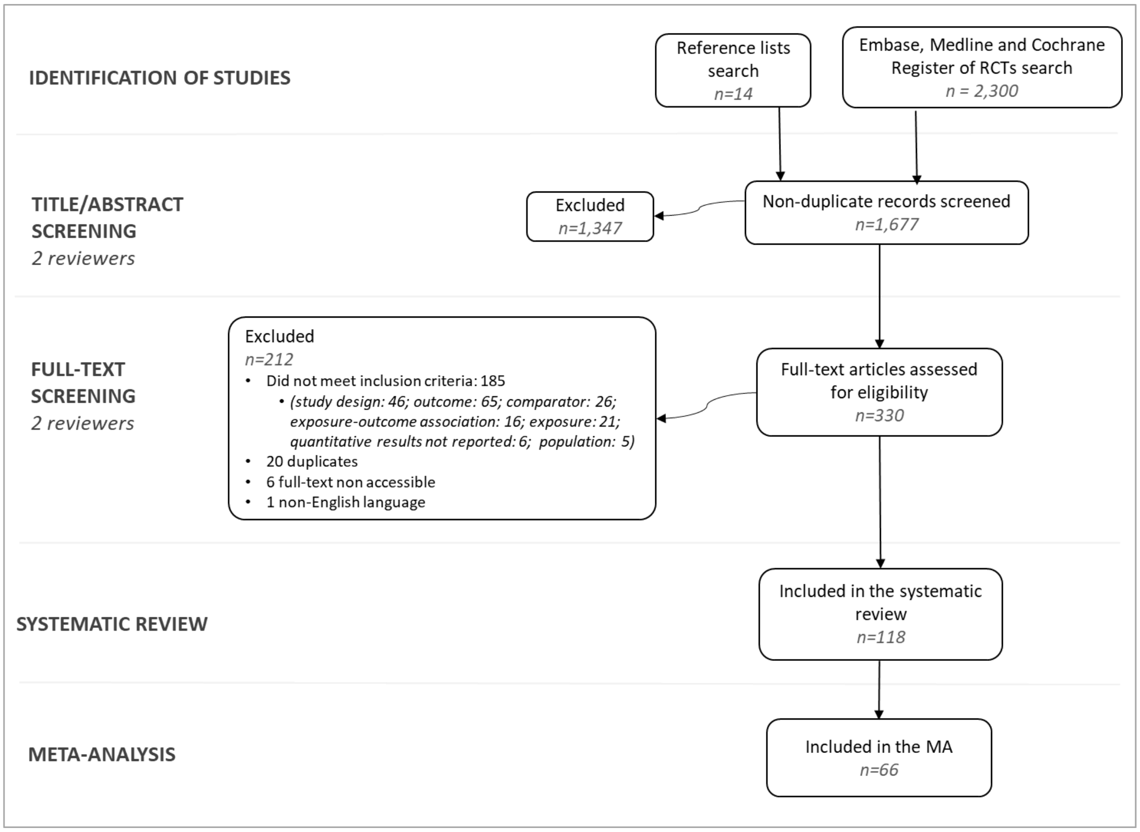


FIGURE 2-1. FLOW CHART FOR THE SELECTION OF STUDIES INCLUDED IN THE SYSTEMATIC REVIEW AND THE META-ANALYSIS.

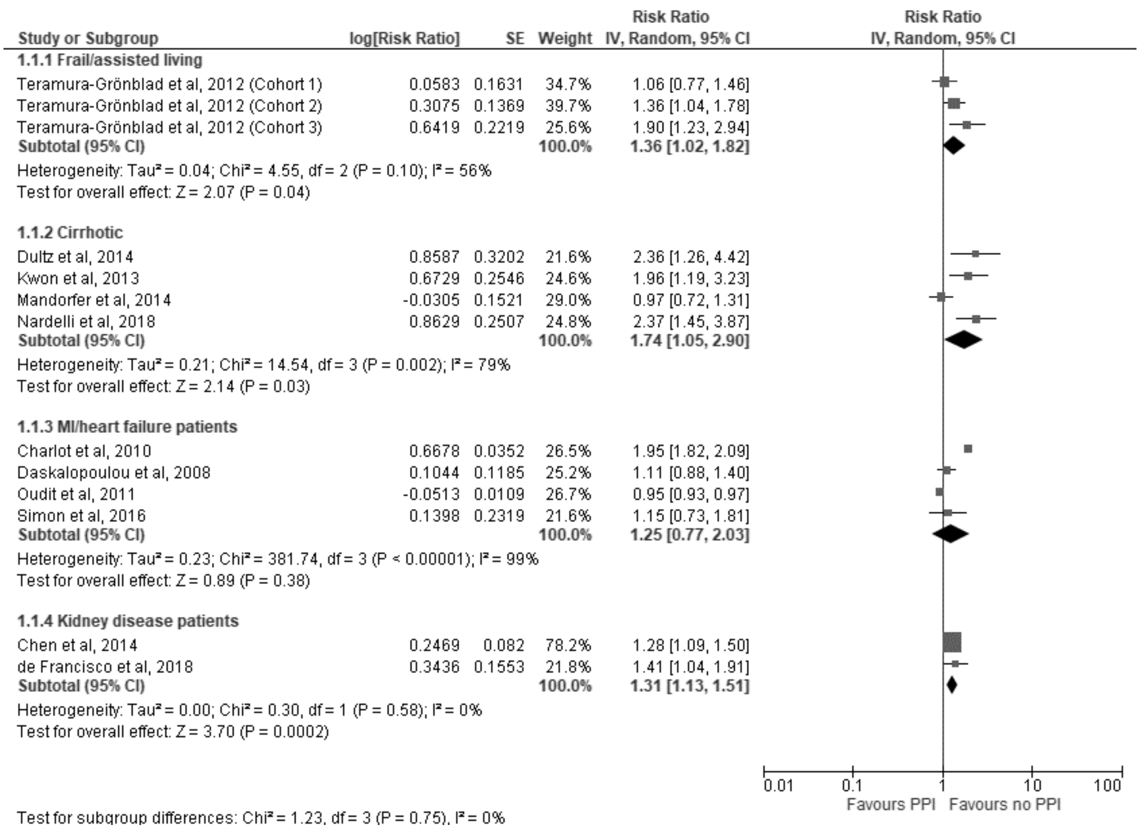


FIGURE 2- 2. POOLED RISK RATIOS (RRS) FOR GROUP A OBSERVATIONAL STUDIES THAT ASSESSED THE RISK OF ACM WITH PPI USE VS NONUSE. STUDIES WERE SUBGROUPED BASED ON PATIENT POPULATIONS.

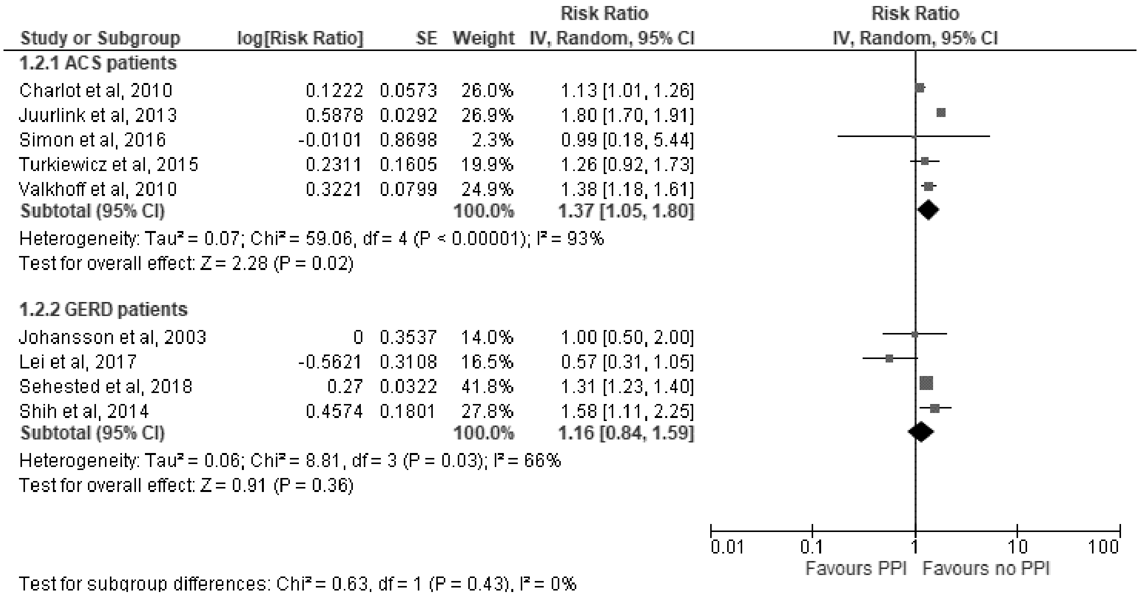


FIGURE 2- 3. POOLED RISK RATIOS (RRS) FOR GROUP A OBSERVATIONAL STUDIES THAT ASSESSED THE RISK OF MI WITH PPI USE VS NONUSE. STUDIES WERE SUBGROUPED BASED ON PATIENT POPULATIONS.

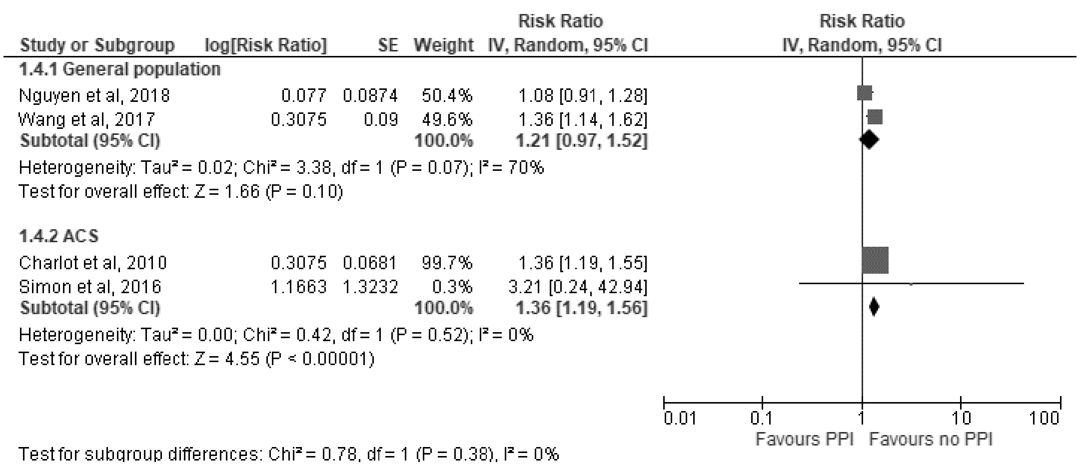
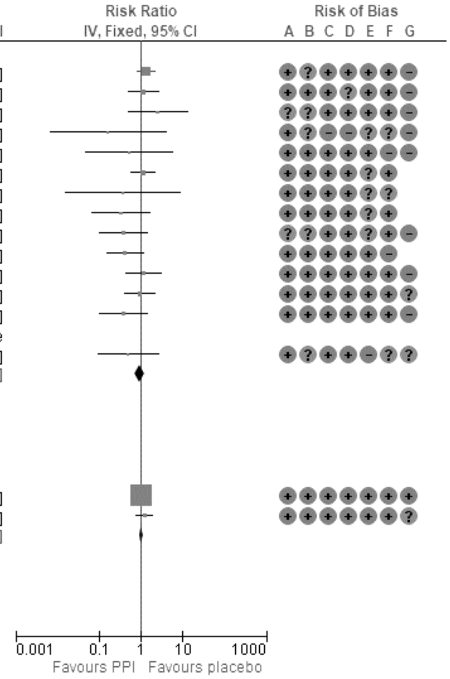


FIGURE 2- 4. POOLED RISK RATIOS (RRS) FOR GROUP A OBSERVATIONAL STUDIES THAT ASSESSED THE RISK OF STROKE WITH PPI USE VS NONUSE. STUDIES WERE SUBGROUPED BASED ON PATIENT POPULATIONS.

Study or Subgroup	PPI Events	PPI Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
3.1.1 UGIB patients						
Daneshmend et al, 1992	40	578	30	569	32.8%	1.31 [0.83, 2.08]
Hasselgren et al, 1997	11	159	10	163	10.1%	1.13 [0.49, 2.58]
Hawkey et al, 2001	5	102	2	103	2.6%	2.52 [0.50, 12.72]
Hung et al, 2007	0	103	1	50	0.7%	0.16 [0.01, 3.94]
Javid et al, 2001	1	82	2	84	1.2%	0.51 [0.05, 5.54]
Kantorova et al, 2004	14	72	13	75	14.9%	1.12 [0.57, 2.22]
Kaviani et al, 2003	0	71	1	78	0.7%	0.37 [0.02, 8.84]
Khuroo et al, 1997	2	110	6	110	2.8%	0.33 [0.07, 1.62]
Kuipers et al, 2011	3	375	8	389	4.0%	0.39 [0.10, 1.46]
Lau et al, 2000	5	120	12	120	6.7%	0.42 [0.15, 1.15]
Lau et al, 2007	8	314	7	317	6.9%	1.15 [0.42, 3.14]
Schaffalitzky de Muckadell et al, 1997	10	130	11	135	10.2%	0.94 [0.42, 2.15]
Sung et al, 2009	3	375	8	389	4.0%	0.39 [0.10, 1.46]
Wei et al, 2006	0	35	0	35		Not estimable
Zargar et al, 2006	2	102	4	101	2.5%	0.50 [0.09, 2.64]
Subtotal (95% CI)		2728		2718	100.0%	0.94 [0.72, 1.22]
Total events	104		115			
Heterogeneity: Chi² = 13.96, df = 13 (P = 0.38); I² = 7%						
Test for overall effect: Z = 0.47 (P = 0.64)						
3.1.2 ICU/critically ill patients						
Krag et al, 2018	510	1642	499	1640	95.2%	1.02 [0.92, 1.13]
Selvanderan et al, 2016	30	106	25	108	4.8%	1.22 [0.77, 1.93]
Subtotal (95% CI)		1748		1748	100.0%	1.03 [0.93, 1.14]
Total events	540		524			
Heterogeneity: Chi² = 0.57, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.57 (P = 0.57)						

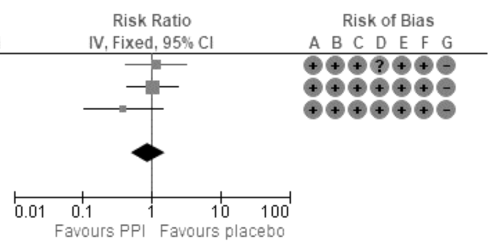


Test for subgroup differences: Chi² = 0.41, df = 1 (P = 0.52), I² = 0%

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

FIGURE 2- 5. POOLED RISK RATIOS (RRS) FOR GROUP A RCTS THAT ASSESSED THE RISK OF ACM WITH PPI USE VS NONUSE. STUDIES WERE SUBGROUPED BASED ON PATIENT POPULATIONS.

Study or Subgroup	PPI Events	PPI Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
Hasselgren et al, 1997	8	314	7	317	33.7%	1.15 [0.42, 3.14]
Lau et al, 2007	10	159	10	163	46.9%	1.03 [0.44, 2.40]
Sung et al, 2009	3	376	8	391	19.4%	0.39 [0.10, 1.46]
Total (95% CI)		849		871	100.0%	0.88 [0.49, 1.58]
Total events	21		25			
Heterogeneity: Chi² = 1.87, df = 2 (P = 0.39); I² = 0%						
Test for overall effect: Z = 0.42 (P = 0.68)						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

FIGURE 2- 6. POOLED RISK RATIO (RR) FOR GROUP A RCTS THAT ASSESSED THE RISK OF MI WITH PPI USE VS NONUSE.

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
2.1.1 Cohort or case-control study				
Ching et al, 2012	0.5822	0.282	2.9%	1.79 [1.03, 3.11]
Douglas et al, 2012	0.3365	0.0418	6.7%	1.40 [1.29, 1.52]
Gaspar et al, 2010	0.0392	0.384	1.9%	1.04 [0.49, 2.21]
Gupta et al, 2010	0.1823	0.4169	1.7%	1.20 [0.53, 2.72]
Harjai et al, 2011	-0.0513	0.2697	3.0%	0.95 [0.56, 1.61]
Ho et al, 2009	-0.0943	0.0657	6.4%	0.91 [0.80, 1.04]
Huang et al, 2010	0.5008	0.1024	5.8%	1.65 [1.35, 2.02]
Juurlink et al, 2009	-0.1165	0.1449	5.0%	0.89 [0.67, 1.18]
Juurlink et al, 2011	0.6098	0.3763	2.0%	1.84 [0.88, 3.85]
Mahabaleshwarkar et al, 2013	0.3365	0.0418	6.7%	1.40 [1.29, 1.52]
Ortolani et al, 2012	-0.3711	0.2782	2.9%	0.69 [0.40, 1.19]
Rassen et al, 2009	0.1823	0.182	4.3%	1.20 [0.84, 1.71]
Rossini et al, 2011	-0.0305	0.6339	0.8%	0.97 [0.28, 3.36]
Sarafoff et al, 2010	0.7885	0.3537	2.1%	2.20 [1.10, 4.40]
Simon et al, 2016	0.0392	0.2722	3.0%	1.04 [0.61, 1.77]
van Boxel et al, 2010	0.5822	0.111	5.7%	1.79 [1.44, 2.22]
Wang et al, 2014	0.6313	0.5041	1.2%	1.88 [0.70, 5.05]
Weisz et al, 2015	0.2469	0.126	5.4%	1.28 [1.00, 1.64]
Yan et al, 2016	0.0953	0.1081	5.7%	1.10 [0.89, 1.36]
Subtotal (95% CI)			**73.3%**	**1.26 [1.11, 1.42]**
Heterogeneity: Tau² = 0.04; Chi² = 71.56, df = 18 (P < 0.00001); I² = 75%				
Test for overall effect: Z = 3.66 (P = 0.0002)				
2.1.2 PS matched or post-hoc analysis of RCT				
Aihara et al, 2012	-0.1165	0.348	2.2%	0.89 [0.45, 1.76]
Banerjee et al, 2011	0.2927	0.3461	2.2%	1.34 [0.68, 2.64]
Charlot et al, 2010	0.7372	0.0706	6.3%	2.09 [1.82, 2.40]
Gargiulo et al, 2016	0.0862	0.184	4.3%	1.09 [0.76, 1.56]
Goodman et al, 2012	0.4055	0.1054	5.8%	1.50 [1.22, 1.84]
O'Donoghue et al, 2009	-0.3857	0.1885	4.2%	0.68 [0.47, 0.98]
Tentzeris et al, 2010	-0.2485	0.4237	1.6%	0.78 [0.34, 1.79]
Subtotal (95% CI)			**26.7%**	**1.17 [0.82, 1.67]**
Heterogeneity: Tau² = 0.17; Chi² = 45.62, df = 6 (P < 0.00001); I² = 87%				
Test for overall effect: Z = 0.89 (P = 0.37)				
Total (95% CI)			**100.0%**	**1.25 [1.11, 1.42]**
Heterogeneity: Tau² = 0.06; Chi² = 130.60, df = 25 (P < 0.00001); I² = 81%				
Test for overall effect: Z = 3.62 (P = 0.0003)				
Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.71), I² = 0%				

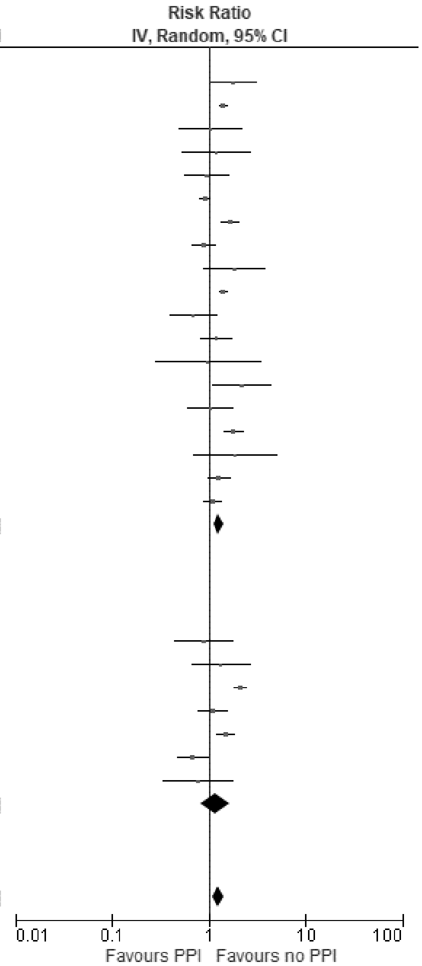


FIGURE 2- 7. POOLED RISK RATIOS (RRS) FOR GROUP B OBSERVATIONAL STUDIES THAT ASSESSED THE RISK OF ACM WITH PPI USE VS NONUSE AMONG CLOPIDOGREL USERS.

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
2.2.1 Cohort or case control				
Douglas et al, 2012	-0.2877	0.1582	5.2%	0.75 [0.55, 1.02]
Evanchan et al, 2009	0.5766	0.0706	6.7%	1.78 [1.55, 2.04]
Harjai et al, 2011	0.0392	0.2477	3.6%	1.04 [0.64, 1.69]
Juurlink et al, 2009	0.207	0.1005	6.3%	1.23 [1.01, 1.50]
Kreutz et al, 2010	0.4886	0.0776	6.6%	1.63 [1.40, 1.90]
Mahabaleshwarkar et al, 2013	-0.1625	0.1863	4.6%	0.85 [0.59, 1.22]
Rassen et al, 2009	0.1989	0.1276	5.8%	1.22 [0.95, 1.57]
Sarafoff et al, 2010	0.2624	0.2477	3.6%	1.30 [0.80, 2.11]
Simon et al, 2016	0.1398	0.3581	2.3%	1.15 [0.57, 2.32]
Valkhoff et al, 2010	0.4824	0.1748	4.9%	1.62 [1.15, 2.28]
van Boxel et al, 2010	0.6575	0.1638	5.1%	1.93 [1.40, 2.66]
Weisz et al, 2015	0.0296	0.1418	5.5%	1.03 [0.78, 1.36]
Yan et al, 2016	-0.1863	0.1017	6.2%	0.83 [0.68, 1.01]
Zairis et al, 2010	0.0953	0.5161	1.4%	1.10 [0.40, 3.02]
Zou et al, 2014	0.5822	0.3623	2.3%	1.79 [0.88, 3.64]
Subtotal (95% CI)			**70.1%**	**1.23 [1.04, 1.47]**
Heterogeneity: Tau² = 0.08; Chi² = 77.01, df = 14 (P < 0.00001); I² = 82%				
Test for overall effect: Z = 2.35 (P = 0.02)				
2.2.2 PS matched obs study or post-hoc analysis of RCT				
Aihara et al, 2012	-0.3711	0.6318	1.0%	0.69 [0.20, 2.38]
Burkard et al, 2011	0.6313	0.2972	3.0%	1.88 [1.05, 3.37]
Charlot et al, 2010	0.1655	0.0644	6.8%	1.18 [1.04, 1.34]
Gargiulo et al, 2016	0.0583	0.2341	3.8%	1.06 [0.67, 1.68]
Goodman et al, 2012	0.1133	0.1116	6.1%	1.12 [0.90, 1.39]
O'Donoghue et al, 2009	-0.0202	0.0909	6.4%	0.98 [0.82, 1.17]
Stockl et al, 2010	0.6575	0.3106	2.8%	1.93 [1.05, 3.55]
Subtotal (95% CI)			**29.9%**	**1.15 [1.00, 1.32]**
Heterogeneity: Tau² = 0.01; Chi² = 9.50, df = 6 (P = 0.15); I² = 37%				
Test for overall effect: Z = 1.93 (P = 0.05)				
Total (95% CI)			**100.0%**	**1.22 [1.07, 1.39]**
Heterogeneity: Tau² = 0.06; Chi² = 94.63, df = 21 (P < 0.00001); I² = 78%				
Test for overall effect: Z = 3.03 (P = 0.002)				
Test for subgroup differences: Chi² = 0.41, df = 1 (P = 0.52), I² = 0%				

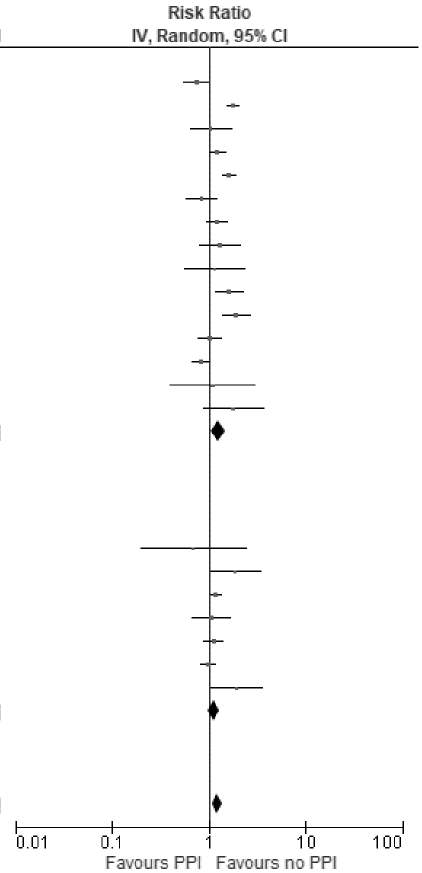


FIGURE 2- 8. POOLED RISK RATIOS (RRS) FOR GROUP B OBSERVATIONAL STUDIES THAT ASSESSED THE RISK OF MI WITH PPI USE VS NONUSE AMONG CLOPIDOGREL USERS.

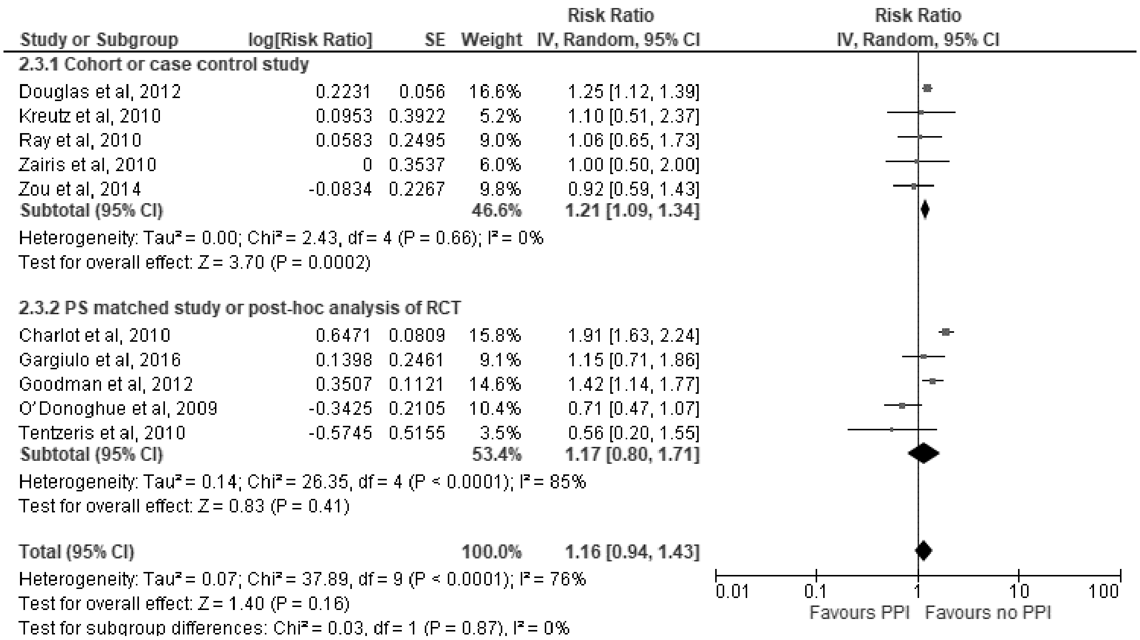


FIGURE 2- 9. POOLED RISK RATIOS (RRS) FOR GROUP B OBSERVATIONAL STUDIES THAT ASSESSED THE RISK OF CARDIOVASCULAR MORTALITY WITH PPI USE VS NONUSE AMONG CLOPIDOGREL USERS.

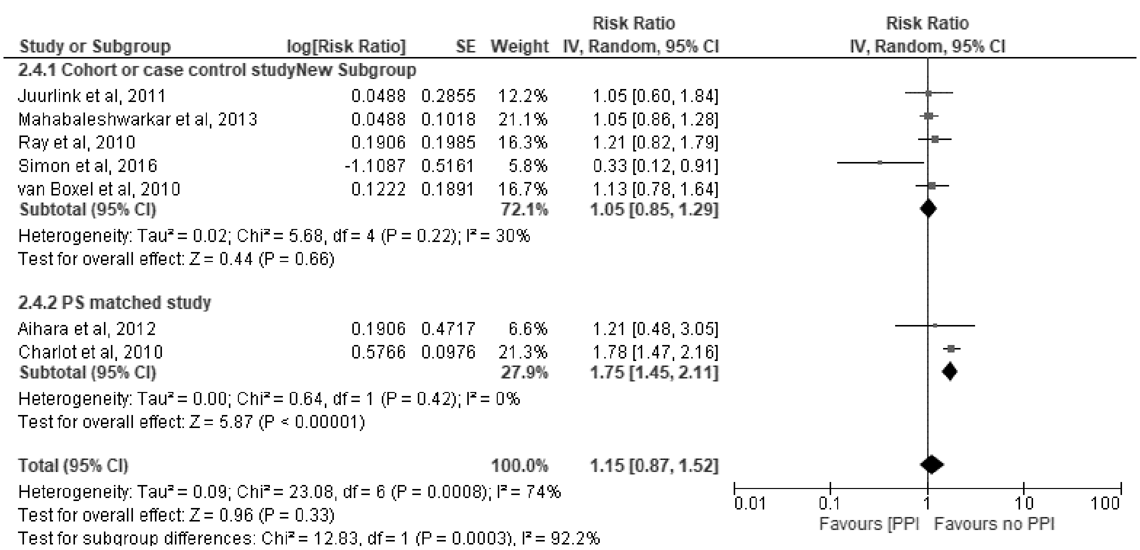


FIGURE 2- 10. POOLED RISK RATIOS (RRS) FOR GROUP B OBSERVATIONAL STUDIES THAT ASSESSED THE RISK OF STROKE WITH PPI USE VS NONUSE AMONG CLOPIDOGREL USERS.

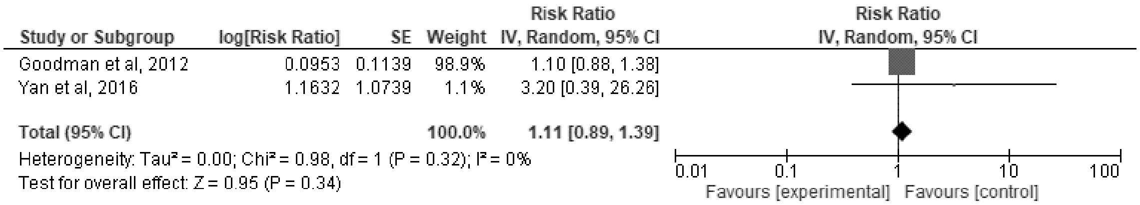


FIGURE 2- 11. POOLED RISK RATIO (RR) FOR GROUP C OBSERVATIONAL STUDIES THAT ASSESSED THE RISK OF ACM WITH PPI USE VS NONUSE AMONG TICAGRELOR USERS.

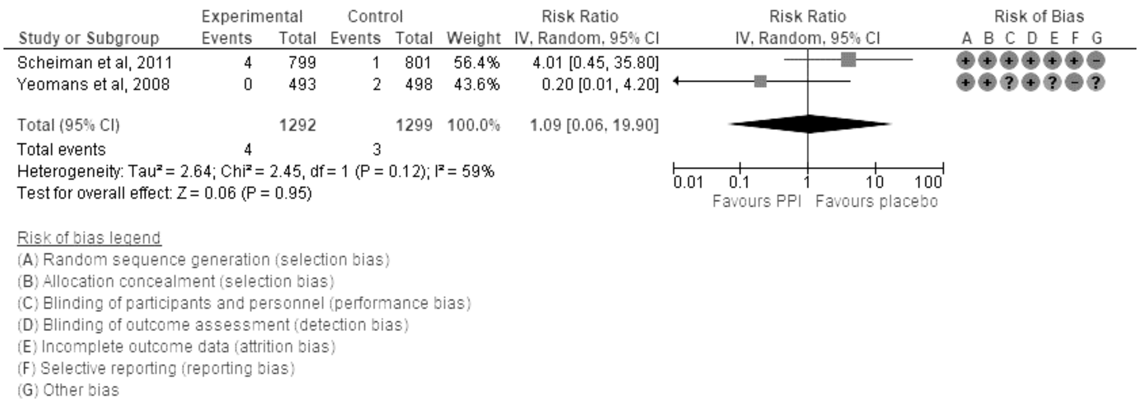


FIGURE 2- 12. POOLED RISK RATIO (RR) FOR GROUP C RCTS THAT ASSESSED THE RISK OF ACM WITH PPI USE VS NONUSE AMONG ASPIRIN USERS.

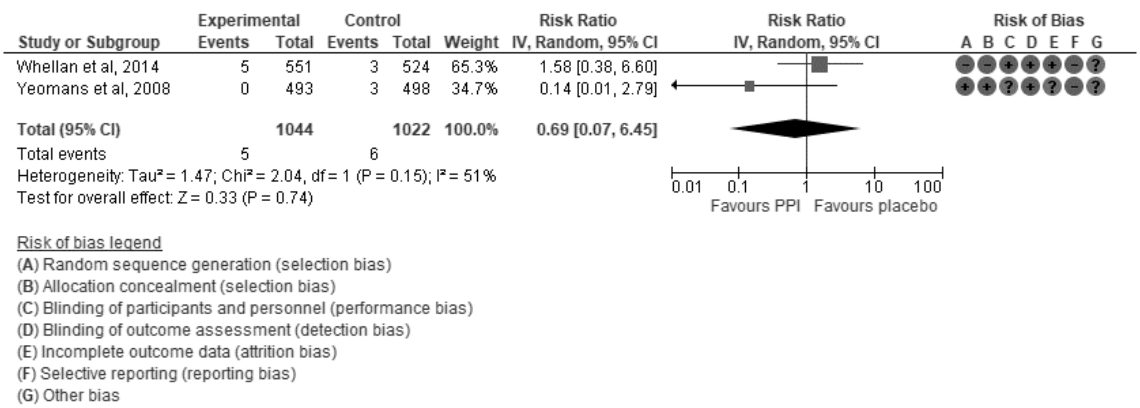


FIGURE 2- 13. POOLED RISK RATIO (RR) FOR GROUP C RCTS THAT ASSESSED THE RISK OF MI WITH PPI USE VS NONUSE AMONG ASPIRIN USERS.

TABLES

TABLE 2- 1. CHARACTERISTICS OF STUDIES THAT ASSESSED THE EFFECT OF PPI USE VS NONUSE (GROUP A).

Citation [location]	Study design	Patient population	Study sample size	Mean age (years) (sd)	Outcome (follow-up)
Observational Studies					
(Antunes et al. 2016) [Portugal] *Abstract only*	Retrospective cohort	Cirrhotic	571; PPI: 180;	NR	ACM (1 and 3 month)
(Arana et al. 2015) [UK]	Nested case-control	UGI disorders	15,811; Cases: 3,239; Controls: 12,572	55 (median)	CVD mortality[1] (up to 7 years)
(Bang and Bendtsen 2018) [Denmark] *Abstract only*	Retrospective cohort	With alcoholic cirrhosis	19,687; PS matched cohort: 2,592;	56 (10)	ACM
(Bell et al. 2017) [USA] *Abstract only*	Retrospective cohort	General population	58,175	NR	Stroke (12 years)
(Bettinger et al. 2018) [Germany]	Retrospective cohort	Pyogenic liver abscess	181; PPI: 100; No PPI: 81;	PPI: 62.3 (13.4); No PPI: 63.2 (14.4);	In hospital mortality
(Caffrey et al. 2016) [USA] *Abstract only*	Retrospective cohort	With S. aureus bacteraemia	12,211 PPI: 809; no PPI: 12,402;	NR	ACM (14-day, 30-day and inpatient)
(Charlot et al. 2010) [Denmark]	Retrospective cohort	MI	Cohort size: 56,406 *PS matched*: PPI: 15,443; No PPI: 15,433	No treatment: 70 (13); PPI only: 73 (12); CP only: 64 (13); Concomitant: 66 (13); PS matched: 73 (13);	MI (1 year); Stroke (1 year); ACM (1 year); CVD mort (1 year)
(Chen et al. 2014) [Taiwan]	Retrospective cohort	ESRD	1,936	65 (11)	Stroke (11 years); ACM (11 years)
(Chitose et al. 2012) [Japan]	Prospective cohort	PCI	1,270 PPI: 331; No PPI: 939	PPI: 72(12); no PPI: 69(12);	MI (18 months); Stroke (18 months); CVD mort (18 months)
(Daskalopoulou et al. 2008) [UK]	Retrospective cohort	MI	9,939 PPI: 3,070; No PPI: 6,869	68 (13)	ACM (1 year)
(Dultz et al. 2015) [Germany]	Prospective cohort	Cirrhosis	272 PPI: 213; No PPI: 59	PPI: 57; no PPI: 57 (median);	ACM (median 266 days; range 1-1,382 days)
(de Francisco et al. 2018) [Spain]	Retrospective cohort	Haemodialysis patients	2242; PPI: 1,776;	PPI: 68.0 (range: 57-76); no PPI: 68.5 (range: 56-76);	ACM (up to 33 months); Cardiovascular mortality (up to 33 months);

Citation [location]	Study design	Patient population	Study sample size	Mean age (years) (sd)	Outcome (follow-up)
			No PPI: 466; PS matched: 410 pairs;		
(Freedberg et al. 2013) [USA]	Retrospective cohort	CDI	894 PPI: 551; No PPIs: 343	PPI: 64 (18); no PPI: 65 (20);	ACM (3 months)
(Gardezi et al. 2018) [UK] *Abstract only*	Retrospective cohort	Non-variceal bleeding	763	NR	NR
(Haider et al. 2012) [USA]	Retrospective cohort	CDI	627 PPI: 172; No PPI: 358	69 (median)	ACM (in-hospital, 6 months)
(Im et al. 2014) [Korea]	Retrospective cohort	PEG	1,021 PPI: 203; No PPI: 472	PPI: 68 (15); no PPI: 66 (14);	ACM (median: 136 days; range 1-2693 days)
(Johansson et al. 2003) [UK]	Nested case-control	GERD	Cases: 7,084; Controls: 10,000	18-79 (range)	MI
(Juurlink et al. 2013) [Canada]	SCCS	MI	5,550	77 (median)	MI (12 weeks)
(Keyvani et al. 2006) [Canada]	Retrospective cohort	UGIB	385 PPI: 132; No PPI: 253	PPI: 65; no PPI: 66;	ACM (in hospital)
(Kwon et al. 2013) [Korea]	Retrospective cohort	Cirrhosis and ascites	1,140 PPI: 82; No PPI: 451;	PPI: 62 (10); no PPI: 63 (9);	ACM (up to 1 month)
(Kwon et al. 2016) [location NR] *Abstract only*	Prospective cohort	Cirrhotic with variceal bleeding	348 PPI: 175; No PPI: 173;	NR	ACM (NR)
(Lee et al. 2015) [Taiwan]	Retrospective cohort	COPD	17,498 PPI: 109; No PPI: 16,863;	>30	ACM (up to 10 years)
(Lei et al. 2017) [Taiwan]	Retrospective cohort	GERD	54,422;	51.6 (17)	MI (12 years, median: 3.3 years)
(Maggio et al. 2013) [Italy]	Prospective cohort	Elderly (≥65)	491 PPI: 174; no PPI 317	PPI: 80 (6); no PPI 80 (6);	ACM (1 year)
(Mandorfer et al. 2014) [Austria]	Retrospective cohort	Cirrhosis and ascites	607 PPI: 520; No PPI: 87	PPI: 57 (12); no PPI: 60 (12);	ACM (up to 5 years)[1]
(Myles et al. 2009) [UK]	Retrospective cohort	Pneumonia	3,681 PPI: 1,060; No PPI: 2,621	>40	ACM (1 month, median follow up of 2.8 years)
(Nardelli et al. 2018) [Italy]	Prospective cohort	Cirrhotic	310; PPI: 125; no PPI: 185	62.2 (11.8); PPI: 63.3 (11.6); no PPI: 61.5 (11.9)	ACM
(Nguyen et al. 2018) [USA]	Prospective cohort	No history of stroke	97,503; PPI: 9,122; no PPI: 88,381	69 (8); Nurses' Health Study: 65.7 (7.1);	Stroke (12 years)

Citation [location]	Study design	Patient population	Study sample size	Mean age (years) (sd)	Outcome (follow-up)
				Health Professionals Follow-up Study: 69.9 (8.6);	
(Oudit et al. 2011) [Canada]	Retrospective cohort	Heart failure	22,107 PPI: 6,431; No PPI: 15,676	PPI: 80 (median); no PPI: 81 (median);	ACM (1 year)
(Sehested et al. 2018) [Denmark]	Retrospective cohort (6 nationwide registries)	UGIB	214, 998	PPI nonusers: 53 (median); Short-term PPI users: 55 (median); long-term PPI users: 59 (median);	Stroke (up to 16 years); MI (up to 16 years); Median follow-up: 5.8 years
(Shah et al. 2015) [USA]	Prospective cohort	Shortness of breath/ abnormal stress test	1,503	66 (11)	CVDM (8 years)
(Shih et al. 2014) [Taiwan]	Retrospective cohort	Receiving PPIs	252,734 PPI: 126,367; No PPI: 126,367	PPI: 49 (15); no PPI: 49 (15);	MI (120 days); ACM (120 days)
(Simon et al. 2011) [France]	Retrospective cohort	MI	2,744 PPI: 1611; No PPI: 1,133	PS matched cohorts: PPI: 65 (12); no PPI: 66 (13);	MI (1 year); Stroke (1 year); ACM (1 year)
(Taha et al. 2013) [NR] - *abstract only*	Prospective cohort	UGIB	Cohort size: 404; PPI: 292;	NR	ACM (1 month)
(Teramura-Gronblad et al. 2012) -Cohort 2 [Finland]	Retrospective cohort	Chronic disease patients requiring 24-hr care	1,004; PPI: 231; No PPI: 773;	PPI: 81 (11); no PPI: 82 (11);	ACM (1 year)
(Teramura-Gronblad et al. 2012) –Cohort 1 [Finland]	Retrospective cohort	In assisted-living facilities	1,389 (Cohort 1); PPI: 367; No PPI: 1,022;	PPI: 84 (8); no PPI: 82 (8);	ACM (1 year)
(Teramura-Gronblad et al. 2012) –Cohort 3 [Finland]	Retrospective cohort	Geriatric, frail patients	425; PPI: 91; No PPI: 334;	PPI: 86 (7); no PPI: 86 (7);	ACM (1 year)
(Turkiewicz et al. 2015) [Sweden]	SCCS	MI	3,490	73 (12)	MI
(Valkhoff et al. 2011) [Netherlands]	Nested case-control	MI	Cases: 616; Controls 126,817;	65 (13)	recurrent MI (up to 9 years; median: 3.6 years)
(van der Hoorn et al. 2015) [Australia]	Prospective cohort	Elderly women	4,432; PPI: 2,328; No PPI: 2,104;	PPI: 78 (1); no PPI: 78 (2);	ACM (mean 6.6 years)
(Wang et al. 2017) [Taiwan]	Retrospective cohort	General population	396,296; PPI: 198,148; No PPI: 198,148.	51.7 (15.4)	First time stroke (4 months)
(Win et al. 2010) [USA] *Abstract only*	Retrospective cohort	UGIB	658; PPI: 110; No PPI: 548;	59 (15)	ACM (not clear)
Intervention studies					

Citation [location]	Study design	Patient population	Study sample size	Mean age (years) (sd)	Outcome (follow-up)
(Daneshmend et al. 1992) [England]	RCT	UGIB	1,147; PPI (omep): 578; No PPI: 569;	PPI: 59 (19); no PPI: 60 (19);	ACM (40 days)
(Gao et al. 2009) [China]	RCT	MI	237; PPI (omep): 114; No PPI: 123;	PPI: 58 (9); no PPI: 58 (9);	ACM (2 weeks)
(Hasselgren et al. 1997) [Sweden and Norway]	RCT	UGIB	322; PPI (omep): 159; No PPI: 163;	PPI: 75 (8) no PPI: 74 (7)	MI (3 weeks); Stroke (3 weeks); ACM (3 weeks)
(Hawkey et al. 2001) [UK]	RCT	UGIB	PPI (lanso): 102; No PPI (placebo): 103; Other groups: 209;	PPI: 59; no PPI: 56;	ACM (unclear)
(Hung et al. 2007) [China]	RCT	UGIB	168; PPI: 114; No PPI: 54;	PPI infusion: 64; PPI bolus: 58; no PPI: 63;	ACM (1 month)
(Javid et al. 2001) [India]	RCT	UGIB	166; PPI (omep): 82; No PPI: 84;	PPI: 55 (10); no PPI: 56 (8);	ACM (not clear)
(Kantorova et al. 2004) [Czech Republic]	RCT	High UGIB risk	323; PPI (omep); No PPI: 75;	PPI: 44 (15); no PPI: 46 (19);	ACM (in hospital)
(Kaviani et al. 2003) [Iran]	RCT	UGIB	160; PPI (omep): 80; No PPI: 80’	PPI: 53 (18); no PPI: 52 (19);	ACM (3 weeks)
(Khuroo et al. 1997) [India]	RCT	UGIB	220; PPI: 110; No PPI 110;	PPI: 58 (8); no PPI: 56 (8);	ACM (1 month)[1]
(Krag et al. 2018) [Multicenter - 6 European countries]	RCT	ICU patients at risk for GI bleeding	3,298; PPI (panto): 1,645; Placebo: 1,653;	Panto: 67 (IQR 56-75); Placebo: 67 (IQR 55-75);	ACM (3 months)
(Kuipers et al. 2011) [16 countries]	RCT	UGIB	767; PPI: 376; No PPI:391;	PPI: 62; no PPI: 60;	ACM (up to 1 month)
(Lau et al. 2000) [Hong Kong]	RCT	UGIB	PPI: 120; no PPI: 120;	PPI: 64 (17); no PPI: 37 (16);	ACM (1 month)
(Lau et al. 2007) [Hong Kong]	RCT	UGIB	PPI: 319; no PPI: 319;	PPI: 62 (18); no PPI: 62 (18);	MI (unclear); ACM (1 month)
(Leung et al. 2018) [China]	RCT (open label)	Undergoing ERCP sphincterotomy	125; PPI (esomep): 60; No PPI: 65;	Esomep: 70 (14); No PPI: 72 (16);	ACM (1 month)
(Liu et al. 2013) [China]	RCT	Intracerebral hemorrhage	165; PPI (omep): 58; No PPI: 53;	>18 years (range)	ACM (1 month)
(Nikcevic et al. 2011) [NR] *abstract only*	RCT	ACS	300; PPI (panto): 150; No PPI: 150;	Not reported	ACM (not reported)
(Schaffalitzky de Muckadell et al. 1997) [Denmark, Holland and France]	RCT	UGIB	274; PPI (omep): 134; No PPI: 140;	PPI: 66 (15); no PPI: 67 (16);	ACM (3 days, 21 days, 35 days)

Citation [location]	Study design	Patient population	Study sample size	Mean age (years) (sd)	Outcome (follow-up)
(Selvanderan et al. 2016) [Australia]	RCT	Mechanically ventilated/critically ill	216; PPI (panto): 107; no PPI: 109;	Panto: 52 (18); Placebo: 52 (17);	ACM (3 months)
(Sung et al. 2009) [16 countries]	RCT	UGIB	767; PPI (esomep): 376; No PPI: 391;	PPI: 62; no PPI: 60;	MI (1 month); ACM (1 month)
(Wei et al. 2007) [Taiwan]	RCT	UGIB	70; PPI: 35; No PPI: 35;	PPI: 57 (13); no PPI: 64 (11);	ACM
(Zargar et al. 2006) [India]	RCT	UGIB	PPI (panto) 102; no PPI: 101;	PPI: 55 (9); no PPI: 52 (9);	ACM (maximum of 6 weeks)

[1]defined as transplant-free survival: time to liver transplantation, death or end of follow-up

Abbreviations: ACM: all-cause mortality; CDI: Clostridium difficile infection; esomep: esomeprazole; ERGP: endoscopic retrograde cholangiopancreatography; esomep: esomeprazole; GERD: Gastroesophageal reflux disease; lanso: lansoprazole; MI: myocardial infarction; NR: not reported; omep: omeprazole; panto: pantoprazole; PEG: Percutaneous endoscopic gastrostomy; PPI: proton pump inhibitor; PS: propensity score; SD: standard deviation; SCCS: self-controlled case-series; UGIB: Upper gastrointestinal bleeding;

TABLE 2- 2. FINDINGS FROM OBSERVATIONAL STUDIES THAT REPORTED ADJUSTED EFFECT ESTIMATES FOR PPI USE VS NONUSE CLASSIFIED BY OUTCOME (GROUP A).

Study	Patient population	Follow-up period	Adjusted effect estimates (95% CI) [1]	Variables adjusted for	Authors' conclusion on the PPI-outcome of interest association
All-cause mortality					
(Dultz et al. 2015)	Cirrhosis	Median: 266 days; Range: 1-1,382 days	**aHR, 2.36 (1.26–4.43)**,	Adjusted for differences between groups compared and for severity of cirrhosis.	Possible association with mortality among cirrhotic patients.
(Antunes et al. 2016) *Abstract only*	Cirrhosis	up to 90 days after admission	1-month ACM: non-significant association with PPIs (OR not reported); 3-month ACM: aOR 1.89 (p-value 0.000)'	NR	Association between continuous PPI exposure and 90-day mortality cirrhotic patients;
(Bang and Bendtsen 201 *Abstract only*	Alcoholic cirrhosis	NR	PS matched, aHR, 1.0 (0.9-1.1);	NR	No association between PPI and ACM in patients with alcoholic cirrhosis;
(Kwon et al. 2016) *Abstract only*	Cirrhosis with variceal bleeding	NR	aHR, 0.5 (0.4-0.7);	NR	Reduced mortality with long-term PPI use in liver cirrhosis patients with variceal bleeding;
(Caffrey et al. 2016) *Abstract only*	with S. aureus bacteremia	14-days and 30-days	PS matched, 14-day ACM, aHR, 0.48 (0.30-0.78); PS matched, 1-month ACM, aHR, 0.96 (0.69-1.33); PS matched, inpatient mortality, aHR, 0.58, (0.36-0.94);	PS (antibiotic treatment, concomitant medications, comorbidities and medical history);	Association between PPI use and lower mortality rates among patients with S. aureus bacteremia;
(Bettinger et al. 2018)	Pyogenic liver abscess	Mean hospital stay: 27 days	In-hospital mortality, aOR, 2.56 (1.01-6.46);	Intrahepatic abscess expansion, bile duct compression, intensive care treatment, Charlson index;	PPI treatment in patients with pyogenic liver abscess is associated with higher in-hospital mortality;
(de Francisco et al. 2018	Hemodialysis	up to 33 months. Mean follow up 22.8 +/-9.2 months.	**PS matched, aHR, 1.41 (1.04-1.93);**	PS (demographic features, HD clinical parameters, laboratory values, and concomitant antithrombotic medication);	PPI use is associated with excess mortality risk in hemodialysis patients; findings need to be confirmed in RCTs;
(Nardelli et al. 2018)	Cirrhosis	Mean follow up: 14.1 +/- 12.3 months	**ACM, aHR, 2.37 (1.45-3.87);**	MELD score, PPIs use, previous history of HE, development of overt HE, MHE, age, albumin and sodium levels;	PPI use was independently associated with mortality among cirrhotic patients. Causative role cannot be deduced;
(Kwon et al. 2013)	Cirrhosis and ascites	up to 1 month	**SBP patients, within 30 days after SBP, aOR, 1.96 (1.19–3.23);** SBP patients excluding deaths from HCC, within 30 days after SBP, aOR, 3.31 (1.23–8.92);	Not clear.	PPIs associated with SBP-related mortality. Requires further investigation.

TABLE 2- 2. FINDINGS FROM OBSERVATIONAL STUDIES THAT REPORTED ADJUSTED EFFECT ESTIMATES FOR PPI USE VS NONUSE CLASSIFIED BY OUTCOME (GROUP A).

Study	Patient population	Follow-up period	Adjusted effect estimates (95% CI) [1]	Variables adjusted for	Authors' conclusion on the PPI-outcome of interest association
(Mandorfer et al. 2014)	Cirrhosis and ascites	up to 5 years	**All patients[2], aHR, 0.97 (0.72-1.32);** Patients with no SBP at first paracentesis, aHR, 1.01 (0.72-1.42); Patients with no SBP or systemic infection at first paracentesis, aHR, 0.94, (0.67-1.33)	Age, HCC, history of variceal bleeding, varices and MELD score	No association between PPIs and mortality among cirrhotic patients.
(Taha et al. 2013) - *abstract*	UGIB	1 month	aOR, 1.34 (0.50-3.59);	Age, Blatchford and Charlson scores;	PPI (intravenously) before endoscopy did not affect mortality among UGIB patients.
(Charlot et al. 2010)	MI	1 year	**PS matched, aHR, 1.95 (1.82–2.09);**	Age, sex, PCI, income, concomitant medications and comorbidities.	PPIs associated with an increased risk for adverse cardiovascular outcomes regardless of clopidogrel use, likely due to unmeasured confounding.
(Daskalopoulou et al. 2008)	MI	1 year	**Use of PPI before and after MI, aHR, 1.03 (0.82–1.31)** Use of PPI after MI, aHR,1.11 (0.88–1.43);	Age, sex, smoking, alcohol, obesity, prior hospitalization, concomitant medications and comorbidities.	No association between PPI use and mortality in patients that have had a first MI.
(Simon et al. 2011)	MI	1 year	In hospital mortality: aOR, 1.47 (0.67-3.25); **PS matched, aHR, 1.15 (0.73 - 1.83);**	Adjusted for age, gender, BMI, smoking, family history, prior treatments, GRACE score, comorbidities, comedications, PCI.	PPI use not associated with increased MACE or mortality in clopidogrel treated patients for recent MI.
(Oudit et al. 2011)	Heart failure	1 year	**Nested case-control analyses, PS matched, aOR 0.95 (0.93-0.97):** All cohort: Any PPI, Excluding deaths within 30 days of HF, aOR, 0.93 (0.87-1.01); Any PPI, only deaths within 30 days of HF, aOR, 0.80 (0.72–0.89); Omep, aOR 0.84, (0.77–0.90); Panto, aOR, 0.85 (0.77–0.93) ;	Adjusted for age, sex, concomitant medications, and comorbidities. Case control matched by age and gender.	No association between PPI use and risk of mortality in chronic HF patients in an ambulatory setting.
(Teramura-Gronblad et al. 2012) (Cohort 1)	In assisted living facilities	1 year	**aHR, 1.06, (0.77-1.46);**	Adjusted for age, gender, Charlson comorbidity index, immobility, and SSRIs	Possible association between PPIs and increased mortality.
(Teramura-Gronblad et al. 2012) (Cohort 2)	Chronic patients requiring 24-hr care	1 year	**aHR, 1.36 (1.04-1.77);**	Adjusted for: age, sex, Charlson comorbidity index, use of SSRIs and malnutrition;	Possible association between PPIs and increased mortality.

TABLE 2- 2. FINDINGS FROM OBSERVATIONAL STUDIES THAT REPORTED ADJUSTED EFFECT ESTIMATES FOR PPI USE VS NONUSE CLASSIFIED BY OUTCOME (GROUP A).

Study	Patient population	Follow-up period	Adjusted effect estimates (95% CI) [1]	Variables adjusted for	Authors' conclusion on the PPI-outcome of interest association
(Teramura-Gronblad et al. 2012) (Cohort 3)	Geriatric, frail patients	1 year	aHR, 1.90 (1.23-2.94);	Adjusted for: age, sex, Charlson comorbidity index, delirium, and use of aspirin and SSRIs.	Possible association between PPIs and increased mortality
(Lee et al. 2015)	COPD	up to 10 years	All patients, aHR, 2.39 (1.92-2.97); <70 years, aHR, 5.20 (3.60-7.51); ≥70 years, aHR, 1.71 (1.30-2.23);	Adjusted for age, sex, glucocorticoids and comorbidities,	Higher risk of mortality in PPI users vs nonusers.
(Maggio et al. 2013)	Elderly (≥65)	1 year	aHR, 1.51 (1.03-2.77);	Adjusted for: age, sex, BMI, cognitive impairment, dependency in activities of daily living, gastrointestinal conditions, fracture, medications at discharge, concomitant medications.	Association between PPI use and an increased risk of ACM in older patients discharged from acute care hospitals.
(Chen et al. 2014)	ESRD	11 years	aHR, 1.28(1.09–1.51);	Adjusted for: antiplatelet use (aspirin or clopidogrel), age, gender, cirrhosis type and complication, geographical region, comorbidities and concomitant drugs;	PPI use is an independent factor predicting increased risk of death or readmission due to ischemic stroke - recommended further investigation.
(Im et al. 2014)	PEG	median: 136 days; range 1-2693 days	aOR, 1.71 (1.15, 2.56);	Adjusted for age, comorbidities and concomitant medications and stroke.	Possible association between PPI use and ACM after PEG -requires further investigation.
(Myles et al. 2009)	Pneumonia	1 month; median follow up of 2.8 years	30-day follow-up, PPI use within 30 days of diagnosis, aHR, 0.90 (0.72-1.12); 2.8-year median follow up, PPI use within 30 days of diagnosis, aHR, 1.03 (0.88–1.21);	Adjusted for age, sex, smoking, Charlson comorbidity index, co-prescriptions, concomitant medications, Townsend's deprivation score.	No association between PPI use and long term or short-term ACM in pneumonia patients.
(Shih et al. 2014)	PPI users	4 months	aHR, 2.04 (1.63-2.56);	Propensity score adjusted for: age, sex, index date, prior outpatient visits, income, urbanization level, Charlson comorbidity score, concomitant medications and comorbidities.	PPI use is associated with a greater risk of MI in patients with normal cardiovascular risk.
Cardiovascular mortality					

TABLE 2- 2. FINDINGS FROM OBSERVATIONAL STUDIES THAT REPORTED ADJUSTED EFFECT ESTIMATES FOR PPI USE VS NONUSE CLASSIFIED BY OUTCOME (GROUP A).

Study	Patient population	Follow-up period	Adjusted effect estimates (95% CI) [1]	Variables adjusted for	Authors' conclusion on the PPI-outcome of interest association
(Charlot et al. 2010)	MI	1 year	PS matched, aHR, 1.83 (1.69–1.98);	Adjusted for: age, sex, PCI, income, concomitant medications and comorbidities.	PPI use is associated with an increased risk for adverse cardiovascular outcomes regardless of clopidogrel use, likely due to unmeasured confounding.
(de Francisco et al. 2018	Hemodialysis patients	up to 33 months. Mean follow up 22.8 +/-9.2 months.	PS matched, aHR, 1.67 (1.03-2.71);	PS (demographic features, HD clinical parameters, laboratory values, and concomitant antithrombotic medication);	PPI use is associated with excess mortality risk in hemodialysis patients; findings need to be confirmed in RCTs;
(Arana et al. 2015)	On PPIs, domperidone or metoclopramide	up to 7 years	aOR, 1.35 (1.21–1.51);	Matched by: age, sex, and practice. Adjusted for: prior heart conditions and procedures, concomitant medications, smoking, alcohol, and other variables.	***Positive association[4].***
(Shah et al. 2015)	Shortness of breath or abnormal stress test	8 years	aHR, 2.00 (1.07–3.78);	Adjusted for: gender, race, smoking, comorbidities, and concomitant medications.	Potential association between PPI use and CVD mortality -requires further investigation.
Myocardial infarction					
(Turkiewicz et al. 2015)	MI	self-controlled	Based on dispensation of PPIs: **All patients, OR, 1.26 (0.92–1.72);** Patients with no prior AMI, OR, 1.29 (0.92–1.83); Based on prescriptions of PPIs: All patients, OR, 1.36 (0.82-2.25); Patients with no prior AMI, OR, 1.66 (1.00–2.76);	Self-controlled	No evidence of association between PPI and MI.
(Lei et al. 2017) [Taiwan]	GERD	up to 12 years	aHR, 0.57 (0.31-1.04);	Age, sex, hypertension, diabetes mellitus, hyperlipidemia, congestive heart failure, and ischemic stroke;	GERD patients using PPIs for more than one year had slightly decreased the risk of future MI. Further research needed;
(Charlot et al. 2010)	MI	1 year	**PS matched, aHR, 1.13 (1.01–1.25);**	PS matched for: age, sex, PCI, income, concomitant medications and comorbidities.	PPI use is associated with an increased risk for adverse cardiovascular outcomes regardless

TABLE 2- 2. FINDINGS FROM OBSERVATIONAL STUDIES THAT REPORTED ADJUSTED EFFECT ESTIMATES FOR PPI USE VS NONUSE CLASSIFIED BY OUTCOME (GROUP A).

Study	Patient population	Follow-up period	Adjusted effect estimates (95% CI) [1]	Variables adjusted for	Authors' conclusion on the PPI-outcome of interest association
					of clopidogrel use, likely due to unmeasured confounding.
(Sehested et al. 2018)	UGIB	5.8 years (median)	aHR, 1.31 (1.23-1.39);	Age, sex, comorbidities, concomitant medications;	Association between use of PPI and first-time ischemic stroke and MI;
(Simon et al. 2011)	MI	1 year	**Recurrent MI, aOR, 0.99 (0.18–5.53);**	Adjusted for age, gender, BMI, smoking, family history, prior treatments, GRACE score, comorbidities, comedications, PCI.	PPI use not associated with increased MACE or mortality in CP treated patients for recent MI.
(Juurlink et al. 2013)	MI	4 months	**aOR, 1.8 (1.7 - 1.9);**	Self-matched	PPI not associated with cardiac events (similar magnitude risk also detected for H2RAs).
(Valkhoff et al. 2011)	MI	Median 3.6 years (up to 9 years)	Recurrent MI: **current PPI vs no PPI, aOR, 1.38 (1.18–1.61)**; current PPI vs past PPI, aOR, 1.22 (0.79–1.88);	Matched for age: gender, risk of recurrent MI and calendar time. Adjusted for: follow-up time in days and total number of prescriptions one year prior to baseline MI.	No association between concomitant therapy and recurrent MI;
(Johansson et al. 2003)	GERD	case control	**Current use of PPI[3], aOR, 1.0 (0.5–2.1);** Short duration use of PPI, aOR, 1.1 (0.4–2.9); Long duration use PPI, aOR, 0.9 (0.3–2.4);	Adjusted for age, sex, calendar year, smoking and co-morbidities.	No association between PPI use and MI risk in GERD patients.
(Shih et al. 2014)	On PPIs	4 months	**All patients, aHR, 1.58 (1.11-2.25);** >=45, aHR, 1.44(1.00-2.78); <45, aHR, 8.0(1.00-63.92); Males, aHR, 1.72 (1.11-2.66); Females, aHR, 1.34 (0.72-2.46); Patients with diabetes mellitus, aHR, 1.34 (0.81-2.20); Nondiabetics, aHR, 1.87 (1.13-3.1); Patients on AP agents, aHR, 2.07(1.16-3.7); Patients not on AP agents, aHR, 1.33 (0.85-2.09); Patients on clopidogrel, aHR, 2.02 (0.75-5.40) Patients not on clopidogrel, aHR, 1.53 (1.04-2.23) Patients on NSAID, aHR, 1.86 (0.97-3.55); Patients not on NSAID, aHR, 1.48 (0.97-2.26);	PS (includes age, sex, index date, number of outpatient visits in prior year, SES, urbanization level, Charlson comorbidity score, concomitant medications and comorbidities)	PPI use is associated with a greater risk of MI in patients with normal cardiovascular risk.
Stroke					

TABLE 2- 2. FINDINGS FROM OBSERVATIONAL STUDIES THAT REPORTED ADJUSTED EFFECT ESTIMATES FOR PPI USE VS NONUSE CLASSIFIED BY OUTCOME (GROUP A).

Study	Patient population	Follow-up period	Adjusted effect estimates (95% CI) [1]	Variables adjusted for	Authors' conclusion on the PPI-outcome of interest association
(Charlot et al. 2010)	MI	1 year	**PS matched, aHR, 1.36 (1.19–1.55).**	PS matched for age, sex, PCI, income, concomitant medical treatment and comorbid conditions.	PPI use is associated with an increased risk for adverse cardiovascular outcomes regardless of clopidogrel use, likely due to unmeasured confounding.
(Nguyen et al. 2018)	No history of stroke	Up to 12 years	**aHR, 1.08 (0.91– 1.27).**	Age, smoking, BMI, physical activity, dietary quality, alcohol use, hormone use in women, vitamin use, aspirin use, NSAID used, hypertension, hyperlipidemia, CAD, diabetes, clinical indications for PPIs;	No association between PPI use and ischemic stroke, after accounting for indications for PPI use;
(Wang et al. 2017)	General population	First time stroke (4 months)	**PS matched, aHR, 1.36 (1.14–1.62);** *By sex:* Males, aHR, 1.22 (0.98–1.54); Females, aHR, 1.58 (1.19–2.08); *By age:* 20-59 years, aHR, 1.89 (1.31–2.74); 60+ years, aHR, 1.23 (1.01–1.50); *By PPI type:* Esomep, aHR, 1.36 (0.96–1.90); Lanso, aHR,1.39 (0.97–2.01); Omep, aHR 1.54 (1.06–2.23); Panto, aHR 1.46 (0.67–2.21); Rabep, aHR 0.81 (0.46–1.44);	Propensity score (age, index date, gender, income, urbanization, outpatient visits in prior year, Charlson comorbidity index, antiplatelet use, concomitant medications, comorbidities;	PPI use may be associated with an increased risk of first-time ischemic stroke in the general population. Further research needed;
(Bell et al. 2017) *Abstract only*	General population	up to 12 years	aHR, 1.49 (1.35-1.65);	Age, sex, race, education, hypertension, hyperlipidemia, diabetes and BMI;	Positive association between PPI use and stroke;
(Sehested et al. 2018)	Upper GI bleeding	5.8 years (median)	aHR, 1.13 (1.08-1.19);	Age, sex, comorbidities, concomitant medications;	Association between use of PPI and first-time ischemic stroke and MI;
(Simon et al. 2011)	MI	1 year	**aOR, 3.21 (0.24–42.5)**	Adjusted for age, gender, BMI, smoking, family history, prior treatments, GRACE score, comorbidities, comedications, PCI.	PPI use not associated with increased MACE or mortality in CP treated patients for recent MI.

TABLE 2- 2. FINDINGS FROM OBSERVATIONAL STUDIES THAT REPORTED ADJUSTED EFFECT ESTIMATES FOR PPI USE VS NONUSE CLASSIFIED BY OUTCOME (GROUP A).

Study	Patient population	Follow-up period	Adjusted effect estimates (95% CI) [1]	Variables adjusted for	Authors' conclusion on the PPI-outcome of interest association
(Chen et al. 2014)	ESRD	11 years	aHR, 1.25, (1.01–1.56) (Outcome: readmission for stroke).	Adjusted for: antiplatelet use (aspirin or clopidogrel), age, gender, cirrhosis type and complication, geographical region, comorbidities, concomitant drugs;	PPI use is an independent factor predicting increased risk of death or readmission due to IS -recommend further investigation.

[1] *Effect estimates included in the meta-analysis are bolded.*

[2] *Mortality defined as transplant free mortality;*

[3] *Current use: drug supply lasted until index date or ended in previous month; short duration treatment use: less than 3 months; long duration use: treatment more than 3 months;*

Abbreviations: ACM: all-cause mortality; ACS: acute coronary syndrome; aHR: adjusted HR; aOR: adjusted OR; AP: antiplatelet; CAD: coronary artery disease; CVD: cardiovascular disease; ESRD: end stage renal disease; esomep: esomeprazole; DES: drug eluting stent; GRACE: Global Registry of Acute Coronary Events; HCC: hepatocellular carcinoma; HF: heart failure; lanso: lansoprazole; MELD: model for end-stage liver disease; MI: myocardial infarction; NSAIDs: Nonsteroidal anti-inflammatory drugs; NR: not reported; omep: omeprazole; PAD: Peripheral arterial disease ; panto: pantoprazole; PEG: Percutaneous endoscopic gastrostomy; PCI: Percutaneous coronary intervention; PPI: proton pump inhibitor; PS: propensity score; rabep: rabeprazole; SBP: spontaneous bacterial peritonitis; SSRIs: selective serotonin reuptake inhibitors; UGIB: Upper gastrointestinal bleeding;

[4] When the authors' conclusions regarding the association in question was not reported, the reviewers arrived at a conclusion based on whether there was a statistically significant difference in the proportion of events between the treatment groups; these conclusions are bolded in this column.

TABLE 2- 3. FINDINGS FROM RCTS FOR PPI USE VS NONUSE CLASSIFIED BY OUTCOME (GROUP A).

Citation (Study design)	Patient population	Outcome (follow up period)	Percentage of events or unadjusted effect estimates[1] (95% CI) and number of patients (N) in each exposure group	Overall author conclusion on the PPI-outcome of interest association[2]
All-cause mortality				
(Daneshmend et al. 1992)	UGIB	ACM (40 days)	PPI (omep): 7% (N=578); no PPI: 5% (N=569); p-value: 0.23;	No difference in mortality between omep treatment and placebo groups among UGIB patients.
(Krag et al. 2018)	ICU patients at risk for GI bleeding	ACM (3 months)	PPI (panto): 510/1642; placebo: 499/1640; RR 1.02 (0.91-1.13);	3-month mortality was the same among study groups.
(Leung et al. 2018)	Undergoing ERCP sphincterotomy	ACM (1 month)	PPI (esomep): 3.3% (n=60); no PPI: 1.5% (n=65); p-value: 0.61;	No difference in 1-month mortality between the PPI and standard care groups.
(Selvanderan et al. 2016)	Mechanically ventilated/critically ill	ACM (3 months)	PPI (panto): 30/106; placebo: 25/108; PPI vs placebo, aHR 1.68 (0.97-2.90);	No difference between the groups in the 3-day month.
(Gao et al. 2009)	MI	ACM (14 days)	PPI (omep) 2% (N=114); no PPI: 11% (N=123); p-value: 0.035;	Possible lower mortality rate with the use of omep in MI patients.
(Hasselgren et al. 1997)	UGIB	ACM (3 days, 21 days)	*3 days* PPI (omep): 1% (N=159); no PPI: 1% (N=163); p-value >0.2; *21 days* PPI (omep): 7% (N=159); no PPI: 1% (N=163); p-value 0.012;	No difference in mortality between treatment groups; observed difference likely due to imbalance in risk factors.
(Hawkey et al. 2001)	UGIB	ACM (unclear)	PPI (lanso): 2% (N=102); no PPI: 5% (N=102); p-value: 0.242;	*Difference in mortality between treatment groups is not statistically significant.*
(Hung et al. 2007)	UGIB	ACM: 30 days	PPI: 0 (N=103); no PPI: 2% (N=50); p-value: 0.15;	No difference in mortality between bolus/infusion of PPI and no PPI treatment.
(Javid et al. 2001)	UGIB	ACM (not clear)	PPI (omep): 1% (N=82); no PPI: 2% (N=84); p-value: 0.98; (based on 3 deaths)	*Difference in mortality between groups not statistically significant.*
(Kantorova et al. 2004)	High risk for UGIB	ACM (in hospital)-(unclear)	*ICU mortality* PPI (omep): 13% (N=72); no PPI: 11% (N=75); p-value: 0.71; *Hospital mortality* PPI (omep): 19% (N=72); no PPI: 17% (N=5); p-value: 0.75;	No difference in in-hospital mortality between PPI treatment and placebo among critically ill patients with high risk of UGIB.
(Kaviani et al. 2003)	UGIB	ACM (3 weeks)	PPI (omep): 0 (N=71); no PPI: 1% (N=78); p-value: 0.4;	No difference in ACM between groups.
(Khuroo et al. 1997)	UGIB	ACM (1 month)	PPI (omep): 2% (N=110); no PPI: 5% (N=110); p-value	No significant difference in ACM between groups.

TABLE 2- 3. FINDINGS FROM RCTS FOR PPI USE VS NONUSE CLASSIFIED BY OUTCOME (GROUP A).

Citation (Study design)	Patient population	Outcome (follow up period)	Percentage of events or unadjusted effect estimates[1] (95% CI) and number of patients (N) in each exposure group	Overall author conclusion on the PPI-outcome of interest association[2]
(Kuipers et al. 2011)	UGIB	ACM (up to 30 days)	PPI (esomep): 1% (N=375); no PPI: 2% (N=389); p-value: 0.26;	No significant difference in ACM in patients with high risk of peptic ulcer rebleeding after successful endoscopic hemostatis for PUB.
(Lau et al. 2000)	UGIB	ACM (30 days)	PPI (omep): RR 2.40 (0.87-6.60);	*Effect measure for mortality not statistically significant.*
(Lau et al. 2007)	UGIB	ACM (30 days)	PPI: 3% (N=314); no PPI 2% (N=317); p-value 0.78;	*Difference in mortality between groups not statistically significant.*
(Liu et al. 2013)	Intracerebral hemorrhage	ACM (30 days)	PPI (omep): 29% (N=58); no PPI: 38% (N=53); p-value: 0.31;	Nonsignificant difference in death counts between groups.
(Nikcevic et al. 2011) *-abstract*	ACS	ACM (NR)	PPI: 2% (N=150); no PPI: 4.7% (N=150); p-value <0.05	Lower in-hospital mortality with panto among ACS patients.
(Schaffalitzky de Muckadell et al. 1997)	UGIB	ACM (3, 21 and 35 days)	*3 days* PPI (omep): 2% (N=130); no PPI: 0 (N=135); p-value: 0.1; *21 days* PPI (omep): 6% (N=130); no PPI: 6% (N=135); p-value: 1; *35 days* PPI (omep): 8% (N=130); no PPI: 8% (N=135); p-value: 1;	No difference in mortality between treatment groups.
(Sung et al. 2009)	UGIB	ACM (1 month)	PPI (esomep): 1% (N=375); no PPI: 2% (N=389); p value: 0.22;	*Difference in mortality between groups not statistically significant.*
(Wei et al. 2007)	UGIB	ACM (1 month)	No deaths in either group; PPI: N=35; no PPI: N=35;	No difference in mortality among high-risk ulcer bleeders treated with either esomeprazole or placebo.
(Zargar et al. 2006)	UGIB	ACM (unclear - maximum of 6 weeks)	RR 0.49 (0.09-2.71) *(based on 6 counts of death)*	Nonsignificant differences in mortality between groups.
Myocardial infarction				
(Hasselgren et al. 1997)	UGIB	MI (21 days)	PPI (omep): 3.1% (N=159); no PPI: 1.2% (N=163); p-value: 0.24;	No difference in mortality between treatment groups (observed difference likely due to imbalance in risk factors).
(Lau et al. 2007)	UGIB	MI (unclear)	PPI: 0.3% (N=314); no PPI: 0% (N=317); p-value: 0.5	*Difference in mortality between groups not statistically significant.*
(Sung et al. 2009)	UGIB	MI (1 month)	PPI (esomep): 1.1% (N=375); no PPI: 1.0% (N=389); p-value: 0.59;	*Difference in mortality between groups not statistically significant.*
Stroke				
(Hasselgren et al. 1997)	UGIB	Stroke (21 days)	PPI (omep): 1.3% (N=159); no PPI: 0 (N=163); p-value: 0.14;	No difference in mortality between treatment groups (observed difference likely due to imbalance in risk factors).

[1] *Quantitative findings included in the meta-analysis are bolded.*
[2] When the authors' conclusions regarding the association in question was not reported, the reviewers arrived at a conclusion based on whether there was a statistically significant difference in the proportion of events between the treatment groups; these conclusions are bolded in this column.
Abbreviations: ACM: all-cause mortality; ACS: acute coronary syndrome; esomep: esomeprazole; ICU: intensive care unit; lanso: lansoprazole; MI: myocardial infarction; NR: not reported; omep: omeprazole; PPI: proton pump inhibitor; UGIB: Upper gastrointestinal bleeding;

TABLE 2- 4. CHARACTERISTICS OF STUDIES THAT ASSESSED THE EFFECT OF CONCOMITANT TREATMENT OF PPIS AND CLOPIDOGREL VS CLOPIDOGREL ONLY (GROUP B).

Citation (Location)	Study design (Setting)	Patient population	Study sample size	Mean age (years) (sd)	Outcome(s) of interest (follow-up period)
Observational Studies					
(Aihara et al. 2012) [Japan]	Retrospective cohort	PCI with stent	1,887 PPI: 1,068; No PPI: 819	PPI: 69 (11) no PPI: 68 (10)	MI (1 year); Stroke (1 year); ACM (1 year);
(Gargiulo et al. 2016) [Italy]	Post-hoc analysis of RCT	PCI	1,970; PPI: 738;	No PPI: 59-77 (range); PPI: 62-78 (range) ;	ACM (2 years); MI (2 years); Cardiovascular mortality (2 years);
(Yan et al. 2016) [Multi-country - 11 countries]	Retrospective cohort	ACS, PCI	Cohort size: 9,429; PPIs: 5,165; No PPI: 4265;	PPI: 66.2; No PPI: 61.3	ACM (1 year); MI (1 year);
(Yi et al. 2018) [China]	Prospective cohort	Stroke patients receiving clopidogrel	523; PPI: 161; no PPI: 362;	Patients that experienced an event: 71.0 (13.2); Patients that did not experience an event: 67.2 (12.4);	Recurrent stroke (1 year); MI (1 year); Cardiovascular mortality (1 year)
(Banerjee et al. 2011) [USA]	Retrospective cohort	PCI	4,545 PPI: 867; No PPI: 3,678	PPI 65: (10) no PPI: 64 (10)	ACM (1 year, 6 years)
(Bhurke et al. 2012) [USA]	Retrospective cohort	ACS	10,101 PPI: 2,958; No PPI: 7,143	PS matched cohorts PPI: 61 (12) no PPI: 61 (12)	MI (mean 268 days)
(Burkard et al. 2012) [Netherlands]	Post-hoc analyses of RCT	PCI	801 PPI: 109; No PPI: 692	PPI: 66(11) no PPI: 63 (11)	MI (3 years); ACM (3 years);
(Charlot et al. 2010) [Denmark]	Retrospective cohort	MI	Cohort size : 56406 *PS matched* PPI: 15,443; No PPI: 15,433	no treatment: 70(13) PPI only: 73(12) CP only: 64 (13) Concomitant: 66(13) PS matched: 73 (13)	MI (1 year); Stroke (1 year); ACM (1 year); CVD mort (1 year);
(Ching et al. 2012) [USA]	Retrospective cohort	PCI	3,287 PPI: 1,128; No PPI: 2,159	PPI: 66 (13) no PPI: 62(13)	ACM (9 months)
(Chitose et al. 2012) [Japan]	Prospective cohort	PCI	1,270 PPI: 331; No PPI: 939	PPI: 72(12) no PPI: 69(12)	MI (18 months); Stroke, CVD mort (18 months);
(Depta et al. 2015) [USA]	Prospective cohort	ACS	2,062 PPI: 372; No PPI: 1,690	PPI: 60 (12) no PPI: 58 (12)	ACM (1 year); Stroke (1 year);

TABLE 2- 4. CHARACTERISTICS OF STUDIES THAT ASSESSED THE EFFECT OF CONCOMITANT TREATMENT OF PPIS AND CLOPIDOGREL VS CLOPIDOGREL ONLY (GROUP B).

Citation (Location)	Study design (Setting)	Patient population	Study sample size	Mean age (years) (sd)	Outcome(s) of interest (follow-up period)
(Douglas et al. 2012) [UK]	Retrospective cohort	Receiving clopidogrel and aspirin	24,471 PPI: 9,111; No PPI: 15,360	PPI: 71 no PPI: 68	MI (median 303 days); ACM (median 303 days); CVD mort (median 303 days);
(Evanchan et al. 2010) [USA]	Retrospective cohort	MI and stent	5,794 PPI: 1369; No PPI: 4,425	PPI: 64 no PPI: 63	MI (1 year)
(Gaglia et al. 2010) [USA]	Retrospective cohort	PCI with DES	820 PPI: 318; No PPI: 502	PPI: 64 (12) no PPI: 64 (12)	MI (in-hospital, 1 year); ACM (1 month, 1 year);
(Galante et al. 2012) [Brazil]	Retrospective cohort	PCI	2,823 PPI (omep): 1,273; No PPI: 1,295;	63 (12)	ACM (not reported)
(Gaspar et al. 2010) [Portugal]	Retrospective cohort	ACS	802 PPI: 274; no PPI: 528	PPI: 64(13) no PPI: 61 (13)	ACM (6 months)
(Goodman et al. 2012) [43 countries]	Post-hoc analyses of RCT	ACS	18,601 PPI: 6,539; No PPI: 12,060	PPI: 63 no PPI: 62	MI (1 year); ACM (1 year); CVD mort (1 year);
(Gupta et al. 2010) [USA]	Retrospective cohort	PCI	315 PPI: 72; No PPI: 342	PPI: 62(1) no PPI: 62 (1)	ACM (4 years)
(Harjai et al. 2011) [USA]	Retrospective cohort	CAD with PCI	2651 PPI: 751; no PPI: 1902	PPI: 64(12) no PPI: 66 (11)	MI (6 months); ACM (6 months);
(Ho et al. 2009) [USA]	Retrospective cohort	ACS	8205 PPI: 5,244; No PPI: 2,961	PPI: 68 (11) no PPI: 66 (12)	ACM (1,080 days)
(Hokimoto and Ogawa 2010) [Japan] –*abstract only*	Prospective cohort	ACS	170 PPI (rabep): 37; no PPI: 133	NR	MI (1 year); Stroke (1 year); CVD mort (1 year);
(Huang et al. 2010) [Taiwan]	Retrospective cohort	PCI	3,278 PPI: 572; No PPI: 2,706	PPI: 69(11) no PPI: 65 (12)	ACM (up to 6 years (from Kaplan Meir curve)
(Hudzik et al. 2010) [Poland]	Prospective cohort	Stent	38 PPI (omep): 18; No PPI: 20	PPI: 63(9) no PPI: 61 (12)	Stroke (1 year); ACM (1 year); Death (1 year);
(Juurlink et al. 2009) [Canada]	Nested case-control	MI	Cases: 734; Controls: 2057	77 (median)	MI (3 months); ACM (3 months);
(Juurlink et al. 2011) [Canada]	Nested case-control	Stroke	Cases: 118; Controls: 472	77 (median)	Stroke (readmission) (up to 6 months); ACM (up to 6 months);
(Kim et al. 2014) [Korea] -*abstract*	Case crossover	MI	43,822	30-99 (range)	recurrent MI (not reported)
(Kreutz et al. 2010) [USA]	Retrospective cohort	PCI with stent	16,690 PPI: 6,828; No PPI 9,682	PPI: 68 (10) no PPI: 65 (11)	MI (1 year); CVD (1 year);

TABLE 2- 4. CHARACTERISTICS OF STUDIES THAT ASSESSED THE EFFECT OF CONCOMITANT TREATMENT OF PPIS AND CLOPIDOGREL VS CLOPIDOGREL ONLY (GROUP B).

Citation (Location)	Study design (Setting)	Patient population	Study sample size	Mean age (years) (sd)	Outcome(s) of interest (follow-up period)
(Mahabaleshwarkar et al. 2013) [USA]	Nested case-control	Elderly clopidogrel users	Cases: 9,908; Controls: 9,908	All patients: 77 (7) Cases: 79 (8) Controls: 79 (8)	MI; Stroke; ACM;
(Munoz-Torrero et al. 2011) [Spain]	Retrospective cohort	CAD, cerebrovascular or PAD	1,222 PPI: 519; No PPI: 703	PPI: 68 (11) no PPI: 64 (12)	MI (at least 1 year); Stroke (at least 1 year); ACM (at least 1 year);
(O'Donoghue et al. 2009) [30 countries]	Post-hoc analyses of RCT	ACS with PCI	PPI: 4,529; No PPI: 9,079	PPI: 62 no PPI: 61	MI (400 days); ACM (400 days); CVD mort (400 days);
(Ortolani et al. 2012) [Italy]	Retrospective cohort	ACS	3,896 PPI: 3,519; No PPI: 377	PPI: 69(12); no PPI: 63 (12)	ACM (1 year)
(Rassen et al. 2009) [USA and Canada]	Retrospective cohort	ACS or PCI	*British Columbia cohort*: 10,391 PPI: 1,353; No PPI: 9,038 *Pennsylvania cohort*: 4,176 PPI: 1,352; No PPI: 2,824 *New Jersey cohort* 3,998 PPI: 1,291; No PPI: 2,707	*BC cohort* PPI: 76 (7); no PPI: 74 (6) *PA cohort* PPI: 79 (7); no PPI: 78 (7) *NJ cohort* PPI: 78 (7); no PPI: 78 (7)	MI (6 months); ACM (6 months);
(Ray et al. 2010) [USA]	Retrospective cohort	ACS	20,596 PPI: 7,593; No PPI: 13,003	PPI: 61 (11) no PPI: 60 (11)	Stroke (6 years); CVD mort (6 years);
(Rossini et al. 2011) [Italy]	Retrospective cohort	PCI with DES	1328 PPI: 1,158; No PPI: 170	PPI: 64 (11) no PPI: 63 (11)	ACM (1 year)
(Sarafoff et al. 2010) [Germany]	Retrospective cohort	DES	3,338 PPI: 698; No PPI: 2,640	PPI: 69 (11) no PPI: 66 (11)	MI (30 days); ACM (30 days);
(Simon et al. 2011) [France]	Retrospective cohort	MI	2,744 PPI: 1611; No PPI: 1,133	PS matched cohorts: PPI: 65 (12) no PPI: 66 (13)	MI (1 year); Stroke (1 year); ACM (1 year);
(Stockl et al. 2010) [USA]	Retrospective cohort	MI or stent	7,049 PPI: 1,041; No PPI: 6,008 PS matched: 1,033 in each group.	PPI: 69 (11) no PPI: 69 (11)	MI (1 year)
(Sweeny et al. 2009) [USA] -*abstract*	Retrospective cohort	PCI with DES	8,311 PPI: 1,385; no PPI: 6,926	Not reported	ACM (mean 2 years)
(Tentzeris et al. 2010) [Austria]	Retrospective cohort	PCI with stent	1,210 PPI: 691; No PPI: 519	PPI: 64 (12) no PPI: 64 (12)	ACM (mean 7.8 months); CVD mort (mean 7.8 months);
(Ulhaq et al. 2011) [UK]	Retrospective cohort	MI	184 PPI: 96; no PPI: 88	67	MI (1 year)

TABLE 2- 4. CHARACTERISTICS OF STUDIES THAT ASSESSED THE EFFECT OF CONCOMITANT TREATMENT OF PPIS AND CLOPIDOGREL VS CLOPIDOGREL ONLY (GROUP B).

Citation (Location)	Study design (Setting)	Patient population	Study sample size	Mean age (years) (sd)	Outcome(s) of interest (follow-up period)
(Valkhoff et al. 2011) [Netherlands]	Nested case-control	MI	Cases: 616; Controls 126,817	65 (13)	recurrent MI (up to 9 years; median: 3.6 years)
(van Boxel et al. 2010) [Netherlands]	Retrospective cohort	New clopidogrel users	18,139 PPI: 5,734; No PPI: 12,405	PPI: 69 (12) no PPI: 66 (12)	MI (750 days); Stroke (750 days); ACM (750 days);
(Wang et al. 2014) [Sweden]	Retrospective cohort	CVD and high risk for UGIB	2,285 (cohort)	67% of sample >75 years	ACM (3 months)
(Weisz et al. 2015) [US and Germany]	Prospective cohort	CAD with DES	8,582 PPI: 2,697; No PPI 5,885	PPI: 64 (11) no PPI: 63 (11)	MI (2 years); ACM (2 years);
(Wu et al. 2010) [Taiwan]	Retrospective cohort	ACS	6,552 PPI: 514; No PPI: 5,551; others	PPI: 72 (1) no PPI: 66 (0)	ACM (3 months)
(Zairis et al. 2010) [Greece]	Retrospective cohort	ACS with stent	588 PPI (omep): 340; No PPI: 248	PPI: 62 (11) no PPI: 62 (11)	MI (1 year); CVD mort[1] (1 year);
(Zou et al. 2014) [China]	Retrospective cohort	PCI with DES	7906 (enrolled) PPI: 6,188; No PPI: 1,465	PPI: 66 (10) no PPI: 66 (11)	MI (1 year); CVD mort (1 year);
Intervention Studies					
(Bhatt et al. 2010) [15 countries]	RCT	ACS	3,873 PPI: 1,876; No PPI: 1,885	PPI: 69 no PPI: 69	MI (6 months); Stroke (6 months); ACM (6 months); CVD mort (6 months);
(Hsu et al. 2011) [Taiwan]	RCT (open label)	Atherosclerosis and history of peptic ulcers	PPI: 83; no PPI: 82	PPI: 71 (12) no PPI: 73 (11)	MI (6 months); Stroke (6 months); CVD mort (6 months);
(Wu et al. 2011) [China]	RCT	ACS and high risk for UGIB	665 PPI: 333; No PPI: 332	76% were over 75+	ACM (1 month)

Abbreviations: ACM: all-cause mortality; ACS: acute coronary syndrome; CAD: coronary artery disease; CVD: cardiovascular disease; DES: drug eluting stent; MI: myocardial infarction; NR: not reported; omep: omeprazole; PAD: Peripheral arterial disease; panto: pantoprazole; PEG: PCI: Percutaneous coronary intervention; PPI: proton pump inhibitor; PS: propensity score; rabep: rabeprazole; SD: standard deviation; UGIB: Upper gastrointestinal bleeding;

TABLE 2- 5. FINDINGS FROM OBSERVATIONAL STUDIES THAT REPORTED ADJUSTED EFFECT ESTIMATES FOR CONCOMITANT PPI/CLOPIDOGREL TREATMENT VS CLOPIDOGREL ALONE CLASSIFIED BY OUTCOME (GROUP B).[1]

Study	Patient population	Follow up period	Adjusted effect estimates[1] (95% CI)	Variables adjusted for	Authors' conclusion on the PPI-outcome of interest association
All-cause mortality					
(Rossini et al. 2011)	PCI with DES	1 year	**aOR, 0.97, (0.28–3.31);**	Adjusted for age, gender, BMI, smoking, comorbidities, comedications, admission diagnosis, family history of CAD;	No interaction between PPI and clopidogrel among patients with DES implantation -recommend further investigation.
(Gargiulo et al. 2016)	PCI	up to 24 months	Note that HRs are reported for PPI non-use vs PPI use. **aHR, 0.92 (0.64-1.31);**	Sex, age, creatinine clearance, clinical presentation, and CRUSADE score;	No association between PPI use and ischemic events.
(Yan et al. 2016)	ACS, PCI	1 year	**aHR, 1.10 (0.89-1.36);**	Age, sex, comorbidities, propensity to receive PPI at discharge;	No association between concomitant use of PPIs with either clopidogrel or ticagrelor among patients with ACS following PCI.
(Ortolani et al. 2012)	ACS	1 year	**aHR, 0.69 (0.40–1.16);**	Adjusted for age, sex, Charlson index, length of stay, comedications, and comorbidities.	Concomitant use of clopidogrel and PPIs is not associated with ACM, but associated with higher risk of nonfatal hospitalization for ACS in ACS patients at low risk for GI bleeding -recommend further investigation.
(Simon et al. 2011)	MI	1 year	In hospital mortality: **All types of PPI, aOR, 1.04 (0.61-1.77);** Omep, aOR, 1.16 (0.66–2.05); Esomep, aOR, 0.72 (0.30–1.7); Lanso, aOR, 1.30 (0.15–11.5); Panto, aOR, 1.00 (0.27–3.68);	Adjusted for age, gender, BMI, smoking, family history, prior treatments, GRACE score, comorbidities, comedications, PCI.	PPI use not associated with increased MACE or mortality in CP treated patients for recent MI.
(Weisz et al. 2015)	CAD with DES	2 years	**aHR, 1.28 (1.00, 1.63);**	Adjusted for: age, sex, comorbidities, prior events, smoking, hemoglobin, WBC, platelet count, PS (quintile variable);	Nonsignificant association between PPI and mortality or MI.
(Juurlink et al. 2009)	MI	3 months 1 year	Within 90 days of discharge, aOR, 0.82 (0.57-1.18); **Within 1 year of discharge, aOR, 0.89 (0.67-1.18);**	Adjusted for: age, sex, income, Charlson comorbidity index, length of stay in hospital, comorbidities, and concomitant medications.	Association between concomitant PPI (omep, lanso or rabep) and clopidogrel treatment and increased risk of recurrent MI among MI patients. No similar association with panto.

TABLE 2- 5. FINDINGS FROM OBSERVATIONAL STUDIES THAT REPORTED ADJUSTED EFFECT ESTIMATES FOR CONCOMITANT PPI/CLOPIDOGREL TREATMENT VS CLOPIDOGREL ALONE CLASSIFIED BY OUTCOME (GROUP B).[1]

Study	Patient population	Follow up period	Adjusted effect estimates[1] (95% CI)	Variables adjusted for	Authors' conclusion on the PPI-outcome of interest association
(Sarafoff et al. 2010)	DES	1 month	**aHR, 2.2 (1.1–4.3);**	Adjusted for: age, sex, MI, comorbidities, BMI, GI disease.	No association between concomitant treatment and death or MI in patients receiving drug-eluting stents.
(Gupta et al. 2010)	PCI	4 years	**aOR, 1.20 (0.53–2.70);**	Adjusted for: age, smoking, comedications, comorbidities, prior procedures;	Possible association between concomitant treatment and MACE in PCI patients.
(Harjai et al. 2011)	PCI	6 months	**PS adjusted, PPI use, aHR, 0.95 (0.56-1.63);** PS adjusted, omep or esomep, aHR, 0.49 (0.17-1.37);	Age, prior conditions, comorbidities, stent, concomitant medications.	No association between PPI use and MACE at 6 months follow up.
(Gaspar et al. 2010)	ACS	6 months	**6 months, aOR, 1.04, (0.49-2.18);**	Age, gender, comorbidities, prior CVD, Killip class.	No association between PPI use and death at 6 months among ACS patients treated with clopidogrel and aspirin.
(Rassen et al. 2009)	ACS or PCI	6 months	*British Columbia cohort* PS adjusted, aRR, 1.39 (0.73–2.64); *Pennsylvania cohort* PS adjusted, aRR, 1.57 (0.88–2.81); *New Jersey cohort* PS adjusted, aRR, 0.89 (0.49–1.60); ***All cohorts*** **PS adjusted, aRR, 1.20 (0.84–1.70);**	Age, gender, race, calendar year, prior hospitalization, prior medications, prior diagnoses, medical service use, and 400 covariates for PS calculation.	No association between concomitant treatment and MI or mortality in elderly patients after PCI or ACS.
(van Boxel et al. 2010)	New clopidogrel users	2.05 years	**aHR, 1.79 (1.44- 2.22);**	Age, gender, concomitant medications.	Increased risk for MI and ACM among new clopidogrel users taking PPIs concurrently. No association between concomitant treatment and stroke.
(Ching et al. 2012)	PCI	9 months	**PS adjusted, aHR, 1.79 (1.03-3.12),**	Age, sex, smoking, body surface area, GI bleeding and comorbidities.	Possible association; recommend further investigation.
(Douglas et al. 2012)	On clopidogrel and aspirin	10.1 months	**All PPIs, aHR, 1.40 (1.29 to 1.52);** Omen, esomep and lanso, aHR, 1.43 (1.31 to 1.56);	Age, sex, BMI, smoking, alcohol, comorbidities.	No association between PPI use and MACE.
(Juurlink et al. 2011)	Stroke	up to 6 months	**Current PPI use, aOR, 1.84 (0.88 to 3.89);** Recent PPI use, aOR,0.80 (0.24 to 2.68); *Current PPI use: within 60 days before index date;*	Age, gender, income, Charlson comorbidity index, length of stay in the hospital during the first admission for stroke, hospital	No association between concomitant clopidogrel and PPI treatment and readmission for

TABLE 2- 5. FINDINGS FROM OBSERVATIONAL STUDIES THAT REPORTED ADJUSTED EFFECT ESTIMATES FOR CONCOMITANT PPI/CLOPIDOGREL TREATMENT VS CLOPIDOGREL ALONE CLASSIFIED BY OUTCOME (GROUP B).[1]

Study	Patient population	Follow up period	Adjusted effect estimates[1] (95% CI)	Variables adjusted for	Authors' conclusion on the PPI-outcome of interest association
			Recent PPI use: 61-180 days before index date;	type, comorbidities, prior events, and concomitant medications.	stroke or death in patients that have had a stroke.
(Huang et al. 2010)	PCI	up to 6 years	**aHR, 1.65, (1.35–2.01);**	Age, gender, and pre-existing diseases.	Increased incidence of mortality with concomitant use of clopidogrel and PPI after PCI among East Asian population.
(Ho et al. 2009)	ACS	2.96 years	**aOR, 0.91 (0.80-1.05);**	Age, prior CVD and procedures, comorbidities, discharge medications and others.	Combine treatment of PPIs and clopidogrel was associated with an increased risk of adverse outcomes after hospital discharge among ACS patients.
(Sweeny et al. 2009) -abstract	PCI with DES	mean 2 years	aHR, 1.3 (1.06-1.60);	Adjusting variables not reported	Combined treatment with clopidogrel and PPIs was associated with an increased risk in mortality following PCI with a DES.
(Mahabaleshwarkar et al. 2013)	ACS	unclear	**aOR, 1.40 (1.29–1.53).**	Matched by: age and time to cohort entry. Adjusted for: gender, race, comorbidities, prior procedures, concomitant medications.	Possible association with ACM.
(Wang et al. 2014)	CVD and high risk for UGIB	3 months	CVD cohort, aHR, 1.14 (0.53-2.45); Patients with UGI bleeding before cohort entry, aHR, 1.25 (0.57-2.72); **MI cohort, aHR, 1.88 (0.70-5.03);** MI patients with UGI bleeding before cohort entry, aHR, 2.26 (0.82-6.26).	Age, sex, history of CVD, bleeding, comorbidity.	No association with concomitant treatment in patients with a high risk of UGIB. Use of clopidogrel or PPIs alone seems to increase the risk of mortality and recurrent cardiovascular disease compared with concomitant use of these drugs.
(Tentzeris et al. 2010)	PCI with stent	mean 7.8 months	**PS matched, aHR, 0.78 (0.34-1.761).**	PS matched by: age, gender, comorbidities, smoking, prior procedures, stent, concomitant medications, ACS.	No association between PPI/DAPT and ACM or CV death.
(Charlot et al. 2010)	MI	1 year	**PS matched, aHR, 2.09 (1.82–2.41);**	Age, sex, PCI, income, concomitant medications and comorbidities.	PPI use is associated with an increased risk for adverse cardiovascular outcomes regardless of clopidogrel use, likely due to unmeasured confounding.

TABLE 2- 5. FINDINGS FROM OBSERVATIONAL STUDIES THAT REPORTED ADJUSTED EFFECT ESTIMATES FOR CONCOMITANT PPI/CLOPIDOGREL TREATMENT VS CLOPIDOGREL ALONE CLASSIFIED BY OUTCOME (GROUP B).[1]

Study	Patient population	Follow up period	Adjusted effect estimates[1] (95% CI)	Variables adjusted for	Authors' conclusion on the PPI-outcome of interest association
				Propensity score matched (based on age, gender, income, baseline conditions).	
(Aihara et al. 2012)	PCI with stent	1 year	**PS matched, aHR, 0.89 (0.45–1.74);**	Adjusted for factors found to be different between two groups and PS matched using comorbidities, prior PCI, stent size.	Concomitant therapy of a PPI and clopidogrel after coronary stenting not associated with a higher risk of adverse outcomes than use of clopidogrel without a PPI in a Japanese population.
(Banerjee et al. 2011)	PCI	1 year, 6 years	**PS matched, 1 year post PCI, aOR, 1.34 (0.68–2.66);** PS matched, within 6yrs post PCI, aOR,1.18 (0.64–2.16); N=278 matched cases and controls	Age, comorbidities, prior procedures, smoking, PCI. For PS matching: variables not listed but reported "rigorous control of confounders".	No association between concomitant clopidogrel and PPI treatment and increase risk of MACE in post-PCI patients treated with stent implants.
(Goodman et al. 2012)	ACS	1 year	**aHR, 1.5 (1.22–1.83);**	Propensity score (based on race, sex, region, ulcer, prior MI, blood pressure, heart rate, hemoglobin, co-medications) and the percentage of time the patient was on a PPI from randomization to the start of the landmark.	Possible association between PPI use and higher rates of cardiovascular events.
(O'Donoghue et al. 2009)	ACS with PCI	1.1 years	**aHR, 0.68 (0.47–0.96);**	Potential confounders and the propensity to treat with a PPI.	No association between PPI use MACE risk in patients treated with either clopidogrel or prasugrel.
Cardiovascular mortality					
(Kreutz et al. 2010)	PCI with stent	1 year	**aHR, 1.10 (0.51–2.40);**	Age, sex, prior hospitalization, prior stent, heart conditions, comorbidities, UGIB.	Association between concomitant PPI/clopidogrel treatment and MACE within 1 year after coronary stenting.
(Gargiulo et al. 2016)	PCI	up to 24 months	Note that HRs are reported for PPI non-use vs PPI use. **aHR, 0.87 (0.53-1.40)**	Sex, age, creatinine clearance, clinical presentation, and CRUSADE score;	No association between PPI use and ischemic events.
(Zou et al. 2014)	PCI with DES	1 year	**aHR, 0.92 (0.59–1.23)[2];**	Age, comorbidities, GI disease, and stents.	No significant differences in the risk of MI, cardiovascular death and other adverse events,

TABLE 2- 5. FINDINGS FROM OBSERVATIONAL STUDIES THAT REPORTED ADJUSTED EFFECT ESTIMATES FOR CONCOMITANT PPI/CLOPIDOGREL TREATMENT VS CLOPIDOGREL ALONE CLASSIFIED BY OUTCOME (GROUP B).[1]

Study	Patient population	Follow up period	Adjusted effect estimates[1] (95% CI)	Variables adjusted for	Authors' conclusion on the PPI-outcome of interest association
					regardless of combination of clopidogrel and a PPI in PCI patients.
(Zairis et al. 2010)	ACS with stent	1 year	aHR, 1.0 (0.5 -1.9);	Adjusting variables not reported.	Omep had no impact on the clinical efficacy of clopidogrel drug therapy during the first year after successful coronary stenting.
(Ray et al. 2010)	ACS	6 years	aHR, 1.06 (0.65-1.74);	Age, gender, TennCare uninsured enrolment, race, calendar year, qualifying hospitalization diagnosis and procedures and the propensity score.	Possible association between concomitant treatment and MACE - recommend further investigation.
(Douglas et al. 2012)	On clopidogrel and aspirin	median 10.1 months	Any PPI vs no PPI, aHR, 1.25 (1.12 to 1.40)[3]; Strong inhibitors[4]; aHR, 1.28 (1.15 to 1.44);	Age, sex, BMI, smoking, alcohol, diabetes, and heart conditions.	No association between PPI use and MACE.
(Tentzeris et al. 2010)	PCI with stent	mean 7.8 months	PS matched, aHR, 0.563 (0.205-1.55);	PS matched: age, gender, smoking, prior heart procedures and conditions, concomitant medications, comorbidities.	No association between PPI/DAPT and ACM or CV death.
(Charlot et al. 2010)	MI	1 year	PS matched, aHR, 1.91 (1.63–2.24);	Age, sex, PCI, income, concomitant medications and comorbidities.	PPI use is associated with an increased risk for adverse cardiovascular outcomes regardless of clopidogrel use, likely due to unmeasured confounding.
(Goodman et al. 2012)	ACS	1 year	aHR, 1.42 (1.14–1.76);	Propensity score (based on race, sex, region, ulcer, prior MI, blood pressure, heart rate, hemoglobin, comedications) and time on PPIs.	Possible association between PPI use and higher rates of cardiovascular events.
(O'Donoghue et al. 2009)	ACS with PCI	1.1 years	aHR, 0.71 (0.47–1.07);	Potential confounders and the propensity to treat with a PPI.	No association between PPI use MACE risk in patients treated with either clopidogrel or prasugrel.
Myocardial infarction					
(Zairis et al. 2010)	ACS with stent	1 year	aHR, 1.1, (0.4-2.7);	Adjusting variables not reported.	Omep had no impact on the clinical efficacy of clopidogrel therapy in 1st year after stent.

TABLE 2- 5. FINDINGS FROM OBSERVATIONAL STUDIES THAT REPORTED ADJUSTED EFFECT ESTIMATES FOR CONCOMITANT PPI/CLOPIDOGREL TREATMENT VS CLOPIDOGREL ALONE CLASSIFIED BY OUTCOME (GROUP B).[1]

Study	Patient population	Follow up period	Adjusted effect estimates[1] (95% CI)	Variables adjusted for	Authors' conclusion on the PPI-outcome of interest association
(Gargiulo et al. 2016)	PCI	up to 24 months	Note that HRs are reported for PPI non-use vs PPI use. **aHR, 0.94 (0.60-1.49);**	Sex, age, creatinine clearance, clinical presentation, and CRUSADE score;	No association between PPI use and ischemic events.
(Yan et al. 2016)	ACS, PCI	1 year	**aHR, 0.83 (0.68 - 1.01);**	Age, sex, comorbidities, propensity to receive PPI at discharge;	No association between concomitant use of PPIs with either clopidogrel or ticagrelor among patients with ACS following PCI.
(Simon et al. 2011)	MI	1 year	Recurrent MI **All PPIs, aOR, 1.15 (0.57–2.32);** Omep, aOR 1.18 (0.55–2.52); Esomep, aOR 1.20 (0.44–3.30); Panto, aOR 1.22 (0.26–5.77);	Adjusted for age, gender, BMI, smoking, family history, prior treatments, GRACE score, comorbidities, comedications, PCI.	PPI use not associated with increased MACE or mortality in CP treated patients for recent MI.
(Evanchan et al. 2010)	MI and stent	1 year	**recurrent MI, aOR, 1.78, (1.55–2.07);**	Age, comorbidities and concomitant medications.	Possible association between concomitant treatment and recurrent MI within 1 year in PCI patients.
(Zou et al. 2014)	PCI with DES	1 year	**aHR, 1.79 (0.88–3.72);**	Age, comorbidities and prior events.	No significant differences in the risk of MI, cardiovascular death and other adverse events, regardless of combination of clopidogrel and a PPI in PCI patients.
(Kreutz et al. 2010)	PCI with stent	1 year	**aHR, 1.63 (1.40–1.90);**	Age, sex, prior hospitalizations, prior events, comorbidities, prior PPI use.	Association between concomitant PPI/clopidogrel treatment and MACE within 1 year after coronary stenting.
(Weisz et al. 2015)	CAD with DES	2 years	**aHR, 1.03 (0.78, 1.35);**	Age, sex, smoking, prior events, comorbidities, and PS as a quintile variable.	Nonsignificant association between PPI and mortality or MI.
(Juurlink et al. 2009)	MI	3 months	*Outcome: readmission for MI* Within 90 days, CP users, current use of PPI vs no use, aOR, 1.27 (1.03-1.57); Within 90 days, CP users, previous use of PPI vs no use, aOR, 0.86 (0.63–1.19); Within 90 days, CP users, remote use of PPI vs no use, aOR, 0.81 (0.46–1.41); Within 90 days, CP users, current use of	Age, sex, income, Charlson comorbidity index, length of stay in hospital during the index admission, comorbidities, and concomitant medications.	Association between concomitant PPI (omep, lanso or rabep) and clopidogrel treatment and increased risk of recurrent MI among MI patients. No similar association with panto.

TABLE 2- 5. FINDINGS FROM OBSERVATIONAL STUDIES THAT REPORTED ADJUSTED EFFECT ESTIMATES FOR CONCOMITANT PPI/CLOPIDOGREL TREATMENT VS CLOPIDOGREL ALONE CLASSIFIED BY OUTCOME (GROUP B).[1]

Study	Patient population	Follow up period	Adjusted effect estimates[1] (95% CI)	Variables adjusted for	Authors' conclusion on the PPI-outcome of interest association
			panto vs no use, aOR, 1.02 (0.70–1.47) ; Within 90 days, CP users, Previous use of panto vs no use, aOR, 0.89 (0.48–1.67); Within 90 days, CP users, remote use of panto vs no use, aOR,2.09 (0.74–5.92); Within 90 days, CP users, current use of PPI other than panto vs no use, aOR, 1.40 (1.10–1.77) ; Within 90 days, CP users, Previous use of PPI other than panto vs no use, aOR, 0.86 (0.60–1.23); Within 90 days, CP users, remote use of PPI other than panto vs no use, aOR, 0.60 (0.31–1.17); **Within 1 year, CP users, PPI use vs no use, aOR, 1.23 (1.01–1.49);**		
(Sarafoff et al. 2010)	DES	1 month	**aHR, 1.3 (0.8–2.3);**	Age, sex, BMI, prior events, comorbidities.	No association between concomitant treatment and death or MI in patients receiving drug-eluting stents.
(Harjai et al. 2011)	CAD with PCI	6 months	**PS adjusted, all PPIs, aHR, 1.04 (0.64-1.69);** PS adjusted, omep or esomep, aHR, 0.65 (0.29-1.43);	Prior CV events and procedures, discharge medications (for all types of PPIs); Adjusted for prior CV events and procedures, and comorbidities (for omep and esomep).	No association between PPI use and MACE at 6 months follow up.
(Rassen et al. 2009)	ACS or PCI	6 months	*British Columbia cohort,* PS adjusted, aRR (rate ratio), 1.18 (0.88–1.60); *Pennsylvania cohort*, PS adjusted, aRR (rate ratio), 1.95 (1.03–3.70); *New Jersey cohort*, PS adjusted, aRR (rate ratio), 1.05 (0.56–1.98); **Pooled cohorts, PS adjusted, aRR (rate ratio), 1.22 (0.95–1.57);**	Age, gender, race, calendar year, prior hospitalization, prior medications, prior diagnoses, medical service use, and 400 covariates for PS calculation.	No association between concomitant treatment and MI or mortality in elderly patients after PCI or ACS.
(van Boxel et al. 2010)	New clopidogrel users	2.05 years	**aHR, 1.93 (1.40-2.65);**	Age, gender, concomitant medications.	Increased risk for MI and ACM among new clopidogrel users taking PPIs concurrently.

TABLE 2- 5. FINDINGS FROM OBSERVATIONAL STUDIES THAT REPORTED ADJUSTED EFFECT ESTIMATES FOR CONCOMITANT PPI/CLOPIDOGREL TREATMENT VS CLOPIDOGREL ALONE CLASSIFIED BY OUTCOME (GROUP B).[1]

Study	Patient population	Follow up period	Adjusted effect estimates[1] (95% CI)	Variables adjusted for	Authors' conclusion on the PPI-outcome of interest association
					No association between concomitant treatment and stroke.
(Douglas et al. 2012)	On clopidogrel and aspirin	median 10.1 months	Any PPI, aHR, 1.30 (1.12 to 1.50); Strong CYP2C19 inhibiting PPI vs no PPI; aHR, 1.29 (1.12 to 1.49); *Strong PPIs: omep, esomep, and lanso;* SCCS analyses **PPI vs no PPI, aIRR (incident rate ratio), 0.75 (0.55 to 1.01);** Strong PPI vs no PPI, aIRR (incident rate ratio), 0.77 (0.57 to 1.03);	Main analyses (not SCCS): Adjusted for age, sex, BMI, smoking, alcohol, comorbidities and prior events.	No association between PPI use and MACE.
(Valkhoff et al. 2011)	MI	nested case control	recurrent MI **Current CP+PPI vs Current CP but no PPI, aOR, 1.62 (1.15–2.27);** Current CP +PPI vs Current CP but past PPI, aOR, 0.95 (0.38–2.41);	Matched for age: gender, risk of recurrent MI and calendar time. Adjusted for: follow-up time in days and prescriptions in year prior to index MI.	No association between concomitant therapy and recurrent MI;
(Mahabaleshwarkar et al. 2013)	Elderly clopidogrel users	nested case control	**aOR, 0.85 (0.59–1.23);**	Age, time to cohort entry; Adjusted for: gender, race, comorbidities, prior procedures, concomitant medications	Possible association with ACM.
(Aihara et al. 2012)	PCI with stent	1 year	**PS matched, aHR, 0.69 (0.20–2.32);**	PS calculated using multi-vessel disease, left anterior descending culprit, and AHA/ACC type B2/C lesion, hypertension, diabetes mellitus, previous PCI, stent size, and stent length.	Concomitant therapy of a PPI and clopidogrel after coronary stenting not associated with a higher risk of adverse outcomes than use of clopidogrel without a PPI in a Japanese population.
(Stockl et al. 2010)	MI or stent	1 year	**PS matched, all PPIs, aHR, 1.93 (1.05-3.54);** PS matched, panto, aHR, 2.18 (0.88-5.39);	PS matched and adjusted for Charlson comorbidity index score (all PPIs); PS matched, and adjusted for Charlson comorbidity index score, geographical state, pre-period hospitalization for other ischemic heart disease, and pre-period history	Possible association between concomitant treatment and higher risk of adverse outcomes - recommend further investigation.

TABLE 2- 5. FINDINGS FROM OBSERVATIONAL STUDIES THAT REPORTED ADJUSTED EFFECT ESTIMATES FOR CONCOMITANT PPI/CLOPIDOGREL TREATMENT VS CLOPIDOGREL ALONE CLASSIFIED BY OUTCOME (GROUP B).[1]

Study	Patient population	Follow up period	Adjusted effect estimates[1] (95% CI)	Variables adjusted for	Authors' conclusion on the PPI-outcome of interest association
				of 2 outpatient medical claims for heart failure (panto);	
(Charlot et al. 2010)	MI	1 year	**PS matched, aHR, 1.18 (1.04–1.35);**	PS matched for: age, sex, PCI, income, concomitant medications and comorbidities.	PPI use is associated with an increased risk for adverse cardiovascular outcomes regardless of clopidogrel use, likely due to unmeasured confounding.
(Burkard et al. 2012)	PCI	3 years	**aHR, 1.88 (1.05–3.37);**	Age, sex, weight, concomitant medications, ulcer disease history, concomitant medications (baseline differences)	Concomitant PPI and clopidogrel treatment was associated with increased MI rates 3 years after PCI.
(Goodman et al. 2012)	ACS	1 year	**aHR, 1.12 (0.9–1.4);**	Propensity score (based on sex, race, region, medical history, medications, prior events)	Possible association between PPI use and higher rates of cardiovascular events.
(O'Donoghue et al. 2009)	ACS with PCI	1.1 years	**all PPIs, aHR, 0.98 (0.82–1.17);** Omep, aHR, 0.95 (0.73–1.23); Panto, aHR, 0.97 (0.75–1.24); Esomep, aHR, 1.18 (0.81–1.73); Lanso, aHR, 0.86 (0.51–1.46);	Adjusted for potential confounders and the propensity to be treated with a PPI.	No association between PPI use MACE risk in patients treated with either clopidogrel or prasugrel.
(Kim et al. 2014) - *abstract*	MI	not reported	PPI use vs nonuse, aOR, 1.35 (1.05-1.75); All PPIs except panto + DAPT vs DAPT, aOR, 1.56 (1.16-2.10);	Concomitant medications	Possible association between concomitant PPI use of clopidogrel and PPI in AMI patients receiving DAPT.
Stroke					
(Mahabaleshwarkar et al. 2013)	Elderly clopidogrel users	nested case control	**aOR, 1.05 (0.86–1.28)**	Matched by age and time to cohort entry; Adjusted for gender, race, comorbidities, prior procedures, concomitant medications.	Possible association with ACM.
(Charlot et al. 2010)	MI	1 year	**aHR, 1.78 (1.47–2.16);**	PS matched for age, sex, PCI, income, concomitant medical treatment and comorbid conditions.	PPI use is associated with an increased risk for adverse cardiovascular outcomes regardless of clopidogrel use, likely due to unmeasured confounding.

TABLE 2- 5. FINDINGS FROM OBSERVATIONAL STUDIES THAT REPORTED ADJUSTED EFFECT ESTIMATES FOR CONCOMITANT PPI/CLOPIDOGREL TREATMENT VS CLOPIDOGREL ALONE CLASSIFIED BY OUTCOME (GROUP B).[1]

Study	Patient population	Follow up period	Adjusted effect estimates[1] (95% CI)	Variables adjusted for	Authors' conclusion on the PPI-outcome of interest association
(Simon et al. 2011)	MI	1 year	**All PPIs, aOR, 0.33 (0.12–0.92)**; Omep, aOR 0.14 (0.03–0.67) Esomep, aOR, 0.54 (0.14–2.16); Panto, aOR, 1.78 (0.36–8.83	Age, gender, BMI, smoking, family history, prior treatments, GRACE score, comorbidities, comedications, PCI.	PPI use not associated with increased MACE or mortality in CP treated patients for recent MI.
(Ray et al. 2010)	ACS	6 years	**aHR, 1.21 (0.82-1.78);**	Age, sex, year of study entry, race, Medicaid enrolment, prior procedures, comorbidities, concomitant medications, smoking, BMI, medical care utilization, prior CV medical visits number, prior hospital stay;	Possible association between concomitant treatment and MACE - recommend further investigation.
(van Boxel et al. 2010)	New clopidogrel users	2.05 years	**aHR, 1.13 (0.78 – 1.65);**	Age, gender, concomitant medications.	Increased risk for MI and ACM among new clopidogrel users taking PPIs concurrently. No association between concomitant treatment and stroke.
(Juurlink et al. 2011)	Stroke	6 months	**Current PPI use (within 60 days before index date), aOR, 1.05 (0.60 to 1.82),** Recent PPI use (61-180 days before index date), aOR, 1.22 (0.55 to 2.68), Remote PPI use (181-365 days before index date), aOR, 0.24 (0.03 to 2.12);	Adjusted for age, gender, income, Charlson comorbidity index, length of stay in the hospital during the first admission for stroke, hospital type, comorbidities, prior events, and concomitant medications.	No association between concomitant clopidogrel and PPI treatment and readmission for stroke or death in patients that have had a stroke.
(Aihara et al. 2012)	PCI with stent	1 year	**PS matched, aHR, 1.21 (0.48–3.19)**	Adjusted for factors identified through univariate analysis ($P < 0.20$) and other variables. For PS matched analyses: multivessel disease, left anterior descending culprit, and AHA/ACC type B2/C lesion, hypertension, diabetes mellitus, previous PCI, stent size, and stent length.	Concomitant therapy of a PPI and clopidogrel after coronary stenting not associated with a higher risk of adverse outcomes than use of clopidogrel without a PPI in a Japanese population.

[1]Bolded results were included in the meta-analysis
[2] Cardiovascular mortality was defined as all death cases unless otherwise stated.
[3]Vascular mortality defined as diseases of the circulatory system.
[4]Strong inhibitors defined as omeprazole, lansoprazole and esomeprazole.

Abbreviations: ACM: all-cause mortality; ACS: acute coronary syndrome; aHR: adjusted HR; aIRR: adjusted incidence rate ratio; aOR: adjusted OR; AP: antiplatelet; BMI: body mass index; CAD: coronary artery disease; CV: cardiovascular; DAPT: dual antiplatelet therapy; DES: drug eluting stent; esomep: esomeprazole; GI: gastrointestinal; GRACE: Global Registry of Acute Coronary Events; lanso: lansoprazole; MACE: major adverse cardiovascular events; MI: myocardial infarction; NSAIDs: Nonsteroidal anti-inflammatory drugs; NR: not reported; omep: omeprazole; PAD: Peripheral arterial disease ; panto: pantoprazole; PCI: Percutaneous coronary intervention; PPI: proton pump inhibitor; PS: propensity score; rabep: rabeprazole;

TABLE 2- 6. FINDINGS FROM RCTS FOR CONCOMITANT PPI/CLOPIDOGREL TREATMENT VS CLOPIDOGREL ALONE CLASSIFIED BY OUTCOME (GROUP B).

Citation (Study design)	Patient population	Outcome (follow up period)	Counts/rates of events or unadjusted effect estimates and number of patients (N) in each exposure group[1]	Overall author conclusion on the PPI-outcome of interest association
All-cause mortality				
(Bhatt et al. 2010)	ACS	ACM (6 months)	*Clopidogrel and aspirin users* Event rate, PPI (omep): 0.4 (95% CI: 0.0–0.7) *(N=1,876)*; no PPI, event rate, 0.5 (95% CI: 0.0–1.1) (N=1,885); p-value: 1.00;	No association between PPI/clopidogrel treatment and MACE.
(Wu et al. 2011)	ACS and high risk for UGIB	ACM (30 day)	*Clopidogrel and aspirin users* PPI (panto): 11% (N=333); no PPI: 10% (N=332); p-value: 1;	Panto prophylactic treatment has no significant effect on 30-day mortality.
Cardiovascular mortality				
(Bhatt et al. 2010)	ACS	CV mort (6 months)	*Clopidogrel and aspirin users* Event rate: PPI (omep), 0.4 (95% CI: 0.0–0.7) *(N=1,876)*; no PPI: 0.3 (0.0–0.8) (N=1,885); p-value: 0.49;	No association between PPI/clopidogrel treatment and MACE.
(Hsu et al. 2011)	Atherosclerosis and history of peptic ulcers	CV mort (6 months)	*Clopidogrel users* PPI (esomep): 0 (N=83); no PPI (esomep): 0 (N=82);	No evidence of increased risk of MACE when esomep is given before breakfast and clopidogrel is administered at bedtime.
Myocardial infarction				
(Bhatt et al. 2010)	ACS	MI (6 months)	*Clopidogrel and aspirin users* PPI/omep use vs nonuse, aHR, 0.92 (0.44–1.90); *Event rate* *PPI (omep): 1.2 (0.5–2.0) (N=1,876); no PPI: 1.5 (0.6–2.4) (N=1,885);*	No association between PPI/clopidogrel treatment and MACE.
(Hsu et al. 2011)	Atherosclerosis and history of peptic ulcers	MI (6 months)	*Clopidogrel users* PPI (esomep): 2.4% (N=83); no PPI (esomep): 2.4% (N=82); p-value: 1;	No evidence of increased risk of MACE when esomep is given before breakfast and clopidogrel is administered at bedtime.
Stroke				
(Bhatt et al. 2010)	ACS	Stroke (6 months)	*Clopidogrel and aspirin users* Event rate, PPI (omep): 0.2 (0.0–0.5) (N=1,876); no PPI: 0.3 (0.0–0.7) (N=1,885); p-value: 0.43;	No association between PPI/clopidogrel treatment and MACE.
(Hsu et al. 2011)	Atherosclerosis and history of peptic ulcers	Stroke (6 months)	*Clopidogrel users* PPI (esomep): 1.2% (N=83); no PPI (esomep): 0% (N=82); p-value: 1.	No evidence of increased risk of MACE when esomep is given before breakfast and clopidogrel is administered at bedtime.

Abbreviations: ACS: acute coronary syndrome; CV: cardiovascular; esomep: esomeprazole; lanso: lansoprazole; MACE: major adverse cardiovascular events; MI: myocardial infarction; omep: omeprazole; PAD: Peripheral arterial disease; panto: pantoprazole; PPI: proton pump inhibitor; UGIB: upper gastrointestinal bleeding;

TABLE 2- 7. CHARACTERISTICS OF STUDIES THAT ASSESSED THE EFFECT OF CONCOMITANT TREATMENT OF PPIS WITH OTHER ANTIPLATELETS (GROUP C).

Citation [Location]	Study design (Setting)	Patient population	Study sample size	Mean age (years) (sd)	Outcome(s) of interest (follow-up period)
Observational studies					
(Charlot et al. 2011) [Denmark]	Retrospective cohort	MI; Aspirin users;	19,925; PPI: 4,306; No PPI: 15,619	PPI: 73 (12) no PPI: 70 (13)	MI (1 year) Stroke (1 year) ACM (1 year) CVD mort (1 year)
(Yan et al. 2016) [International -11 countries]	Retrospective cohort	ACS, PCI; Ticagrelor users;	9,429; PPIs: 5,165; No PPI: 4265;	PPI: 66.2; No PPI: 61.3	ACM (1 year); MI (1 year);
(Goodman et al. 2012) [43 countries]	Post-hoc analyses of RCT	ACS; Ticagrelor users;	18,601; PPI: 6,539; No PPI: 12,060	PPI: 63 no PPI: 62	MI (1 year) ACM (1 year) CVD mort (1 year)
(Kimura et al. 2011) [Japan]	Retrospective cohort	PCI; Ticlopidine users;	12,446 ; PPI: 3223; No PPI: 9223	PPI: 69 (11) no PPI: 68 (11)	MI (3 years) Stroke (3 years) ACM (3 years) CVD mort (3 years)
(O'Donoghue et al. 2009) [30 countries]	Post-hoc analyses of RCT	ACS with PCI; Prasugrel users;	PPI: 4,529; No PPI: 9,079	PPI: 62 no PPI: 61	MI (400 days) ACM (400 days) CVD mort (400 days)
Intervention studies					
(Angiolillo et al. 2014) and (Goldstein et al, 2010)[1]	RCT	On NSAIDs	*Study 1*: 438; PPI: 218; No PPI: 220; *Study 2*: 423; PPI: 212; No PPI:211;	Study 301: 61 Study 302: 60	MI (6 months) ACM (6 months)
(Yeomans et al. 2008) [10 countries]	RCT	60 or over; Aspirin users;	991; PPI (esomep): 493; placebo: 498;	Esomep: 69.5 (6.6); Placebo: 69.1 (6.5);	ACM (26 weeks); MI (26 weeks);
(Scheiman et al. 2011) [Multinational -20 countries]	RCT	Cardiovascular disease at high risk for ulcers; Aspirin users;	2,426; PPI (esomep 40 mg): 817; PPI (esomep 20 mg): 804; placebo: 805;	Esomep 40 mg: 67.7 (range: 21-87); Esomep 20 mg: 67.7 (range: 24-89); Placebo: 67.4 (range: 24-94);	ACM (26 weeks)
(Chan et al. 2007) [China]	RCT	UGIB; Celecoxib;	273; PPI: 137; No PPI: 136;	PPI: 70 (12) no PPI: 72(11)	Stroke: 13 months ACM : 13 months
(Lai et al. 2002) [Hong Kong]	RCT	Peptic ulcers; Aspirin users;	123; PPI (lanso): 62; No PPI: 61;	PPI: 72 (8) no PPI: 69 (8)	ACM (median 1 year)
(Sofia et al. 2000) [Portugal]	RCT	UGIB	208 PPI (omep): 40; No PPI: 44	PPI: 59 (17) no PPI: 65 (15)	ACM (not clear)

TABLE 2- 7. CHARACTERISTICS OF STUDIES THAT ASSESSED THE EFFECT OF CONCOMITANT TREATMENT OF PPIS WITH OTHER ANTIPLATELETS (GROUP C).

Citation [Location]	Study design (Setting)	Patient population	Study sample size	Mean age (years) (sd)	Outcome(s) of interest (follow-up period)
(Sugano et al. 2014) [Japan, Korea and Taiwan]	RCT	CVD and peptic ulcers; Aspirin and gefarnate users;	430 PPI (esomep): 215; No PPI: 215	PPI: 66 (10) no PPI: 68 (9)	MI (72 weeks) ACM (72 weeks)
(Whellan et al. 2014) [USA]	RCT	CVD disease/ high risk for gastric ulcers; Aspirin users;	1,049 PPI: 524; No PPI: 525	PPI 66; No PPI: 66	MI (1,3, 6 months) Stroke (1,3, 6 months) CVD mort (1,3, 6 months)

Abbreviations: ACM: all-cause mortality; ACS: acute coronary syndrome; CVD: cardiovascular disease; esomep: esomeprazole; DES: drug eluting stent; lanso: lansoprazole; MI: myocardial infarction; NSAIDs: Nonsteroidal anti-inflammatory drugs; omep: omeprazole; panto: pantoprazole; PCI: Percutaneous coronary intervention; PPI: proton pump inhibitor; rabep: rabeprazole; SD: standard deviation; UGIB: Upper gastrointestinal bleeding;

TABLE 2- 8. FINDINGS FROM OBSERVATIONAL STUDIES THAT REPORTED ADJUSTED EFFECT ESTIMATES FOR CONCOMITANT USE OF PPIS AND OTHER ANTIPLATELET AGENTS VS ANTIPLATELET AGENTS ALONE CLASSIFIED BY OUTCOME (GROUP C).

Study	Patient population	Follow up period	Adjusted effect estimates[1] (95% CI) (those used in MA are bolded)	Variables adjusted for	Authors' conclusion on the PPI-outcome of interest association
All-cause mortality					
(Charlot et al. 2011)	MI	1 year	Aspirin users: PS matched aHR, 2.38 (2.12 to 2.67),	PS models: score calculated based on: age, gender, income group, PCI, comorbidities, co medications.	Association between PPI use and MACE in aspirin treated patients with first time MI -recommended further investigation.
(Yan et al. 2016)	ACS, PCI	1 year	Ticagrelor users: **aHR, 3.20 (0.39 - 26.4);**	Age, sex, comorbidities, propensity to receive PPI at discharge;	No association between concomitant use of PPIs with ticagrelor among patients with ACS following PCI.
(Goodman et al. 2012)	ACS	1 year	Ticagrelor users **aHR, 1.10 (0.88–1.39);**	Propensity score (based on race, sex, region, ulcer, prior MI, blood pressure, heart rate, hemoglobin, comedications) and the percentage of time the patient was on a PPI from randomization to the start of the landmark.	Association between PPI use and composite cardiovascular end points may be due to confounding.
(O'Donoghue et al. 2009)	ACS with PCI	1.1 years	Prasugrel users aHR, 1.00 (0.71–1.41);	Potential confounders and the propensity to treat with a PPI.	No association between PPI use and MACE risk in patients treated with either clopidogrel or prasugrel.
Cardiovascular mortality					
(Charlot et al. 2011)	MI	1 year	Aspirin users PS aHR, 2.19 (1.92- 2.49);	PS score calculated based on: age, gender, income group, PCI, comorbidities, concomitant medications.	Association between PPI use and MACE in aspirin treated patients with first time MI -recommend further investigation.
(Goodman et al. 2012)	ACS	1 year	Ticagrelor users aHR, 1.13 (0.88–1.44);	Propensity score (based on race, sex, region, ulcer, prior MI, blood pressure, heart rate, hemoglobin, comedications) and the percentage of time the patient was on a PPI from randomization to the start of the landmark.	Association between PPI use and composite cardiovascular endpoints may be due to confounding.
(O'Donoghue et al. 2009)	ACS with PCI	1.1 years	Prasugrel users aHR, 1·06 (0·70–1·62);	Potential confounders and the propensity to treat with a PPI.	No association between PPI use and MACE risk in patients treated with either clopidogrel or prasugrel.
Myocardial infarction					
(Charlot et al. 2011)	MI	1 year	Aspirin users PS models, aHR, 1.33 (1.13- 1.56); N PPI: 4159; no PPI: 4159;	Cox models: age, sex, year of inclusion, PCI, income, concomitant medications and comorbidities. PS based on: age, gender, income group,	Association between PPI use and MACE in aspirin treated patients with first time MI -recommend further investigation.

TABLE 2- 8. FINDINGS FROM OBSERVATIONAL STUDIES THAT REPORTED ADJUSTED EFFECT ESTIMATES FOR CONCOMITANT USE OF PPIS AND OTHER ANTIPLATELET AGENTS VS ANTIPLATELET AGENTS ALONE CLASSIFIED BY OUTCOME (GROUP C).

Study	Patient population	Follow up period	Adjusted effect estimates[1] (95% CI) (those used in MA are bolded)	Variables adjusted for	Authors' conclusion on the PPI-outcome of interest association
				PCI, comorbidities, concomitant medications.	
(Goodman et al. 2012)	ACS	1 year	Ticagrelor users aHR, 1.14 (0.89–1.45);	Propensity score (based on sex, race, region, medical history, concomitant medications, prior events)	Association between PPI use and composite cardiovascular endpoints may be due to confounding.
(O'Donoghue et al. 2009)	ACS with PCI	1.1 years	Prasugrel users: All PPIs, aHR, 1.02 (0.84–1.25); Omep, aHR, 1.02 (0.76–1.36); Panto, aHR, 1.09 (0.83–1.43); Esomep, aHR, 0.92 (0.57–1.48); Lanso, aHR, 1.08 (0.66–1.79);	Potential confounders and the propensity to be treated with a PPI.	No association between PPI use and MACE in patients treated with either clopidogrel or prasugrel.
Stroke					
(Charlot et al. 2011)	MI	1 year	Aspirin users PS analyses, aHR, 1.20 (0.99-1.46),	PS models: score calculated based on: age, gender, income group, PCI, comorbidities, co medications.	Association between PPI use and MACE in aspirin treated patients with first time MI -recommended further investigation.

[1]Bolded findings were included in the meta-analysis

Abbreviations: ACS: acute coronary syndrome; aHR: adjusted HR; esomep: esomeprazole; lanso: lansoprazole; MACE: major adverse cardiovascular events; MI: myocardial infarction; omep: omeprazole; PAD: Peripheral arterial disease; panto: pantoprazole; PCI: Percutaneous coronary intervention; PPI: proton pump inhibitor; PS: propensity score;

TABLE 2- 9. FINDINGS FROM RCTS FOR CONCOMITANT USE OF PPIS AND OTHER ANTIPLATELET AGENTS VS ANTIPLATELET AGENTS ALONE CLASSIFIED BY OUTCOME (GROUP C).

Citation	Patient population	Outcome (follow up period)	Counts/rates of events or unadjusted effect estimates and number of patients (N) in each exposure group[1]	Overall author conclusion on the PPI-outcome of interest association[2]
All-cause mortality				
(Angiolillo et al. 2014) and (Goldstein et al, 2010)	On NSAIDs	ACM (6 months)	*Naproxen users* PPI: 0 (N=800); no PPI: 0 (N=426);	***No difference***
(Yeomans et al. 2008)	60 or over and receiving low dose aspirin.	ACM (26 weeks); MI (26 weeks);	*Aspirin users* **Esomep: 0/493;** **Placebo: 2/498;**	Esomeprazole in combination with low-dose aspirin showed no safety concerns.
(Scheiman et al. 2011)	Cardiovascular disease at high risk for ulcers	ACM (26 weeks)	*Aspirin users* Esomep 40 mg: 4/814; **Esomep 20mg: 4/799;** **Placebo: 1/801;**	Esomeprazole in combination with low-dose aspirin was well tolerated and there were no safety concerns.
(Chan et al. 2007)	UGIB	ACM (13 months)	*Celecoxib users* PPI (esomep): 1% (N=137); no PPI: 1% (N=136); p-value: 0.62	No difference in mortality between concomitant celecoxib/PPI treatment vs celecoxib alone among UGIB patients
(Sofia et al. 2000)	UGIB	ACM (not clear)	*Ethanol users* PPI (omep): 4% (N= 40); no PPI: 4% (N= 44); p-value: 1;	No difference in mortality between groups.
(Sugano et al. 2014)	CVD and peptic ulcers	ACM (72 weeks)	*Aspirin and gefarnate users* PPI: 0% (N=215); no PPI: 0% (N=215);	***No difference***
Cardiovascular mortality				
(Whellan et al. 2014)	CVD or CVA disease/ high risk for gastric ulcers	CVD mortality (1,3, 6 months)	*Aspirin users* PPI: 0% (N=521); no PPI: 0.1% (N=524); p-value: 0.47	***No difference***
Myocardial infarction				
(Angiolillo et al. 2014) and (Goldstein et al, 2010)	On NSAIDs	MI (6 months)	*Naproxen users* PPI (esomep): 0.1% (N= 1,157); no PPI: 0 deaths (N=426); p-value: 0.52;	***No difference***
(Yeomans et al. 2008)	60 or over and receiving low dose aspirin.	ACM (26 weeks); MI (26 weeks);	*Aspirin users* **Esomep: 0/493;** **Placebo: 3/498;**	Esomeprazole in combination with low-dose aspirin showed no safety concerns.
(Sugano et al. 2014)	CVD and peptic ulcers	MI (72 weeks)	*Aspirin and gefarnate users* PPI: 0 (N=214); no PPI: 1% (N=213); p-value: 0.14;	***No difference***
(Whellan et al. 2014)	CVD or CVA disease/ high risk for gastric ulcers	MI (1,3, 6 months)	*Aspirin users* **PPI (omep): 0.96% (N=521); no PPI: 0.57% (N=524);** p-value: 0.47;	***No difference***
Stroke				
(Chan et al. 2007)	UGIB	Stroke (13 months)	*Celecoxib users* PPI: 0 (N=137); no PPI: 1% (N=136); p-value: 0.25;	No difference in mortality between concomitant celecoxib/PPI treatment vs celecoxib alone among UGIB patients

Citation	Patient population	Outcome (follow up period)	Counts/rates of events or unadjusted effect estimates and number of patients (N) in each exposure group[1]	Overall author conclusion on the PPI-outcome of interest association[2]
(Whellan et al. 2014)	CVD or CVA disease/ high risk for gastric ulcers	Stroke (1,3, 6 months)	*Aspirin users* PPI (omep): 0 (N=521); no PPI: 0 (N=524)	***No difference***

[1]Bolded results were included in the meta-analysis

[2] When the authors' conclusions regarding the association in question was not reported, the reviewers arrived at a conclusion based on whether there was a statistically significant difference in the proportion of events between the treatment groups; these conclusions are bolded in this column.

Abbreviations: ACM: all-cause mortality; CVA: cerebrovascular accident; CVD: cardiovascular disease; esomep: esomeprazole; MI: myocardial infarction; NSAIDs: Nonsteroidal anti-inflammatory drugs; omep: omeprazole; PPI: proton pump inhibitor; UGIB: upper gastrointestinal bleeding.

SUPPLEMENTAL MATERIAL

SUPPLEMENTAL MATERIAL I - SEARCH STRATEGIES

EMBASE (WITH SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK FILTERS)

	Search terms	Results
1	Proton pump inhibitor$.tw.	15682
2	Ppi$.tw.	22015
3	*proton pump inhibitor/	6465
4	Esomeprazole.tw.	2064
5	Pantoprazole.tw.	2307
6	Lansoprazole.tw.	2985
7	Omeprazole.tw.	10010
8	Rabeprazole.tw.	1583
9	*Esomeprazole/	1254
10	*Pantoprazole/	1483
11	*Lansoprazole/	2238
12	*omeprazole/	8388
13	*Rabeprazole/	1115
14	or/1-13	45500
15	myocardial infarction$.tw.	195179
16	heart infarction$.tw.	977
17	heart attack$.tw.	5719
18	heart infarction/	217265
19	cerebrovascular accident$.tw.	7478
20	stroke$.tw.	251045
21	cerebrovascular accident/	111017
22	mortality.tw.	705132
23	mortality/	594725
24	death$.tw.	776905
25	death/	182715
26	cardiovascular mortality/	16475
27	or/15-26	1921157
28	14 and 27	3260
29	limit 28 to (human and English language)	2519
30	Clinical trial/	852915
31	Randomized controlled trial/	388215
32	Randomization/	68660
33	Single blind procedure/	21256
34	Double blind procedure/	124707
35	Crossover procedure/	45093
36	Placebo/	266122
37	Randomi?ed controlled trial$.tw.	126586
38	Rct.tw.	18750
39	Random allocation.tw.	1466
40	Allocated randomly.tw.	2073
41	Randomly allocated.tw.	23605

	Search terms	Results
42	(allocated adj2 random).tw.	741
43	Single blind$.tw.	16593
44	Double blind$.tw.	156454
45	((treble or triple) adj blind$).tw.	502
46	Placebo$.tw.	223606
47	Prospective study/	313531
48	or/30-47	1520035
49	Case study/	34656
50	Case report.tw.	294365
51	Abstract report/ or letter/	944138
52	or/49-51	1266554
53	48 not 52	1479906
54	Clinical study/	71067
55	case control study/	99837
56	Family study/	10950
57	Longitudinal study/	82996
58	Retrospective study/	435645
59	Prospective study/	313531
60	Randomized controlled trials/	86770
61	59 not 60	311111
62	Cohort analysis/	222382
63	(Cohort adj (study or studies)).mp.	151743
64	(Case control adj (study or studies)).tw.	89202
65	(follow up adj (study or studies)).tw.	48109
66	(observational adj (study or studies)).tw.	83399
67	(epidemiologic$ adj (study or studies)).tw.	81050
68	(cross sectional adj (study or studies)).tw.	110429
69	or/54-58,61-68	1428334
70	exp Meta Analysis/	101478
71	((meta adj analy$) or metaanalys$).tw.	109987
72	(systematic adj (review$1 or overview$1)).tw.	90438
73	or/70-72	197971
74	cancerlit.ab.	674
75	cochrane.ab.	48937
76	embase.ab.	48668
77	(psychlit or psyclit).ab.	963
78	(psychinfo or psycinfo).ab.	11510
79	(cinahl or cinhal).ab.	14940
80	science citation index.ab.	2518
81	bids.ab.	482
82	or/74-81	77679
83	reference lists.ab.	11930
84	bibliograph$.ab.	15793
85	hand-search$.ab.	5446
86	manual search$.ab.	3307
87	relevant journals.ab.	960
88	or/83-87	33648
89	data extraction.ab.	14316
90	selection criteria.ab.	23030

	Search terms	Results
91	89 or 90	35974
92	review.pt.	2096963
93	91 and 92	17606
94	letter.pt.	909295
95	editorial.pt.	492388
96	animal/	1695032
97	human/	16366505
98	96 not (96 and 97)	1271960
99	or/94-95,98	2658216
100	73 or 82 or 88 or 93	237029
101	100 not 99	229519
102	48 or 69 or 101	2680283
103	29 and 102	1105

MEDLINE (WITH SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK FILTERS)

Searched Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

	Search terms	Results
1	proton pump inhibitor$.tw.	10107
2	ppi$.tw.	15427
3	esomeprazole.tw.	1122
4	pantoprazole.tw.	1346
5	lansoprazole.tw.	2083
6	omeprazole.tw.	7292
7	rabeprazole.tw.	969
8	Proton Pump Inhibitors/	8279
9	esomeprazole/	781
10	pantoprazole/	0
11	lansoprazole/	1973
12	omeprazole/	8346
13	rabeprazole/	869
14	or/1-13	32654
15	myocardial infarction$.tw.	145835
16	heart infarction$.tw.	218
17	heart attack$.tw.	4376
18	myocardial infarction/	149423
19	cerebrovascular accident$.tw.	5550
20	stroke$.tw.	173130
21	stroke/	69428
22	mortality.tw.	530062
23	mortality/	36648
24	death$.tw.	606795
25	death/	12620
26	cardiovascular mortality/	0

	Search terms	Results
27	or/15-26	1318764
28	14 and 27	1601
29	limit 28 to (english language and humans)	1188
30	limit 29 to yr="1980 -Current"	1182
31	Epidemiologic studies/	6448
32	exp case control studies/	762625
33	exp cohort studies/	1512988
34	Case control.tw.	90849
35	(cohort adj (study or studies)).tw.	110344
36	Cohort analy$.tw.	4554
37	(Follow up adj (study or studies)).tw.	40507
38	(observational adj (study or studies)).tw.	57146
39	Longitudinal.tw.	164309
40	Retrospective.tw.	327471
41	Cross sectional.tw.	207413
42	Cross-sectional studies/	207789
43	or/31-42	2157945
44	Meta-Analysis as Topic/	15046
45	meta analy$.tw.	84578
46	metaanaly$.tw.	1540
47	Meta-Analysis/	62186
48	(systematic adj (review$1 or overview$1)).tw.	73746
49	exp Review Literature as Topic/	8485
50	or/44-49	158682
51	cochrane.ab.	40289
52	embase.ab.	40550
53	(psychlit or psyclit).ab.	898
54	(psychinfo or psycinfo).ab.	10418
55	(cinahl or cinhal).ab.	13468
56	science citation index.ab.	2338
57	bids.ab.	384
58	cancerlit.ab.	612
59	or/51-58	64423
60	reference list$.ab.	11860
61	bibliograph$.ab.	13096
62	hand-search$.ab.	4680
63	relevant journals.ab.	853
64	manual search$.ab.	2896
65	or/60-64	29917
66	selection criteria.ab.	22865
67	data extraction.ab.	11912
68	66 or 67	32947
69	Review/	2078265
70	68 and 69	21919
71	Comment/	673946
72	Letter/	956717
73	Editorial/	400060
74	animal/	5648637
75	human/	14553252

	Search terms	Results
76	74 not (74 and 75)	4053214
77	or/71-73,76	5514207
78	50 or 59 or 65 or 70	190931
79	78 not 77	179513
80	Randomized Controlled Trials as Topic/	104215
81	randomized controlled trial/	416556
82	Random Allocation/	86926
83	Double Blind Method/	136065
84	Single Blind Method/	21606
85	clinical trial/	508511
86	clinical trial, phase i.pt.	16133
87	clinical trial, phase ii.pt.	25900
88	clinical trial, phase iii.pt.	10999
89	clinical trial, phase iv.pt.	1103
90	controlled clinical trial.pt.	92193
91	randomized controlled trial.pt.	416556
92	multicenter study.pt.	199128
93	clinical trial.pt.	508511
94	exp Clinical Trials as topic/	303963
95	or/80-94	1131907
96	(clinical adj trial$).tw.	250905
97	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	141670
98	PLACEBOS/	34122
99	placebo$.tw.	175469
100	randomly allocated.tw.	19887
101	(allocated adj2 random$).tw.	22672
102	or/96-101	474957
103	95 or 102	1305549
104	case report.tw.	229815
105	letter/	956717
106	historical article/	332255
107	or/104-106	1505772
108	103 not 107	1270783
109	43 or 79 or 108	3209343
110	30 and 109	635

COCHRANE CENTRAL REGISTER FOR CONTROLLED TRIALS (WITH SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK FILTERS)

	Keywords	Results
1	proton pump inhibitor$.tw.	1548
2	ppi$.tw.	1106
3	Proton Pump Inhibitors/	816
4	esomeprazole.tw.	531
5	esomeprazole/	289
6	pantoprazole.tw.	561
7	pantoprazole/	0
8	lansoprazole.tw.	893
9	lansoprazole/	543
10	omeprazole.tw.	2473

	Keywords	Results
11	omeprazole/	1956
12	rabeprazole.tw.	459
13	rabeprazole/	257
14	or/1-13	5283
15	myocardial infarction$.tw.	14964
16	heart attack$.tw.	326
17	heart infarction$.tw.	18
18	Myocardial Infarction/	7742
19	cerebrovascular accident$.tw.	309
20	stroke$.tw.	22617
21	Stroke/	3643
22	mortality.tw.	25644
23	Mortality/	283
24	death$.tw.	24668
25	Death/	59
26	or/15-25	69642
27	14 and 26	183
28	limit 27 to English language	166

SUPPLEMENTAL MATERIAL II - SCREENING FORMS

Screening forms specific to this project were designed using DistillerSR (Evidence Partners) and are presented below.

Stage 1 –Title and abstract screening

SUBMIT FORM and go to This Form - Next Reference or **Skip to Next**

1. Should this study be included in Stage 2 screening?

- ( ) Yes
- ( ) Unsure
- (•) No

2. Reason for exclusion:

- [ ] Population
- [ ] Intervention(s)/Exposure(s)
- [ ] Comparison(s)
- [ ] Outcome(s)
- [ ] Study design

Inclusion/Exclusion criteria

Population
Humans over 18 years

Intervention/exposure
PPI as a class or specific types of PPIs (Omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole, dexlans
PPI + other drugs

Exclude: Studies comparing effect of PPI to effect of other drugs (ex. H2RA, H2 antagonist,...)

Comparator
Placebo/no treatment with PPIs
Other drugs (without PPIs)
In general, exposure here should be the same as the treatment/intervention group minus the PPI.

Outcomes
Myocardial infarction/heart attack
Cerebrovascular accident/stroke
Mortality
MACE/composite outcomes

Study design
RCTs (also post hoc analyses)
Observational (cohort, case control, case crossover, self-controlled, controlled before and after)
Systematic reviews and meta analyses

Exclude: Literature reviews, cross-sectional studies, editorials/commentaries, case reports and case series

SUBMIT FORM and go to This Form - Next Reference or **Skip to Next**

Stage 2 – Full-text screening

SUBMIT FORM and go to ▼ or **Skip to Next**

1. **Do the title and authors match those on PDF?**
   - (●) Yes ( ) No

2. **This study should be:**
   - (●) Excluded ( ) Included ( ) Discussed with 2nd reviewer

For included studies, ensure that effect estimates (or raw data that allows the calculation of effect estimates) are reported for atleast one of the outcomes of interest.

3. **Reason for exclusion (check first that applies):**
   - (●) Does not meet inclusion criteria.
   - ( ) Published in non-English language.
   - ( ) Duplicate study (enter refID)
   - ( ) Full-text not accessible.
   - ( ) Other

4. **Which inclusion criteria is not satisfied (check first that applies)?**
   - ( ) Population
   - ( ) Exposure(s) or intervention(s)
   - ( ) Comparator(s)
   - ( ) Outcome(s)
   - ( ) Study design
   - ( ) Exposure-outcome association
   - ( ) Quantitative results not reported

Comments

SUPPLEMENTAL MATERIAL III - DATA EXTRACTION FORM

The following data extraction forms were designed using DistillerSR (Evidence Partners) for this project.

SUBMIT FORM and go to ▾ or **Skip to Next**

1. **In-text citation: ex Smith et al, 2010**

...

A- Study population

2. **If the study is based on the analysis of a large database, specify name and type of database (EHR, administrative data, pharmacy records,...)**

3. **Country/countries**

...

4. **Setting of study**

...

5. **Patient population (ex. ACS patients, diabetics,...)**

...

6. **For cohort study, specify name of cohort if reported.**

7. **Inclusion criteria**

8. **Exclusion criteria**

9. **Calendar year(s) of sampling (ex. 2005-2006)**

...

B- Methods

10. **Was investigating the effect of PPIs on the outcome of interest a pre-specified objective of the study?**

- Yes
- No
- Unclear
- Comment

Clear Response

11. **Study design.** *If the article reports results from two separate designs, check both and be sure to indicate data extracted refers to which design.*

- Abstract only (indicate whether attempt was made to locate full-text)
- Prospective cohort
- Retrospective cohort
- Case control (also nested case control)
- SCCS
- RCT
- Crossover trial
- Post hoc analyses of RCT
- Other (specify)
- Comments

12. **Sample size** (of the study, regardless of those analysed for the outcome reported)
- [ ] For cohort (cohort size)
- [ ] For case-control (cases/controls)
- [ ] For RCT (intervention/control)
- [ ] For self controlled case series/case cross-over
- [ ] Other design, specify

13. **Briefly describe the statistical methods used.**

Exposure

14. **Exposure groups compared**
- [ ] (PPI vs placebo) or (PPI use vs no PPI use)
- [ ] (PPI + clopidogrel) vs clopidogrel (specify if other drugs in addition to clopidogrel, ex aspirin)
- [ ] (PPI + other agent(s)) vs other agent(s)

15. **PPI type** (check specific types only if outcomes were stratified by type)
- [ ] PPI (general)
- [ ] Omeprazole
- [ ] Lansoprazole
- [ ] Esomeprazole
- [ ] Pantoprazole
- [ ] Rabeprazole
- [ ] Dexlansoprazole
- [ ] Other

16. **Notes on exposure ascertainment.**

17. **PPI exposure details (duration, dose, form,...)**

18. **If exposure to clopidogrel (including DAT) was assessed, specify details (dose, duration,...)**

19. **If exposure to PPI + other agents was assessed, specify details of other agents**

Outcomes

20. **Outcome(s) of interest assessed (check all that apply).** *Specify follow up duration for each.*

- [ ] Myocardial infarction
- [ ] Stroke
- [ ] All-cause mortality
- [ ] Cardiovascular mortality
- [ ] Comments on outcomes

21. **Notes on outcome ascertainment**

C- Results

22. **Age of study participants**

- ☐ Range of ages
- ☐ Mean age (SD)
- ☐ Median age
- ☐ No age data reported

23. **Sex of study participants**

- ○ Males only
- ○ Females only
- ○ Males and females. Enter % males
- ○ Not reported

Clear Response

24. **Ethnicity of study participants**

- ☐ Caucasian
- ☐ Asian
- ☐ African american
- ☐ Hispanic
- ☐ Other
- ☐ Not reported

Outcome 1: Myocardial infarction *(leave blank if not relevant)*

25. **Effect estimates.**
Indicate whether estimate reported is HR, OR, RR (95% CI) and the factors each adjusted/matched for or stratified by +95% CI. Include the number analysed for the outcome and the SE and p-value for each estimate if provided.
If there's a long list of variables adjusted for, copy to box below.
Ex. (HR, 1.5, 1.4-1.6) or (OR, females, 1.5, 1.4-1.6)

26. **Variables that the effect estimates reported above were adjusted for**

27. **Number of subjects analysed for the above outcome**

- ☐ Total Analysed
- ☐ Number exposed to PPIs
- ☐ Number not exposed to PPIs

28. **If effect estimates not reported, enter raw data/counts for 2x2 table (exposed/nonexposed and events/nonevents)**

Outcome 2: Stroke *(leave blank if not relevant)*

29. **Effect estimates.**
Indicate whether estimate reported is HR, OR, RR (95% CI) and the factors each adjusted/matched for or stratified by +95% CI. Include the number analysed for the outcome and the SE and p-value for each estimate if provided.
If there's a long list of variables adjusted for, copy to box below.
Ex. (HR, 1.5, 1.4-1.6) or (OR, females, 1.5, 1.4-1.6)

30. **Variables that the effect estimates reported above were adjusted for**

31. **Number of subjects analysed for the above outcome**

- ☐ Total Analysed
- ☐ Number exposed to PPIs
- ☐ Number not exposed to PPIs

32. **If effect estimates not reported, enter raw data/counts for 2x2 table (exposed/nonexposed and events/nonevents)**

Outcome 3: All-cause mortality *(leave blank if not relevant)*

33. **Effect estimates.**
Indicate whether estimate reported is HR, OR, RR (95% CI) and the factors each adjusted/matched for or stratified by +95% CI. Include the number analysed for the outcome and the SE and p-value for each estimate if provided.
If there's a long list of variables adjusted for, copy to box below.
Ex. (HR, 1.5, 1.4-1.6) or (OR, females, 1.5, 1.4-1.6)

34. **Variables that the effect estimates reported above were adjusted for**

35. **Number of subjects analysed for the above outcome**

- ☐ Total Analysed
- ☐ Number exposed to PPIs
- ☐ Number not exposed to PPIs

36. **If effect estimates not reported, enter raw data/counts for 2x2 table (exposed/nonexposed and events/nonevents)**

Outcome 4: CVD mortality *(leave blank if not relevant)*

37. **Effect estimates.**
Indicate whether estimate reported is HR, OR, RR (95% CI) and the factors each adjusted/matched for or stratified by +95% CI. Include the number analysed for the outcome and the SE and p-value for each estimate if provided.
If there's a long list of variables adjusted for, copy to box below.
Ex. (HR, 1.5, 1.4-1.6) or (OR, females, 1.5, 1.4-1.6)

38. **Variables that the effect estimates reported above were adjusted for**

39. **Number of subjects analysed for the above outcome**

- ☐ Total Analysed
- ☐ Number exposed to PPIs
- ☐ Number not exposed to PPIs

40. **If effect estimates not reported, enter raw data/counts for 2x2 table (exposed/nonexposed and events/nonevents)**

D- Conclusions

41. **Study strengths reported by authors.**

42. **Study limitations reported by authors.**

43. **Other study strengths noted by reviewer.**

44. **Other study limitations noted by reviewer.**

45. **Overall conclusion reported by authors on the associations between PPIs and outcomes of interest (ex. no association, positive association, unclear,...)**

SUPPLEMENTAL MATERIAL IV - DETAILED TABLES

TABLE S2- 1. CHARACTERISTICS OF STUDY DESIGN AND PATIENT POPULATION OF STUDIES THAT ASSESSED THE EFFECT OF PPI USE VS NO PPI USE (GROUP A).

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
Observational studies								
(Antunes et al. 2016) (Portugal) Abstract	Retrospective cohort (1 tertiary center)		Cirrhotic	*Inclusion:* - hospitalization with cirrhosis - patients with ascites and microbiological cultures at admission	Cohort size: 571; PPI: 180	NR	NR	NR
(Arana et al. 2015a) (UK)	Nested case-control (database analysis, population based)	Clinical Practice Research Datalink-Global initiative for Chronic Obstructive Lung Disease (CPRD-GOLD	UGI disorders	*Inclusion*: - registered in database - has linkable data to HES (hospital episode statistics) and ONS (office of national statistics) - at least 1 continuous year of enrollment in CPRD GOLD after first exposure to either study drugs between 2005-2011 *Exclusion*: - residing in institutions on or before cohort entry - cancer diagnosis before cohort entry date	15,811 (Cases: 3,239; Controls: 12,572	55 (median)	43%	Not reported
(Bang el al 2018) (Denmark) Abstract	Retrospective cohort (Database analysis)	Danish Prescription Database	With alcoholic cirrhosis	*Inclusion:* - with alcoholic cirrhosis -history of opioid claims (for PS matching) *Exclusion*: -cancer, chronic viral hepatitis, non-alcoholic fatty liver disease, follow-up time <30 days.	Cohort size: 19,687; PS matched cohort: 2,592	56 (10)	65%	NR

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
(Bell el al 2017) (USA) Abstract	Retrospective cohort (Database analysis)	Rochester Epidemiology Project's medical records system	General population	*Inclusion:* - resident of Olmsted County, MS *Exclusion*: - <18 years old -history of CVD - missing data for variables needed in the analysis - PPI use in prior year	Cohort size: 58,175	NR	NR	NR
(Bettinger et al 2018) (Germany)	Retrospective cohort (Database analysis)		Pyogenic liver abscess	*Inclusion:* - with pyogenic liver abscess and information on diagnosis, treatment and clinical course	Cohort size: 181; PPI: 100; No PPI: 81;	PPI: 62.3 (13.4); No PPI: 63.2 (14.4);	PPI: 67%: no PPI: 68%;	NR
(Caffrey et al 2016) (USA) Abstract	Retrospective cohort (Veteran Affairs hospitals)		With S. aureus bacteremia	*Inclusion:* - admitted to Veterans Affairs hospitals -positive S. aureus blood culture and receiving antibiotics within 2 days of culture collection	Cohort size: 12,211 PPI: 809; no PPI: 12,402	NR	NR	NR
(de Francisco et al 2018) (Spain)	Retrospective cohort; (Database analysis - 40 Clinics)	EuCliD database	Hemodialysis patients	*Inclusion:* - 3 sessions per week hemodialysis *Exclusion*: - < 18 years old -prescription for diuretics	Cohort: 2242; PPI: 1,776; No PPI: 466; PS matched: 410 pairs;	PPI: 68.0 (range: 57-76); no PPI: 68.5 (range: 56-76);	PPI: 62%; no PPI: 66%;	NR
(Charlot et al. 2010) (Denmark)	Retrospective cohort (database, hospitals)	Danish National Patient Registry	MI	*Inclusion*: - >30 years - hospitalized with MI between 2000-2006 *Exclusion*: - prior MI - partially missing data	Cohort size : 56,406 PS matched: (PPI: 15,443; No PPI: 15,433)	No treatment: 70 (13) PPI only: 73 (12) CP only: 64 (13) Concomitant: 66 (13) PS matched: 73 (13)	No treatment: 61% PPI only: 53% Clopidogrel only: 71% Concomitant: 62%	(largely Caucasian population)

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
							PS matched: 54%	
(Chen et al. 2014) (Taiwan)	Retrospective cohort (database study)	National Health Insurance Research database	ESRD	Inclusion: - ESRD on dialysis with first catastrophic illness certificate and had hemodialysis, peritoneal dialysis, or hemofiltration - >18 years admitted to hospital for first time ischemic stroke between 1998-2006 - received standard dose of aspirin or clopidogrel once daily - had 3 years of medical data *Exclusion*: - prior stroke (other than index stroke) - missing data -receiving antiplatelets other than clopidogrel	1,936	65 (11)	50%	Not reported
(Chitose et al. 2012) (Japan)	Prospective cohort (registry, hospitals - 16 centers)	Kumamoto Intervention Conference Study (KICS)	PCI	*Inclusion*: - consecutive patients undergoing PCI at one of 16 centers in Japan between June 2008 - March 2009 - written consent *Exclusion*: - in-hospital death - not on thienopyridines at time of discharge - re-intervention after first registration - planned staged interventional procedure	1,270 (PPI: 331; No PPI: 939)	PPI: 72(12) no PPI: 69(12)	PPI: 68% no PPI: 71%	Not reported
(Daskalopoulou et al. 2008) (UK)	Retrospective cohort (database, general practice)	UK General Practice Research Database (GPRD)	MI	*Inclusion*: ->20 years -survived at least 90 days following a first MI between Jan 2002 and Dec 2004 - minimum of 3 years of records in GPRD	9,939 (PPI: 3,070; No PPI: 6,869)	68 (13)	60%	Not reported
(Dultz et al. 2015) (Germany)	Prospective cohort (hospital)		Cirrhosis	*Inclusion*: - attending clinic with cirrhosis between 2009-2011	272 (PPI: 213; No PPI: 59)	PPI: 57 no PPI: 57 (median)	67%	Not reported

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
				- cirrhosis confirmed by liver histopathological exam or pathognomonic results in MRI or CT *Exclusion*: - cancer history other than hepatocellular carcinoma in prior 5 years - prior solid organ transplant at age less than 18 years				
(Freedberg et al. 2013) (USA)	Retrospective cohort (database analysis)		CDI	*Inclusion*: - incident CDI between Dec 1, 2009 and June 30, 2012 and no prior positive test within 90 days *Exclusion*: - did not meet study endpoints - no proven clinical follow-up in medical system after the 90-day study period	894 (PPI: 551; No PPIs: 343)	PPI: 64 (18) no PPI: 65 (20)	48%	Caucasian, African American, Hispanic, Other
(Gardezi et al 2018) Abstract	Hospitals		Non-variceal bleeding	*Inclusion:* - received upper GI endoscopy for nonvariceal bleeding	763	NR	NR	NR
(Haider et al. 2012) (USA)	Retrospective cohort (records of hospital patients - 1 center)		CDI	*Inclusion*: ->18 years - positive for C. difficile between Jan 2001 - Oct 2009 *Exclusion:* - pregnant women - prior history of CDI	627 (PPI: 172; No PPI: 358, others)	69 (median)	47%	98% Caucasian
(Im et al. 2014) (Korea)	Retrospective cohort (University hospitals - 7 centers)		Percutaneous endoscopic gastrostomy (PEG)	*Inclusion:* - consecutive patients that underwent PEG between June 2006 -Jan 2012 *Exclusion:* - <18 years - personal history of gastrectomy - insufficient data on patient - simple PEG changes during the study period after an initial PEG placement	1,021 (PPI: 203; No PPI: 472)	Mean (SD) : PP: 68 (15) no PPI: 66 (14)	67%	Not reported

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
(Johansson et al. 2003) (UK)	Nested case-control (database, general practice)	UK General Practice Research Database (GPRD)	GERD	*Inclusion:* **GERD cohort** - 18-79 years - registered in database and 2+ years of enrolment with the GP before 1996 - first recorded diagnosis of GERD during 1996 <u>Cases</u> - MI and from GERD cohort <u>Controls</u> - free of GERD - randomly sample from the source population - matched by age and sex to case *Exclusion*: - GERD diagnosis or cancer diagnosis before 1996 - pregnant women -past history and long term use of acid suppressing drugs without specific treatment indication	(Cases: 7,084; Controls: 10,000)	18-79 (range)	Not reported	Not reported
(Juurlink et al. 2013) (Canada)	Self-controlled case series (database)	Ontario Drug Benefit Claims Databases, Canadian Institute for Health Information's Discharge Abstract Database (CIHI-DAD), Registered Persons Database, Ontario	MI	*Inclusion*: - Ontario residents - 66+ years - hospitalizations occurring within 12 weeks of initiation of PPI treatment *Exclusion*: - hospitalizations for MI and hospital length of stay <3 days	5,550	77 (median)	51%	Not reported

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
		Health Insurance Plan Database						
(Keyvani et al. 2006) (Canada)	Retrospective cohort (tertiary care - 2 centers)		Acute non-variceal UGIB	*Inclusion*: - primary diagnosis with acute non-variceal UGIB between April 1999-March 2004 *Exclusion*: - evidence of only chronic GI bleeding (iron deficiency, stools positive for occult blood); - GI bleeding related to portal hypertension - transferred from another health care institution more than 6 hours after initial presentation - did not undergo endoscopy within 24 hours of initial presentation	385 (PPI: 132; No PPI: 253)	PPI: 65 no PPI: 66	PPI: 37% no PPI: 40%	Not reported
(Kwon et al. 2013) (Korea)	Retrospective cohort (Medical centers -2 centers)		Cirrhosis and ascites	*Inclusion*: - cirrhotic patients with ascites - underwent diagnostic paracentesis after hospitalisation from January 2003 to December 2010 - liver cirrhosis confirmed biopsy or by clinical evidence of cirrhosis *Exclusion*: - GI bleeding within 14 days prior to admission - organ transplantation - antibiotic use within 2 weeks prior to admission - no access to medication list on admission - tuberculous peritonitis - carcinomatosis - HIV	1,140 (PPI: 82; No PPI: 451; Others)	PPI: 62 (10) no PPI: 63 (9)	75%	Not reported

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
(Kwon et al 2016) Abstract	Prospective cohort (Single center)		Cirrhotic with variceal bleeding	*Inclusion:* - with gastroesophageal variceal bleeding and cirrhosis	Cohort size: 348 PPI: 175; No PPI: 173	NR	NR	NR
(Lei et al 2017) (Taiwan)	Retrospective cohort (Database analysis)	National Health Insurance (NHI)	GERD	*Inclusion:* - newly diagnosed with GERD *Exclusion*: - diagnosis with CAD, peripheral artery disease, or AMI before enrollment.	Cohort size: 54,422;	51.6 (17)	46.50%	NR
(Lee et al. 2015) (Taiwan)	Retrospective cohort (database analysis)	National Health Insurance Program (Taiwan)	COPD	*Inclusion*: - COPD diagnosis between 2001-2005 -randomly sampled from database - 30+ years	17,498 (PPI: 109; No PPI: 16,863; Others)	>30	59%	Not reported
(Maggio et al. 2013) (Italy)	Prospective cohort (acute care medical wards - 11 centers)	Pharmaco-surveillance in the Elderly Care	Elderly (≥65)	*Inclusion*: - ≥65 years -admitted to participating wards *Exclusion*: - in-hospital death - enrolled in long term care units - declined participation	491 (PPI: 174; no PPI 317)	PPI: 80 (6) no PPI 80 (6)	PPI: 47% no PPI: 45%	Not reported
(Mandorfer et al. 2014) (Austria)	Retrospective cohort (medical records, hospitals -1 center)		Cirrhosis and ascites	*Inclusion*: -with cirrhosis and underwent first paracentesis at the medical university between 2006-2011 *Exclusion*: - with other causes of ascites (such as severe cardiovascular disease, renal insufficiency, extra-hepatic malignancies and non-cirrhotic portal hypertension)	607 (PPI: 520; No PPI: 87)	PPI: 57 (12) no PPI: 60 (12)	70%	Not reported

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
(Myles et al. 2009) (UK)	Retrospective cohort (database, general practice)	The Health Improvement network (THIN)	Pneumonia	*Inclusion*: - ≥40 years -pneumonia diagnosis between July 2001-July 2002 *Exclusion:* - date of death recorded before pneumonia diagnosis date (errors)	3,681 (PPI: 1,060; No PPI: 2,621)	>40	Not reported	Not reported
(Nardelli et al 2018) (Italy)	Prospective cohort		Cirrhotic	*Inclusion:* - cirrhotic patients without overt hepatic encephalopathy - cirrhosis confirmed by clinical, biochemical and radiological signs. *Exclusion*: - overt HE based on West-Haven criteria - alcohol/psychoactive drugs -neurological disease - lack of compliance with psychometric evaluations due to language barriers or reduced vision -dementia - advance hepatocellular carcinoma - TIPS and/or large porto- systemic shunts and patients with a history of persistent or recurrent HE defined by two or more than two episodes within the last six months, even if without overt HE on first observation were also excluded.	Cohort size: 310; PPI: 125; no PPI: 185;	62.2 (11.8); PPI: 63.3 (11.6); no PPI: 61.5 (11.9);	71.3%; PPI: 67.2%; no PPI: 74.0%;	NR
(Nguyen et al 2018) (USA)	Prospective cohort	Nurse's Health Study and Health Professionals Follow-up Study	No history of stroke	*Inclusion:* - female nurses between 30-55 years at enrollment, since year 2000 (Nurse's Health Study); - male health care professionals between 40-75 years at enrollment, since 2004 (Health Professionals Follow-up Study) *Exclusion*:	Cohort size: 97,503; PPI: 9,122; no PPI: 88,381;	69 (8); Nurses' Health Study: 65.7 (7.1); Health Professionals Follow-up	29.70%	NR

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
				- history of stroke or cancer -missing data on exposure of interest		Study: 69.9 (8.6);		
(Oudit et al. 2011) (Canada)	Retrospective cohort (database analysis)	Ambulatory Care Database, Alberta Inpatient Discharge Abstract Database, Alberta Health Care Insurance Registry, Blue Cross Medication Database	Heart failure	*Inclusion*: - >65 years - diagnosed with heart failure as most responsible diagnosis between 1 Apr 1, 1999 – Dec 31, 2005	22,107 (PPI: 6,431; No PPI: 15,676	PPI: 80 no PPI: 81 (median)	55%	Not reported
(Sehested et al 2018) (Denmark)	Retrospective cohort (Database analysis)	Six nationwide administrative registers	UGIB	*Inclusion:* - elective upper endoscopy *Exclusion*: - <30 or >100 years of age - patients with prior coronary heart disease, stroke, atherosclerosis of extremities, users of adenosine diphosphate receptor antagonists or dipyridamole.	Cohort size: 214, 998	PPI nonusers: 53 (median); Short-term PPI users: 55 (median); long-term PPI users: 59 (median);	43.30%	NR
(Shah et al. 2015) (USA)	Prospective cohort (medical centers)	GenePAD cohort (the Genetic Determinants of Peripheral	Shortness of breath or abnormal stress test and underwent	*Inclusion*: - underwent non-emergent coronary angiogram for angina, shortness of breath or an abnormal stress test at one of the medical enters	1,503	66 (11)	65%	Caucasian, Asian, African American, Hispanic, Other

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
		Arterial Disease)	coronary angiogram	*Exclusion*: - History of radiation treatment, organ transplant or viral diseases				
(Shih et al. 2014) (Taiwan)	Retrospective cohort (database analysis)	Longitudinal Health Insurance Database (Taiwan)	On PPIs	*Inclusion*: - PPI prescription during ambulatory visits between 2000 and 2009 - 18-80 years - no history of MI, acquired immunodeficiency syndrome, HIV infection, or cancer before PPI prescription - no prior PPI prescription within 120 days *Exclusion*: - prescription of PPI within 60 days after an episode of severe UGI bleeding that needed hospitalization, blood transfusion, or inotropic agent	252,734 (PPI: 126,367; No PPI: 126,367)	PPI: 49 (15) no PPI: 49 (15)	51%	Not reported
(Simon et al. 2011) (France)	Retrospective cohort (Hospitals and private clinics with ICU - 223 centers)	French Registry of Acute ST-Elevation and Non–ST-Elevation Myocardial Infarction (FAST-MI) Registry	MI	*Inclusion*: - >18 years - admitted to ICU with definite MI *Exclusion*: - diagnosed with iatrogenic MI (invalidated for an alternative diagnosis) - unstable angina with no elevation of cardiac necrosis	2,744 (PPI: 1611; No PPI: 1,133)	PS matched cohorts: PPI: 65 (12) no PPI: 66 (13)	27%- 42% between groups	Not reported
(Taha et al. 2013) (NR) [abstract]	Prospective cohort/ (Hospitals)		UGIB	*Inclusion*: - undergoing endoscopy for UGIB	Cohort size : 404 (202 PPI, others no PPI)	NR	NR	Not reported
(Teramura-Gronblad et al. 2012) -Cohort 2 (Finland)	Retrospective cohort (Long term		Chronic patients requiring 24-hr care	*Inclusion*: - agree to participate in study	1004 (PPI: 231; No PPI: 773)	PPI: 81 (11) no PPI: 82 (11)	PPI: 29% no PPI: 24%	Not reported

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
	care hospitals)			*Exclusion*: - incomplete medical data				
(Teramura-Gronblad et al. 2012) –Cohort 1 (Finland)	Retrospective cohort (assisted living facilities - 69 centers)		In assisted-living facilities	*Inclusion*: - residents in assisted living facilities in Helsinki and Espoo in 2007 *Exclusion*: - decline to participate - incomplete medication data - residents of temporary respite care	1,389 (Cohort 1) (PPI: 367; No PPI: 1,022)	PPI: 84 (8) no PPI: 82 (8)	PPI: 24% no PPI: 20%	Not reported
(Teramura-Gronblad et al. 2012) –Cohort 3 (Finland)	Retrospective cohort (hospital and nursing home)		Geriatric, frail patients	*Inclusion*: - in geriatric wards and nursing homes in Helsinki - agree to participate in study *Exclusion*: - <70 years	425 (PPI: 91; No PPI: 334)	PPI: 86 (7) no PPI: 86 (7)	PPI: 21% no PPI: 18%	Not reported
(Turkiewicz et al. 2015) (Sweden)	Self-controlled case series (hospital records)	Swedish Population Register and Skåne Healthcare Register	MI	*Inclusion*: - included in database - AMI event between Oct 14, 2005 and Dec 31, 2006 - age 40 to 90 at AMI event	3,490	73 (12)	61%	Not reported
(Valkhoff et al. 2011) (Netherlands)	Nested case-control (database analysis)	PHARMO Record Linkage System (Netherlands)	MI	*Inclusion*: Cohort: patients admitted for MI between Jan 1999- Dec 2008 -required to have had one prescription filled at least 1 year preceding the date of cohort entry *Cases* - recurrent MI 30 days of baseline MI *Controls* - randomly selected from cohort, matched	(Cases: 616; Controls 126,817)	65 (13)	67%	Not reported

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
				on gender, age, risk of recurrent MI, and calendar time;				
(van der Hoorn et al. 2015) (Australia)	Prospective cohort (database analysis)	Australian Longitudinal Study data linked to Pharmaceutical Benefits Scheme	Elderly women	*Inclusion*: - Australian citizens and permanent residents - women born 1921-1926 - included in Medicare database *Exclusion*: - completed a short version of the survey - did not consent to data linkage - died before 2003 - received PPI and/or osteoporosis medication in 2002 - missing confounder data	4,432 (PPI: 2,328; No PPI: 2,104)	PPI: 78 (1); no PPI: 78 (2)	0	Not reported
(Wang 2017) (Taiwan)	Retrospective cohort (Database analysis)	Longitudinal Health Insurance Database	General population	*Inclusion:* - ≥ 20 years - no prior diagnosis of atrial fibrillation, AIDS, HIV infection, cerebrovascular disease, or cancer before the prescription of PPI - no use of any PPI within 30 days before the current prescription - no hospitalizations in prior 30 days	Cohort size: 396,296; PPI: 198,148; No PPI: 198,148;	51.7 (15.4)	53.60%	NR
(Win et al. 2010) (USA) [abstract]	Retrospective cohort (chart review, hospital)		UGIB	*Inclusion*: - endoscopic evaluation of UGIB between Jan 2005-Dec 2008 *Exclusion*: - no significant finding on upper endoscopy	658 (PPI: 110; No PPI: 548)	59 (15)	60%	African American (95%); others;
Intervention studies								
(Daneshmend et al. 1992) (England)	RCT (hospitals - 2 centers)		UGIB	*Inclusion*: - UGIB - history of hematemesis or melena within 24 hours preceding admission *Exclusion*:	1,147 (PPI (omeprazole): 578; No PPI: 569)	PPI: 59 (19) no PPI: 60 (19)	PPI: 62% no PPI: 65%	Not reported

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
				- <18 years - pregnant - severe illness making active treatment inappropriate (terminal disease, advanced malignancy) or inability to start treatment within 12 hours of admission - severe bleeding that needs surgery, trivial bleeding, bleeding for other reasons - potential to drug interactions with concomitant medications (such as warfarin)				
(Gao et al. 2009) (China)	RCT (hospitals – 2 centers)		MI	*Inclusion*: - hospitalized for MI from Jan 2003 - Dec 2007 - underwent "canalization" *Exclusion*: - did not undergo "canalization" - had presented UGIB in 6 months before hospitalization	237 (PPI (omeprazole): 114; No PPI: 123)	PPI: 58 (9) no PPI: 58 (9)	53%	Not reported
(Hasselgren et al. 1997) (Sweden and Norway)	RCT (hospitals - 29 centers)		UGIB	*Inclusion*: - >60 years - admitted with melena or hematemesis, endoscoped within 12 hours of admission - UGIB *Exclusion*: - UGI malignancy - deficient hemostasis - renal, hepatic or cardiac failure - significant abnormalities in laboratory screening - anticoagulation therapy within 5 days of admission	322 (PPI (omeprazole): 159; No PPI: 163)	PPI: 75 (8) no PPI: 74 (7)	PPI: 56% no PPI: 60%	Not reported
(Hawkey et al. 2001) (UK)	RCT (hospitals - 2 centers)		UGIB	*Inclusion*: - admitted for suspected UGIB *Exclusion*: - absence of UGIB upon endoscopy -severe bleeding requiring surgical	PPI (lansoprazole): 102 No PPI (placebo):	PPI: 59 no PPI: 56	PPI: 80% no PPI: 77%	Not reported

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
				interventions - other conditions: pregnancy, lactation, active thromboembolism or intravascular coagulopathy, high creatinine levels	103 Other groups: 209			
(Hung et al. 2007) (China)	RCT (hospital)		UGIB	*Inclusion*: -with UGIB that had upper endoscopy -with successful haemostasis *Exclusion*: with previous gastrectomy or vagotomy, those that had taken warfarin , H2RAs or PPI in the previous 48 hours	168 (PPI: 114; No PPI: 54)	PPI infusion: 64 PPI bolus: 58 no PPI: 63	PPI infusion: 59% PPI bolus: 72% no PPI: 74%	Asian
(Javid et al. 2001) (India)	RCT (hospital)		UGIB	*Inclusion*: - UGIB - underwent GI endoscopy within 12 hours of admission and showed peptic ulcers or stigmata of recent hemorrhage *Exclusion*: - terminal cancer - perfuse hemorrhage accompanied by persistent shock - continued bleeding within 34 hours of endoscopic treatment and needed emergency surgery - could not provide consent	166 (PPI (omeprazole): 82; No PPI: 84)	PPI: 55 (10) no PPI: 56 (8)	PPI: 63% no PPI: 61%	Not reported
(Kantorova et al. 2004) (Czech Republic)	RCT (hospital)		high UGIB risk	*Inclusion*: - >18 years - admitted to ICU for major abdominal or thoracic surgery between Feb 2000 - June 2002 - need mechanical ventilation for at least 48 hours or had coagulopathy, and nasogastric tube in place *Exclusion*: - <48 hours expected length of stay - history of esophago-gastric surgery - GI bleeding at time of admission or in	323 (PPI (omeprazole); No PPI: 75; others)	PPI: 44 (15) no PPI: 46 (19)	PPI: 67% no PPI: 67%	Not reported

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
				previous year - pneumonia - treatment with PPIs, H2RAs, antacids or sucralfate in prior 72 hours - peptic ulcer disease in prior year - use of anticoagulants, high dose oral corticosteroids or thrombolytic agents during previous week - renal insufficiency needing hemodialysis - thrombocytopenia <30,000/ml - life expectancy < 3 months - cannot give informed consent				
(Kaviani et al. 2003) (Iran)	RCT (hospitals - 2 centers)		UGIB	*Inclusion*: - >15 years - UGIB - successful endoscopic treatment of actively bleeding ulcers or ulcers with non-bleeding visible vessels between April 1999 and May 2000 *Exclusion*: - low risk bleeders - unknown source of bleeding - on anti-secretory drugs (PPIs or H2RAs) - highly probable gastric malignancies - unsuccessful endoscopic treatment	160 (PPI-omeprazole: 80; No PPI: 80)	PPI: 53 (18) no PPI: 52 (19)	PPI: 80% no PPI: 80%	Not reported
(Khuroo et al. 1997) (India)	RCT (hospital)		UGIB	*Inclusion*: - UGIB - endoscopy between Jan 1992 - Aug 1994 *Exclusion*: - terminal illness preventing endoscopy - profuse hemorrhage with persistent shock	220 (PPI: 110; No PPI 110)	PPI: 58 (8) no PPI: 56 (8)	PPI: 62% no PPI: 60%	Not reported
(Krag et al 2018) [Multicenter - 2 European countries]	RCT (33 Intensive care units)	NCT02467621	ICU patients at risk for GI bleeding	*Inclusion* - 18 or over admitted to ICU for acute conditions -had at least one risk factor for GI bleeding;	3,298; PPI (pantoprazole 40 mg): 1,645; Placebo: 1,653;	Pantoprazole: 67 (IQR 56-75); Placebo: 67 (IQR 55-75);	Pantoprazole: 63%; Placebo: 65%.	NR

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
				Exclusion: -ongoing daily treatment with acid suppressants - consent could not be obtained - gastrointestinal bleeding during index hospital admission - withdrawn from active therapy or were brain dead - underwent organ transplantation during index hospital admission - peptic ulcer confirmed by endoscopy or other method during index hospital admission - contraindication to pantoprazole 17 Were pregnant - pregnancy				
(Kuipers et al. 2011) (16 countries)	RCT (emergency departments (91 centers))	NCT00251979	UGIB	*Inclusion*: - 18+ years - successful hemostatic treatment of a bleeding peptic ulcer by endoscopy - single peptic ulcer (≥55 mm in diameter) and current or recent bleeding	767 (PPI: 376; No PPI:391)	PPI: 62 no PPI: 60	PPI: 68% no PPI: 69%	(88% Caucasian)
(Lau et al. 2000) (Hong Kong)	RCT (hospital)		UGIB	*Inclusion*: -admitted for UGIB -underwent successful endoscopy of active ulcers (or ulcers with nonbleeding vessels) *Exclusion*: -unsuccessful endoscopy	(PPI: 120; no PPI: 120)	PPI: 64 (17) no PPI: 37 (16)	PPI: 67% no PPI: 67%	Not reported
(Lau et al. 2007) (Hong Kong)	RCT (hospital)		UGIB	*Inclusion*: - presenting with UGIB to hospital *Exclusion*: - continued shock despite resuscitation - <18 years - cannot provide consent - pregnant	(PPI: 319; no PPI: 319)	PPI: 62 (18) no PPI: 62 (18)	PPI: 66% no PPI: 63%	Not reported

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
				- allergy to PPI - on aspirin for CV protection				
(Leung et al 2018) [China]	RCT (hospital)	NCT01873079	Undergoing ERCP sphincterotomy	*Inclusion*: - 18 or older -scheduled for elective ERCP and EST *Exclusion*: - prior EST, history of gastrectomy, acid-reduction surgery, sphincterotomy, sphincteroplasty or liver transplantation - receiving PPIs or H2RAs within the previous week - on warfarin, novel anticoagulants or other new antiplatelet agents; (- pregnant or lactating - did not consent	125; PPI (esomeprazole): 60; No PPI: 65;	Esomeprazole: 70 (14); No PPI: 72 (16);	Esomeprazole: 57; no PPI: 43%	NR
(Liu et al. 2013) (China)	RCT (hospital)	ChiCTR-TRC-12001871, (Chinese clinical trial registry)	Intracerebral hemorrhage	*Inclusion*: - hospitalized at neurosurgical ICU between April 2006-Dec 2008 - 18+ years - intracerebral hemorrhage requiring surgery - nasogastric tube in place - baseline intragastric pH <4 on 2 consecutive measurements - informed consent *Exclusion:* - arteriovenous malformation or aneurysmal hemorrhage, - history of peptic ulcers - patients likely to swallow blood (for example, those with severe facial trauma) - underwent antiplatelet and anticoagulation therapy - renal insufficiency requiring hemodialysis	165 (PPI -omeprazole: 58; No PPI: 53; others)	>18 years (range)	PPI: 53% no PPI: 66%	Not reported

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
				- thrombocytopenia less than 30,000/ml - died within 72 hours after the ictus				
(Nikcevic et al. 2011) (NR) [abstract]	RCT (Hospital)		ACS	*Inclusion*: - admitted to hospital with ACS between Jan 2008 - Dec 2008	300 (PPI - Pantoprazole: 150; No PPI: 150)	Not reported	Not reported	Not reported
(Schaffalitzky de Muckadell et al. 1997) (Denmark, Holland and France)	RCT (hospital - 34 centers)		UGIB	*Inclusion*: ->18 years - UGIB with peptic ulcer - endoscoped within 12 hours after admission - history of circulatory failure and bleeding *Exclusion*: - oesophageal varices, Mallory Weiss lesion, deficient hemostasis - anticoagulant therapy, need for NSAIDS during study - upper GI malignancy - expected life expectancy <6 months - phenytoin treatment - pregnancy, lactation or childbearing potential with no use of contraception -omeprazole treatment less than 5 days before enrollment	274 (PPI-omeprazole: 134; No PPI:140)	PPI: 66 (15) no PPI: 67 (16)	PPI: 58% no PPI: 58%	Not reported
(Selvanderan et al 2016) [Australia]	RCT (1 ICU unit)	Australian New Zealand Clinical Trials Registry: ACTRN12613000807752	Mechanically ventilated/critically ill	*Inclusion*: - admitted to Royal Adelaide Hospital ICU - anticipated to be mechanically ventilated for more than 24 hours and receive enteral nutrition within 48 hours of admission; *Exclusion*: - use of acid-suppressive therapy prior to admission	216; PPI (pantoprazole): 107; no PPI: 109;	Pantoprazole: 52 (18); Placebo: 52 (17);	Pantoprazole: 72%; Placebo: 68%;	NR

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
				- admission with gastrointestinal bleeding - history of proven peptic ulcer disease - administration of greater than 100 mg daily of prednisolone (or equivalent of other corticosteroid) - surgery on the upper gastrointestinal tract or cardiac surgery during the current hospital admission - pregnancy -Jehovah's witnesses - patients who could not receive their first dose of study medication within 36 hours of initiation of mechanical ventilation - admission for the sole purpose of providing palliative care -patients readmitted to the ICU.				
(Sung et al. 2009) (16 countries)	RCT (emergency departments (91 centers))	NCT00251979	UGIB	*Inclusion*: - ≥18 years - UGIB in prior 24 hours to hospitalization - 1 bleeding gastric or duodenal ulcer that was at least 5 mm in diameter *Exclusion*: - bleeding from multiple ulcers or concomitant UGI sources, - another major disease - life expectancy <6 months - needed treatment with NSAID, aspirin or CP during first 7 days of the study - received more than 40 mg of PPI intravenously in 24 hours before enrollment -needed a drug known to interact with PPI	767 (PPI-esomeprazole: 376; No PPI: 391)	PPI: 62 no PPI: 60	PPI: 67% no PPI: 69%	Caucasian, Asian, African American, Other (>87% Caucasian)
(Wei et al. 2007) (Taiwan)	RCT (hospital)		UGIB	*Inclusion*: ->16 years - UGIB and admitted to hospital between Sept 2002 and March 2004 - successful endoscopy treatment for actively bleeding of ulcers or ulcers with nonbleeding	70 (PPI: 35; No PPI: 35)	PPI: 57 (13) no PPI: 64 (11)	PPI: 69% no PPI: 60%	Not reported

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
				visible vessels *Exclusion*: - unsuccessful endoscopy				
(Zargar et al. 2006) (India)	RCT (hospital)		UGIB	*Inclusion*: -history of hematemesis and/or melena -underwent endoscopy within 12 hours of bleeding or after resuscitation *Exclusion*: - <18 years - cannot give informed consent - pregnant or lactating women - on anticoagulants - more than one possible source of bleeding - severe coagulopathy - previous acid reducing surgeries - terminally ill	(PPI-pantoprazole: 102; no PPI: 101)	PPI: 55 (9) no PPI: 52 (9)	PPI: 62% no PPI: 69%	Not reported

TABLE S2- 2. CHARACTERISTICS OF THE EXPOSURE, OUTCOMES AND SOURCE OF FUNDING OF STUDIES THAT ASSESSED THE EFFECT OF PPI USE VS NO PPI USE (GROUP A).

Citation	PPI type assessed	Exposure ascertainment	Outcome(s) of interest (follow-up period)	Outcome ascertainment	Calendar year(s) of sampling	Source of funding
Observational Studies						
(Arana et al. 2015b)	PPIs (general)	From EMRs (prescription dates, quantity and duration).	CVD mortality[1] (up to 7 years)	EMRs and linkage with ONS death certificate.	2005-2011	Industry
(Antunes et al. 2016) Abstract	PPIs (general)	NR	ACM (1 and 3 month)	NR	2010-2014	NR
(Bang el al 2018) Abstract	PPIs (general)	NR	ACM	NR	1994-2014	NR
(Bell el al 2017) Abstract	PPIs (general)	Electronic health records and outpatient prescriptions	Stroke (12 years)	Diagnosis codes	2004-2016	NR
(Kwon et al 2016) Abstract	Omeprazole	NR	ACM (NR)	MR	2007-2013	NR
(Sehested et al 2018)	PPIs (general)	Prescription records	Stroke (up to 16 years); MI (up to 16 years); Median follow-up: 5.8 years	Database/registry (ICD codes)	1997-2012	Public/non profit
(Caffrey et al 2016) Abstract	PPIs (general)	NR	ACM (14-day, 30-day and inpatient)	NR	2002-2013	NR
(Bettinger et al 2018)	PPIs (general)	EMRs	In hospital mortality	In hospital	2005-2017	None.

Citation	PPI type assessed	Exposure ascertainment	Outcome(s) of interest (follow-up period)	Outcome ascertainment	Calendar year(s) of sampling	Source of funding
(de Francisco et al 2018)	PPIs (general)	Database (at baseline)	ACM (up to 33 months); Cardiovascular mortality (up to 33 months);	NR	2013	Private (Fresenius Medical Care)
(Nardelli et al 2018)	PPIs (general)	Hospital and physician records; follow up visits.	ACM	NR	2014-2016	NO financial support.
(Nguyen et al 2018)	PPIs (general)	Biennial questionnaires.	Stroke (12 years)	Medical records.	2000-2012	Public/non profit
(Wang et al 2017)	PPIs (general)	Prescription records/ database	First time stroke (4 months)	Database	2002-2012	Public/non profit
(Lei et al 2017)	PPI (general)	Outpatient pharmacy prescription records database	MI (12 years, median: 3.3 years)	Database	2000-2011	Non-profit
(Charlot et al. 2010)	PPIs (general)	National prescription registry (PPI prescriptions obtained up till 1 year after discharge)	MI (1 year) Stroke (1 year) ACM (1 year) CVD mort (1 year)	Danish National Patient Registry	2000-2006	Public/non profit
(Chen et al. 2014)	PPIs (general)	Health insurance database	Stroke (11 years) ACM (11 years)	Patient records	1998-2006	Public/non profit
(Chitose et al. 2012)	PPIs (general)	Registry. Compliance with drugs was confirmed.	MI (18 months) Stroke (18 months) CVD mort (18 months)	Hospital records; clinical and radiological evidence (stroke)	2008-2009	Public/non profit
(Daskalopoulou et al. 2008)	PPIs (general)	Prescription records	ACM (1 year)	NR	2002-2004	Public/non profit

Citation	PPI type assessed	Exposure ascertainment	Outcome(s) of interest (follow-up period)	Outcome ascertainment	Calendar year(s) of sampling	Source of funding
(Dultz et al. 2015)	PPIs (general)	PPI exposure assessed at hospital admission.	ACM (median 266 days; range 1-1,382 days)	Not clear	2009 -2011	Public/non profit
(Freedberg et al. 2013)	PPIs (general) (98% of patients on esomeprazole)	Discharge summaries were manually reviewed to extract information regarding discharge PPIs	ACM (3 months)	EMRs cross is cross-indexed with the National Social Security Death Index.	2009 - 2012	Public/non profit
(Haider et al. 2012)	PPIs (general)	No info where data was from (assuming hospital records)	ACM (in-hospital, 6 months)	NR	2001-2009	No statement
(Im et al. 2014)	PPIs (general)	Hospital records	ACM (median: 136 days; range 1-2693 days)	Not clear	2006- 2012	No statement
(Johansson et al. 2003)	PPIs (general)	Electronic health records.	MI	Electronic records; MI events confirmed with GP questionnaire.	1996-2000	Industry
(Juurlink et al. 2013)	PPIs (general)	Medical records.	MI (12 weeks)	Database records	1996-2008	Public/non profit
(Keyvani et al. 2006)	PPIs (general) (majority of patients received omeprazole and pantroprazole)	Medical chart abstraction.	ACM (in hospital)	Medical records	1999-2004	Industry and public/non profit
(Kwon et al. 2013)	PPIs (general)	Use of electronic medical records from hospital.	ACM (up to 1 month)	EMRs	2003 - 2010	None
(Lee et al. 2015)	PPIs (general)	Prescriptions records.	ACM (up to 10 years)	Patient records	2001-2005	Public/non profit

Citation	PPI type assessed	Exposure ascertainment	Outcome(s) of interest (follow-up period)	Outcome ascertainment	Calendar year(s) of sampling	Source of funding
(Maggio et al. 2013)	PPI (general)	Questionnaires during hospitalization and follow up visits (every 3 months for 1 year).	ACM (1 year)	Contact with relatives; death certificates and registers;	2007	Public/non profit
(Mandorfer et al. 2014)	PPIs (general)	Medical records.	ACM (up to 5 years) (defined as transplant-free survival: time to liver transplantation, death or end of follow-up.)	Not clear.	2006-2011	None
(Myles et al. 2009)	PPIs (general)	Prescription records;	ACM (1 month, median follow up of 2.8 years)	Not reported	2001-2002	Public/non profit
(Oudit et al. 2011)	PPIs (general) Omeprazole Pantoprazole	Medication databases in the year prior to index HF diagnosis.	ACM (1 year)	Database	1999-2005	Public/non profit
(Shah et al. 2015)	PPIs (general)	Assessed at enrollment	CVDM (8 years)	Medical and contact of patients/relatives. Deaths confirmed in Social Security Death Index	2004-2008	Public and private
(Shih et al. 2014)	PPIs (general)	Prescription records (drugs, dispensing date, quantity, dose collected).	MI (120 days) ACM (120 days)	Insurance records	2000-2009	Public/non profit
(Simon et al. 2011)	PPIs (general) Omeprazole Lansoprazole Omeprazole Pantoprazole	EMRs	MI (1 year) Stroke (1 year) ACM (1 year)	EMRs	2005	Industry and Public/non profit

Citation	PPI type assessed	Exposure ascertainment	Outcome(s) of interest (follow-up period)	Outcome ascertainment	Calendar year(s) of sampling	Source of funding
(Taha et al. 2013)	Omeprazole	NR	ACM (1 month)	NR	NR	No statement
(Teramura-Gronblad et al. 2012) (Cohort 2)	PPIs (general)	Medical charts	ACM (1 year)	National registers	Sept 2003	Public/non profit
(Teramura-Gronblad et al. 2012) (Cohort 1)	PPIs (general)	Medical charts	ACM (1 year)	Central national registers	2007	Public/non profit
(Teramura-Gronblad et al. 2012) (Cohort 3)	PPIs (general)	Medical charts	ACM (1 year)	National registers	NR	Public/non profit
(Turkiewicz et al. 2015)	PPIs (general)	Prescription records and pharmacy dispensing records for PPI exposure;	MI	Hospital records, discharge diagnosis	2005-2006	Public/non profit
(Valkhoff et al. 2011)	PPIs (general)	Electronic health records, outpatient drug dispensing files of pharmacies.	recurrent MI (up to 9 years; median: 3.6 years)	Hospital records	1999-2008	Public/non profit
(van der Hoorn et al. 2015)	PPIs (general)	Pharmaceutical Benefits Scheme (PBS) administrative database	ACM (mean 6.6 years)	National death index	1996	Public/non profit
(Win et al. 2010)	PPIs (general)	Chart review	ACM (not clear)	Not clear if in-hospital mortality. No details on ascertainment.	2005-2008	
Intervention studies						

Citation	PPI type assessed	Exposure ascertainment	Outcome(s) of interest (follow-up period)	Outcome ascertainment	Calendar year(s) of sampling	Source of funding
(Daneshmend et al. 1992)	Omeprazole	Randomized PPI exposure	ACM (40 days)	NR	1986-1989	Industry
(Krag et al 2018)	Pantoprazole (40 mg once daily)	Medication received intravenously at hospital until discharge or death	ACM (3 months)	Patient files, contact with patients or family, regional and national registries.	2016-2017	Public/non profit
(Leung et al 2018)	Esomeprazole (40 mg twice daily for 10 days)	Medication received in hospital	ACM (1 month)	Follow up visits and national mortality records.	2013-2016	Public/non profit
(Selvanderan et al 2016)	Pantoprazole IV (40 mg once daily)	Randomized. Medication dispensed in hospital ICU	ACM (3 months)	Not reported	2014-2015	Public/non profit
(Gao et al. 2009)	Omeprazole	Randomized PPI exposure	ACM (2 weeks)	NR	2003-2007	No statement
(Hasselgren et al. 1997)	Omeprazole	Randomized PPI exposure	MI (3 weeks) Stroke (3 weeks) ACM (3 weeks)	NR	NR	Industry
(Hawkey et al. 2001)	Lansoprazole	Randomized PPI exposure (4 groups)	ACM (unclear)	Personal visits by research staff	Not reported	Industry
(Hung et al. 2007)	Pantoprazole	Randomized PPI exposure (3 groups)	ACM (1 month)	Monitoring of patients	2002-2005	Public/non profit
(Javid et al. 2001)	Omeprazole	Randomized PPI exposure	ACM (not clear)	Not clear	1996-1999	No statement

Citation	PPI type assessed	Exposure ascertainment	Outcome(s) of interest (follow-up period)	Outcome ascertainment	Calendar year(s) of sampling	Source of funding
(Kantorova et al. 2004)	Omeprazole	Randomized PPI exposure	ACM (in hospital)	NR	2000-2002	Public/non profit
(Kaviani et al. 2003)	Omeprazole	Randomized PPI exposure	ACM (3 weeks)	NR	1999-2000	Public/non profit
(Khuroo et al. 1997)	Omeprazole	Randomized PPI exposure	ACM (1 month)[1]	NR	1992-1994	Public/non profit
(Kuipers et al. 2011)	Esomeprazole	Randomized PPI exposure	ACM (up to 1 month)	At each center	2005-2007	Industry
(Lau et al. 2000)	Omeprazole	Randomized PPI exposure	ACM (1 month)	Monitoring of patients	1998-1999	Public/non profit
(Lau et al. 2007)	Omeprazole	Randomized PPI exposure	MI (unclear) ACM (1 month)	Hospital records; Patient contact; Clinic follow up;	2004-2005	Public/non profit
(Liu et al. 2013)	Omeprazole	Randomized PPI exposure	ACM (1 month)	NR	2006 - 2008	Public/non profit
(Nikcevic et al. 2011)	Pantoprazole	Randomized PPI exposure; not blinded.	ACM (not reported)	Not blinded	2008	No statement
(Schaffalitzky de Muckadell et al. 1997)	Omeprazole	Randomized PPI exposure	ACM (3 days, 21 days, 35 days)	Survey; Deaths reviewed by external group.	NR	No statement
(Sung et al. 2009)	Esomeprazole	Randomized PPI exposure	MI (1 month) ACM (1 month)	Blinded committee (for mortality)	2005-2007	Industry

Citation	PPI type assessed	Exposure ascertainment	Outcome(s) of interest (follow-up period)	Outcome ascertainment	Calendar year(s) of sampling	Source of funding
(Wei et al. 2007)	Esomeprazole	Randomized PPI exposure	ACM	NR	2002-2004	No statement
(Zargar et al. 2006)	Pantoprazole	Randomized PPI exposure	ACM (unclear - maximum of 6 weeks)	Follow up visits;	2001-2003	No statement

[1]*Cardiac death, defined as an unexpected natural death from circulatory arrest, usually due to a life-threatening ventricular arrhythmia, and that was consistent with an underlying cardiac cause*

TABLE S2- 3. CHARACTERISTICS OF STUDY DESIGN AND PATIENT POPULATION OF STUDIES THAT ASSESSED THE EFFECT OF CONCOMITANT PPI AND CLOPIDOGREL TREATMENT VS CLOPIDOGREL ALONE (GROUP B).

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
Observational Studies								
(Aihara et al. 2012) (Japan)	Retrospective cohort (hospital registries (12 centers)	Ibaraki Cardiac Assessment Study (ICAS) registry	PCI with stent	*Inclusion*: -informed consent -underwent PCI +stenting between Feb 2006-Aug 2009 -treated with CP following stenting *Exclusion*: -not prescribed CP after discharge -patients confirmed to have discontinued or newly started PPIs after discharge -non Ibaraki residents -patients that could not be linked to hospital discharge billing (to avoid loss to follow up)	1,887 (PPI: 1,068; No PPI: 819)	PPI: 69 (11) no PPI: 68 (10)	no PPI: 76 PPI: 74%	Asian
(Banerjee et al. 2011) (USA)	Retrospective cohort (database analysis, hospitalized patients)	Veterans Affairs Pharmacy Benefits Management database, National Patient Care Database	PCI	*Inclusion*: - in Veterans affairs pharmacy benefits management database and national patient care database - PCI with stent implantation between Jan 2003-Dec 2008 - discharged on clopidogrel - complete demographic and drug refill data	4,545 (PPI: 867; No PPI: 3,678)	PPI 65: (10) no PPI: 64 (10)	98 (veterans)	Caucasian, African American, Hispanic, Other
(Bhurke et al. 2012) (USA)	Retrospective cohort (database analysis,, population based)	IMS LifeLink Health Plan	ACS	*Inclusion*: - ACS patients - 18+ - ER visit or hospitalization - new clopidogrel users (within 90 days after diagnosis) and no clopidogrel use 180 days prior to ACS diagnosis *Exclusion*: - ACS diagnosis during 180 days prior to index date (first clopidogrel prescription)	10,101 (PPI: 2,958; No PPI: 7,143)	PPI: 61 (12) no PPI: 61 (12) (PS matched cohorts)	70	Not reported

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
(Burkard et al. 2012) (Netherlands)	Post-hoc analyses of RCT (hospitals)	BASKET trial (post-hoc)	PCI	*Inclusion*: - undergoing PCI *Exclusion*: - no discharge medication	801 (PPI: 109; No PPI: 692)	PPI: 66(11) no PPI: 63 (11)	PPI: 69 no PPI: 80	Not reported
(Charlot et al. 2010) (Denmark)	Retrospective cohort (database analysis,, hospitals)	Danish National Patient Registry	MI	Inclusion: - >30 years - hospitalized with AMI between 2000-2006 Exclusion: - prior MI - partially missing data	Cohort size : 56406 PS matched: (PPI: 15,443; No PPI: 15,433)	no treatment: 70(13) PPI only: 73(12) CP only: 64 (13) Concomitant: 66(13) PS matched: 73 (13)	no treatment: 61 PPI only: 53 Clopidogrel only: 71 Concomitant: 62 PS matched: 54	(largely Caucasian population)
(Ching et al. 2012) (US)	Retrospective cohort (hospital)		PCI	Inclusion: - PCI at Hartford Hospital Cardiac Catheterization Lab between Jan 2004-Nov 2008 - discharged on clopidogrel and aspirin	3,287 (PPI: 1,128; No PPI: 2,159)	PPI: 66 (13) no PPI: 62(13)	PPI: 60 no PPI: 71	Not reported
(Chitose et al. 2012) (Japan)	Prospective cohort (hospital registries (16 centers))	Kumamoto Intervention Conference Study (KICS)	PCI	Inclusion: - consecutive patients undergoing PCI at one of 16 centers in Japan between June 2008 - March 2009 - written consent Exclusion: - in-hospital death - not on thienopyridines at time of discharge - re-intervention after first registration - planned staged interventional procedure	1,270 (PPI: 331; No PPI: 939)	PPI: 72(12) no PPI: 69(12)	PPI: 68 no PPI: 71	Not reported
(Depta et al. 2015) (USA)	Prospective cohort (medical centers (24 centers))	TRIUMPH cohort (Translational Research Investigating	ACS	Inclusion: - AMI (elevated troponin level and documented clinical ischemia - Caucasian or African American - discharged on clopidogrel after AMI	2,062 (PPI: 372; No PPI: 1,690)	PPI: 60 (12) no PPI: 58 (12)	70	Caucasian, African American

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
		Underlying disparities in acute Myocardial infarction Patients' Health status)						
(Douglas et al. 2012) (UK)	Retrospective cohort (database analysis)	UK General Practice Research Database (GPRD), Myocardial Ischemia National Audit Project (MINAP), Office for National Statistics	On clopidogrel and aspirin	Inclusion: - active within GPRD from Jan 2003 onwards with at least 12 months between first registration and first recorded CP prescription - concurrently prescribed aspirin	24,471 (PPI: 9,111; No PPI: 15,360)	PPI: 71 no PPI: 68	PPI: 58 no PPI: 65	Not reported
(Evanchan et al. 2010) (US)	Retrospective cohort (electronic and paper records)		MI and stent	Inclusion: - admitted with AMI and underwent PCI with stent between Jan 2003-Jan 2008 - discharged on clopidogrel	5,794 (PPI: 1369; No PPI: 4,425)	PPI: 64 no PPI: 63	Not reported	Not reported
(Gaglia et al. 2010) (USA)	Retrospective cohort (database analysis, hospital (1 center))		PCI with DES	Inclusion: - underwent PCI with DES - randomly selected from database	820 (PPI: 318; No PPI: 502)	PPI: 64 (12) no PPI: 64 (12)	PPI: 62 no PPI: 64	Caucasian (70%), Asian, African American, Hispanic
(Galante et al. 2012) (Brazil)	Retrospective cohort (database analysis, hospital)		PCI	*Inclusion*: - treated with clopidogrel between Jan 2007-Nov 2009 at the Heart Institute in Sao Paulo	2,823 (PPI (omeprazole): 1,273; No PPI: 1,295; Others)	63 (12)	64	Not reported

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
(Gargiulo et al 2016) (Italy)	Post-hoc analysis of RCT (3 hospitals)	PRODIGY trial NCT00611286.	PCI	*Inclusion*: - PCI patients receiving DES at 3 Italian sites randomized to either 6 or 24 months of DAPT (clopidogrel + aspirin).	1,970; PPI: 738;	No PPI: 59-77 (range); PPI: 62-78 (range) ;	No PPI: 79.2%; PPI: 72.5%;	NR
(Gaspar et al. 2010) (Portugal)	Retrospective cohort (database analysis, hospital (1 center))		ACS	Inclusion: -admitted with ACS -discharge on aspirin and CP for at least 6 months Exclusion: - incomplete prescription data to allow exposure assessment	802 (PPI: 274; no PPI: 528)	PPI: 64(13) no PPI: 61 (13)	PPI: 74 no PPI: 77	Not reported
(Goodman et al. 2012) (43 countries)	Post-hoc analyses of RCT (hospitals, 3 centers)	PLATO trial (post-hoc)	ACS	Inclusion: - hospitalized for ACS and had ST segment elevation or new left bundle branch block and were to undergo PCI - or had at least 2 of the following: ST-segment deviation; positive biomarker indicating myocardial necrosis; age 60 years; prior myocardial infarction (MI) or coronary artery bypass grafting; coronary artery disease (with 50% stenosis in 2 vessels); prior ischemic stroke, transient ischemic attack, carotid stenosis (50%), or cerebral revascularization; diabetes mellitus; peripheral arterial disease; or chronic renal dysfunction (creatinine clearance 60 mL/min per 1.73 m2) Exclusion: - increased risk of bleeding (ex, active bleeding, major surgery 30 days), - clinically important anemia or thrombocytopenia - need for ongoing oral anticoagulation therapy - moderate/severe liver disease.	18,601 (PPI: 6,539; No PPI: 12,060)	PPI: 63 no PPI: 62	PPI: 72 no PPI: 71	Caucasian, Asian, African American, Other (>90% Caucasian)

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
(Gupta et al. 2010) (USA)	Retrospective cohort (hospital records (1 center))		PCI	Inclusion: - underwent PCI between Jan 2003-Aug 2004 - discharged on clopidogrel Exclusion: -not discharged on CP	315 (PPI: 72; No PPI: 342)	PPI: 62(1) no PPI: 62 (1)	Not reported	Not reported
(Harjai et al. 2011) (USA)	Retrospective cohort (registry, hospitals)	Guthrie PCI registry	CAD with OCI	Inclusion: -underwent PCI -stable or unstable CAD -discharged alive without MI, TVR or stroke Exclusion: -enrolled in an RCT on AP treatment -incomplete/lack of discharge data on PPI use - did not complete 6 month follow-up	2651 (PPI: 751; no PPI: 1902)	PPI: 64(12) no PPI: 66 (11)	PPI: 72 no PPI: 62	99% Caucasian
(Ho et al. 2009) (USA)	Retrospective cohort (records of patients/charts, hospitals (127 VHA centers))	Veterans Health Administration	ACS	Inclusion: - discharged with MI or unstable angina between Oct 2003 - Jan 2006 - prescribed clopidogrel at discharge	8205 (PPI: 5,244; No PPI: 2,961)	PPI: 68 (11) no PPI: 66 (12)	99 (veterans)	Not reported
(Hokimoto and Ogawa 2010) (Japan) [abstract]	Prospective cohort (Hospital)			Inclusion: - on aspirin 100 mg/day and clopidogrel 75 mg/day and treated with either rabeprazole or no PPI	170 (PPI (rabeprazole): 37; no PPI: 133)	NR	Not reported	Not reported
(Huang et al. 2010) (Taiwan)	Retrospective cohort (database analysis)	National Health Insurance database (Taiwan)	PCI	Inclusion: - underwent PCI after Jan 1, 2002 - on clopidogrel	3,278 (PPI: 572; No PPI: 2,706)	PPI: 69(11) no PPI: 65 (12)	72	Asian

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
(Hudzik et al. 2010) (Poland)	Prospective cohort (Hospitals)		Stent	Inclusion: - with prior stent implantation, and underwent coronary angiography between Jan 2006 - July 2008 Exclusion: - co-existing autoimmune disorders, acute infectious diseases, chronic inflammatory diseases, renal failure - known malignant diseases, decompensated diabetes mellitus, hepatitis - severe trauma or burns during the 12 months prior to coronary angiography - ischemic or hemorrhagic stroke during the 12 months prior to coronary angiography - glucocorticoids and/or androgen therapy - psychiatric disorders - lack of patient consent to participate	38 (PPI (omeprazole): 18; No PPI: 20)	PPI: 63(9) no PPI: 61 (12)	PPI: 83 no PPI: 65	Not reported
(Juurlink et al. 2009) (Canada)	Nested case-control (database analysis, hospitals)	Ontario Public Drug Program, Canadian Institute for Health Information Discharge Abstract Database, Ontario Health Insurance Plan database, Registered Persons Database	MI	Inclusion: Cohort - ≥66 years -discharged for MI between Apr 2002 - Dec 2007 - universal access to health care and drug coverage - filled clopidogrel prescription within 3 days of discharge Cases - readmitted for MI within 90 days of discharge (readmission is index date) Controls - 3 controls per case - no MI before index date of case - matched by age (+/- 3 years), in-hospital PCI, date of hospital discharge, date of hospital discharge (+/- 5 days), predicted probability of short term mortality	(Cases: 734; Controls: 2057)	77 (median)	Cases: 52 Controls: 55	Not reported

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
				Exclusion: -received clopidogrel, ticlopidine or dipyridamole in the year before admission - in long term care facilities - received PPI within 90 days before or after the index date to eradicate H pylori				
(Juurlink et al. 2011) (Canada)	Nested case-control (database analysis, hospitals)	Canadian Institute for Health Information Discharge Abstract Database , Ontario Public Drug Program Benefit Program, Ontario Health Insurance Plan, Registered Persons Database	Stroke	Inclusion: Cohort - ≥66 years in Ontario - discharged after stroke between April 2002-Sept 2008 - filled prescription for clopidogrel within 30 days of discharge after stroke Cases -experienced outcome of interest within 180 days of discharge after stroke Controls - sampled randomly with replacement from cohort - event free but at risk on the index date - matched on age (+/- 1 year), gender, and outcome Exclusion: Received clopidogrel in year prior to hospitalization or ticlopidine or dipyridamole in the 90 days before hospitalization -patients in long term care facilities -those who received PPI products to eradicate Helicobacter pylori in the year preceding the index date or 90 days thereafter -patients who underwent carotid endarterectomy within 90 days after hospitalization -patients readmitted for stroke between cohort entry and first CP prescription	(Cases: 118; Controls: 472)	77 (median)	Cases: 42 Controls: 42	Not reported

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
(Kim et al. 2014) (Korea) [abstract]	Case crossover (database analysis, hospitals)	Korean Health Insurance Review and Assessment Service database	MI	Inclusion: - MI and received clopidogrel and aspirin between Jan 2008- Dec 2010 (after MI hospitalization) - 20-99 years	43822	30-99 (range)	NR	Not reported
(Kreutz et al. 2010) (US)	Retrospective cohort (database analysis)	Medco Health Solutions	PCI with stent	Inclusion: - ≥18 years - PCI with coronary stent between Oct 2005-Sept 2006 - continuous eligibility data 6 months prior to index PCI and 12 months after	16,690 (PPI: 6,828; No PPI 9,682)	PPI: 68 (10) no PPI: 65 (11)	PPI: 62 no PPI: 74	Not reported
(Mahabaleshwarkar et al. 2013) (USA)	Nested case-control (database)	Medicare	Elderly clopidogrel users	Inclusion: Cohort of clopidogrel users: - 65 years of age as of January 1, 2006 - continuous Medicare part A coverage and at least 1 month of Part B coverage from January 1, 2006 to December 31, 2008 or until death - initiated clopidogrel therapy and did not have any gap of 30 days or more between clopidogrel fills between July 1, 2006 and December 31, 2008, - no clopidogrel claims in the 6 months prior to start of study Cases - had an index event: (AMI, stroke, receiving CABG surgery, or PCI) or death, between date of first prescription claim for clopidogrel and Dec 2008; Controls - did not experience an index event - matched by age (+/- 5 years) and time to cohort entry (+/-7 days);	(Cases: 9,908; Controls: 9,908)	All patients: 77 (7) Cases: 79 (8) Controls: 79 (8)	38	Caucasian, African American, Other (85% Caucasian)

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
(Munoz-Torrero et al. 2011) (Spain)	Retrospective cohort (hospital registries (14 centers))	Factores de Riesgo y ENfermedad Arterial (FRENA), Registry	CAD, cerebrovascular or PAD	Inclusion: - outpatients with symptomatic artery disease with at least one episode of CAD, CVD or PAD. - receiving clopidogrel at baseline -oral consent to be in registry	1,222 (PPI: 519; No PPI: 703)	PPI: 68 (11) no PPI: 64 (12)	PPI: 75 no PPI: 77	Not reported
(O'Donoghue et al. 2009) (30 countries)	Post-hoc analyses of RCT (hospitals)	TRITON-Timi 38 trial (post-hoc)	ACS with PCI	Inclusion: - ACS patients undergoing planned PCI - randomized to either prasugrel or clopidogrel Exclusion: - high risk of bleeding - history of anemia, thrombocytopenia, pathological intracranial findings - use of thienopyridine within 5 days before randomization	(PPI: 4,529; No PPI: 9,079)	PPI: 62 no PPI: 61	CP users: PPI: 70 no PPI: 75 Prasugrel users: PPI: 73 no PPI 76;	Not reported
(Ortolani et al. 2012) (Italy)	Retrospective cohort (database analyses)		ACS	Inclusion: - primary discharge of ACS diagnosis from private and public hospitals between Jan 2008 - Aug 2008 - filled prescription for clopidogrel within 30 days after discharge Exclusion: - hospitalization more than 180 days - residence outside Emilia-Romagna region - prior diagnosis that increases hemorrhagic risk	3,896 (PPI: 3,519; No PPI: 377)	PPI: 69(12); no PPI: 63 (12)	PPI: 69 no PPI: 77	Not reported
(Rassen et al. 2009) (USA and Canada)	Retrospective cohort (database analysis, hospitals)	PHARMNET (British Columbia), Pharmaceutical Assistance Contract for the Elderly (Pennsylvania), Pharmaceutic	ACS or PCI	Inclusion: - ≥65 years -underwent PCI or hospitalized for ACS (AMI or unstable angina) in British Columbia, Pennsylvania or New Jersey between Jan 2001-Dec 2005, - hospitalization was between 3-180 days - initiated clopidogrel within 7 days of index date - no clopidogrel use in 180 days before index,	BC: 10,391 (PPI: 1,353; No PPI: 9,038) PA 4,176 (PPI: 1,352; No PPI: 2,824) NJ 3,998 (PPI: 1,291; No PPI: 2,707)	BC cohort PPI: 76 (7) no PPI: 74 (6) PA cohort PPI: 79 (7) no PPI: 78 (7) NJ cohort PPI: 78 (7) no PPI: 78 (7)	BC cohort PPI: 54 no PPI: 64 PA cohort PPI: 22 no PPI: 27 NJ cohort PPI: 31 no PPI: 36	Caucasian, Other (US cohort: Caucasians and others; BC cohort: not reported)

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
		al Assistance to the Aged and Disabled (New Jersey)		- at least 1 medical service and filled at least 1 prescription in each of the two 6 months periods preceding the index event.				
(Ray et al. 2010) (US)	Retrospective cohort (Database analysis, hospitals (multiple centers))	Tennessee Medicaid program	ACS	Inclusion: - hospitalized for AMI, coronary artery revascularization, or unstable angina - prescribed clopidogrel between Jan 1999-Dec 2005 - enrolled in Medicaid - ≥30 years - on clopidogrel for at least 1 day during study period - 1 year or more Medicaid enrolment prior to index hospitalization - available data to classify patients - evidence of regular medical care during the 1 year preceding index hospitalization, defined as at least 1 prescription or outpatient visit Exclusion: - diagnosed cocaine use, alcohol abuse, cancer, HIV, renal, hepatic or respiratory failure, organ transplant, liver cirrhosis, esophageal varices, bariatric or other surgery resulting in gastrojejunal anastomosis - nursing home residents	20,596 (PPI: 7,593; No PPI: 13,003)	PPI: 61 (11) no PPI: 60 (11)	PPI: 46 no PPI: 53	Caucasian, Other (78% Caucasian)
(Rossini et al. 2011) (Italy)	Retrospective cohort (Registry (2 centers))		PCI with DES	Inclusion: - PCI with DES implantation at one of two institutes in Northern Italy - discharge on DAT (aspirin and clopidogrel) Exclusion: - incomplete data	1328 (PPI: 1,158; No PPI: 170)	PPI: 64 (11) no PPI: 63 (11)	PPI: 76 no PPI: 81	Not reported

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
(Sarafoff et al. 2010) (Germany)	Retrospective cohort (hospital)		DES	Inclusion: - DES implantation between July 2002-Dec 2006 - received clopidogrel and Aspirin prior to DES as well as for follow-up period	3,338 (PPI: 698; No PPI: 2,640)	PPI: 69 (11) no PPI: 66 (11)	PPI: 70 no PPI: 77	Not reported
(Simon et al. 2011) (France)	Retrospective cohort (hospitals and private clinics with ICU (223 centers))	French Registry of Acute ST-Elevation and Non–ST-Elevation MI (FAST-MI) Registry	MI	Inclusion: - 18+ years - admitted to ICU with definite MI Exclusion: - diagnosed with iatrogenic MI (invalidated for an alternative diagnosis) - unstable angina with no elevation of cardiac necrosis	2,744 (PPI: 1611; No PPI: 1,133)	PS matched cohorts: PPI: 65 (12) no PPI: 66 (13)	27 - 42% between groups	Not reported
(Stockl et al. 2010) (US)	Retrospective cohort (database analysis)	(Insurance claims database (pharmacy and medical claims), hospital data , from Western US)	MI or stent	Inclusion: - 18-84 years - filled prescription for clopidogrel between Jan 2004-Dec 2006 - inpatient hospitalization with primary code for acute MI or coronary stent placement within 30 days before identification - continuous enrollment in the health plan during the 180 days before the index date Exclusion: - clopidogrel prescription filled in the 180 days before index date - diagnosis of renal disease, renal failure, liver failure, abnormal secretion of gastrin, GERD, helicobacter pylori, or gastric ulcers	7,049 (PPI: 1,041; No PPI: 6,008) PS matched: 1,033 in each group.	PPI: 69 (11) no PPI: 69 (11) (matched cohorts)	56	Not reported
(Sweeny et al. 2009) (USA) [abstract]	Retrospective cohort (database analysis, hospitals)	New York State Interventional database	PCI with DES	- underwent PCI with DES between Apr 2003-June 2007	8,311 (PPI: 1,385; no PPI: 6,926)	Not reported	Not reported	Not reported

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
(Tentzeris et al. 2010) (Austria)	Retrospective cohort (registry, hospital)		PCI with stent	Inclusion: For registry inclusion - consecutive patients, successful PCI with stent implantation between Jan 2003 - Dec 2006 -on DAPT (aspirin and clopidogrel)	1,210 (PPI: 691; No PPI: 519)	PPI: 64 (12) no PPI: 64 (12)	PPI: 65 no PPI: 73	Not reported
(Ulhaq et al. 2011) (UK)	Retrospective cohort -letter to the editor (hospital -1 center)		MI	Inclusion: ACS on DAPT	184 (PPI: 96; no PPI:88)	67	66	Caucasian, Asian
(Valkhoff et al. 2011) (Netherlands)	Nested case-control (database analysis)	PHARMO Record Linkage System (Netherlands)	MI	Inclusion: Cohort: patients admitted for AMI between Jan 1999- Dec 2008 (primary diagnosis) -required to have had one prescription filled at least 1 year preceding the date of cohort entry Cases - recurrent MI (primary diagnosis) with 30 day period between discharge from baseline MI and recurrent MI Controls - randomly selected from cohort, matched on gender, age and risk of recurrent MI, and calendar time;	(Cases: 616; Controls 126,817)	65 (13)	67	Not reported
(van Boxel et al. 2010) (Netherlands)	Retrospective cohort (database analysis)	Two Dutch health insurance databases	New clopidogrel users	Inclusion: - insured, ≥18 years - registered for at least 1 year in database - at least 1 prescription for clopidogrel between Jan 2006-Dec 2007 Exclusion: - use of clopidogrel in the 180 days before the index clopidogrel prescription date	18,139 (PPI: 5,734; No PPI: 12,405)	PPI: 69 (12) no PPI: 66 (12)	PPI: 59 no PPI: 67	Not reported

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
(Wang et al. 2014) (Sweden)	Retrospective cohort (Population based database)	Swedish Patient Register and Swedish Prescribed Drug Register (SPDR)	CVD and high risk for UGIB	Inclusion: - high risk for UGIB - first hospitalization for CVD (AMI, stroke, angina) between 2006-2008 Exclusion: - prescription of aspirin - prior MI, stroke or angina within 1 year before entry other than index hospitalization - emigrated before January 1, 2006 - cardiovascular rehospitalisation or had died less than 7 days after study entry	2,285 (cohort)	67% of sample >75 years	56	Caucasian
(Weisz et al. 2015) (US and Germany)	Prospective cohort (registries, hospitals -10-15 US and European centers)	ADAPT-DES multicenter registry	CAD with DES	Inclusion: - all comers with CAD - treated with aspirin and clopidogrel - underwent placement of one or more DES Exclusion: - major complication during the procedure or before platelet function testing - planned bypass surgery after stenting - significant anemia preventing accurate measurement of platelet reactivity - unable to take DAPT were excluded	8,582 (PPI: 2,697; No PPI 5,885)	PPI: 64 (11) no PPI: 63 (11)	PPI: 70 no PPI: 76	Caucasian, Other (90% Caucasian)
(Wu et al. 2010) (Taiwan)	Retrospective cohort (database analysis, hospitals)	National Health Insurance Research Database (Taiwan)	ACS	Inclusion: - primary diagnosis of ACS between July 2002-June 2005 - Clopidogrel treatment Exclusion: - ACS events within first month after discharge - <20 years	6,552 (PPI: 514; No PPI: 5,551; others)	PPI: 72 (1) no PPI: 66 (0)	PPI: 61 no PPI: 71	Not reported
(Yan et al 2016) (Multiple countries)	Retrospective cohort (Registry analysis)	BleeMACS registry NCT02466854	ACS, PCI	Inclusion: - 18 years of age or older - discharged alive with a diagnosis of ACS and treated with PCI - users of ticagrelor or clopidogrel	Cohort size: 9,429; PPIs: 5,165; No PPI: 4265;	PPI: 66.2; No PPI: 61.3;	PPI: 75%; No PPI: 79%;	NR

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
(Yi et al 2018)	Stroke patients receiving clopidogrel	http://www.chictr.org ChiCTR-OCH-14004724	Stroke patients receiving clopidogrel	Inclusion: - first time stroke within 7 days of enrollment - visiting one of two participating centers - written consent - 40+ years - no history of clopidogrel treatment for at least 14 days before admission Exclusion: - allergy to clopidogrel - cerebral embolism and other determined etiology or undetermined etiology IS - taking other nonsteroidal anti-inflammatory drugs except aspirin, or anticoagulants with warfarin or heparin within 2 weeks; - very low or very high platelet count - any major surgical procedure or severe trauma within 1 week prior to enrollment - fever, hypoxia, or any relevant hemodynamic compromise on admission; - myelodysplastic syndrome or other blood diseases - a history of carotid endoartectomy or carotid stent therapy or carotid endoartectomy or carotid stent therapy during the follow-up period.	523; PPI: 161; no PPI: 362;	Patients that experienced MI, stroke or death: 71.0 (13.2); Patients that did not experience an event: 67.2 (12.4);	Patients that experienced MI, stroke or death: 63.8%; Patients that did not experience an event: 64.4%;	NR
(Zairis et al. 2010) (Greece)	Retrospective cohort (hospital -1 center)		ACS with stent	Inclusion: - successful coronary stent in Tzanio hospital due to stable angina or ACS between April 2003- Jan 2005 - treated with acetylsalicylic acid and clopidogrel for at least 12 hrs before stent	588 (PPI (Omeprazole): 340; No PPI:: 248)	PPI: 62 (11) no PPI: 62 (11)	82	Not reported

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
(Zou et al. 2014) (China)	Retrospective cohort (hospital)		PCI with DES	Inclusion: - complete medication data for 1 month before PCI and stent and for 12 month follow-up thereafter - PPI users had to have at least 3 PPI prescriptions or took PPI more than 6 days throughout the follow up period Exclusion: - no discharge medication data were excluded from the analysis - interrupted clopidogrel medication or were not on clopidogrel	7906 (enrolled) (PPI: 6,188; No PPI: 1,465)	PPI: 66 (10) no PPI: 66 (11)	73	Asian
Intervention studies								
(Bhatt et al. 2010) (15 countries)	RCT (hospitals)		ACS	Inclusion: - ≥21 years - anticipated use of clopidogrel and aspirin for the next 12 months (including ACS patients or undergoing stent placement) Exclusion: - discharge from hospital was not anticipated within 48 hours of admission - need for short-term or long-term use of PPIs, H2RAs, sucralfate, misoprostol - pre-existing erosive esophagitis, esophageal, gastric variceal disease or previous non-endoscopic gastric surgery - receipt of clopidogrel or another thienopyridine for more than 21 days before randomization - receipt of oral anticoagulation therapy that could not be safely discontinued for the duration of the study - recent fibrinolytic therapy	3,873 (PPI: 1,876; No PPI: 1,885)	PPI: 69 no PPI: 69	PPI: 67 no PPI: 70	Caucasian, Other (94% Caucasian)

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
(Hsu et al. 2011) (Taiwan)	RCT Comments : open label (hospital)		Atherosclerosis and history of peptic ulcers	Inclusion: -history or peptic ulcer -underwent endoscopy for dyspeptic symptoms or routine screening -on CP to prevent ischemic events for at least 2 weeks Exclusion: - peptic surgery other than oversewing of a perforation - allergies to study drugs - need for long term NSAID, corticosteroids, aspirin or anticoagulants - pregnancy - active cancer - acute serious medical illness or terminal illness. - GERD - received PPI or antibiotic therapy within 2 weeks before endoscopy	(PPI: 83; no PPI: 82)	PPI: 71 (12) no PPI: 73 (11)	PPI: 78 no PPI:72	Not reported
(Wu et al. 2011) (China)	RCT (hospitals (3 cardiology centers))		ACS and high risk for UGIB	Inclusion: -diagnosis of ACS, consecutively admitted to 3 cardiology hospitals between May 2008-April 2010 -confirmed ACS diagnosis AND 1 or more of these risk factor for GI bleeding: 75+ years, history of peptic ulcer disease, history of GI bleeding, cardiogenic shock and chronic renal dysfunction;	665 (PPI: 333; No PPI: 332)	76% were over 75+	PPI:74 no PPI: 73	Not reported

TABLE S2- 4. CHARACTERISTICS OF THE EXPOSURE, OUTCOMES AND SOURCE OF FUNDING OF STUDIES THAT ASSESSED THE EFFECT OF CONCOMITANT PPI AND CLOPIDOGREL TREATMENT VS CLOPIDOGREL ALONE (GROUP B).

Citation	PPI type assessed	Patients taking aspirin	Exposure ascertainment	Outcome(s) of interest (follow-up period)	Outcome ascertainment	Calendar year(s) of sampling	Source of funding
Observational Studies							
(Aihara et al. 2012)	PPIs (general)	Yes	Follow up at 30 days, 6 months and 1 year after PCI.	MI (1 year) Stroke (1 year) ACM (1 year)	Medical records	2006-2009	No statement
(Banerjee et al. 2011)	PPIs (general)	No	Dispensing records using the prescription release dates and days of supply.	ACM (1 year, 6 years)	National Patient Care database	2003-2008	Public/non profit
(Bhurke et al. 2012)	PPIs (general)	No	Medical records (fill dates and supply)	MI (mean 268 days)	Medical records (ICD codes)	2001-2008	Public/non profit
(Burkard et al. 2012)	PPIs (general)	Yes	PPI from discharge records. Antiplatelet randomised.	MI (3 years) ACM (3 years)	Hospital records, lab confirmation (MI); Death (not clear);	2003-2004	Public/non profit
(Charlot et al. 2010)	PPIs (general)	No	National prescription registry (PPI prescriptions obtained up till 1 year after discharge)	MI (1 year) Stroke (1 year) ACM (1 year) CVD mort (1 year)	Danish National Patient Registry	2000-2006	Public/non profit
(Ching et al. 2012)	PPIs (general)	Yes	Patient charts.	ACM (9 months)	Chart reveiw or direct contact with patients/relatives	2004-2008	Public/non profit
(Chitose et al. 2012)	PPIs (general)	No	Registry. Compliance with drugs was confirmed.	MI (18 months) Stroke, CVD mort (18 months)	Hospital records; clinical and radiological evidence (for stroke)	2008-2009	Public/non profit
(Depta et al. 2015)	PPIs (general)	No	Chart abstraction at admission	ACM (1 year) Stroke (1 year)	Social Security Administration Death Master File	2005-2008	Public/non profit

Citation	PPI type assessed	Patients taking aspirin	Exposure ascertainment	Outcome(s) of interest (follow-up period)	Outcome ascertainment	Calendar year(s) of sampling	Source of funding
(Douglas et al. 2012)	PPIs (general) strong PPIs grouped together (omeprazole, esomeprazole, lansoprazole)	Yes	EMRs.	MI (median 303 days) ACM (median 303 days) CVD mort (median 303 days)	Office for National Statistics Mortality records (mortality); Myocardial Ischemia National Audit Project records (MI);	2003-2009	Public/non profit
(Evanchan et al. 2010)	PPIs (general)	No	Discharge records.	MI (1 year)	Chart review	2003-2008	None
(Gaglia et al. 2010)	PPI (general) Omeprazole Lansoprazole Esomeprazole Pantoprazole Rabeprazole	Yes	Hospital charts	MI (in-hospital, 1 year) ACM (1 month, 1 year)	Phone or in person interview. Events adjudicated by independent committee;	2003-2007	No statement
(Galante et al. 2012)	Omeprazole	Some patients	Hospital records	ACM (not reported)	Not clear	2007-2009	No statement
(Gargiulo et al 2016)	PPIs (general)	Yes	Interview (baseline and follow-up)	ACM (2 years); MI (2 years); Cardiovascular mortality (2 years);	Hospital records and adjudication by committee	NR	None.
(Gaspar et al. 2010)	PPI (general) (excluding those on pantoprazole	Yes	Clinical records	ACM (6 months)	By phone interviews and hospital record review.	2004-2008	No statement
(Goodman et al. 2012)	PPIs (general)	No	Self-reported and assessment during follow up at 20, 60, 90 and 180 days.	MI (1 year) ACM (1 year) CVD mort (1 year)	Ascertained by an independent clinical events committee (blinded)	2006-2009	None for this analysis; Industry

Citation	PPI type assessed	Patients taking aspirin	Exposure ascertainment	Outcome(s) of interest (follow-up period)	Outcome ascertainment	Calendar year(s) of sampling	Source of funding
							funding for PLATO trial
(Gupta et al. 2010)	PPIs (general) (78% of patients on rabeprazole)	No	Discharge records.	ACM (4 years)	EMRs	2003-2004	No statement
(Harjai et al. 2011)	PPI (general) Omeprazole Esomeprazole	Yes	Patients records; Self-reported compliance to PPI at 6 months	MI (6 months) ACM (6 months)	Patients records (MI); Social Security Death Index (ACM)	2001-2007	None
(Ho et al. 2009)	PPIs (general)	No	Pharmacy refill data	ACM (1,080 days)	Vital status file (mortality)	2003-2006	Public/non profit
(Hokimoto and Ogawa 2010)	Rabeprazole	Yes		MI (1 year) Stroke (1 year) CVD mort (1 year)	Not reported	Not reported	No statement
(Huang et al. 2010)	PPIs (general)	No	Claims database records	ACM (up to 6 years (from Kaplan Meir curve)	Database	2002-2007	Public/non profit
(Hudzik et al. 2010)	Omeprazole	Yes	Not reported.	Stroke (1 year) ACM (1 year) Death (1 year)	Follow up	2006-2008	No statement
(Juurlink et al. 2009)	PPIs (general)	No	Prescription records	MI (3 months) ACM (3 months)	Hospital admissions database	2002-2009	Public/non profit

Citation	PPI type assessed	Patients taking aspirin	Exposure ascertainment	Outcome(s) of interest (follow-up period)	Outcome ascertainment	Calendar year(s) of sampling	Source of funding
(Juurlink et al. 2011)	PPIs (general)	No	Drug program database	Stroke (readmission) (up to 6 months) ACM (up to 6 months)	Database	2002-2008	Public/non profit
(Kim et al. 2014) [abstract]	PPIs (general)	Yes	Database	recurrent MI (not reported)	Database	2008 - 2010	No statement
(Kreutz et al. 2010)	PPIs (general)	No	Prescription claims database.	MI (1 year) CVD (1 year)	Claims records	2005-2006	Industry and Public/non profit
(Mahabaleshwarkar et al. 2013)	PPIs (general)	No	Medicare drug event file	MI Stroke ACM	Inpatient claims (MI and stroke); Medicare Beneficiary Summary file (ACM).	2006 - 2008	Public/non profit
(Munoz-Torrero et al. 2011)	PPIs (general)	No	Collected info within 3 months of study entry.	MI (at least 1 year) Stroke (at least 1 year) ACM (at least 1 year)	Case report forms	2003-2009	Industry
(O'Donoghue et al. 2009)	PPIs (general)	No	PPI exposure determined at study entry and at follow up	MI (400 days) ACM (400 days) CVD mort (400 days)	Independent committee (blinded)	2004-2007	None for this analysis; trial funded by industry

Citation	PPI type assessed	Patients taking aspirin	Exposure ascertainment	Outcome(s) of interest (follow-up period)	Outcome ascertainment	Calendar year(s) of sampling	Source of funding
(Ortolani et al. 2012)	PPIs (general)	No	Pharmacy refill data (dispensing date and the number of days supplied for each dispensed medication)	ACM (1 year)	Municipal registries and hospital discharge records.	2008	Public/non profit
(Rassen et al. 2009)	PPIs (general)	No	Insurance claims records	MI (6 months) ACM (6 months)	Insurance claims records (MI); Vital statistics and government agencies (mortality)	2001-2005	Public/non profit
(Ray et al. 2010)	PPIs (general)	Yes	Medicaid files of medications dispensed at the pharmacy;	Stroke (6 years) CVD mort (6 years)	Hospital admissions data; Death certificates (CVD mortality);	1999-2005	Public/non profit
(Rossini et al. 2011)	PPIs (general)	Yes	Telephone contact or outpatient clinical visits at 1, 6, and 12 months after the index procedure.	ACM (1 year)	In-hospital death	NR	No statement
(Sarafoff et al. 2010)	PPIs (general) (77% of patients were on pantroprazole)	Yes	Hospital charts and discharge data	MI (30 days) ACM (30 days)	Phone/in person interview.	2002-2006	No statement
(Simon et al. 2011)	PPIs (general) Omeprazole Lansoprazole Omeprazole Pantoprazole	No	EMR	MI (1 year) Stroke (1 year) ACM (1 year)	EMRs	2005	Industry and Public/non profit
(Stockl et al. 2010)	PPIs (general) Pantoprazole	No	Prescription records	MI (1 year)	Database claims	2004-2006	No statement
(Sweeny et al. 2009)	PPIs (general)	No	Database	ACM (mean 2 years)	Social Security Index	2003-2007	No statement

Citation	PPI type assessed	Patients taking aspirin	Exposure ascertainment	Outcome(s) of interest (follow-up period)	Outcome ascertainment	Calendar year(s) of sampling	Source of funding
[abstract]							
(Tentzeris et al. 2010)	PPIs (general)	Yes	Discharge summaries.	ACM (mean 7.8 months) CVD mort (mean 7.8 months)	Follow up; Statistics Austria (mortality)	2003-2006	Public/non profit
(Ulhaq et al. 2011)	PPI (general)	Yes	NR	MI (1 year)	Not reported	Not reported (1 year)	
(Valkhoff et al. 2011)	PPIs (general)	No	Electronic health records, outpatient drug dispensing files of pharmacies.	recurrent MI (up to 9 years; median: 3.6 years)	Hospital records	1999-2008	Public/non profit
(van Boxel et al. 2010)	PPIs (general)	No	Prescriptions records from insurance database	MI (750 days) Stroke (750 days) ACM (750 days)	Database	2004-2007	Industry
(Wang et al. 2014)	PPIs (general)	No	Swedish Prescribed Drug Register	ACM (3 months)	Swedish Cause of Death Register	2006-2008	Public/non profit
(Weisz et al. 2015)	PPIs (general)	Yes	Case report forms and hospital discharge data.	MI (2 years) ACM (2 years)	Follow up	2008-2010	No statement
(Wu et al. 2010)	PPIs (general)	No	Prescription records	ACM (3 months)	Database	2002-2005	Public/non profit
(Yan et al 2016)	PPIs (general)	Some patients	Discharge records	ACM (1 year); MI (1 year);	Telephone or in person interviews; medical records	2003-2014	NR
(Yi et al 2018)	PPIs (general)	Not clear	BR	MI, recurrent stroke, Cardiovascular mortality	Medical chart review, interviews, and adjudication by independent committee	2014-2015	Public/non profit

Citation	PPI type assessed	Patients taking aspirin	Exposure ascertainment	Outcome(s) of interest (follow-up period)	Outcome ascertainment	Calendar year(s) of sampling	Source of funding
(Zairis et al. 2010)	Omeprazole	Yes	Follow up data collected prospectively, at 1, 6, 9 and 12 months after discharge.	MI (1 year) CVD mort[1] (1 year)	Discharge reports, physician contact, death certifications.	2003-2005	No statement
(Zou et al. 2014)	PPIs (general) (90.% of patients on omeprazole)	Yes	Hospital discharge records, outpatient clinical visits, questionnaires or telephone interviews	MI (1 year) CVD mort (1 year)	Hospital records, outpatient clinical visits, written questionnaires, and telephone interviews	2005-2010	Public/non profit
Intervention studies							
(Bhatt et al. 2010)	Omeprazole	Yes	Randomized PPI exposure (stratified permuted blocks)	MI (6 months) Stroke (6 months) ACM (6 months) CVD mort (6 months)	Independent cardiologists (blinded)	2008	Industry
(Hsu et al. 2011)	Esomeprazole	No	PPI exposure randomized.	MI (6 months) Stroke (6 months) CVD mort (6 months)	Independent committee	2008-2010	Public/non profit
(Wu et al. 2011)	Pantoprazole	Yes	PPI randomized.	ACM (1 month)	Medical records and telephone contact with relatives.	2008-2010	No statement

[1](Cardiac death defined as sudden unexplained death, death due to fatal myocardial infarction, or death after rehospitalisation because of heart failure or possible acute myocardial ischemia

TABLE S2- 5. CHARACTERISTICS OF STUDY DESIGN AND PATIENT POPULATION OF STUDIES THAT ASSESSED THE EFFECT OF CONCOMITANT TREATMENT OF PPIS AND OTHER DRUGS VS OTHER DRUGS ALONE (GROUP C).

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection Criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
Observational studies								
(Charlot et al. 2011) (Denmark)	Retrospective cohort (database analysis, hospitals)	Danish national patient registry, National prescription registry, Danish civil registry	MI	Inclusion: -consecutive patients >30 years -admitted with first MI (1ry or 2nd diagnosis) between 1997-2006 -filled prescription for aspirin within 30 days of discharge Exclusion: - treated with clopidogrel - partially missing data - emigrating patients censored at time of emigration	19,925 (PPI: 4,306; No PPI: 15,619)	PPI: 73 (12) no PPI: 70 (13)	PPI: 54 no PPI: 61	Not reported
(Goodman et al. 2012) (43 countries)	Post-hoc analyses of RCT (hospitals (3 centers))	PLATO trial (post-hoc analysis)	ACS	Inclusion: - hospitalized for ACS and had ST segment elevation or new left bundle branch block and were to undergo PCI - or had at least 2 of the following: ST-segment deviation; positive biomarker indicating myocardial necrosis; age 60 years; prior MI or coronary artery bypass grafting; coronary artery disease; prior ischemic stroke, transient ischemic attack, carotid stenosis, or cerebral revascularization; diabetes mellitus; peripheral arterial disease; or chronic renal dysfunction Exclusion: - increased risk of bleeding	18,601 (PPI: 6,539; No PPI: 12,060)	PPI: 63 no PPI: 62	PPI: 72 no PPI: 71	Caucasian, Asian, African American, Other (>90% Caucasian)

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection Criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
				- clinically important anemia or thrombocytopenia - need for ongoing oral anticoagulation therapy - moderate/severe liver disease.				
(Kimura et al. 2011) (Japan)	Retrospective cohort (database analysis, hospitals -26 centers)	CREDO-Kyoto (Coronary REvascularization Demonstrating Outcome Study in Kyoto) PCI/CABG registry Cohort-2	PCI	Inclusion: - PCI or CABG as first coronary revascularization between Jan 2005- Dec 2007 -discharged on thienopyridines Exclusion: -refused participation in study upon follow-up -in-hospital deaths	12,446 (PPI: 3223; No PPI: 9223)	PPI: 69 (11) no PPI: 68 (11)	PPI: 69 no PPI: 73	Not reported
(O'Donoghue et al. 2009) (30 countries)	Post-hoc analyses of RCT (hospitals)	TRITON-Timi 38 trial (post-hoc)	ACS with PCI	Inclusion: - ACS patients undergoing planned PCI - randomized to either prasugrel or clopidogrel Exclusion: - high risk of bleeding - history of anemia, thrombocytopenia, pathological intracranial findings - use of thienopyridine within 5 days before randomization	(PPI: 4,529; No PPI: 9,079)	PPI: 62 no PPI: 61	CP users: PPI: 70 no PPI: 75 Prasugrel users: PPI: 73 no PPI 76;	Not reported
Yan et al 2016 (Multiple countries)	Retrospective cohort (Registry analysis)	BleeMACS registry NCT02466854	ACS, PCI	Inclusion criteria: - 18 years of age or older - discharged alive with a diagnosis of ACS and treated with PCI - users of ticagrelor or clopidogrel	Cohort size: 9,429; PPIs: 5,165; No PPI: 4265;	PPI: 66.2; No PPI: 61.3;	PPI: 75%; No PPI: 79%;	NR

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection Criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
Intervention studies								
(Angiolillo et al. 2014) and (Goldstein et al, 2010)[1]	RCT (59 centers (Angiolillo); 70 centers (Goldstein))	NCT00527787	On NSAIDs	Inclusion: - helicobacter pylori negative patients - clinical diagnosed osteoarthritis, rheumatoid arthritis, ankylosing spondylitis or any other condition expected to required daily NSAID therapy for at least 6 months - 18-49 years with documented history of uncomplicated gastric or duodenal ulcer within past 5 years or 50+ years Exclusion: - peptic ulcer (3+mm diameter with depth) determined by endoscopy at baseline were excluded from these studies, - history of hypersensitivity or allergy to any PPI or NSAID and/or any uncontrolled acute or chronic medical illness - prior GI disorders or surgery -history of alcohol or drug abuse	Study 1: 438 (PPI: 218; No PPI: 220); Study 2: 423 (PPI: 212; No PPI:211)	Study 301: 61 Study 302: 60	over 63%	Caucasian, Asian, Other (>84% Caucasian)
(F.K.L. et al. 2007) (China)	RCT (hospital -1 center)	NCT00365313	UGIB	Inclusion: - at Prince of Wales Hospital in Hong Kong - UGIB and taking NSAIDs for arthritis - endoscoped to confirm ulcer bleeding - 8 weeks course of PPI to heal ulcer and ulcers were healed - negative for H pylori - NSAIDS indicated for duration of the trial; Exclusion: - unhealed ulcers - use of low dose aspirin, anticoagulants, or	273 (PPI: 137; No PPI: 136)	PPI: 70 (12) no PPI: 72(11)	PPI: 47 no PPI: 49	Not reported

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection Criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
				corticosteroids before index bleeding - previous gastric or duodenal surgery other than a patch repair - allergy to celecoxib - erosive esophagitis, gastric outlet obstruction, terminal illness, cancer or renal failure				
(Lai et al. 2002) (Hong Kong)	RCT (hospital -1 center)		Peptic ulcers and on low dose aspirin	Inclusion: - peptic ulcer at least 5 mm in diameter - on low dose aspirin for at least 1 month before complications - had disease such as stroke or heart disease, that required long term aspirin treatment -18-80 years -positive for H pylori infection Exclusion: - esophagitis revealed by endoscopy - history of gastric or duodenal surgery other than oversewing of a perforation - allergy to study drugs - concomitant treatment with NSAIDS, corticosteroids, anticoagulants - active cancer - H Pylori infection that could not be eradicated after two attempts	123 (PPI (lansoprazole): 62; No PPI: 61)	PPI: 72 (8) no PPI: 69 (8)	PPI: 75 no PPI: 69	Not reported
(Scheiman et al 2011) [Multinational -20 countries]	RCT (multicenter)	OBERON NCT00441727	Cardiovascular disease at high risk for ulcers	Inclusion: - prescribed low dose aspirin daily - helicobacter pylori negative - 18 or older with documented history of uncomplicated peptic ulcer; 60 or older with specific risk factors	2,426; PPI (esomeprazole 40 mg): 817; PPI	Esomeprazole 40 mg: 67.7 (range: 21-87);	Esomeprazole 40 mg: 53.5%; Esomeprazole 20 mg: 53.4%;	> 80% white

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection Criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
				Exclusion: - Cardiovascular exclusion criteria: unstable hypertension; recent ACS, PCI, CABG, clinically relevant valvular disease, serious cardiac failure and stroke. - Gastrointestinal exclusion criteria: Los Angeles grade C or D erosive (reflux) oesophagitis at baseline; patient-reported severe oesophagitis within 1 year; peptic ulcer at baseline; history of peptic ulcer complications (eg, clinically significant bleeding and/or perforation) and previous gastric or duodenal surgery (patients who had undergone laparoscopic fundoplication were eligible). - Other exclusion criteria	(esomeprazole 20 mg): 804; Placebo: 805;	Esomeprazole 20 mg: 67.7 (range: 24-89); Placebo: 67.4 (range: 24-94);	Placebo: 50.1%	
(Sofia et al. 2000) (Portugal)	RCT (hospital -1 center)		UGIB	Inclusion: - UGIB, endoscoped within 24 hours of admission - Peptic ulcer with active bleeding, a non-bleeding visible vessel or an adherent fresh clot	208 (PPI (omeprazole): 40; No PPI: 44)	PPI: 59 (17) no PPI: 65 (15)	PPI: 66 no PPI: 57	Not reported
(Sugano et al. 2014) (Japan, Korea and Taiwan)	RCT (hospitals)	LAVENDER study (Low-dose Aspirin-related ulcer recurrence preVENtion unDER esomeprazole) ; NCT01069939	CVD and peptic ulcers	Inclusion: - 20+ years - medical history of peptic ulcer - ulcer scarring or clear evidence of open ulcer according confirmed by endoscopy -thrombotic condition (MI, cerebrovascular disease, etc., taking ASA for) - non-lactating and negative pregnancy test (for women)	430 (PPI (esomeprazole):215; No PPI: 215)	PPI: 66 (10) no PPI: 68 (9)	80	Asian

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection Criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
				Exclusion: - active ulcer at enrolment (confirmed by endoscopy) - history of GI surgery - current or past evidence of GI disorder or gastric outlet obstruction - malignancy - severe disease - uncontrolled diabetes - unstable hypertension - pancreatitis - severe pulmonary disease - scarring related to other conditions or endoscopic therapy, such as endoscopic mucosal resection or endoscopic submucosal dissection				
(Whellan et al. 2014) (USA)	RCT (hospitals (78 centers))	NCT00960869 and NCT00961350	CVD or CVA disease/ high risk for gastric ulcers	Inclusion: - established CV or cerebrovascular disease - taking ASA from 6 months or more - at risk for ASA associated gastric ulcerations (either 55+ years, or 18-45 years with documented history peptic ulcer in the 5 years before study entry Exclusion: -ulcer 3mm or more3 with depth at screening/baseline endoscopy -positive H pylori at screening -history of serious UGI event/disorder -surgery leading to impaired drug absorption -recent coronary revascularization	1,049 (PPI: 524; No PPI: 525)	PPI 66; No PPI: 66	PPI: 72 no PPI:71	Caucasian, Asian, African American, Other (90% Caucasian)

Citation (Location)	Study design (Setting)	Database/cohort name or NCT identifier	Patient population	Selection Criteria	Study sample size	Mean age (years) (sd)	% Males	Ethnicity
(Yeomans et al 2008) [10 countries]	RCT (78 centers)	NCT00251966; AstraZeneca study code: D9617C00011	60 or over and receiving low dose aspirin	Inclusion: - 60 or over -clinical diagnosis that requires low dose treatment with aspiring expected to continue for 26-weeks - negative for infection with H. pylori -no evidence of duodenal ulcer at baseline Exclusion: - erosive esophagitis (Grade B-D) at baseline - Barrett's esophagus -dysplastic changes in esophagus -other gastroduodenal pathology - unstable angina, MI, stroke, TIA in prior 3 months - upper GI symptoms requiring treatment - receiving specific medications - received a PPI, prostaglandin analogue, or H2RA during in the prior 14 days	991; Esomeprazole 493; Placebo: 498;	Esomeprazole: 69.5 (6.6); Placebo: 69.1 (6.5);	Esomeprazole; 56.8%; Placebo: 57.4%;	NR

[1] These two publications referred to the same study. Data was extracted from both papers.

TABLE S2- 6. CHARACTERISTICS OF THE EXPOSURE, OUTCOMES AND SOURCE OF FUNDING OF STUDIES THAT ASSESSED THE EFFECT OF CONCOMITANT TREATMENT OF PPIS AND OTHER DRUGS VS OTHER DRUGS ALONE (GROUP C).

Citation	PPI type assessed	Exposure groups compared	Exposure ascertainment	Outcome(s) of interest (follow-up period)	Outcome ascertainment	Calendar year(s) of sampling	Source of funding
Observational Studies							
(Charlot et al. 2011)	PPIs (general)	(PPI+aspirin) vs (aspirin)	Prescription claims database (date dispensed, type, quantity, dose, days of supply);	MI (1 year) Stroke (1 year) ACM (1 year) CVD mort (1 year)	National patient registry	1997-2006	Public/non profit
(Goodman et al. 2012)	PPIs (general)	(PPI+ ticagrelor) vs (ticagrelor)	Self-reported and assessment during follow up at 20, 60, 90 and 180 days.	MI (1 year) ACM (1 year) CVD mort (1 year)	Ascertained by an independent clinical events committee (blinded)	2006-2009	Other: No funding for the analyses; AstraZeneca funded PLATO trial.
(Kimura et al. 2011)	PPIs (general)	(PPI +ticlopidine) vs (ticlopidine) (90% of patients) (PPI+CP) vs (CP) (10% of patients) (all patients on aspirin)	Hospital charts or databases and from follow up forms.	MI (3 years) Stroke (3 years) ACM (3 years) CVD mort (3 years)	Hospital charts, referring physician or patient/relative contact; All outcomes were adjudicated by committee;	2005-2007	
(O'Donoghue et al. 2009)	PPIs (general)	(PPI+prasugrel) vs (prasugrel)	PPI exposure determined at study entry and at follow up	MI (400 days) ACM (400 days) CVD mort (400 days)	Independent committee (blinded)	2004-2007	None for this analysis; original trial funded by industry
(Yan et al 2016)	PPIs (general)	(PPI+ticagrelor) vs (ticagrelor)	Discharge records	ACM (1 year); MI (1 year);	Telephone or in person interviews; medical records	2003-2014	NR

Citation	PPI type assessed	Exposure groups compared	Exposure ascertainment	Outcome(s) of interest (follow-up period)	Outcome ascertainment	Calendar year(s) of sampling	Source of funding
Intervention studies							
(Angiolillo et al. 2014) and (Goldstein et al, 2010)	Esomeprazole	(PPI+naproxen) vs (naproxen)	Randomized to receive either EC naproxen + esomeprazole or EC naproxen;	MI (6 months) ACM (6 months)	NR	2007-2008	Industry
(F.K.L. et al. 2007)	Esomeprazole	(PPI+celecoxib) vs (celecoxib)	Randomized PPI exposure. (compliance assessed by pill counts)	Stroke: 13 months ACM : 13 months	Independent committee (blinded)	2002-2004	Public/non profit
(Lai et al. 2002)	Lansoprazole	(PPI+aspirin) vs (aspirin)	Randomized PPI exposure	ACM (median 1 year)	Follow up visits	1999-2001	Public/non profit
(Scheiman et al 2011)	Esomeprazole (40 mg and 20 mg once daily)	(PPI+ aspirin) vs (aspirin)	Adherence to esomeprazole was assessed during follow up visits; Adherence to aspirin was not assessed;	ACM (26 weeks)	Follow up visits	2007-2008	Industry
(Sofia et al. 2000)	Omeprazole	(PPI+ethanol) vs (ethanol)	Randomized PPI exposure	ACM (not clear)	NR	1994-1997	No statement
(Sugano et al. 2014)	Esomeprazole	(PPI+aspirin+gefarnate) vs (aspirin+gefarnate)	Randomized.	MI (72 weeks) ACM (72 weeks)	Not clear	2010-2012	Industry
(Whellan et al. 2014)	Omeprazole	(PPI+ aspirin) vs (aspirin)	Randomized.	MI (1,3, 6 months) Stroke (1,3, 6 months) CVD mort (1,3, 6 months)	Independent blinded committees;	2009-2012	Industry

Citation	PPI type assessed	Exposure groups compared	Exposure ascertainment	Outcome(s) of interest (follow-up period)	Outcome ascertainment	Calendar year(s) of sampling	Source of funding
(Yeomans et al 2008)	Esomeprazole (20 mg once daily)	(PPI+ aspirin) vs (aspirin)	Follow up visits and inspection of medication containers	ACM (26 weeks); MI (26 weeks);	Not reported	2004-2005	Industry

SUPPLEMENTAL MATERIAL V - REASONS FOR EXCLUSION OF STUDIES FROM META-ANALYSIS

The studies listed in the following table were included in the systematic review but excluded from the meta-analysis. Reasons for exclusion are presented by study and outcome.

TABLE S2- 7. REASONS FOR EXCLUSION OF STUDIES FROM THE META-ANALYSES.

Study	Outcome	Reason
Group A – observational studies		
(Antunes et al. 2016)	All-cause mortality	Abstract only; full text not found.
(Bang el al, 2018	All-cause mortality	Abstract only; full text not found.
(Bell et al, 2017)	Stroke	Abstract only; full text not found.
(Bettinger et al, 2018)	In hospital mortality	Patient population (pyogenic liver disease patients) cannot be combined with other study populations for this outcome.
(Caffrey et al, 2016)	All-cause mortality	Abstract only; full text not found.
(Kwon et al. 2016)	All-cause mortality	Abstract only; full text not found.
(de Francisco el al. 2018)	Cardiovascular mortality	Patient population (hemodialysis patients) cannot be combined with other study populations for this outcome.
(Taha et al. 2013)	All-cause mortality	Abstract only; full text not found.
(Lee et al. 2015)	All-cause mortality	Patient population (COPD patients) cannot be combined with other study populations.
(Maggio et al. 2013)	All-cause mortality	Patient population (elderly) cannot be combined with other study populations.
(Chen et al. 2014)	All-cause mortality	Patient population (ESRD patients) cannot be combined with other study populations.
(Im et al. 2014)	All-cause mortality	Patient population (PEG patients) cannot be combined with other study populations.
(Myles et al. 2009)	All-cause mortality	Patient population (pneumonia patients) cannot be combined with other study populations.
(Shih et al. 2014)	All-cause mortality	Patient population (PPI users) cannot be combined with other study populations.
(Sehested et al, 2018)	Stroke	Patient population (UGIB) cannot be combined with other study populations.
(Charlot et al. 2010)	Cardiovascular mortality	Patient population (MI patients) cannot be combined with other study populations.
(Arana et al. 2015)	Cardiovascular mortality	Patient population (patients on PPIs, domperidone or metoclopramide) cannot be combined with other study populations.
(Shah et al. 2015)	Cardiovascular mortality	Patient population (patients with shortness of breath or abnormal stress test) cannot be combined with other study populations.
(Chen et al. 2014)	Myocardial infarction	Patient population (ESRD patients) cannot be combined with other study populations.
Group A – RCTs		
(Liu et al. 2013)	Myocardial infarction	Patient population (Intracerebral hemorrhage patients) cannot be combined with other study populations.

(Leung et al 2018)	All-cause mortality	Patient population (patients undergoing ERCP sphincterotomy) cannot be combined with other study populations.
(Nikcevic et al. 2011)	Myocardial infarction	Abstract only; full text not found.
(Gao et al. 2009)	Myocardial infarction	Patient population (MI patients) cannot be combined with other study populations.
(Wei et al. 2007)	Myocardial infarction	No deaths in either group
(Hasselgren et al. 1997)	Stroke	The only Group A RCT for this outcome.
Group B –observational studies		
(Sweeny et al. 2009)	All-cause mortality	Abstract only; full text not found.
(Kim et al. 2014)	All-cause mortality	Abstract only; full text not found.
Groub B – RCTs		
(Bhatt et al. 2010)	All-cause mortality	Patient population (ACS patients) cannot be combined with other study populations.
(Wu et al. 2011)	All-cause mortality	Patient population (ACS and high risk for UGIB) cannot be combined with other study populations.
(Bhatt et al. 2010)	Cardiovascular mortality	Patient population (ACS patients) cannot be combined with other study populations.
(Hsu et al. 2011)	Cardiovascular mortality	Patient population (atherosclerosis patients with peptic ulcer history) cannot be combined with other study populations.
(Bhatt et al. 2010)	Stroke	Patient population (ACS patients) cannot be combined with other study populations.
(Hsu et al. 2011)	Stroke	Patient population (atherosclerosis patients with peptic ulcer history) cannot be combined with other study populations.
Group C – observational studies		
(Charlot et al. 2011)	All-cause mortality, myocardial infarction and cardiovascular mortality	Different interventions across studies.
(O'Donoghue et al. 2009)	All-cause mortality, myocardial infarction and cardiovascular mortality	Different interventions across studies.
(Charlot et al. 2011)	Stroke	The only observational study in Group C for this outcome.
Group C – RCTs		
(Angiolillo et al. 2014) and (Goldstein et al, 2010)	All-cause mortality and myocardial infarction	Different interventions across studies.
(Chan et al. 2007)	All-cause mortality and stroke	Different interventions across studies.
(Sofia et al. 2000)	All-cause mortality	Different interventions across studies.
(Sugano et al. 2014)	All-cause mortality	Different interventions across studies.
(Angiolillo et al. 2014) and (Goldstein et al, 2010)	All-cause mortality	Different interventions across studies.
(Sofia et al. 2000)	All-cause mortality	Different interventions across studies.
(Whellan et al. 2014)	Cardiovascular mortality and stroke	The only RCT in Group C for this outcome
(Angiolillo et al. 2014) and (Goldstein et al, 2010)	Myocardial infarction	Different interventions across studies.
(Sugano et al. 2014)	Myocardial infarction	Different interventions across studies.

SUPPLEMENTAL MATERIAL VI - GROUP B SUBGROUP AND SENSITIVITY ANALYSES

TABLE S2- 8. SUBGROUP ANALYSIS BY PPI ASSESSED AMONG GROUP B STUDIES THAT EVALUATED THE EFFECT OF CONCOMITANT CLOPIDOGREL/PPI TREATMENT ON MYOCARDIAL INFARCTION. THE NUMBER OF STUDIES POOLED FOR EACH OUTCOME IS REPRESENTED BY "N".

PPI type	Risk Ratio for MI (95% CI)	Number of studies pooled
Omeprazole	0.97 (0.76-1.22)	*n=3*
Esomeprazole	1.18 (0.83-1.68)	*n=2*
Pantoprazole	1.18 (0.72-1.95)	*n=3*
Overall	1.03 (0.88-1.20)	

Study or Subgroup	PPI Events	PPI Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Fixed, 95% CI
12.1.1 nonprofit/public/no funding						
Hung et al, 2007	0	103	1	50	0.8%	0.16 [0.01, 3.98]
Kantorova et al, 2004	14	72	13	75	11.4%	1.15 [0.50, 2.65]
Kaviani et al, 2003	0	71	1	78	0.8%	0.36 [0.01, 9.01]
Khuroo et al, 1997	2	110	6	110	3.0%	0.32 [0.06, 1.63]
Lau et al, 2000	5	120	12	120	6.9%	0.39 [0.13, 1.15]
Lau et al, 2007	8	314	7	317	7.6%	1.16 [0.41, 3.23]
Subtotal (95% CI)		**790**		**750**	**30.5%**	**0.73 [0.44, 1.23]**
Total events	29		40			
Heterogeneity: Chi² = 5.23, df = 5 (P = 0.39); I² = 4%						
Test for overall effect: Z = 1.18 (P = 0.24)						
12.1.2 Industry						
Daneshmend et al, 1992	40	578	30	569	33.5%	1.34 [0.82, 2.18]
Hasselgren et al, 1997	11	159	10	163	10.2%	1.14 [0.47, 2.76]
Hawkey et al, 2001	5	102	2	103	2.9%	2.60 [0.49, 13.74]
Kuipers et al, 2011	3	375	8	389	4.5%	0.38 [0.10, 1.46]
Sung et al, 2009	3	375	8	389	4.5%	0.38 [0.10, 1.46]
Subtotal (95% CI)		**1589**		**1613**	**55.5%**	**1.10 [0.75, 1.60]**
Total events	62		58			
Heterogeneity: Chi² = 6.42, df = 4 (P = 0.17); I² = 38%						
Test for overall effect: Z = 0.48 (P = 0.63)						
12.1.3 Not reported						
Javid et al, 2001	1	82	2	84	1.4%	0.51 [0.05, 5.69]
Schaffalitzky de Muckadell et al, 1997	10	130	11	135	10.0%	0.94 [0.38, 2.29]
Wei et al, 2006	0	35	0	35		Not estimable
Zargar et al, 2006	2	102	4	101	2.7%	0.48 [0.09, 2.71]
Subtotal (95% CI)		**349**		**355**	**14.1%**	**0.78 [0.37, 1.66]**
Total events	13		17			
Heterogeneity: Chi² = 0.58, df = 2 (P = 0.75); I² = 0%						
Test for overall effect: Z = 0.65 (P = 0.52)						
Total (95% CI)		**2728**		**2718**	**100.0%**	**0.93 [0.70, 1.23]**
Total events	104		115			
Heterogeneity: Chi² = 14.00, df = 13 (P = 0.37); I² = 7%						
Test for overall effect: Z = 0.54 (P = 0.59)						
Test for subgroup differences: Chi² = 1.76, df = 2 (P = 0.41), I² = 0%						

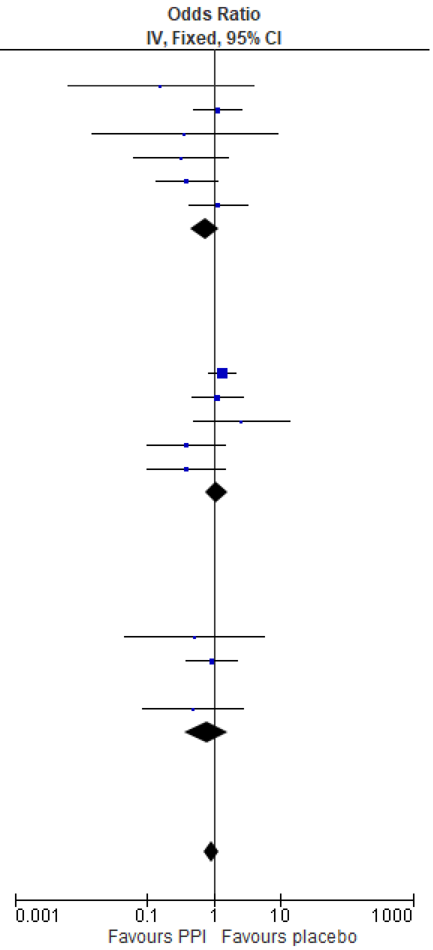
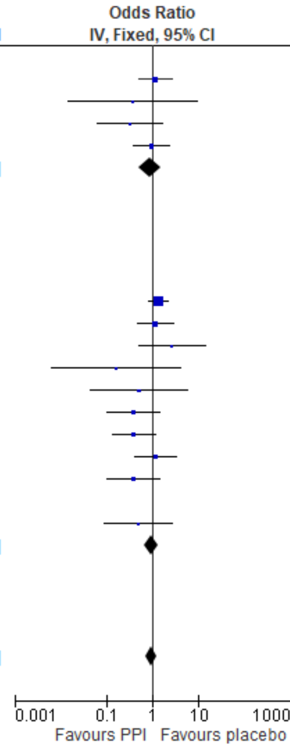


FIGURE S2- 1. SENSITIVITY ANALYSES BY SOURCE OF FUNDING FOR GROUP A RCTS THAT ASSESSED THE ASSOCIATION BETWEEN PPI USE VS NONUSE WITH ACM AMONG UGIB PATIENTS.

Study or Subgroup	PPI Events	PPI Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Fixed, 95% CI	A	B	C	D	E	F	G
12.2.1 No domains with high risk													
Kantorova et al, 2004	14	72	13	75	11.4%	1.15 [0.50, 2.65]	+	+	+	+	?	+	
Kaviani et al, 2003	0	71	1	78	0.8%	0.36 [0.01, 9.01]	+	+	+	+	?	?	
Khuroo et al, 1997	2	110	6	110	3.0%	0.32 [0.06, 1.63]	+	+	+	+	?	+	
Schaffalitzky de Muckadell et al, 1997	10	130	11	135	10.0%	0.94 [0.38, 2.29]	+	+	+	+	+	+	?
Subtotal (95% CI)		**383**		**398**	**25.2%**	**0.88 [0.50, 1.54]**							
Total events	26		31										
Heterogeneity: Chi² = 2.20, df = 3 (P = 0.53); I² = 0%													
Test for overall effect: Z = 0.45 (P = 0.65)													
12.2.2 1 or more domains with high risk													
Daneshmend et al, 1992	40	578	30	569	33.5%	1.34 [0.82, 2.18]	+	?	+	+	+	+	−
Hasselgren et al, 1997	11	159	10	163	10.2%	1.14 [0.47, 2.76]	+	+	+	?	+	+	−
Hawkey et al, 2001	5	102	2	103	2.9%	2.60 [0.49, 13.74]	?	?	+	+	+	+	−
Hung et al, 2007	0	103	1	50	0.8%	0.16 [0.01, 3.98]	+	?	−	−	?	?	−
Javid et al, 2001	1	82	2	84	1.4%	0.51 [0.05, 5.69]	+	+	+	+	+	−	−
Kuipers et al, 2011	3	375	8	389	4.5%	0.38 [0.10, 1.46]	?	?	+	+	?	+	−
Lau et al, 2000	5	120	12	120	6.9%	0.39 [0.13, 1.15]	+	+	+	+	+	−	
Lau et al, 2007	8	314	7	317	7.6%	1.16 [0.41, 3.23]	+	+	+	+	+	+	−
Sung et al, 2009	3	375	8	389	4.5%	0.38 [0.10, 1.46]	+	+	+	+	+	+	−
Wei et al, 2006	0	35	0	35		Not estimable							
Zargar et al, 2006	2	102	4	101	2.7%	0.48 [0.09, 2.71]	+	?	+	+	−	?	?
Subtotal (95% CI)		**2345**		**2320**	**74.8%**	**0.94 [0.68, 1.31]**							
Total events	78		84										
Heterogeneity: Chi² = 11.76, df = 9 (P = 0.23); I² = 23%													
Test for overall effect: Z = 0.36 (P = 0.72)													
Total (95% CI)		**2728**		**2718**	**100.0%**	**0.93 [0.70, 1.23]**							
Total events	104		115										
Heterogeneity: Chi² = 14.00, df = 13 (P = 0.37); I² = 7%													
Test for overall effect: Z = 0.54 (P = 0.59)													
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), I² = 0%													



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

FIGURE S2- 2. SENSITIVITY ANALYSES BY RISK OF BIAS IN GROUP A RCTS THAT ASSESSED THE ASSOCIATION BETWEEN PPI USE VS NONUSE WITH ACM AMONG UGIB PATIENTS.

TABLE S2- 9. SENSITIVITY ANALYSES ASSESSING THE EFFECT OF STUDY FUNDING SOURCE ON THE POOLED EFFECT ESTIMATES AMONG GROUP B OBSERVATIONAL STUDIES. N REPRESENTS THE NUMBER OF STUDIES POOLED FOR EACH OUTCOME.

	Risk Ratio (95% CI)							
Variable	All-cause mortality		Myocardial infarction		Cardiovascular mortality		Stroke	
Funding source								
Public/non-profit	1.21 (1.02-1.43)	*(n=16)*	1.20 (1.03-1.39)	*(n=13)*	1.17 (0.93-1.48)	*(n=8)*	1.34 (1.18-1.53)	*(n=4)*
Industry	1.44 (0.86-2.43)	*(n=2)*	1.59 (1.28-1.97)	*(n=4)*	1.10 (0.51-2.37)	*(n=1)*	0.98 (0.69-1.38)	*(n=2)*
Not reported	1.18 (1.02-1.37)	*(n=7)*	1.06 (0.83-1.36)	*(n=6)*	1.00 (0.50-2.00)	*(n=1)*	1.21 (0.48-3.05)	*(n=1)*
Overall	**1.23 (1.08-1.41)**		**1.22 (1.07-1.38)**		**1.16 (0.94-1.43)**		**1.29 (1.15-1.46)**	

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
3.1.1 Omeprazole				
Bhatt et al, 2010	-0.0834	0.3763	4.3%	0.92 [0.44, 1.92]
O'Donoghue et al, 2009	-0.0513	0.1344	33.7%	0.95 [0.73, 1.24]
Simon et al, 2016	0.1655	0.3895	4.0%	1.18 [0.55, 2.53]
Subtotal (95% CI)			**42.0%**	**0.97 [0.76, 1.22]**
Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 2 (P = 0.86); I² = 0%				
Test for overall effect: Z = 0.28 (P = 0.78)				
3.1.2 Esomeprazole				
O'Donoghue et al, 2009	0.1655	0.192	16.5%	1.18 [0.81, 1.72]
Simon et al, 2016	0.1823	0.5119	2.3%	1.20 [0.44, 3.27]
Subtotal (95% CI)			**18.8%**	**1.18 [0.83, 1.68]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%				
Test for overall effect: Z = 0.93 (P = 0.35)				
3.1.3 Pantoprazole				
O'Donoghue et al, 2009	-0.0305	0.1312	35.4%	0.97 [0.75, 1.25]
Simon et al, 2016	0.1989	0.7888	1.0%	1.22 [0.26, 5.73]
Stockl et al, 2010	0.7793	0.4628	2.8%	2.18 [0.88, 5.40]
Subtotal (95% CI)			**39.2%**	**1.18 [0.72, 1.95]**
Heterogeneity: Tau² = 0.08; Chi² = 2.88, df = 2 (P = 0.24); I² = 31%				
Test for overall effect: Z = 0.67 (P = 0.50)				
Total (95% CI)			**100.0%**	**1.03 [0.88, 1.20]**
Heterogeneity: Tau² = 0.00; Chi² = 4.04, df = 7 (P = 0.77); I² = 0%				
Test for overall effect: Z = 0.39 (P = 0.69)				
Test for subgroup differences: Chi² = 1.13, df = 2 (P = 0.57), I² = 0%				

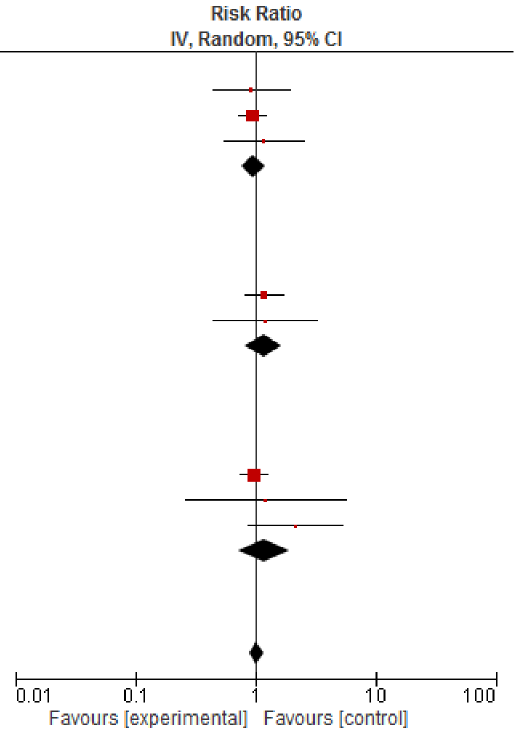


FIGURE S2- 3. SENSITIVITY ANALYSES BY TYPE OF PPI FOR GROUP B OBSERVATIONAL STUDIES THAT ASSESSED THE ASSOCIATION BETWEEN PPI USE VS NONUSE AND MI AMONG CLOPIDOGREL USERS.

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
13.1.1 Nonprofit/public/ no funding				
Banerjee et al, 2011	0.2927	0.3461	2.5%	1.34 [0.68, 2.64]
Charlot et al, 2010	0.7372	0.0706	6.2%	2.09 [1.82, 2.40]
Ching et al, 2012	0.5822	0.282	3.1%	1.79 [1.03, 3.11]
Douglas et al, 2012	0.3365	0.0418	6.5%	1.40 [1.29, 1.52]
Gargiulo et al, 2016	0.0862	0.184	4.5%	1.09 [0.76, 1.56]
Goodman et al, 2012	0.4055	0.1054	5.7%	1.50 [1.22, 1.84]
Harjai et al, 2011	-0.0513	0.2697	3.3%	0.95 [0.56, 1.61]
Ho et al, 2009	-0.0943	0.0657	6.2%	0.91 [0.80, 1.04]
Huang et al, 2010	0.5008	0.1024	5.8%	1.65 [1.35, 2.02]
Juurlink et al, 2009	-0.1165	0.1449	5.1%	0.89 [0.67, 1.18]
Ortolani et al, 2012	-0.3711	0.2782	3.2%	0.69 [0.40, 1.19]
O'Donoghue et al, 2009	-0.3857	0.1885	4.4%	0.68 [0.47, 0.98]
Rassen et al, 2009	0.1823	0.182	4.5%	1.20 [0.84, 1.71]
Sweeney et al, 2009	0.2624	0.1041	5.8%	1.30 [1.06, 1.59]
Tentzeris et al, 2010	-0.2485	0.4237	1.9%	0.78 [0.34, 1.79]
Wang et al, 2014	0.6313	0.5041	1.4%	1.88 [0.70, 5.05]
Subtotal (95% CI)			**70.1%**	**1.21 [1.02, 1.43]**
Heterogeneity: Tau² = 0.08; Chi² = 113.77, df = 15 (P < 0.00001); I² = 87%				
Test for overall effect: Z = 2.15 (P = 0.03)				
13.1.2 Industry				
Simon et al, 2016	0.0392	0.2722	3.2%	1.04 [0.61, 1.77]
van Boxel et al, 2010	0.5822	0.111	5.6%	1.79 [1.44, 2.22]
Subtotal (95% CI)			**8.9%**	**1.44 [0.86, 2.43]**
Heterogeneity: Tau² = 0.10; Chi² = 3.41, df = 1 (P = 0.06); I² = 71%				
Test for overall effect: Z = 1.38 (P = 0.17)				
13.1.4 Not reported				
Aihara et al, 2012	-0.1165	0.348	2.4%	0.89 [0.45, 1.76]
Gaspar et al, 2010	0.0392	0.384	2.2%	1.04 [0.49, 2.21]
Gupta et al, 2010	0.1823	0.4169	1.9%	1.20 [0.53, 2.72]
Rossini et al, 2011	-0.0305	0.6339	1.0%	0.97 [0.28, 3.36]
Sarafoff et al, 2010	0.7885	0.3537	2.4%	2.20 [1.10, 4.40]
Weisz et al, 2015	0.2469	0.126	5.4%	1.28 [1.00, 1.64]
Yan et al, 2016	0.0953	0.1081	5.7%	1.10 [0.89, 1.36]
Subtotal (95% CI)			**21.0%**	**1.18 [1.02, 1.37]**
Heterogeneity: Tau² = 0.00; Chi² = 4.80, df = 6 (P = 0.57); I² = 0%				
Test for overall effect: Z = 2.26 (P = 0.02)				
Total (95% CI)			**100.0%**	**1.23 [1.08, 1.41]**
Heterogeneity: Tau² = 0.07; Chi² = 129.00, df = 24 (P < 0.00001); I² = 81%				
Test for overall effect: Z = 3.02 (P = 0.002)				
Test for subgroup differences: Chi² = 0.52, df = 2 (P = 0.77), I² = 0%				

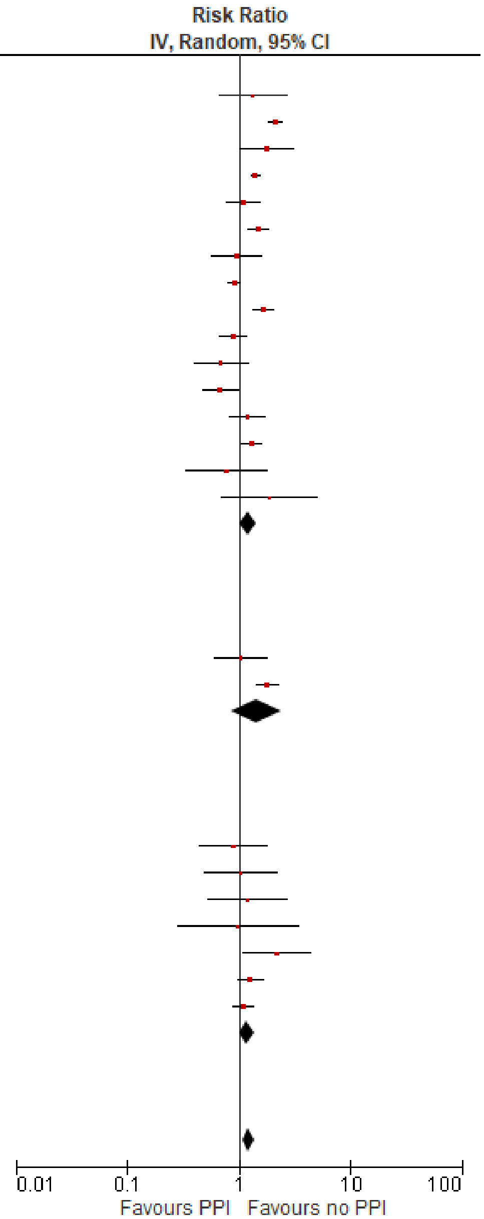


FIGURE S2- 4. SENSITIVITY ANALYSES BY TYPE SOURCE OF FUNDING FOR GROUP B OBSERVATIONAL STUDIES THAT ASSESSED THE ASSOCIATION BETWEEN PPI USE VS NONUSE AND ACM AMONG CLOPIDOGREL USERS.

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
13.2.1 Non profit/public/no funding				
Burkard et al, 2011	0.6313	0.2972	2.9%	1.88 [1.05, 3.37]
Charlot et al, 2010	0.1655	0.0644	6.7%	1.18 [1.04, 1.34]
Douglas et al, 2012	-0.2877	0.1582	5.1%	0.75 [0.55, 1.02]
Evanchan et al, 2009	0.5766	0.0706	6.6%	1.78 [1.55, 2.04]
Gargiulo et al, 2016	0.0583	0.2341	3.7%	1.06 [0.67, 1.68]
Goodman et al, 2012	0.1133	0.1116	5.9%	1.12 [0.90, 1.39]
Harjai et al, 2011	0.0392	0.2477	3.5%	1.04 [0.64, 1.69]
Juurlink et al, 2009	0.207	0.1005	6.1%	1.23 [1.01, 1.50]
Mahabaleshwarkar et al, 2013	-0.1625	0.1863	4.5%	0.85 [0.59, 1.22]
O'Donoghue et al, 2009	-0.0202	0.0909	6.3%	0.98 [0.82, 1.17]
Rassen et al, 2009	0.1989	0.1276	5.6%	1.22 [0.95, 1.57]
Valkhoff et al, 2010	0.4824	0.1748	4.7%	1.62 [1.15, 2.28]
Zou et al, 2014	0.5822	0.3623	2.2%	1.79 [0.88, 3.64]
Subtotal (95% CI)			**64.1%**	**1.20 [1.03, 1.39]**
Heterogeneity: Tau² = 0.05; Chi² = 54.85, df = 12 (P < 0.00001); I² = 78%				
Test for overall effect: Z = 2.29 (P = 0.02)				
13.2.2 Industry				
Bhatt et al, 2010	-0.0834	0.3763	2.1%	0.92 [0.44, 1.92]
Kreutz et al, 2010	0.4886	0.0776	6.5%	1.63 [1.40, 1.90]
Simon et al, 2016	0.1398	0.3581	2.3%	1.15 [0.57, 2.32]
van Boxel et al, 2010	0.6575	0.1638	5.0%	1.93 [1.40, 2.66]
Subtotal (95% CI)			**15.9%**	**1.59 [1.28, 1.97]**
Heterogeneity: Tau² = 0.02; Chi² = 4.32, df = 3 (P = 0.23); I² = 31%				
Test for overall effect: Z = 4.23 (P < 0.0001)				
13.2.3 Not reported				
Aihara et al, 2012	-0.3711	0.6318	0.9%	0.69 [0.20, 2.38]
Sarafoff et al, 2010	0.2624	0.2477	3.5%	1.30 [0.80, 2.11]
Stockl et al, 2010	0.6575	0.3106	2.7%	1.93 [1.05, 3.55]
Weisz et al, 2015	0.0296	0.1418	5.4%	1.03 [0.78, 1.36]
Yan et al, 2016	-0.1863	0.1017	6.1%	0.83 [0.68, 1.01]
Zairis et al, 2010	0.0953	0.5161	1.3%	1.10 [0.40, 3.02]
Subtotal (95% CI)			**20.0%**	**1.06 [0.83, 1.36]**
Heterogeneity: Tau² = 0.04; Chi² = 9.18, df = 5 (P = 0.10); I² = 46%				
Test for overall effect: Z = 0.47 (P = 0.64)				
Total (95% CI)			**100.0%**	**1.22 [1.07, 1.38]**
Heterogeneity: Tau² = 0.06; Chi² = 95.32, df = 22 (P < 0.00001); I² = 77%				
Test for overall effect: Z = 2.99 (P = 0.003)				
Test for subgroup differences: Chi² = 6.76, df = 2 (P = 0.03), I² = 70.4%				

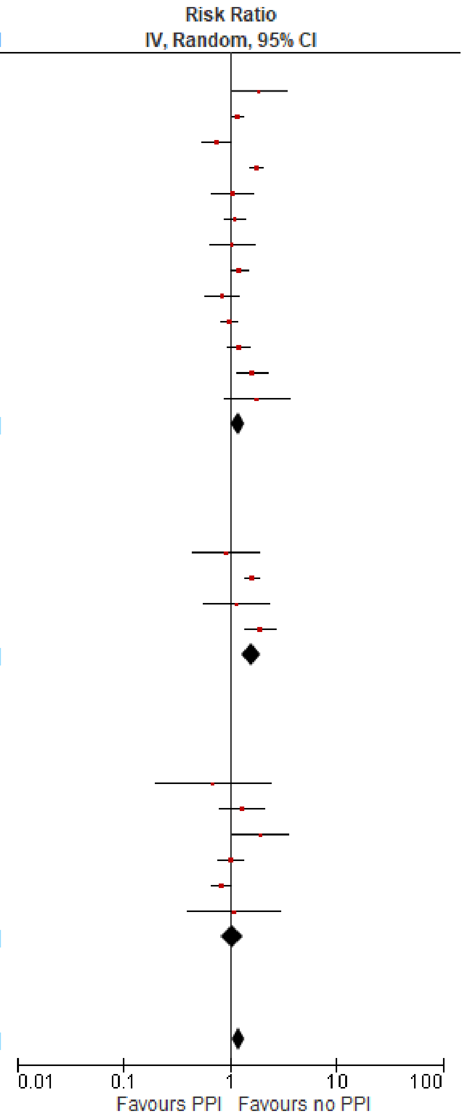


FIGURE S2- 5. SENSITIVITY ANALYSES BY SOURCE OF STUDY FUNDING FOR GROUP B OBSERVATIONAL STUDIES THAT ASSESSED THE ASSOCIATION BETWEEN PPI USE VS NONUSE AND MI AMONG CLOPIDOGREL USERS.

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
13.4.1 Public/non profit/no funding				
Charlot et al, 2010	0.6471	0.0809	15.8%	1.91 [1.63, 2.24]
Douglas et al, 2012	0.2231	0.056	16.6%	1.25 [1.12, 1.39]
Gargiulo et al, 2016	0.1398	0.2461	9.1%	1.15 [0.71, 1.86]
Goodman et al, 2012	0.3507	0.1121	14.6%	1.42 [1.14, 1.77]
O'Donoghue et al, 2009	-0.3425	0.2105	10.4%	0.71 [0.47, 1.07]
Ray et al, 2010	0.0583	0.2495	9.0%	1.06 [0.65, 1.73]
Tentzeris et al, 2010	-0.5745	0.5155	3.5%	0.56 [0.20, 1.55]
Zou et al, 2014	-0.0834	0.2267	9.8%	0.92 [0.59, 1.43]
Subtotal (95% CI)			**88.8%**	**1.17 [0.93, 1.48]**
Heterogeneity: Tau² = 0.07; Chi² = 36.91, df = 7 (P < 0.00001); I² = 81%				
Test for overall effect: Z = 1.36 (P = 0.17)				
13.4.2 Industry				
Kreutz et al, 2010	0.0953	0.3922	5.2%	1.10 [0.51, 2.37]
Subtotal (95% CI)			**5.2%**	**1.10 [0.51, 2.37]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.24 (P = 0.81)				
13.4.3 Not reported				
Zairis et al, 2010	0	0.3537	6.0%	1.00 [0.50, 2.00]
Subtotal (95% CI)			**6.0%**	**1.00 [0.50, 2.00]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.00 (P = 1.00)				
Total (95% CI)			**100.0%**	**1.16 [0.94, 1.43]**
Heterogeneity: Tau² = 0.07; Chi² = 37.89, df = 9 (P < 0.0001); I² = 76%				
Test for overall effect: Z = 1.40 (P = 0.16)				
Test for subgroup differences: Chi² = 0.20, df = 2 (P = 0.91), I² = 0%				

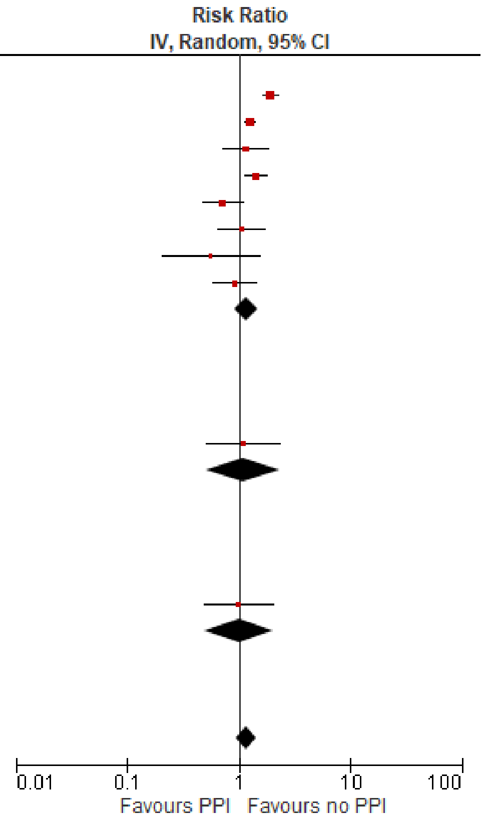


FIGURE S2- 6. SENSITIVITY ANALYSES BY SOURCE OF STUDY FUNDING FOR GROUP B OBSERVATIONAL STUDIES THAT ASSESSED THE ASSOCIATION BETWEEN PPI USE VS NONUSE AND CARDIOVASCULAR MORTALITY AMONG CLOPIDOGREL USERS.

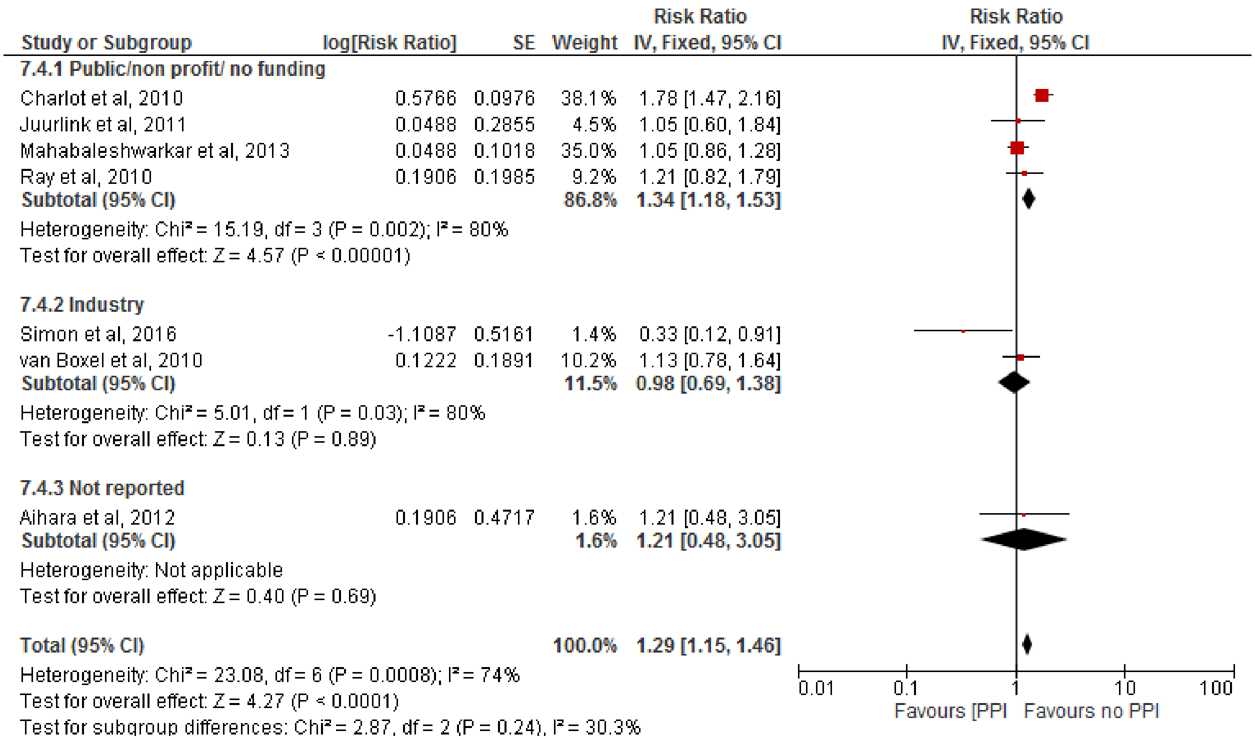


FIGURE S2- 7. SENSITIVITY ANALYSES BY SOURCE OF STUDY FUNDING FOR GROUP B OBSERVATIONAL STUDIES THAT ASSESSED THE ASSOCIATION BETWEEN PPI USE VS NONUSE AND STROKE AMONG CLOPIDOGREL USERS.

SUPPLEMENTAL MATERIAL VII - QUALITY OF OBSERVATIONAL STUDIES INCLUDED IN THE META-ANALYSIS

TABLE S2- 10. NEWCASTLE-OTTAWA SCORES FOR OBSERVATIONAL STUDIES.

Study	Study design	Cohort selections	Outcomes	Comparability	Selection of cases /controls	Exposure
Aihara et al, 2012	Cohort	****	***	**		
Banerjee et al, 2011	Cohort	***	***	**		
Bettinger et al, 2018	Cohort	***	***	*		
Charlot et al, 2010	Cohort	****	***	**		
Charlot et al, 2010	Cohort	****	***	**		
Ching et al, 2012	Cohort	***	***	**		
Daskalopoulou et al, 2008	Cohort	****	**	**		
de Francisco et al, 2018	Cohort	****	**	*		
Douglas et al, 2012	Cohort	****	***	**		
Dultz et al, 2014	Cohort	****	**	**		
Evanchan et al, 2009	Cohort	***	**	**		
Gargiulo et al, 2016	Cohort	****	**	**		
Gaspar et al, 2010	Cohort	****	***	**		
Goodman et al, 2012	Cohort	****	***	**		
Gupta et al, 2010	Cohort	***	**	**		
Harjai et al, 2011	Cohort	****	***	**		
Ho et al, 2009	Cohort	****	**	***		
Huang et al, 2010	Cohort	****	**	**		
Kreutz et al, 2010	Cohort	****	***	**		
Kwon et al, 2013	Cohort	****	***			
Lei et al, 2017	Cohort	****	**	**		
Mandorfer et al, 2014	Cohort	****	**	**		
Nardelli et al, 2018	Cohort	****	*	*		
Nguyen et al, 2018	Cohort	****	**	***		
O'Donoghue et al, 2009	Cohort	***	**	**		

Ortolani et al, 2012	Cohort	****	***	**		
Oudit et al, 2011	Cohort	****	***	**		
Rassen et al, 2009	Cohort	****	***	**		
Ray et al, 2010	Cohort	****	***	**		
Rossini et al, 2011	Cohort	****	***			
Sarafoff et al, 2010	Cohort	****	**	**		
Sehested et al, 2018	Cohort	****	***	**		
Shih et al, 2014	Cohort	****	**	**		
Simon et al, 2016	Cohort	****	***	**		
Simon et al, 2016	Cohort	****	***	**		
Tentzeris et al, 2010	Cohort	****	***	**		
Teramura-Grönblad et al, 2012	Cohort	****	***	**		
van Boxel et al, 2010	Cohort	****	***	**		
Wang et al, 2014	Cohort	****	**	**		
Wang et al, 2017	Cohort	****	**	*		
Weisz et al, 2015	Cohort	****	***	**		
Yan et al, 2016	Cohort	****	*	**		
Zairis et al, 2010	Cohort	****	***			
Zou et al, 2014	Cohort	****	***	**		
Johansson et al, 2003	Case control			**	****	**
Juurlink et al, 2009	Case control			**	****	**
Juurlink et al, 2011	Case control			**	***	**
Juurlink et al, 2013	Case control			**	****	**
Mahabaleshwarkar et al, 2013	Case control			**	***	**
Turkiewicz et al, 2015	Case control			*	****	***
Valkhoff et al, 2010	Case control			**	***	**

2.6.2 SUPPLEMENTAL MATERIALS VIII - FINDINGS FROM OBSERVATIONAL STUDIES THAT REPORTED COUNTS/RATES OF EVENTS.

TABLE S2- 11. FINDINGS FROM OBSERVATIONAL STUDIES THAT REPORTED COUNTS/RATES OF EVENTS AMONG PPI USERS AND NON-USERS (WITH NO CONCOMITANT TREATMENT) (GROUP A). THESE FINDINGS WERE NOT INCLUDED IN THE META-ANALYSIS.

Citation	Patient population	Outcome (follow up)	Percentage of events or unadjusted effect estimates (95% CI) and number of patients (N) in each exposure group	Overall author conclusion on the PPI-outcome of interest association[1]
All-cause mortality				
(Freedberg et al. 2013)	CDI	ACM (90 days)	Within 90 days: PPI: 32% (N=551); no PPI: 25% (N=343); p-value: 0.03.	Higher mortality CDI patients exposed to PPIs.
(Gardezi et al. 2018)	Non-variceal bleeding	ACM (NR)	PPI: 9%; No PPI: 14%; p-value: 0.91;	No association between pre-endoscopy use of PPIs and mortality.
(Haider et al. 2012)	CDI	ACM (in-hospital, 6 months)	***Within 6 months of index CDI*** PPI: 36% (N=172); no PPI: 31% (N=358); p-value: 0.25; ***In hospital mortality*** PPI: 9% (N=172); no PPI: 1% (N=358); p-value: <0.0001	***Difference in mortality between groups not statistically significant within 6 months of index CDI, but statistically significant for in-hospital mortality.***
(Keyvani et al. 2006)	Acute non-variceal UGIB	ACM (in hospital)	PPI: 1.5% (N=132): no PPI: 3% (N=189); p-value: 0.04; *(PPI exposure pre-endoscopy)*	No difference in mortality between groups.
(van der Hoorn et al. 2015)	Elderly women	ACM (mean 6.6 years)	PPI: 20% (N=2,328); No PPI: 23% (N=2,104); p-value: 0.015;	***Difference in mortality is statistically significant between treatment groups.***
(Win et al. 2010)	UGIB	ACM (not clear)	PPI prior to admission: 3.63% (N=110); no PPI prior to admission: 9.12% (N=548); p-value 0.06; *(PPI exposure assessed in the 4 weeks prior to admission)*	***Difference in mortality is not statistically significantly among treatment groups.***
Cardiovascular mortality				
(Chitose et al. 2012)	PCI	CVD mort (18 months)	***All patients:*** PPI: 2% (N=331); no PPI: 1% (N=939); p-value: 0.43; ***ACS patients:*** PPI: 1% (N=171); no PPI: 2% (N=450); p-value: 0.44;	No increased risk of adverse events with PPI after PCI/stent implantation.
Myocardial infarction				
(Chitose et al. 2012)	PCI	MI (18 months)	***All patients:*** PPI: 1% (N=331) ; no PPI: 0.5% (N = 939); p-value 0.2 ***ACS patients:*** PPI: 1.1% (N=171); no PPI: 0.2% (N=450); p-value: 0	No increased risk of adverse events with PPI after PCI/stent implantation.
Stroke				
(Chitose et al. 2012)	PCI	Stroke (18 months)	***All patients:*** PPI: 1% (N=331); no PPI: 1.7% (N=939); p-value: 0.5; ***ACS patients:*** 1.2% (N=171); no PPI: 0.4% (N=450); p-value: 0.28;	No increased risk of adverse events with PPI after PCI/stent implantation.

[1] When the authors' conclusions regarding the association in question was missing, the reviewers arrived at a conclusion based on whether there was a statistically significant difference in the proportion of events between the treatment groups; these conclusions are bolded in this column.

TABLE S2- 12. FINDINGS FROM OBSERVATIONAL STUDIES THAT REPORTED COUNTS/RATES OF EVENTS OR UNADJUSTED RRS AMONG CONCOMITANT PPI/CLOPIDOGREL USERS AND PATIENTS ON CLOPIDOGREL ALONE (GROUP B). THESE FINDINGS WERE NOT INCLUDED IN THE META-ANALYSIS.

Citation	Patient population	Outcome (follow up)	Counts/rates of events or unadjusted effect estimates and number of patients (N) in each exposure group	Overall author conclusion on the PPI-outcome of interest association[1]
All-cause mortality				
(Burkard et al. 2012)	PCI	ACM (36 months)	*Clopidogrel and aspirin users* PPI: 9.2% (N=109); no PPI: 7.4% (N=692); p-value: 0.51	***No difference in deaths among groups. (not authors, authors not relevant to ACM)***.
(Depta et al. 2015)	ACS	ACM (1 year)	*Clopidogrel users* ***Caucasians:*** PPI: 2.9% (N= 307); no PPI: 3.8% (N=1,325); p-value=0.48; ***African Americans:*** PPI: 6.2% (N=65); no PPI: 7.4% (N=365); p-value=0.64;	No association between PPI use and all-cause mortality in either Caucasian or African American race or within each CYP2C19 genotype group.
(Galante et al. 2012)	PCI	ACM (not reported)	Unadjusted RR 1.0 (0.98-1.0); PPI: N=1273; no PPI: N=1295	No statistical difference in MACE risk in concomitant clopidogrel and PPI treatment vs clopidogrel only treatment.
(Gaglia et al. 2010)	PCI with DES	ACM (30 days, 1 year)	*Clopidogrel and aspirin users* ***30 days:*** PPI: 1% (N=318); no PPI: 0.2% (N=502); p-value 0.08; ***1 year:*** PPI 5% (N=318); no PPI: 2% (N=502); p-value 0.02;	Association between PPI/clopidogrel use and MACE and all-cause mortality at 1 year in PCI patients with DES.
(Hudzik et al. 2010)	Stent	ACM (1 year)	*Clopidogrel users* PPI: 0 (N=83); no PPI: 0 (N=65);	***No difference in deaths among groups.***
(Munoz-Torrero et al. 2011)	CAD, cerebrovascular or PAD	ACM (at least 1 year)	*Clopidogrel users* ***All patients:*** Unadjusted RR, 2.2 (1.3–3.7); p value 0.003; PPI: N=519, no PPI: N=703; ***CVD patients:*** Unadjusted RR, 1.6 (0.7–4.0), p-value 0.298; PPI: N=142 , no PPI: N=187; ***PAD patients:*** Unadjusted RR, 1.9 (0.8–4.9), p-value 0.142; PPI: N=130, no PPI:N=168; ***CAD patients***: Unadjusted RR, 3.2 (1.2–8.8); p-value 0.014; PPI: N=247, no PPI: N=348;	***Concomitant use of PPIs and clopidogrel is associated with increased mortality risk in CAD patients but not CVD or PAD patients***
(Wu et al. 2010)	ACS	ACM (3 months)	*Clopidogrel users* PPI: 11.4% (95% CI: 8-16%) (N=311); no PPI: 1.7% (95% CI: 1.4-2.1%) (N=5,551);	Concomitant PPI/clopidogrel treatment after hospital discharge for ACS increases risk of adverse MACE.
Cardiovascular mortality				
(Chitose et al. 2012)	PCI	CVD mort (18 months)	*Clopidogrel users* PPI: 2% (N=187); no PPI: 1% (N=443); p-value: 0.28;	No increased risk of adverse events with PPI after PCI/stent implantation.

Citation	Patient population	Outcome (follow up)	Counts/rates of events or unadjusted effect estimates and number of patients (N) in each exposure group	Overall author conclusion on the PPI-outcome of interest association[1]
(Hokimoto and Ogawa 2010)	On aspirin and clopidogrel	CVD mort (1 year)	*Clopidogrel and aspirin users* PPI: no deaths (N=37); no PPI: 2% (N=133); p-value: 0.38;	No significant difference in clinical outcomes between rabeprazole treated and non-rabeprazole group.
(Yi et al. 2018)	Stroke patients	MI (1 year)	*Clopidogrel users* PPI: 3/155 (1.9%); no PPI: 3/347 (0.9%); p-value: 0.32;	No association between PPI use and MACE among patients with a first time stroke.
Myocardial infarction				
(Bhurke et al. 2012)	ACS	MI (mean 268 days)	*Clopidogrel users* PPI: 6.4% (N=2,674); no PPI: 6.1% (N=2,674); p-value: 0.65;	Concomitant treatment associated with increased MI risk.
(Chitose et al. 2012)	PCI	MI (18 months)	*Clopidogrel users* PPI: 0.5% (N=187); no PPI: 0.7% (N=443); p-value 0.97;	No increased risk of adverse events with PPI after PCI/stent implantation.
(Gaglia et al. 2010)	PCI with DES	MI (in-hospital, 1 year)	*Clopidogrel and aspirin users* ***In hospital mortality:*** PPI: 0.3% (N=318); no PPI: 0.2% (N=502), p-value: 1; ***30-day:*** PPI: 0% (N=318); no PPI: 0.2% (N=502); p-value: 1.	***No difference in MI among groups.***
(Hokimoto and Ogawa 2010)	On aspirin and clopidogrel	MI (1 year)	*Clopidogrel and aspirin users* PPI: 0 (N=37); no PPI: 0 (N=133);	No significant difference in clinical outcomes between rabeprazole treated and non-rabeprazole group.
(Hudzik et al. 2010)	Stent	MI (1 year)	*Clopidogrel and aspirin users* PPI: 33.4% (N=18); no PPI: 5.0% (N=20) ; p-value = 0.03;	Possible association between concomitant CP/omeprazole treatment and MI after stent implantation.
(Munoz-Torrero et al. 2011)	CAD, cerebrovascular or PAD	MI (at least 1 year)	*Clopidogrel users* ***All patients:*** Unadjusted RR, 2.5 (1.3–4.8); N PPI 519, no PPI 703; ***CAD patients:*** Unadjusted RR, 3.4 (1.5–8.2); N, PPI 247, no PPI 348; ***PAD patients:*** Unadjusted RR, 0.9 (0.3–2.8), N PPI 130, no PPI 168;	Concomitant use of PPIs and clopidogrel is associated with an increased incidence MI and stroke in patients with established arterial disease.
(Ulhaq et al. 2011)	MI	MI (1 year)	Clopidogrel and aspirin users: PPI: 10.4% (N=96); no PPI: 2.3% (N=88); p-value: 0.025;	Possible association between PPI/clopidogrel treatments.
(Yi et al. 2018)	Stroke patients	MI (1 year)	*Clopidogrel users* PPI: 3/155 (1.9%); no PPI: 37/347 (1.2%); p-value 0.48;	No association between PPI use and MACE among patients with a first time stroke.

Citation	Patient population	Outcome (follow up)	Counts/rates of events or unadjusted effect estimates and number of patients (N) in each exposure group	Overall author conclusion on the PPI-outcome of interest association[1]
Stroke				
(Chitose et al. 2012)	PCI	Stroke (18 months)	*Clopidogrel users* PPI: 1% (N=187); no PPI: 2% (N=443); p-value: 0.6;	No increased risk of adverse events with PPI after PCI/stent implantation.
(Depta et al. 2015)	ACS	Stroke (1 year)	*Clopidogrel users* Unadjusted rates: PPI: 0% (N=372); no PPI: 0.1% (N=1690); p-value: 1;	PPI use was associated increased cardiac rehospitalisation and risk varied by genotype.
(Hokimoto and Ogawa 2010)	On aspirin and clopidogrel	Stroke (1 year)	*Clopidogrel and aspirin users* PPI (rabep): 3% (N=37); no PPI: 1% (N=133); p-value: 0.37;	No significant difference in clinical outcomes between rabeprazole treated and non-rabeprazole group.
(Hudzik et al. 2010)	Stent	Stroke (1 year)	*Clopidogrel and aspirin users* PPI: 11.1% (N=18); no PPI: 5.0% (N=20); p-value: 0.4;	No association between concomitant clopidogrel/omeprazole treatment and stroke after stent implantation.
(Munoz-Torrero et al. 2011)	CAD, cerebrovascular or PAD	Stroke (at least 1 year)	*Clopidogrel users* ***All patients:*** Unadjusted RR, 1.9 (1.03–3.7), PPI: N= 519, no PPI: N= 703 ***PAD patients:*** Unadjusted RR 10 (1.6–225), PPI: N=130, no PPI: N=168; ***CVD patients:*** Unadjusted RR 1.5 (0.7–3.3) , N PPI: N=142, no PPI: N=187; ***CAD patients:*** Unadjusted RR 1.3 (0.1–12), PPI: N=247, no PPI: N= 348;	Concomitant use of PPIs and clopidogrel is associated with an increased incidence of MI and stroke in patients with established arterial disease.
(Yi et al. 2018)	Stroke patients	MI (1 year)	*Clopidogrel users* PPI: 25/155 (12.3%); no PPI: 44/347 (10.7%); p-value 0.63;	No association between PPI use and MACE among patients with a first time stroke.

[1] When the authors' conclusions regarding the association in question was missing, the reviewers arrived at a conclusion based on whether there was a statistically significant difference in the proportion of events between the treatment groups; these conclusions are bolded in this column.

Table S2- 13. Findings from an observational study that reported counts/rates of events among PPI/ticlopidine users and users of ticlopidine alone (Group C). These findings were not included in the meta-analysis.

Citation/Outcome	Patient population	Outcome (follow up)	Counts/rates of events or unadjusted effect estimates and number of patients (N) in each exposure group	Overall author conclusion on the PPI-outcome of interest association
(Kimura et al. 2011)				
All-cause mortality	PCI	3 years	*Ticlopidine and aspirin users* PPI: 11.9%; no PPI: 6.4%; p-value: <0.0001	Possible association between PPI and MACE in the Japanese practice (antiplatelet therapy is ticlopidine and aspirin).
Cardiovascular mortality	PCI	3 years	*Ticlopidine and aspirin users* PPI: 5% (N=3,223); no PPI: 3% (N=9,223); p-value <0.0001; *(cardiac death)*	
Myocardial infarction	PCI	3 years	*Ticlopidine and aspirin users* PPI: 4.4% (N=3,223); no PPI: 3% (N=9,223); p-value: 0.0004;	
Stroke	PCI	3 years	*Ticlopidine and aspirin users* PPI: 4.5% (N=3,223); no PPI: 4.3% (N=9,223); p-value: 0.52	

SUPPLEMENTAL MATERIAL IX – FUNNEL PLOTS

The following funnel plots correspond to meta-analyses that included ten or more studies are presented below. These plots were visually evaluated for publication bias.

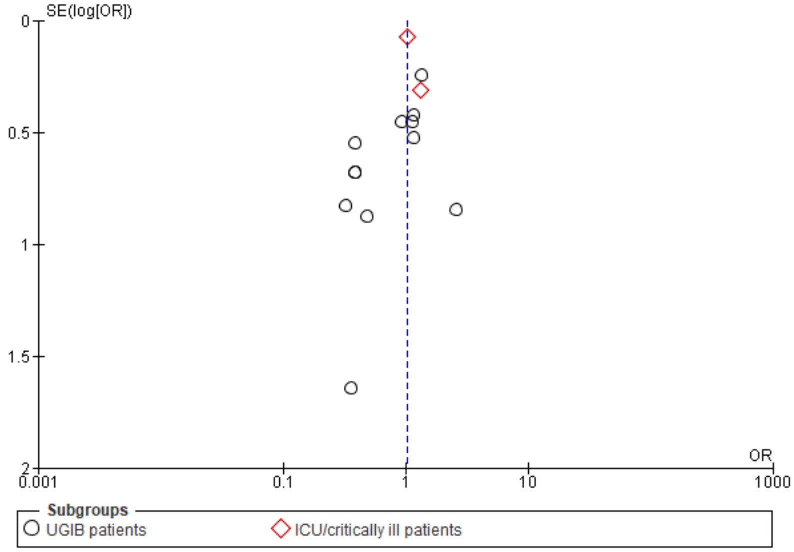


FIGURE S2- 8. FUNNEL PLOT FOR THE META-ANALYSIS OF ACM AMONG GROUP A RCTS.

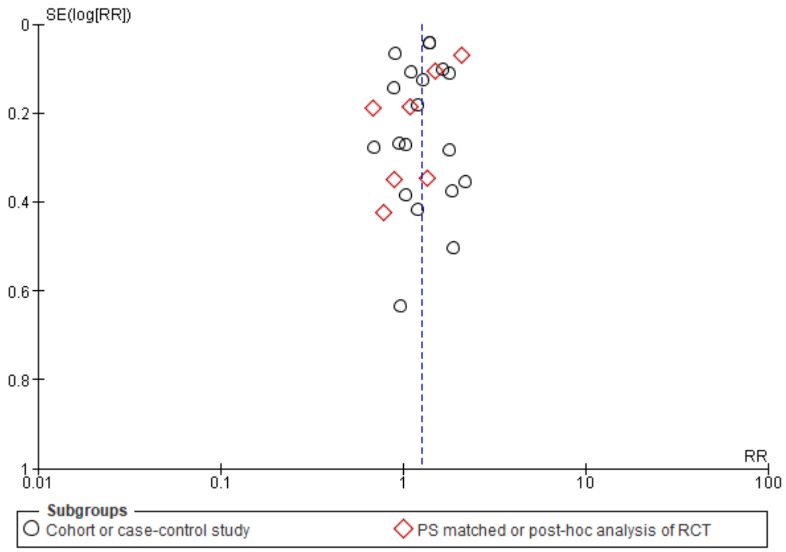


FIGURE S2- 9. FUNNEL PLOT FOR THE META-ANALYSIS OF ACM OUTCOME AMONG GROUP B OBSERVATIONAL STUDIES.

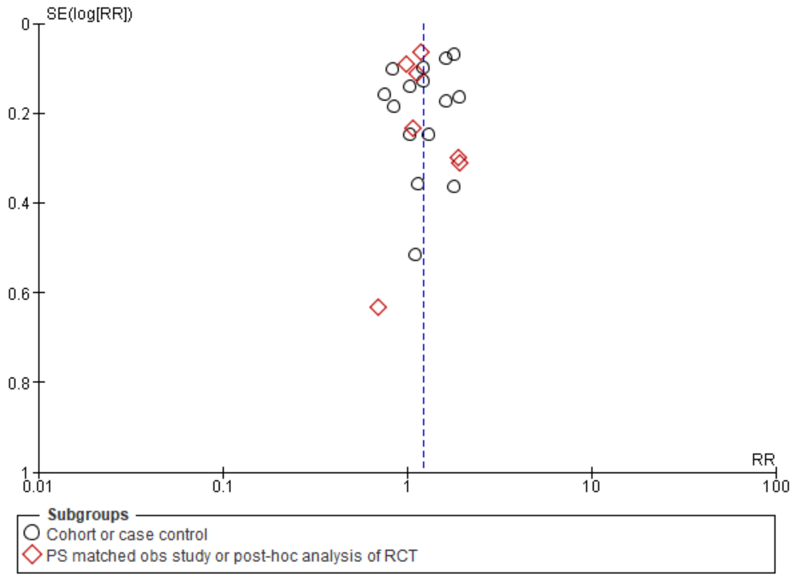


FIGURE S2- 10. FUNNEL PLOT FOR THE META-ANALYSIS OF MI OUTCOME AMONG GROUP B OBSERVATIONAL STUDIES.

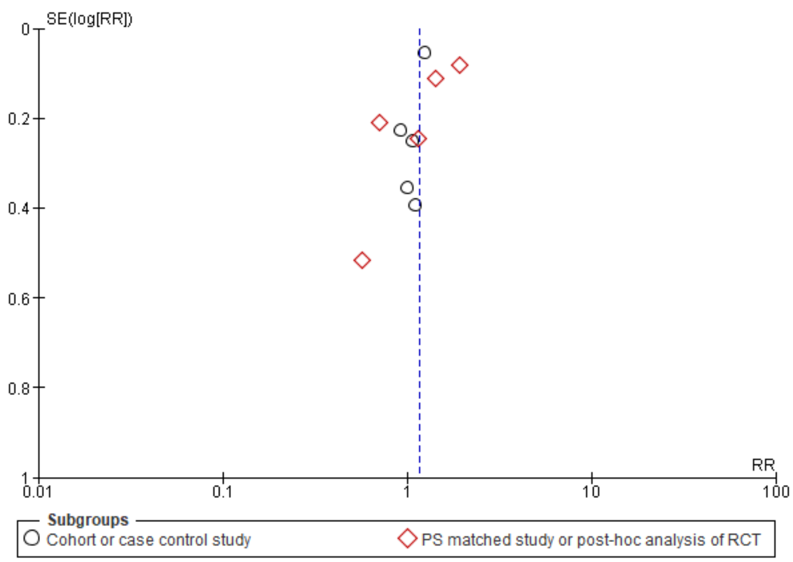


FIGURE S2- 11. FUNNEL PLOT FOR THE META-ANALYSIS OF CARDIOVASCULAR MORTALITY AMONG GROUP B OBSERVATIONAL STUDIES.

CHAPTER 3

TRENDS IN CONCOMITANT CLOPIDOGREL AND PROTON PUMP INHIBITOR TREATMENT AMONG ACS INPATIENTS, 2000-2016

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PREFACE

The current chapter consists of the second manuscript from this thesis. It directly addresses Objective 2 by examining the trends of concomitant treatment with clopidogrel and PPIs in response to the FDA warnings issued in 2009 and 2010. The study allowed us to observe the response to combined treatment in US inpatient settings, as well as to understand rates of concomitant treatment in recent years.

Contributions

For this study, I formulated the study design with guidance from my supervisors. I performed the analysis and wrote the first draft of the manuscript. My supervisors and thesis advisory committee provided feedback and suggestions on all aspects of the study design, statistical analyses, and interpretation of findings during our regular meetings. Ms Nisrine Haddad and Dr James Crispo both contributed to the analyses and interpretation of findings, and revisions of the manuscript. All coauthors were involved in providing suggestions on the draft manuscript.

Ethical approval for this study was obtained from the Ottawa Health Science Network Research Ethics Board at the Ottawa Hospital, Ottawa, Canada (Appendix A).

TRENDS IN CONCOMITANT CLOPIDOGREL AND PROTON PUMP INHIBITOR TREATMENT AMONG ACS INPATIENTS, 2000-2016

ABSTRACT

The US Food and Drug Administration (FDA) issued three safety announcements between January 2009 and October 2010 warning against concomitant use of clopidogrel and proton pump inhibitors (PPIs) due to a potential drug-drug interaction that may attenuate clopidogrel's antiplatelet activity. The primary objective of this study was to examine trends in concomitant clopidogrel/PPI use among acute coronary syndrome (ACS) inpatients in the United States between 2000 and 2016, in relation to the FDA safety communications.

Adult inpatients with a primary diagnosis of ACS were identified from the Cerner Health Facts® database using ICD-9 an ICD-10 codes. The standardized (age, sex, race and census region) prevalence of clopidogrel use with PPIs was calculated yearly and quarterly. Findings were stratified by PPIs' potential to inhibit clopidogrel's activity and by age.

A total of 204,533 inpatients were identified. In 2008, the prevalence of concomitant clopidogrel and PPI treatment was 34.9%, decreasing to 24.4% and 16.4% in 2009 and 2010, respectively, with the decline being similar across age groups. Treatment with inhibiting PPIs (omeprazole and esomeprazole) and clopidogrel has continued to decrease since 2010, with a prevalence of 0.8% in 2016. A similar reduction was not observed with clopidogrel and non-inhibiting PPIs (pantoprazole, lansoprazole, rabeprazole and dexlansoprazole). During the FDA warning period, the combined treatment with

clopidogrel and H_2 receptor antagonists, an alternative to PPIs suggested by the FDA, temporarily increased from 7.8% in 2008 to 12.8% and 14.5% in 2009 and 2010, respectively.

Findings suggest that clinical practice recommendations made by the FDA were followed. Further research is needed to determine how changes in drug labels and the availability of new drugs may have influenced the observed trends.

3.1 INTRODUCTION

Clopidogrel is an antiplatelet agent commonly prescribed to patients with acute coronary syndrome (ACS). Since clopidogrel can increase the risk of gastrointestinal bleeding, treatment guidelines recommend the coprescription of gastric protection, such as proton pump inhibitors (PPIs), with clopidogrel [1]. In January 2009, the FDA released an Early Communication alerting physicians of an ongoing safety review of clopidogrel in light of new study findings suggesting that clopidogrel's antiplatelet activity may be diminished in the presence of PPIs [2]. This initial communication did not specify which PPIs were more likely to interact with clopidogrel. A follow-up to the Early Communication and an advisory were later issued in November 2009, warning physicians against the use of clopidogrel with omeprazole and esomeprazole, which new study results suggested were more likely to inhibit the activation of clopidogrel compared to other PPIs [3, 4]. The communication proposed the use of antacids and certain H_2 receptor antagonists (H2RAs) as alternatives to PPIs for clopidogrel users that require gastric protection. In October 2010, the FDA further issued a reminder against the concomitant use of omeprazole and clopidogrel, suggesting pantoprazole as an alternative [5]. Similar communications warning of the potential interaction were issued by other regulatory agencies outside the United States (US) during this period [6, 7].

The FDA communications were based on studies that assessed the pharmacokinetic and pharmacodynamic effects of concomitant treatment with clopidogrel and PPIs, and a randomized controlled trial measuring platelet reactivity among PCI patients treated with omeprazole and clopidogrel [8–10]. The interaction between both drugs is based on the competitive inhibition of the CYP2C19 enzyme by PPIs. Clopidogrel is a prodrug that is converted to an active metabolite by the P450 system, with CYP2C19 having a principal role; PPIs are also metabolized by this enzyme to various degrees, depending on the type of PPI [11]. The drug interaction is thus not 'class-specific' but 'agent-specific' where the interaction is believed to be stronger with certain PPIs [12]. Numerous observational studies assessing the impact of concomitant treatment with clopidogrel and PPIs on clinical outcomes conducted since 2009 have reached inconsistent conclusions [13–15].

One of FDA's objectives when disseminating drug safety data is to provide patients and physicians with new medical information that may lead to safer use of prescribed medications. Although a previous study reported that FDA drug advisories commonly lead to reductions in use, the response varies from an immediate and strong response to a delayed and low impact response [16]. Prior studies that have examined trends in clopidogrel use in conjunction with PPIs in response to regulatory warnings have been based on outpatient prescription records. In addition to substantial changes in trends of medication use reported in these studies, the trends were found to vary among PPIs in relation to their potential to inhibit clopidogrel's activity [17–20]. In this study, we utilized data from inpatient settings across the US to examine trends in concomitant use of clopidogrel and PPIs among ACS patients, in relation to the FDA warnings.

3.2 METHODS

3.2.1 DATA SOURCE

Study data were derived from Cerner Corporation's HealthFacts® database between January 1, 2000 and December 31, 2016. HealthFacts®, which has previously been used for medication trends analyses [21], includes de-identified patient-level electronic health records collected from more than 500 contributing health facilities. The database included electronic records for over 69 million patients from all US census regions and detailed information from more than 460 million distinct encounters. In addition to demographic data, HealthFacts® includes time stamped laboratory, diagnostic, procedural, and medication information.

3.2.2 STUDY POPULATION

All inpatients 18 years of age or older hospitalized with a primary diagnosis of ACS were identified in each quarter of each calendar year. ICD-9-CM (410.xx, 411.1, 411.81, and 411.89) and ICD-10-CM (I20.0, I21.xx, I22.x, I24.8, and I24.9) codes were used to identify eligible encounters. To ensure that only patients with available pharmacy data in Health Facts were included in the study, eligible encounters had to have at least one recorded medication order. Only encounters with complete information on the patient's age, race, and sex were included to allow for standardization. Patient characteristics, including age, sex (male or female) and race

(Caucasian, African American, Hispanic, or other) were collected at the time of each eligible encounter. Information on census region, urban or rural setting, and teaching status of the healthcare facility was also collected for each eligible encounter. Since each quarter year was analysed cross-sectionally, patients with multiple eligible encounters could be included in multiple quarters, but not in the same quarter. (In instances where the same patient had multiple encounters in the same analysis period, only the earlier encounter was included.)

3.2.3 EXPOSURE ASSESSMENT

Inpatient pharmacy data was used to extract medications ordered during each eligible encounter. Encounters where patients received clopidogrel or PPIs were identified. PPI exposure was further classified into clopidogrel inhibiting PPIs (omeprazole and esomeprazole) and clopidogrel non-inhibiting PPIs (rabeprazole, lansoprazole, dexlansoprazole and pantoprazole). We also identified encounters in which two commonly used antiplatelet agents (ticagrelor and prasugrel) as well as H2RAs (ranitidine, famotidine, cimetidine and nizatidine) were ordered. To ensure that only medication orders that were likely received by the patients were included, orders considered were restricted to those with a valid status. Medications orders with a status of missing, void, cancelled or null were excluded. Further, medication orders with an invalid or missing value for the date that the medication was started were also excluded.

3.2.4 STATISTICAL ANALYSES

Each calendar year was cross-sectionally analysed by year and quarter. The primary outcome was the prevalence of clopidogrel and combined clopidogrel/PPI use among patients admitted for ACS in each time period analysed. Prevalent use of concomitant clopidogrel and PPIs during each time period was defined as the ratio of the number of unique patients that received both medications during a hospital encounter (numerator) to the total number of unique patients during the same time period that met the inclusion criteria (denominator). All drug utilization rates were age-, sex-, race-, and census region- standardized using data from the 2010 American Community Survey (USA Census Bureau).

To better understand patterns of combined PPI and clopidogrel use, we stratified our analyses on PPI type, calculating the prevalence of clopidogrel use with inhibiting PPIs and with non-inhibiting PPIs separately. For comparison with the primary outcome, we also calculated the prevalence of clopidogrel use without PPIs, the prevalence of H2RA use in combination with clopidogrel, as well as the prevalence of ticagrelor and prasugrel use, alone and in combination with a PPI. Comparisons of the prevalence of medication before, during, and after the FDA warning period (2009 and 2010) were made.

Subgroup analyses by age were conducted to examine whether changes in drug use were more pronounced in a specific age group. Prevalent concomitant drug use was stratified into three age groups (18-64, 65-84, and 85+). All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

3.3 RESULTS

A total of 204,533 patients corresponding to 221,008 encounters with a primary diagnosis of ACS met the eligibility criteria during the study period. The mean age of the study patients was 66.6

years (SD =14.0 years) and women comprised 39.5% of the study population (Table 3-1). The majority of patients were of non-Hispanic white race (81.8%) admitted to hospitals in the Northeast and South census regions (73.0%). Characteristics of patients in each quarter of the study period are provided in the supplementary material (Table S3-1).

TABLE 3- 1. CHARACTERISTICS OF ACS PATIENTS INCLUDED IN THE STUDY.

Characteristic	Population (N=204,533)	Percent
Age		
18-64 years	91,260	44.6
65-84 years	88,807	43.4
85+ years	24,466	12.0
Race		
African American	23,590	11.5
Caucasian	167,258	81.8
Hispanic	1,904	0.9
Other	11,781	5.8
Sex		
Female	80,791	39.5
Male	123,742	60.5
Census region		
Midwest	26,499	13.0
Northeast	78,326	38.3
South	71,040	34.7
West	28,668	14.0
Hospital status		
Rural	35,376	17.3
Urban	169,157	82.7
Teaching status		
Teaching	127,398	62.3
Non-teaching	45,021	22.0
Missing	32,114	16.0

The use of clopidogrel, with or without a PPI, among inpatients hospitalized with a primary diagnosis of ACS increased from year 2000 until 2007 (Table 3-2/Figure 3-1). The difference between the prevalence of concomitant treatment and the prevalence of treatment with clopidogrel alone was 4.0% and 5.8% in 2007 and 2008, respectively. In 2008, the FDA pre-warning period, 34.9% of ACS inpatients received concomitant treatment. During the warning period (Q1-2009 to Q4-2010), the mean prevalence of concomitant treatment was 20.4%, corresponding to a 41.5% decline from the pre-warning period. A subsequent 17.3% decline from the warning period to the post-warning year was also observed. During 2011-2014, the mean prevalence of concomitant treatment was in the range of 16.9% - 18.6% and then declined to 16.3% and 14.4% in 2015 and 2016, respectively.

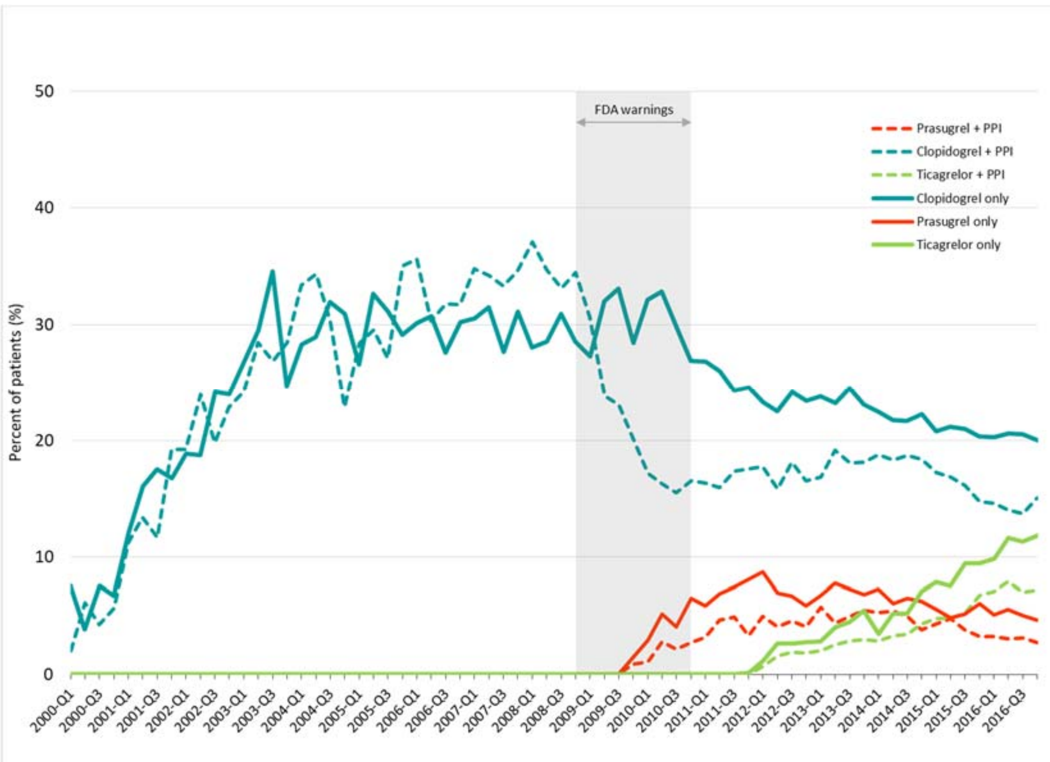


FIGURE 3-1 STANDARDIZED PREVALENCE OF ANTIPLATELET USE, ALONE OR CONCOMITANTLY WITH PPIS, AMONG ACS INPATIENTS. THE SHADED AREA CORRESPONDINGS TO THE TIME PERIOD OF THE FDA WARNINGS REGARDING THE POTENTIAL INTERACTION BETWEEN CLOPIDOGREL AND PPIS.

The mean prevalence of clopidogrel use without PPIs during the FDA warning period was 30.4%. Contrary to concomitant treatment, the mean prevalence of clopidogrel use without PPIs did not drop in the warning period relative to the pre-warning period. However, the use of clopidogrel without PPIs did decline in the post-warning period to reach a mean prevalence of 25.4% in

2011. The annual prevalent use of clopidogrel without PPIs continued to decrease between 2010 and 2016 by an average of 1.7% per year.

TABLE 3- 2. STANDARDIZED ANNUAL PREVALENCE OF ANTIPLATELET USE WITH OR WITHOUT PPIS AMONG ACS INPATIENTS

Year	Clopidogrel	Clopidogrel + PPI	Clopidogrel + inhibiting PPI	Clopidogrel + non-inhibiting PPI	Clopidogrel + H2RA	Prasugrel	Prasugrel + PPI	Ticagrelor	Ticagrelor + PPI
2000	6.4	4.7	2.1	2.6	20.0	-	-	-	-
2001	15.6	14.1	0.5	13.8	12.1	-	-	-	-
2002	21.4	21.4	0.6	21.0	5.2	-	-	-	-
2003	28.4	26.6	0.4	26.3	4.5	-	-	-	-
2004	30.1	29.1	0.1	29.0	6.8	-	-	-	-
2005	29.9	30.1	0.2	29.9	7.7	-	-	-	-
2006	29.7	32.2	7.1	25.6	9.1	-	-	-	-
2007	30.3	34.2	14.1	20.5	6.3	-	-	-	-
2008	29.0	34.9	18.4	16.9	7.8	-	-	-	-
2009	30.2	24.4	14.0	11.1	12.8	0.4	0.2	-	-
2010	30.6	16.4	7.7	9.2	14.5	4.6	2.2	-	-
2011	25.4	16.9	8.1	9.3	11.3	7.2	4.0	0.1	0.0
2012	23.4	17.1	6.6	11.1	8.3	7.1	4.5	2.3	1.5
2013	23.7	18.1	3.2	15.5	7.5	7.2	5.2	4.3	2.7
2014	22.1	18.6	2.4	16.6	7.2	6.5	4.9	5.2	3.5
2015	20.8	16.3	2.5	14.2	7.8	5.4	4.1	8.6	5.4
2016	20.4	14.4	0.8	13.8	7.1	5.1	3.0	11.2	7.3

Two new antiplatelet agents, prasugrel (July 2009) and ticagrelor (July 2011), became available in the US during the study period. Figure 3-1 shows the gradual uptake of these two agents among inpatients, with and without PPIs. The combined prevalence of ticagrelor with and without PPIs increased by an average of 4.6% per year since it was introduced. At the end of 2016, the prevalence of ticagrelor use was 18.5%. While the prevalence of prasugrel increased since it was introduced at an average rate of 3.6% per year until 2012, it remained constant for the following two years, and then started to slowly decline. At the end of the study period, the prevalence of prasugrel use was 8.1%.

Trends of annual prevalent use in concomitant treatment with clopidogrel and PPIs stratified by the inhibiting potential of PPIs type are presented in Figure 3-2. The use of omeprazole and esomeprazole (inhibiting PPIs) was substantially lower than the remaining PPIs until 2006. In 2008, the prevalence of combined clopidogrel treatment with each PPI type was in the 17%-18% range. During the warning period, the annual prevalence of combined treatment declined by approximately 40% for both inhibiting and non-inhibiting PPIs, when compared to the pre-warning period. The prevalence of clopidogrel use with inhibiting PPIs continued to decline thereafter to reach a prevalence of 0.8% at the end of 2016. Conversely, the prevalence of clopidogrel use with non-inhibiting PPIs increased until 2014 to reach approximately 17%, then declined slowly to reach a prevalence of 13.8% at the end of the study period.

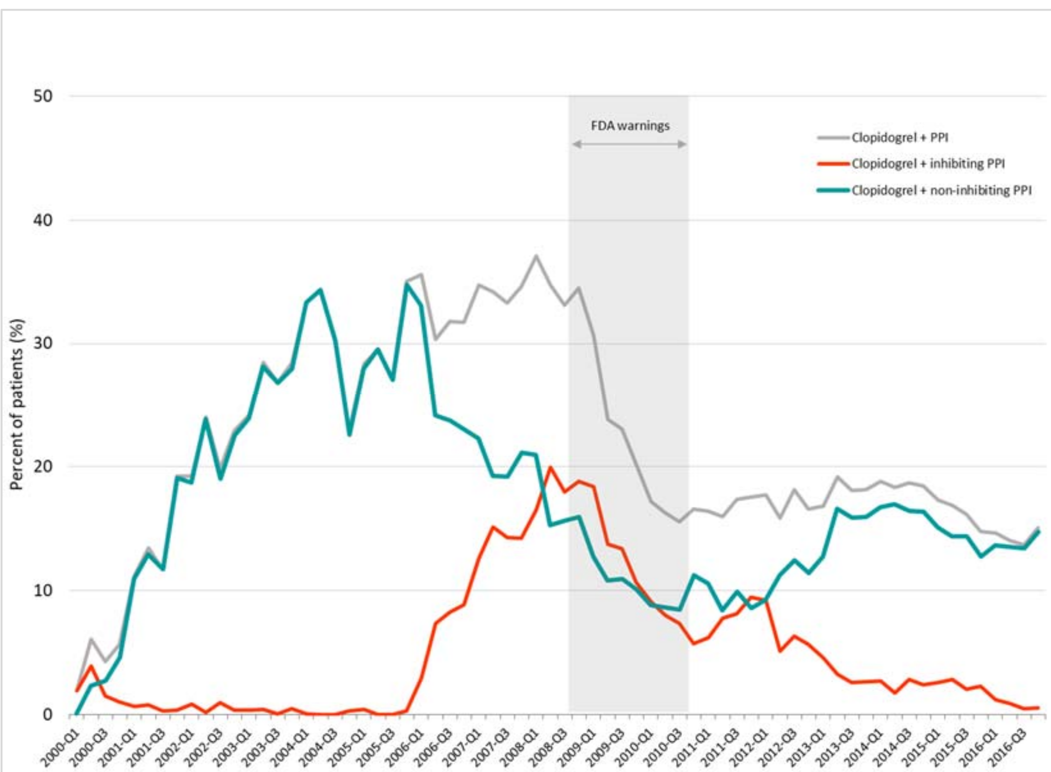


FIGURE 3-2 STANDARDIZED PREVALENCE OF CLOPIDOGREL AND PPI USE, STRATIFIED BY THE POTENTIAL OF PPI TO INHIBIT CLOPIDOGRELS ACTIVITY AMONG ACS INPATIENTS. INHIBITING PPIS: OMEPRAZOLE AND ESOMPEPRAZOLE; NON-INHIBITING PPIS: PANTOPRAZOLE, LANSOPRAZOLE,

DEXLANSOPRAZOLE AND RABEPRAZOLE. THE SHADED AREA CORRESPONDINGS TO THE TIME PERIOD OF THE FDA WARNINGS REGARDING THE POTENTIAL INTERACTION BETWEEN CLOPIDOGREL AND PPIS.

Figure 3-3 shows a marked increase in the use of H2RAs with clopidogrel during the warning period: there was a 74.4% increase in the use of combined clopidogrel and H2RA treatment when comparing the average use in the pre-warning year with the warning period (from 7.8% to 13.6%). This rise in H2RA use with clopidogrel was transient, and was followed by an average decline of 0.8% per year since the end of 2010. In 2016, the average prevalence was 7.1%, indicating a return to rates similar to those observed before the FDA warnings were issued.

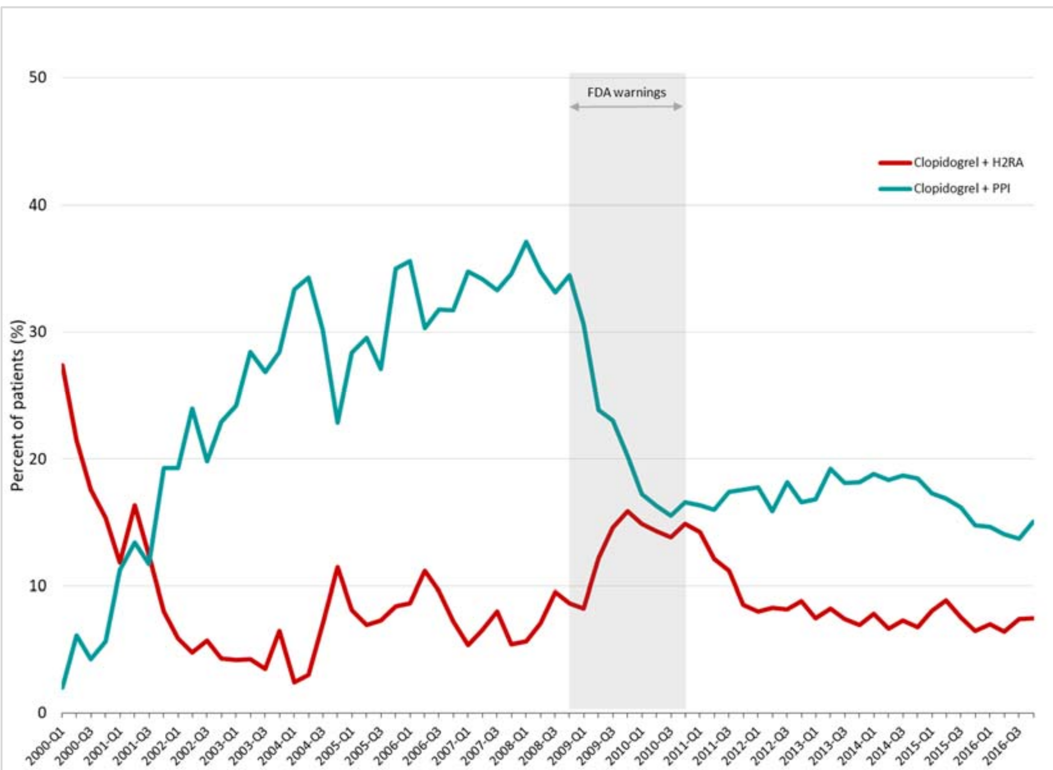


FIGURE 3-3 STANDARDIZED PREVALENCE OF CLOPIDOGREL USE, WITH PPIS OR H2RAS, AMONG ACS INPATIENTS. THE SHADED AREA CORRESPONDINGS TO THE TIME PERIOD OF THE FDA WARNINGS REGARDING THE POTENTIAL INTERACTION BETWEEN CLOPIDOGREL AND PPIS.

3.3.1 SUBGROUP ANALYSES

Standardized rates (for sex, race and census region) of clopidogrel use with PPIs were stratified by age groups to examine whether changes in drug use were more pronounced among a specific group (supplementary material, Figure S3-1). After the first FDA communication in November 2009, the decrease in concomitant PPI and clopidogrel use was similar across the three age groups. However, since 2010, younger inpatients were less likely to receive concomitant treatment compared to older age groups. Among individuals 18-64 years of age, the mean prevalence of concomitant treatment (from 2010-2016) was 16.3%, compared to 19.4% among those 65+ years of age.

Additional figures showing the time trends for the primary analyses stratified by age are presented in the supplementary material (Figures S3-2 to S3-6). The trends observed for clopidogrel, PPIs and H2RAs did not reveal discernable patterns in a particular group when comparing the pre-warning and post warning periods. However, it was apparent that ticagrelor and prasugrel use were the least prevalent among the age group 85+ years of age, when used with or without PPIs.

Prevalence of drug use analyses were repeated on a subset of the ACS study population, limited to the 177,801 patients admitted to the hospital with a primary diagnosis for myocardial infarction (MI) during the study period. For clopidogrel use with and without PPIs, the same patterns were observed as for the ACS cohort. Figures presenting trends of drug use among MI patients are available in the supplementary material (Figures S3-7 to S3-10). Sensitivity analyses also examined the effect of excluding patients with subsequent hospital encounters from the study sample (n=4,816). The same patterns of medication use were observed in the resulting subsample as in the full study sample.

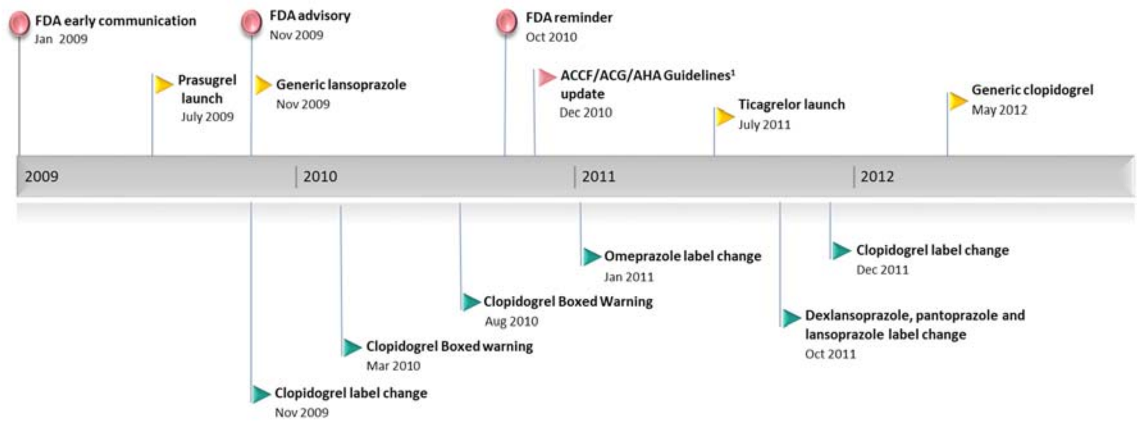
3.4 DISCUSSION

Regulatory agencies such as the FDA play an important role in disseminating emerging safety data about prescription medications to healthcare professionals and the public. Examining patterns of medication use in inpatient and outpatient settings provides information on the response to advisories and the extent to which safer prescribing practices were adopted. This study demonstrated substantial changes in trends of clopidogrel use in combination with PPIs among ACS inpatients following the FDA warnings issued in 2009-2010. Our findings suggest that the use of combined treatment among ACS inpatients decreased immediately after the first FDA advisory was issued in January 2009. However, the prevalence of clopidogrel use without PPIs did not decrease during this period, suggesting that the change in drug use was specific to combined treatment. The decline in concomitant treatment was accompanied by a temporary rise in the use of H2RAs, which had been suggested as an alternative to PPIs in the FDA communication. This suggests that physicians were more likely to prescribe H2RAs during this period, possibly a result of lack of reports of an association between H2RAs and clopidogrel. The second and third safety communications made it clear that the potential interaction with clopidogrel was limited to omeprazole and esomeprazole. Examining the trends, it is likely that some physicians started preferentially prescribing H2RAs to clopidogrel users requiring gastric protection, but later reverted to prescribing PPIs, particularly PPI types that the FDA had viewed as safer. Previous studies in the US and other countries that examined trends of concomitant clopidogrel/PPI among outpatients have reported similar increases in the use of H2RAs [18], as well as in the use of non-inhibiting PPIs [17–20]. It is important to note that although omeprazole is the most prescribed generic PPI, our findings show very low prevalence of omeprazole and esomeprazole use among inpatients from 2000-2006. This observation needs further examination, as it may be due to different formulary lists adopted in the hospitals represented by Health Facts, particularly at the outset of the study period.

Our findings suggest that, although clopidogrel remained the most commonly used antiplatelet compared to prasugrel and ticagrelor among ACS inpatients, its use started to decline slightly as these newer antiplatelets were gradually adopted. The popularity of clopidogrel over these antiplatelets has been reported in the literature [22, 23], and may be due to the availability of generic clopidogrel at a lower cost since 2012. Comparing the prevalence of the newer agents, our results suggest that ticagrelor use is more prevalent than prasugrel use among ACS inpatients. This is likely attributed to the fact that ticagrelor is considered safer among patients with diabetes and renal disease [23] and prasugrel is contraindicated in patients older than 75 years of age with a history of prior stroke [24], both of which may contribute to the higher use of ticagrelor.

This study adds to the current body of literature on trends of the medications in inpatient settings, and shows that physician prescribing practices when caring for ACS patients were consistent with FDA guidelines. However, advisories from the FDA warning against the use of specific drugs are not always met with a prompt response. A recent systematic review found that the effect on the prescribing patterns of physicians is not predictable [16]: the review suggests that FDA advisories on adverse drug interactions were effective in changing physicians prescribing patterns, as opposed to advisories that recommend greater laboratory or clinical monitoring, which were ineffective in achieving large or sustained changes. Since 2007, the FDA has adopted a proactive approach in disseminating preliminary safety information to the public and health care practitioners [25]. This approach is evident in the case of clopidogrel and PPIs, as the FDA first released an Early Communication to alert physicians and the public of a potential interaction between both drugs and to inform them that studies are underway for more information. This type of communication is used by the FDA when a safety issue is still being evaluated. The warnings issued by the FDA also meet the three criteria for effective risk communication reported by Dusetzina et al. (2012), namely having a specific message, providing acceptable alternatives, and reinforcing the message over time.

In addition to the FDA warnings, other events that occurred since 2009 may have had a role in the observed trends in the inpatient use of clopidogrel and PPIs (Figure 4). The clopidogrel label was updated in November 2009 to reflect new information on the interaction with omeprazole [26]. Label changes were also introduced to individual PPIs in 2011-2012 warning against the use of the omeprazole and esomeprazole with clopidogrel, and emphasizing the lack of interaction between pantroprazole, lansoprazole and dexlansoprazole with clopidogrel. Furthermore, guidelines from the American College of Cardiology Foundation, the American College of Gastroenterology, and the American Heart Association were updated to recommend PPI use only in patients that had an elevated risk of upper gastrointestinal bleeding [27].



[1] *American College of Cardiology Foundation / American College of Gastroenterology/ American Heart Association*

FIGURE 3-4 TIME-LINE OF RELEVANT EVENTS IN THE UNITED STATES FOLLOWING THE FIRST FDA SAFETY ALERT.

3.5 STRENGTHS

The prevalence of medication use presented in this study are based on a large sample of ACS patients in the US over a 17 year period. The study sample was comprised of patients from all four Census regions in the US, representing diverse patients with various health care coverage plans. All findings presented were standardized for age, sex, race and census region to take into account the differences in these factors between the HealthFacts population and the US population.

3.6 LIMITATIONS

The changes in medication use demonstrated in this study reflect prescription practices in inpatient settings. The extent to which the findings may be generalized to outpatient settings is unclear, since prescription patterns in outpatient settings may be affected by factors such as health plan formularies, pharmaceutical marketing strategies, and over the counter use of gastric protection. Current guidelines recommend the use of an antiplatelet for up to 12 months in ACS patients. Switching between antiplatelets may occur sometimes for various reasons, including individual response to the medications, genetics and socioeconomic factors such as the cost of brand medications relative to generic formulations [28]. Registry studies have estimated that between 5-50% of clopidogrel users switch ticagrelor or prasugrel. Conversely, patients may switch from ticagrelor or prasugrel to clopidogrel because of the reduced costs of generic formulations and the reduced risk of bleeding [29]. On the other hand, the availability of PPIs as over-the-counter medications may contribute to different prevalence of use of these medications among ACS patients outside of hospital settings.

Although the electronic health records available to us provide information on medication orders placed during encounters, there is no confirmation that the order was dispensed and received by the patients. To increase the likelihood that the medication was received by the patients, we restricted our analysis to medication orders that had a valid status.

Further, the substantial changes in concomitant use of PPIs and clopidogrel cannot be attributed solely to the FDA advisories as other relevant events occurred since 2009, which all may have had an impact on the observed trends. Although many of the events that followed are likely influenced by the FDA advisories, further research is needed to discern the impact of label changes and the availability of generic drugs on the observed response.

3.7 CONCLUSION

The present results suggest that the FDA's clinical practice recommendations related to the co-prescription of clopidogrel and PPIs were generally followed by physicians caring for inpatients. Although clopidogrel continues to be the most prescribed antiplatelet agent, its use in combination with PPIs has declined, particularly in conjunction with omeprazole and esomeprazole. This change is likely due to the clear and specific FDA communications in addition to other relevant events that followed. Since trends in the concomitant use of clopidogrel and PPI varied substantially by the potential of PPIs to inhibit clopidogrel, it is recommended that future studies assessing clinical outcomes take into consideration the type of PPIs administered to patients.

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SUPPLEMENTAL MATERIAL S3

The additional findings are presented in this section include: detailed demographic characteristics of the study sample in each quarter over the study period (Table S3-1); standardized prevalence of medication use stratified in each quarter year in the study period (Table S3-2); standardized prevalence of medications use, stratified by age (Figures S3-1 to S3-6); and standardize prevalence of medication use among MI patients (Figures S3-7 to S3-10).

TABLE S3- 1. DEMOGRAPHIC CHARACTERISTICS OF THE STUDY SAMPLE BY QUARTER.

Characteristic		2000-Q1	2000-Q2	2000-Q3	2000-Q4	2001-Q1	2001-Q2	2001-Q3	2001-Q4	2002-Q1	2002-Q2	2002-Q3	2002-Q4	2003-Q1	2003-Q2	2003-Q3	2003-Q4	2004-Q1
Sex																		
	Female	170	219	217	228	424	467	473	540	467	463	462	508	428	357	255	240	259
	%	*41.2*	*40.9*	*41.3*	*37.5*	*39.4*	*39.2*	*42.6*	*41.4*	*41.0*	*43.3*	*44.0*	*43.1*	*42.3*	*42.4*	*46.1*	*43.6*	*41.2*
	Male	243	317	308	380	651	724	637	765	673	606	588	670	585	485	298	310	370
	%	*58.8*	*59.1*	*58.7*	*62.5*	*60.6*	*60.8*	*57.4*	*58.6*	*59.0*	*56.7*	*56.0*	*56.9*	*57.8*	*57.6*	*53.9*	*56.4*	*58.8*
Age																		
	18-64 years	188	264	253	267	466	481	461	512	448	425	416	453	420	329	186	188	245
	%	*45.5*	*49.3*	*48.2*	*43.9*	*43.4*	*40.4*	*41.5*	*39.2*	*39.3*	*39.8*	*39.6*	*38.5*	*41.5*	*39.1*	*33.6*	*34.2*	*39.0*
	65-84 years	198	228	225	273	494	567	531	646	562	511	521	589	450	395	268	270	282
	%	*47.9*	*42.5*	*42.9*	*44.9*	*46.0*	*47.6*	*47.8*	*49.5*	*49.3*	*47.8*	*49.6*	*50.0*	*44.4*	*46.9*	*48.5*	*49.1*	*44.8*
	85+ years	27	44	47	68	115	143	118	147	130	133	113	136	143	118	99	92	102
	%	*6.5*	*8.2*	*9.0*	*11.2*	*10.7*	*12.0*	*10.6*	*11.3*	*11.4*	*12.4*	*10.8*	*11.5*	*14.1*	*14.0*	*17.9*	*16.7*	*16.2*
Race																		
	African American	89	92	78	79	111	84	90	113	82	66	79	48	61	37	16	18	17
	%	*21.6*	*17.2*	*14.9*	*13.0*	*10.3*	*7.1*	*8.1*	*8.7*	*7.2*	*6.2*	*7.5*	*4.1*	*6.0*	*4.4*	*2.9*	*3.3*	*2.7*
	Caucasian	300	422	420	503	913	1066	986	1148	1023	971	930	1064	902	768	499	491	575
	%	*72.6*	*78.7*	*80.0*	*82.7*	*84.9*	*89.5*	*88.8*	*88.0*	*89.7*	*90.8*	*88.6*	*90.3*	*89.0*	*91.2*	*90.2*	*89.3*	*91.4*
	Hispanic	2	4	5	3	10	9	14	10	10	26	21	38	22	15	15	23	13
	%	*0.5*	*0.8*	*1.0*	*0.5*	*0.9*	*0.8*	*1.3*	*0.8*	*0.9*	*2.4*	*2.0*	*3.2*	*2.2*	*1.8*	*2.7*	*4.2*	*2.1*
	Other	22	18	22	23	41	32	20	34	25	6	20	28	28	22	23	18	24
	%	*5.3*	*3.4*	*4.2*	*3.8*	*3.8*	*2.7*	*1.8*	*2.6*	*2.2*	*0.6*	*1.9*	*2.4*	*2.8*	*2.6*	*4.2*	*3.3*	*3.8*
Census region																		
	Midwest	0	0	0	0	0	37	39	63	36	44	46	77	64	52	58	66	65
	%	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*3.1*	*3.5*	*4.8*	*3.2*	*4.1*	*4.4*	*6.5*	*6.3*	*6.2*	*10.5*	*12.0*	*10.3*
	Northeast	77	145	170	238	691	837	797	867	839	949	845	869	760	676	398	378	457
	%	*18.6*	*27.1*	*32.4*	*39.1*	*64.3*	*70.3*	*71.8*	*66.4*	*73.6*	*88.8*	*80.5*	*73.8*	*75.0*	*80.3*	*72.0*	*68.7*	*72.7*
	South	336	391	355	370	384	317	274	375	265	75	74	112	75	17	0	0	0
	%	*81.4*	*73.0*	*67.6*	*60.9*	*35.7*	*26.6*	*24.7*	*28.7*	*23.3*	*7.0*	*7.1*	*9.5*	*7.4*	*2.0*	*0.0*	*0.0*	*0.0*
	West	0	0	0	0	0	0	0	0	0	1	85	120	114	97	97	106	107
	%	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.1*	*8.1*	*10.2*	*11.3*	*11.5*	*17.5*	*19.3*	*17.0*

Characteristic		2004-Q2	2004-Q3	2004-Q4	2005-Q1	2005-Q2	2005-Q3	2005-Q4	2006-Q1	2006-Q2	2006-Q3	2006-Q4	2007-Q1	2007-Q2	2007-Q3	2007-Q4	2008-Q1	2008-Q2	2008-Q3
Sex																			
	Female	227	204	317	519	530	466	545	528	607	601	672	617	576	595	787	852	838	727
	%	*43.7*	*43.0*	*40.1*	*44.2*	*42.5*	*41.5*	*43.6*	*42.9*	*42.3*	*42.9*	*41.6*	*40.8*	*40.1*	*43.4*	*40.3*	*40.2*	*42.6*	*38.7*
	Male	292	270	473	656	716	656	705	703	829	799	944	894	861	776	1168	1270	1128	1151
	%	*56.3*	*57.0*	*59.9*	*55.8*	*57.5*	*58.5*	*56.4*	*57.1*	*57.7*	*57.1*	*58.4*	*59.2*	*59.9*	*56.6*	*59.7*	*59.9*	*57.4*	*61.3*
Age																			
	18-64 years	199	188	303	405	465	431	475	499	564	542	670	584	605	599	831	841	821	809
	%	*38.3*	*39.7*	*38.4*	*34.5*	*37.3*	*38.4*	*38.0*	*40.5*	*39.3*	*38.7*	*41.5*	*38.7*	*42.1*	*43.7*	*42.5*	*39.6*	*41.8*	*43.1*
	65-84 years	228	208	357	570	578	524	568	554	652	640	689	678	627	588	856	960	862	818
	%	*43.9*	*43.9*	*45.2*	*48.5*	*46.4*	*46.7*	*45.4*	*45.0*	*45.4*	*45.7*	*42.6*	*44.9*	*43.6*	*42.9*	*43.8*	*45.2*	*43.9*	*43.6*
	85+ years	92	78	130	200	203	167	207	178	220	218	257	249	205	184	268	321	283	251
	%	*17.7*	*16.5*	*16.5*	*17.0*	*16.3*	*14.9*	*16.6*	*14.5*	*15.3*	*15.6*	*15.9*	*16.5*	*14.3*	*13.4*	*13.7*	*15.1*	*14.4*	*13.4*
Race																			
	African American	18	14	46	68	86	67	81	89	100	130	183	132	164	184	196	206	249	240
	%	*3.5*	*3.0*	*5.8*	*5.8*	*6.9*	*6.0*	*6.5*	*7.2*	*7.0*	*9.3*	*11.3*	*8.7*	*11.4*	*13.4*	*10.0*	*9.7*	*12.7*	*12.8*
	Caucasian	481	440	715	1079	1121	1024	1128	1101	1292	1218	1380	1336	1233	1138	1680	1812	1646	1559
	%	*92.7*	*92.8*	*90.5*	*91.8*	*90.0*	*91.3*	*90.2*	*89.4*	*90.0*	*87.0*	*85.4*	*88.4*	*85.8*	*83.0*	*85.9*	*85.4*	*83.7*	*83.0*
	Hispanic	10	9	12	8	14	11	14	20	23	17	13	13	13	18	26	28	22	23
	%	*1.9*	*1.9*	*1.5*	*0.7*	*1.1*	*1.0*	*1.1*	*1.6*	*1.6*	*1.2*	*0.8*	*0.9*	*0.9*	*1.3*	*1.3*	*1.3*	*1.1*	*1.2*
	Other	10	11	17	20	25	20	27	21	21	35	40	30	27	31	53	76	49	56
	%	*1.9*	*2.3*	*2.2*	*1.7*	*2.0*	*1.8*	*2.2*	*1.7*	*1.5*	*2.5*	*2.5*	*2.0*	*1.9*	*2.3*	*2.7*	*3.6*	*2.5*	*3.0*
Census region																			
	Midwest	80	60	90	66	71	75	73	84	227	275	390	295	210	180	239	228	243	185
	%	*15.4*	*12.7*	*11.4*	*5.6*	*5.7*	*6.7*	*5.8*	*6.8*	*15.8*	*19.6*	*24.1*	*19.5*	*14.6*	*13.1*	*12.2*	*10.7*	*12.4*	*9.9*
	Northeast	402	346	505	803	835	740	880	862	902	756	808	868	797	710	1061	1087	923	854
	%	*77.5*	*73.0*	*63.9*	*68.3*	*67.0*	*66.0*	*70.4*	*70.0*	*62.8*	*54.0*	*50.0*	*57.5*	*55.5*	*51.8*	*54.3*	*51.2*	*47.0*	*45.5*
	South	0	22	160	278	300	280	254	268	298	357	397	330	414	427	554	600	637	684
	%	*0.0*	*4.6*	*20.3*	*23.7*	*24.1*	*25.0*	*20.3*	*21.8*	*20.8*	*25.5*	*24.6*	*21.8*	*28.8*	*31.2*	*28.3*	*28.3*	*32.4*	*36.4*
	West	37	46	35	28	40	27	43	17	9	12	21	18	16	54	101	207	163	155
	%	*7.1*	*9.7*	*4.4*	*2.4*	*3.2*	*2.4*	*3.4*	*1.4*	*0.6*	*0.9*	*1.3*	*1.2*	*1.1*	*3.9*	*5.2*	*9.8*	*8.3*	*8.3*

Characteristic	2008-Q4	2009-Q1	2009-Q2	2009-Q3	2009-Q4	2010-Q1	2010-Q2	2010-Q3	2010-Q4	2011-Q1	2011-Q2	2011-Q3	2011-Q4	2012-Q1	2012-Q2	2012-Q3	2012-Q4

Sex																		
	Female	813	982	983	960	1052	1305	1255	1136	988	1128	1279	1239	1710	1794	1672	1969	2073
	%	*40.3*	*40.7*	*40.2*	*41.7*	*42.0*	*40.0*	*38.8*	*39.7*	*38.8*	*39.5*	*40.3*	*38.7*	*39.3*	*39.7*	*40.1*	*40.3*	*39.7*
	Male	1203	1434	1464	1342	1451	1959	1982	1724	1559	1726	1896	1967	2639	2725	2497	2916	3154
	%	*59.7*	*59.4*	*59.8*	*58.3*	*58.0*	*60.0*	*61.2*	*60.3*	*61.2*	*60.5*	*59.7*	*61.4*	*60.7*	*60.3*	*59.9*	*59.7*	*60.3*
Age																		
	18-64 years	831	1063	1055	983	1075	1460	1502	1344	1146	1328	1551	1521	2030	2141	2021	2281	2333
	%	*41.2*	*44.0*	*43.1*	*42.7*	*43.0*	*44.7*	*46.4*	*47.0*	*45.0*	*46.5*	*48.9*	*47.4*	*46.7*	*47.4*	*48.5*	*46.7*	*44.6*
	65-84 years	928	1031	1039	1010	1056	1376	1319	1176	1077	1200	1270	1324	1843	1861	1682	2069	2297
	%	*46.0*	*42.7*	*42.5*	*43.9*	*42.2*	*42.2*	*40.8*	*41.1*	*42.3*	*42.1*	*40.0*	*41.3*	*42.4*	*41.2*	*40.4*	*42.4*	*43.9*
	85+ years	257	322	353	309	372	428	416	340	324	326	354	361	476	517	466	535	597
	%	*12.8*	*13.3*	*14.4*	*13.4*	*14.9*	*13.1*	*12.9*	*11.9*	*12.7*	*11.4*	*11.2*	*11.3*	*11.0*	*11.4*	*11.2*	*11.0*	*11.4*
Race																		
	African American	246	289	298	280	336	419	376	371	326	332	504	397	634	669	593	653	696
	%	*12.2*	*12.0*	*12.2*	*12.2*	*13.4*	*12.8*	*11.6*	*13.0*	*12.8*	*11.6*	*15.9*	*12.4*	*14.6*	*14.8*	*14.2*	*13.4*	*13.3*
	Caucasian	1671	2012	2027	1896	2025	2652	2688	2353	2085	2383	2505	2590	3482	3570	3299	3816	4108
	%	*82.9*	*83.3*	*82.8*	*82.4*	*80.9*	*81.3*	*83.0*	*82.3*	*81.9*	*83.5*	*78.9*	*80.8*	*80.1*	*79.0*	*79.1*	*78.1*	*78.6*
	Hispanic	23	33	35	47	45	71	55	56	56	47	42	39	55	48	24	48	34
	%	*1.1*	*1.4*	*1.4*	*2.0*	*1.8*	*2.2*	*1.7*	*2.0*	*2.2*	*1.7*	*1.3*	*1.2*	*1.3*	*1.1*	*0.6*	*1.0*	*0.7*
	Other	76	82	87	79	97	122	118	80	80	92	124	180	178	232	253	368	389
	%	*3.8*	*3.4*	*3.6*	*3.4*	*3.9*	*3.7*	*3.6*	*2.8*	*3.1*	*3.2*	*3.9*	*5.6*	*4.1*	*5.1*	*6.1*	*7.5*	*7.4*
Census region																		
	Midwest	161	275	324	291	311	488	459	450	395	409	570	517	555	548	594	526	555
	%	*8.0*	*11.4*	*13.2*	*12.6*	*12.4*	*15.0*	*14.2*	*15.7*	*15.5*	*14.3*	*18.0*	*16.1*	*12.8*	*12.1*	*14.3*	*10.8*	*10.6*
	Northeast	977	1350	1322	1358	1354	1303	1300	1127	1115	1046	951	1402	1661	1729	1800	2086	2209
	%	*48.5*	*55.9*	*54.0*	*59.0*	*54.1*	*39.9*	*40.2*	*39.4*	*43.8*	*36.7*	*30.0*	*43.7*	*38.2*	*38.3*	*43.2*	*42.7*	*42.3*
	South	696	643	654	523	668	1287	1197	1158	848	1210	1427	1060	1750	1787	1338	1353	1420
	%	*34.5*	*26.6*	*26.7*	*22.7*	*26.7*	*39.4*	*37.0*	*40.5*	*33.3*	*42.4*	*44.9*	*33.1*	*40.2*	*39.5*	*32.1*	*27.7*	*27.2*
	West	182	148	147	130	170	186	281	125	189	189	227	227	383	455	437	920	1043
	%	*9.0*	*6.1*	*6.0*	*5.7*	*6.8*	*5.7*	*8.7*	*4.4*	*7.4*	*6.6*	*7.2*	*7.1*	*8.8*	*10.1*	*10.5*	*18.8*	*20.0*

Characteristic		2013-Q1	2013-Q2	2013-Q3	2013-Q4	2014-Q1	2014-Q2	2014-Q3	2014-Q4	2015-Q1	2015-Q2	2015-Q3	2015-Q4	2016-Q1	2016-Q2	2016-Q3	2016-Q4
Sex																	
	Female	2176	2413	2605	2641	2939	2844	2869	2873	2692	2591	2495	2480	2647	2590	2513	2700
	%	*39.2*	*38.4*	*38.5*	*38.2*	*38.8*	*38.5*	*38.8*	*38.8*	*38.2*	*38.3*	*37.4*	*38.2*	*39.3*	*38.2*	*38.1*	*39.2*
	Male	3376	3877	4158	4266	4630	4541	4532	4532	4356	4176	4174	4009	4094	4196	4092	4194
	%	*60.8*	*61.6*	*61.5*	*61.8*	*61.2*	*61.5*	*61.2*	*61.2*	*61.8*	*61.7*	*62.6*	*61.8*	*60.7*	*61.8*	*62.0*	*60.8*
Age																	
	18-64 years	2539	2914	3240	3197	3478	3373	3396	3262	3097	3146	3119	2838	2993	3110	3028	3032
	%	*45.7*	*46.3*	*47.9*	*46.3*	*46.0*	*45.7*	*45.9*	*44.1*	*43.9*	*46.5*	*46.8*	*43.7*	*44.4*	*45.8*	*45.8*	*44.0*
	65-84 years	2292	2703	2857	2963	3257	3145	3173	3265	3105	2874	2889	2958	2946	2947	2851	3057
	%	*41.3*	*43.0*	*42.2*	*42.9*	*43.0*	*42.6*	*42.9*	*44.1*	*44.1*	*42.5*	*43.3*	*45.6*	*43.7*	*43.4*	*43.2*	*44.3*
	85+ years	721	673	666	747	834	867	832	878	846	747	661	693	802	729	726	805
	%	*13.0*	*10.7*	*9.9*	*10.8*	*11.0*	*11.7*	*11.2*	*11.9*	*12.0*	*11.0*	*9.9*	*10.7*	*11.9*	*10.7*	*11.0*	*11.7*
Race																	
	African American	746	750	728	771	829	757	817	805	819	829	796	750	848	824	849	840
	%	*13.4*	*11.9*	*10.8*	*11.2*	*11.0*	*10.3*	*11.0*	*10.9*	*11.6*	*12.3*	*11.9*	*11.6*	*12.6*	*12.1*	*12.9*	*12.2*
	Caucasian	4370	5053	5506	5597	6109	6008	5980	6057	5719	5397	5322	5211	5352	5406	5204	5441
	%	*78.7*	*80.3*	*81.4*	*81.0*	*80.7*	*81.4*	*80.8*	*81.8*	*81.1*	*79.8*	*79.8*	*80.3*	*79.4*	*79.7*	*78.8*	*78.9*
	Hispanic	33	39	66	48	46	45	48	41	39	43	42	21	26	25	27	23
	%	*0.6*	*0.6*	*1.0*	*0.7*	*0.6*	*0.6*	*0.7*	*0.6*	*0.6*	*0.6*	*0.6*	*0.3*	*0.4*	*0.4*	*0.4*	*0.3*
	Other	403	448	463	491	585	575	556	502	471	498	509	507	515	531	525	590
	%	*7.3*	*7.1*	*6.9*	*7.1*	*7.7*	*7.8*	*7.5*	*6.8*	*6.7*	*7.4*	*7.6*	*7.8*	*7.7*	*7.8*	*8.0*	*8.6*
Census region																	
	Midwest	787	686	773	798	831	829	987	1154	1133	1091	1126	909	881	1142	1049	1177
	%	*14.2*	*10.9*	*11.4*	*11.6*	*11.0*	*11.2*	*13.3*	*15.6*	*16.1*	*16.1*	*16.9*	*14.0*	*13.1*	*16.8*	*15.9*	*17.1*
	Northeast	2223	2440	2360	2007	2200	2370	2349	2281	1856	1661	1428	1397	1557	1312	1224	1439
	%	*40.0*	*38.8*	*34.9*	*29.1*	*29.1*	*32.1*	*31.7*	*30.8*	*26.3*	*24.6*	*21.4*	*21.5*	*23.1*	*19.3*	*18.5*	*20.9*
	South	1486	2052	2502	2900	3200	2891	2813	2670	2769	2636	2736	2555	2694	2798	2865	2774
	%	*26.8*	*32.6*	*37.0*	*42.0*	*42.3*	*39.2*	*38.0*	*36.1*	*39.3*	*39.0*	*41.0*	*39.4*	*40.0*	*41.2*	*43.4*	*40.2*
	West	1056	1112	1128	1202	1338	1295	1252	1300	1290	1379	1379	1628	1609	1534	1467	1504
	%	*19.0*	*17.7*	*16.7*	*17.4*	*17.7*	*17.5*	*16.9*	*17.6*	*18.3*	*20.4*	*20.7*	*25.1*	*23.9*	*22.6*	*22.2*	*21.8*

TABLE S3- 2. STANDARDIZED PREVALENCE OF MEDICATION USE AMONG INPATIENTS HOSPITALIZED FOR ACS STRATIFIED BY EACH QUARTER YEAR IN THE STUDY PERIOD.

Quarter	PPI	Clopidogrel only	Clopidogrel + PPI	Clopidogrel + inhibiting PPI	Clopidogrel + non-inhibiting PPI	Clopidogrel + H2RA	PPI + H2RA	Prasugrel + PPI	Prasugrel only	Ticagrelor + PPI	Ticagrelor only
2000-Q1	29.97	7.58	2.01	1.93	0.08	27.37	26.57	0	0	0	0
2000-Q2	28.88	3.83	6.12	3.93	2.35	21.45	19.33	0	0	0	0
2000-Q3	24.89	7.58	4.28	1.54	2.77	17.61	17.55	0	0	0	0
2000-Q4	31.37	6.75	5.68	1.03	4.64	15.33	19.89	0	0	0	0
2001-Q1	33.15	12.12	11.24	0.64	10.93	11.85	16.43	0	0	0	0
2001-Q2	32.77	16.1	13.44	0.76	12.97	16.33	14.52	0	0	0	0
2001-Q3	32.76	17.57	11.72	0.3	11.72	12.44	16.81	0	0	0	0
2001-Q4	44.94	16.77	19.26	0.39	19.12	8	15.4	0	0	0	0
2002-Q1	46.19	18.9	19.26	0.83	18.72	5.9	15.66	0	0	0	0
2002-Q2	48.6	18.79	24	0.19	23.88	4.77	13.79	0	0	0	0
2002-Q3	40.22	24.22	19.82	0.99	19.05	5.72	10.35	0	0	0	0
2002-Q4	47.47	24	22.9	0.35	22.55	4.34	17.04	0	0	0	0
2003-Q1	44.57	26.72	24.21	0.34	23.9	4.23	13.36	0	0	0	0
2003-Q2	45.91	29.5	28.44	0.42	28.11	4.29	10.48	0	0	0	0
2003-Q3	41.62	34.58	26.83	0.07	26.83	3.5	8.85	0	0	0	0
2003-Q4	44.87	24.7	28.43	0.5	27.93	6.51	10.87	0	0	0	0
2004-Q1	48.19	28.28	33.38	0.08	33.3	2.44	6.68	0	0	0	0
2004-Q2	47	28.94	34.33	0	34.33	3.03	7.06	0	0	0	0
2004-Q3	43.72	31.96	30.22	0	30.22	7.05	6.36	0	0	0	0
2004-Q4	37.9	30.93	22.89	0.31	22.59	11.48	4.74	0	0	0	0
2005-Q1	45.44	26.55	28.37	0.4	27.97	8.16	4.05	0	0	0	0
2005-Q2	46.46	32.62	29.54	0	29.54	6.96	5.43	0	0	0	0

Quarter	PPI	Clopidogrel only	Clopidogrel + PPI	Clopidogrel + inhibiting PPI	Clopidogrel + non-inhibiting PPI	Clopidogrel + H2RA	PPI + H2RA	Prasugrel + PPI	Prasugrel only	Ticagrelor + PPI	Ticagrelor only
2005-Q3	46.22	31.11	27.08	0.02	27.08	7.34	6.77	0	0	0	0
2005-Q4	51.45	29.15	35.04	0.29	34.78	8.43	8.31	0	0	0	0
2006-Q1	50.12	30.17	35.6	2.96	33.08	8.65	6.93	0	0	0	0
2006-Q2	47.53	30.74	30.32	7.39	24.17	11.19	10.13	0	0	0	0
2006-Q3	51.18	27.59	31.78	8.26	23.76	9.59	10.36	0	0	0	0
2006-Q4	49.94	30.18	31.7	8.84	23.02	7.24	7.45	0	0	0	0
2007-Q1	51.9	30.53	34.76	12.59	22.31	5.36	6.13	0	0	0	0
2007-Q2	49.65	31.48	34.18	15.13	19.26	6.56	6.66	0	0	0	0
2007-Q3	49.95	27.67	33.31	14.31	19.23	8.02	7.41	0	0	0	0
2007-Q4	51.66	31.11	34.62	14.25	21.15	5.45	7.06	0	0	0	0
2008-Q1	54.82	28.01	37.11	16.54	20.96	5.7	7.95	0	0	0	0
2008-Q2	51.98	28.53	34.75	19.97	15.31	7.08	6.2	0	0	0	0
2008-Q3	48.48	30.91	33.13	17.96	15.68	9.56	5.54	0	0	0	0
2008-Q4	51.28	28.55	34.48	18.84	15.96	8.64	7.6	0	0	0	0
2009-Q1	49.68	27.3	30.64	18.38	12.75	8.24	10.48	0	0	0	0
2009-Q2	42.7	32.02	23.84	13.75	10.83	12.19	11.21	0	0	0	0
2009-Q3	38.31	33.08	23.06	13.41	10.95	14.57	9.64	0.05	0.02	0	0
2009-Q4	38.53	28.44	20.23	10.67	10.09	15.86	11.63	0.86	1.43	0	0
2010-Q1	33.63	32.11	17.22	9.11	8.83	14.88	11.84	1.1	2.94	0	0
2010-Q2	33.37	32.84	16.3	8.03	8.65	14.28	10.24	2.78	5.16	0	0
2010-Q3	33.57	29.74	15.56	7.38	8.49	13.84	10.85	2.18	4.07	0	0
2010-Q4	34	26.87	16.57	5.72	11.25	14.9	9.36	2.76	6.54	0	0
2011-Q1	33.93	26.83	16.38	6.23	10.61	14.26	9.94	3.17	5.9	0	0

Quarter	PPI	Clopidogrel only	Clopidogrel + PPI	Clopidogrel + inhibiting PPI	Clopidogrel + non-inhibiting PPI	Clopidogrel + H2RA	PPI + H2RA	Prasugrel + PPI	Prasugrel only	Ticagrelor + PPI	Ticagrelor only
2011-Q2	36.21	26.01	16.01	7.77	8.39	12.12	11.66	4.66	6.9	0	0
2011-Q3	36.96	24.33	17.39	8.13	9.95	11.19	10.43	4.92	7.45	0.01	0
2011-Q4	37.14	24.61	17.56	9.48	8.58	8.53	10.74	3.31	8.08	0	0.16
2012-Q1	38.83	23.28	17.75	9.24	9.29	8	11.24	4.99	8.77	0.71	1.17
2012-Q2	37.28	22.52	15.87	5.13	11.26	8.29	9.46	4.1	6.95	1.58	2.65
2012-Q3	39.13	24.2	18.15	6.32	12.43	8.18	10.09	4.62	6.7	1.89	2.66
2012-Q4	38.23	23.41	16.58	5.66	11.46	8.83	10.49	4.1	5.88	1.84	2.77
2013-Q1	39.65	23.79	16.85	4.58	12.74	7.5	9.83	5.77	6.76	2.04	2.83
2013-Q2	41.92	23.23	19.2	3.29	16.64	8.23	11.06	4.43	7.77	2.55	4.04
2013-Q3	40.77	24.55	18.12	2.62	15.91	7.43	11.54	5	7.25	2.85	4.47
2013-Q4	43.17	23.11	18.15	2.66	15.98	6.96	10.85	5.52	6.85	3.01	5.46
2014-Q1	44.01	22.44	18.8	2.7	16.73	7.82	12.16	5.32	7.25	2.84	3.5
2014-Q2	42.94	21.75	18.35	1.75	17	6.66	10.8	5.41	6.06	3.3	5.17
2014-Q3	43.03	21.73	18.7	2.81	16.42	7.32	9.83	4.99	6.52	3.47	5.22
2014-Q4	41.65	22.31	18.44	2.4	16.38	6.8	9.16	3.85	6.23	4.32	7.09
2015-Q1	42.02	20.79	17.29	2.6	15.1	8.06	10.45	4.35	5.53	4.81	7.89
2015-Q2	40.35	21.17	16.87	2.83	14.4	8.92	11.86	4.77	4.88	4.83	7.59
2015-Q3	39.93	20.97	16.16	2.06	14.39	7.55	11.13	3.83	5.18	5.25	9.46
2015-Q4	39.38	20.34	14.76	2.28	12.75	6.47	11.05	3.26	6.06	6.78	9.5
2016-Q1	38.91	20.29	14.66	1.23	13.66	7.05	9.82	3.25	5.08	7.07	9.89
2016-Q2	38.09	20.59	14.08	0.93	13.56	6.46	10.47	3.06	5.53	7.89	11.65
2016-Q3	37.84	20.53	13.72	0.49	13.41	7.46	10.2	3.1	5.04	7.05	11.34
2016-Q4	37.19	20.05	15.07	0.53	14.74	7.49	10.23	2.74	4.64	7.23	11.84

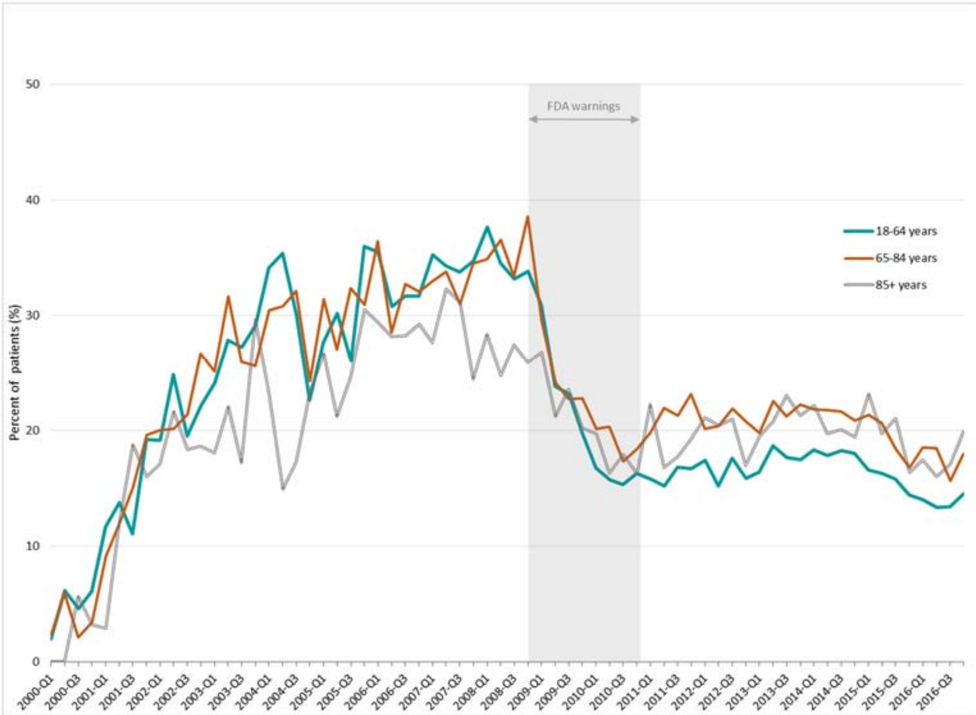

FIGURE S3- 1. STANDARDIZED PREVALENCE OF CLOPIDOGREL AND PPI USE AMONG ACS INPATIENTS, STRATIFIED BY AGE. THE SHADED AREA CORRESPONDS TO THE TIME PERIOD OF THE FDA WARNINGS REGARDING THE POTENTIAL INTERACTION BETWEEN CLOPIDOGREL AND PPIS.

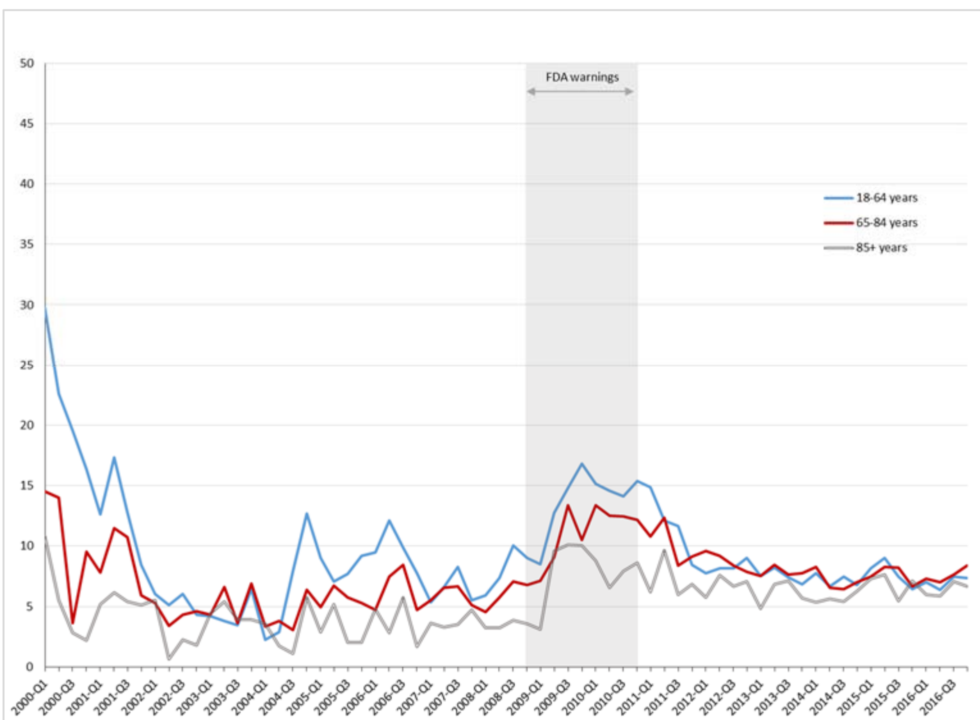

FIGURE S3- 2. STANDARDIZED PREVALENCE OF CLOPIDOGREL AND H2RA USE, AMONG ACS INPATIENTS, STRATIFIED BY AGE.

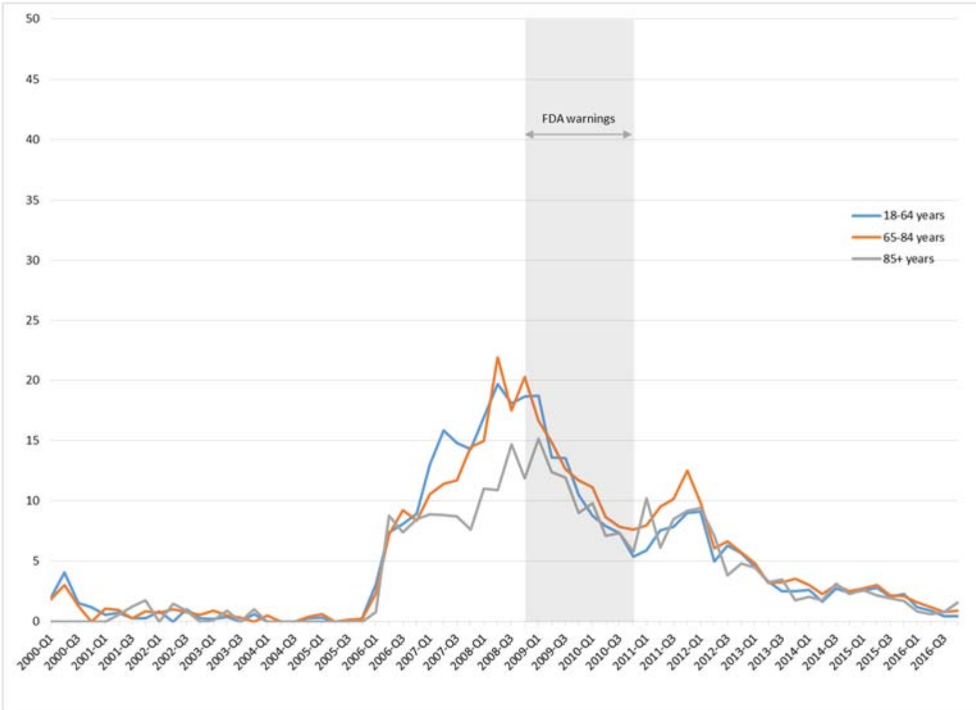

FIGURE S3- 3. STANDARDIZED PREVALENCE OF CLOPIDOGREL AND INHIBITING-PPI USE, AMONG ACS INPATIENTS, STRATIFIED BY AGE.

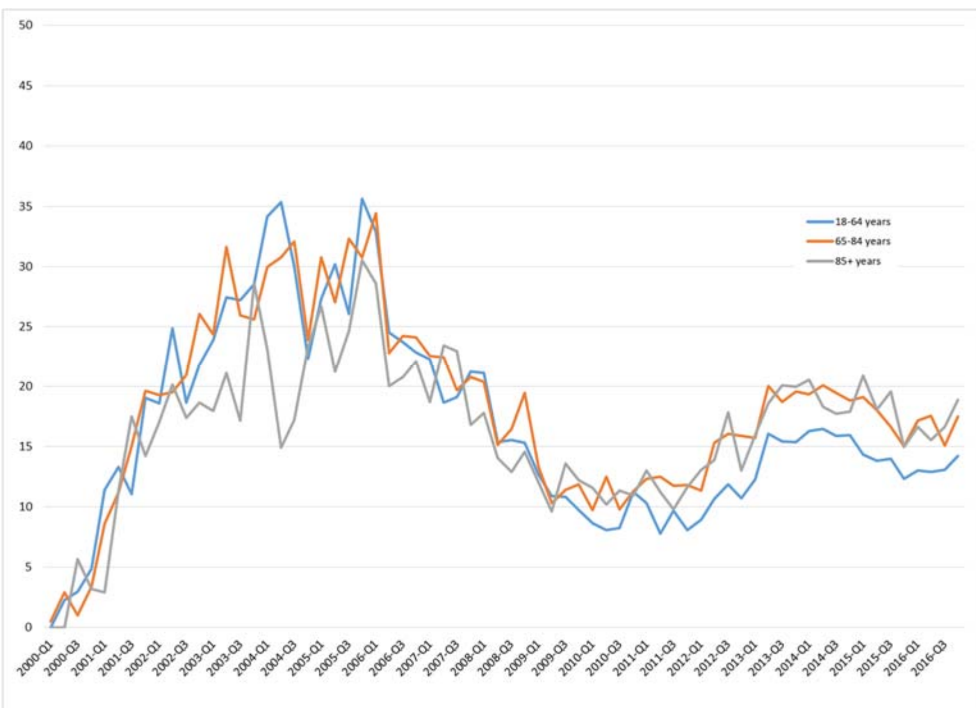

FIGURE S3- 4. STANDARDIZED PREVALENCE OF CLOPIDOGREL AND NON-INHIBITING-PPI USE, AMONG ACS INPATIENTS, STRATIFIED BY AGE.

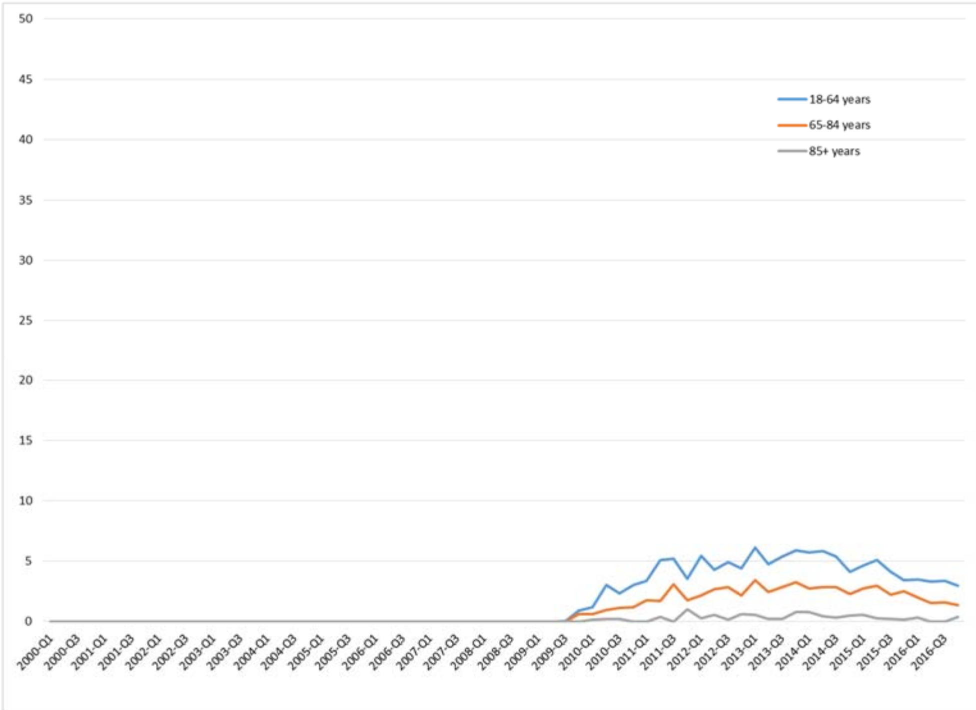

FIGURE S3- 5. STANDARDIZED PREVALENCE OF PRASUGREL AND PPI USE AMONG ACS INPATIENTS, STRATIFIED BY AGE.

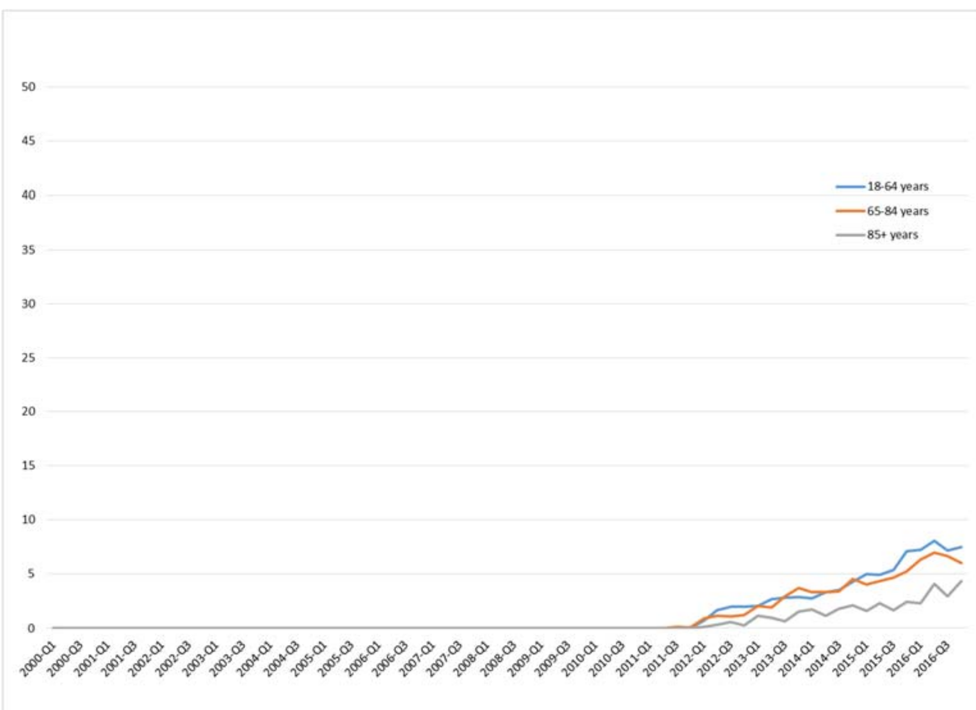

FIGURE S3- 6. STANDARDIZED PREVALENCE OF TICAGRELOR AND PPI USE AMONG ACS INPATIENTS, STRATIFIED BY AGE.

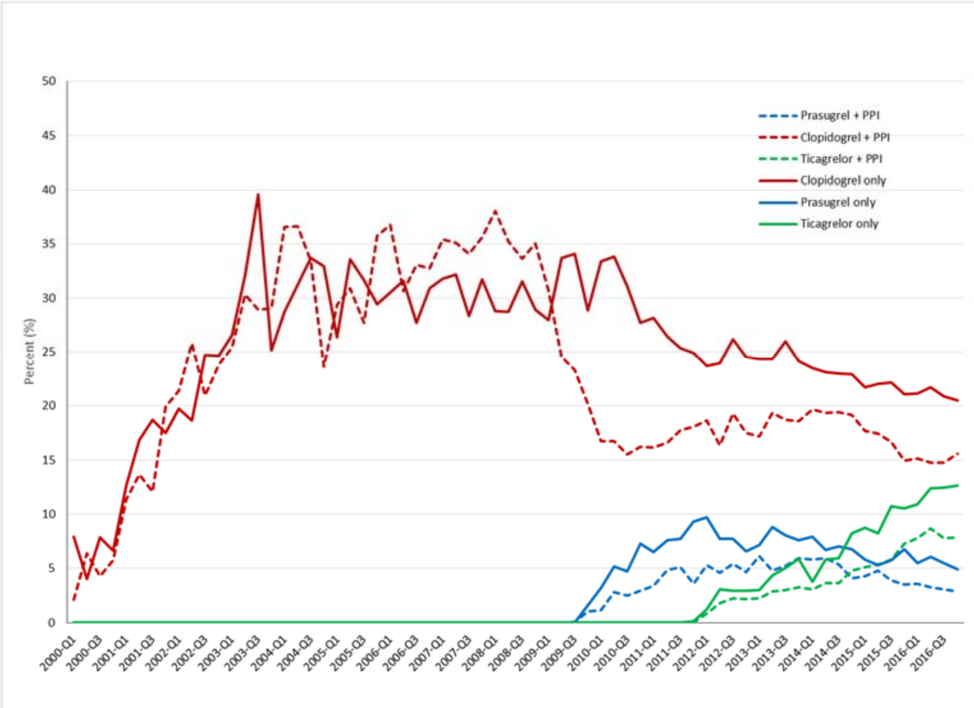

FIGURE S3- 7. STANDARDIZED PREVALENCE OF ANTIPLATELET USE, WITH AND WITHOUT PPIS, AMONG MI INPATIENTS.

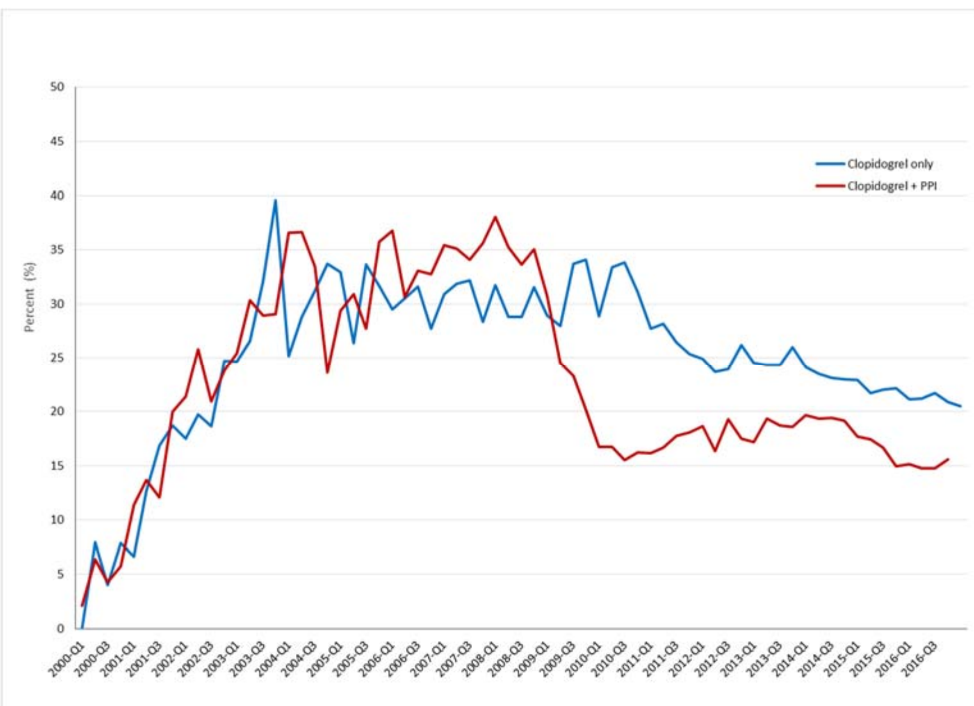

FIGURE S3- 8. STANDARDIZED PREVALENCE OF CLOPIDOGREL USE, WITH AND WITHOUT PPIS, AMONG MI INPATIENTS.

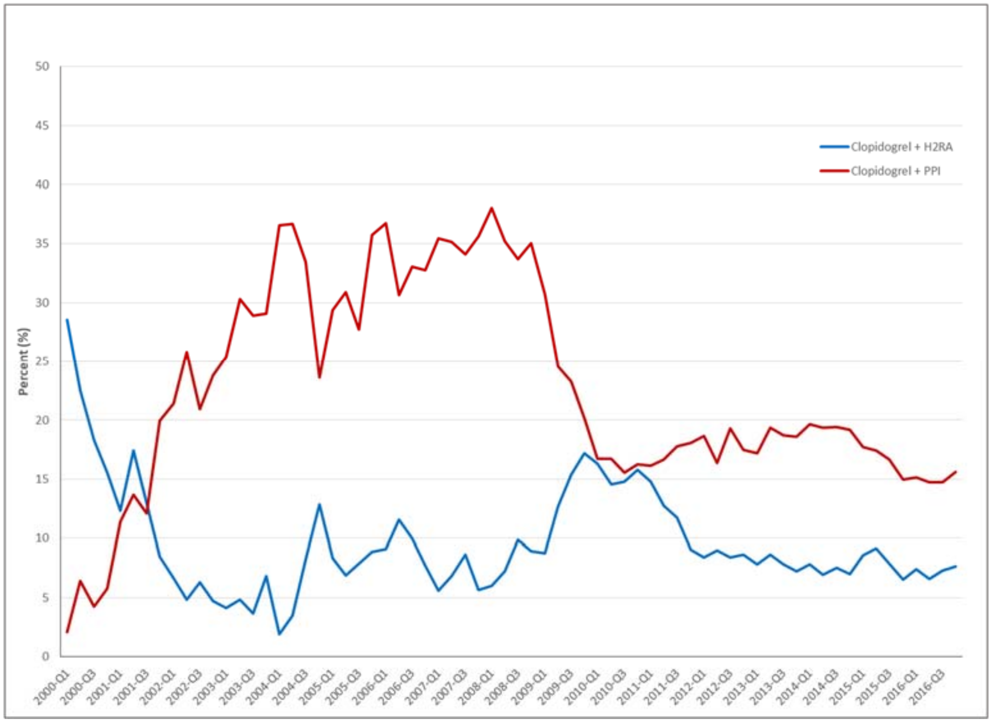

FIGURE S3- 9.   STANDARDIZED PREVALENCE OF CLOPIDOGREL USE WITH PPIS OR H2RAS AMONG MI INPATIENTS.

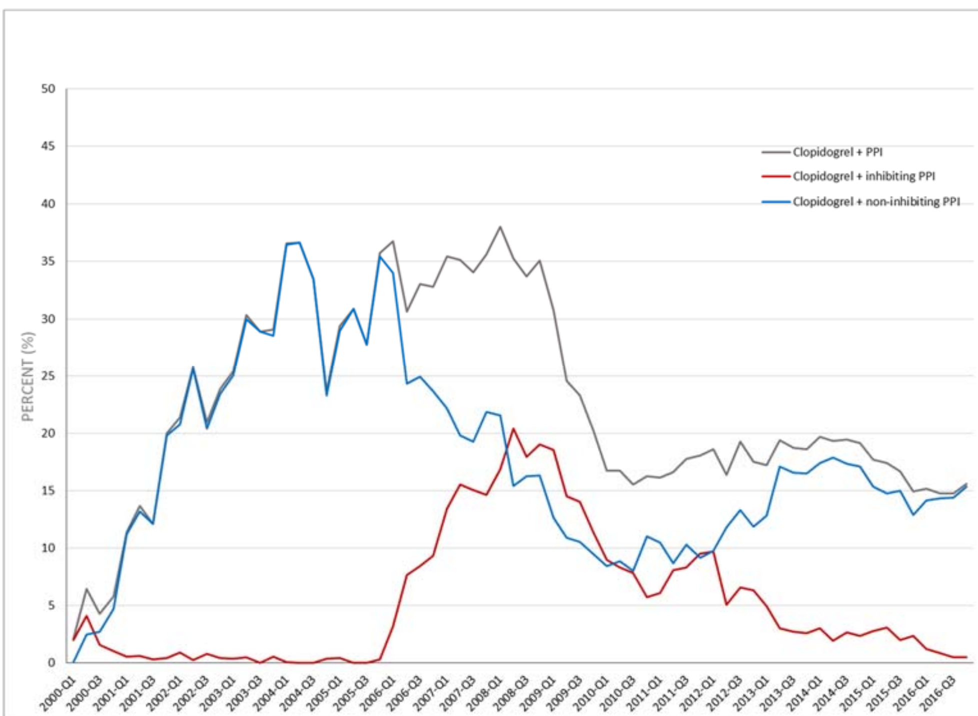

FIGURE S3- 10. STANDARDIZED PREVALENCE OF CLOPIDOGREL USE WITH PPIS, CLASSIFIED BY INHIBITING POTENTIAL OF PPIS, AMONG MI INPATIENTS.

CHAPTER 4

RISK OF ADVERSE CARDIOVASCULAR EVENTS FOLLOWING A MYOCARDIAL INFARCTION IN PATIENTS RECEIVING COMBINED CLOPIDOGREL AND PROTON PUMP INHIBITOR TREATMENT

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PREFACE

The current chapter consists of the third manuscript from this thesis. It directly addresses Objective 3 by quantitatively assessing the risk of four adverse cardiovascular events associated with concomitant clopidogrel and PPI treatment. The study is a nested case-control based on the analysis electronic medical records derived from the Cerner Health Facts® database.

Contributions

I designed the study, performed the analysis and wrote the first draft of the manuscript with guidance from my supervisors. My supervisors and thesis advisory committee provided feedback and suggestions on all aspects of the study design, statistical analyses, and interpretation of findings during our regular meetings and provided suggestions for revisions on the manuscript. Ms Nisrine Haddad contributed to various aspects of the analyses and interpretation of findings as well as revising the draft manuscript. Dr Yannick Fortin contributed to the computation of the Quan Elixhauser Comorbidity Measures index for the statistical analysis, interpreting the findings, and reviewing the manuscript. Dr Andreas Weilgosz provided clinical expert opinion to the selection of covariates (for the statistical analyses) and interpretation of the findings.

Ethical approval for this study was obtained from the Ottawa Health Science Network Research Ethics Board at the Ottawa Hospital, Ottawa, Canada (Appendix A).

RISK OF ADVERSE CARDIOVASCULAR EVENTS FOLLOWING A MYOCARDIAL INFARCTION IN PATIENTS RECEIVING COMBINED CLOPIDOGREL AND PROTON PUMP INHIBITOR TREATMENT

ABSTRACT

Although a drug-drug interaction between PPIs and clopidogrel has been reported in mechanistic studies, the clinical implications of this interaction, investigated in epidemiological studies, have been debated since 2009. In this study, we assess the association between combined clopidogrel-PPI treatment and the risk of the primary outcome of interest – recurrent myocardial infarction (MI) - as well as the risk of three secondary outcomes: stroke, all-cause mortality, and a composite endpoint comprised of all three outcomes.

A nested case control study was conducted within the Cerner Corporation Health Facts® database, comprising electronic medical records (EMRs) for over 69 million patients from 2000 to 2016. The study was based on a retrospective cohort of patients that experienced an MI and started clopidogrel treatment. For each outcome of interest, cases were identified at three, six and 12 months following cohort entry. Each case was matched to a maximum of five controls on age, sex, ethnicity and cohort entry using incidence density sampling. Conditional logistic regression was used to estimate odds ratios (ORs) adjusted for multiple covariates including comedications, comorbidities and hospital characteristics. H2 receptor antagonists (H2RAs) were considered as a negative control exposure; ORs for H2RA use vs non-use were compared to findings for PPI use vs non-use. Findings were

stratified by age group and a number of sensitivity analyses were carried out to evaluate the robustness of the main results.

The study cohort consisted of 52,006 patients, with 2,890 recurrent MI cases identified at 12 months following cohort entry. The adjusted OR for PPI use vs non-use among clopidogrel users was 1.08 (95% CI: 0.95-1.23). Similar ORs, suggesting a lack of an association for both the primary and secondary endpoints, were obtained at three and six months follow-up. A positive association between the combined use of clopidogrel and PPIs was however associated with an increased risk of MI in the 80-89 age group (OR 1.26; 95% CI 1.05-1.51).

The findings of this study generally do not support a significant clinical impact of the combined use of clopidogrel and PPIs among patients that have previously experienced an MI. However, elderly patients receiving combined treatment may be susceptible to an increased risk of MI compared to patients not receiving PPIs.

4.1 INTRODUCTION

Clopidogrel remains a first-choice antiplatelet agent for reducing adverse cardiovascular events in patients with acute coronary syndrome (ACS) or those undergoing percutaneous coronary intervention (PCI) (Pelliccia et al. 2015). Since clopidogrel can increase the risk of gastrointestinal bleeding, treatment guidelines recommend the co-prescription of a proton pump inhibitor (PPI) (Bhatt et al. 2008). The potential for a drug-drug interaction between clopidogrel and PPIs has been investigated in numerous studies since 2009. Pharmacodynamic studies have noted that the antiplatelet activity of clopidogrel is diminished in the presence of PPIs due to competitive inhibition: PPIs are metabolized by hepatic cytochrome (CYP) P450 isoenzyme 2C19 (CYP2C19) which is the enzyme with a major role in the two oxidative steps that are necessary to activate clopidogrel into its active form in the human body (Kazui et al. 2010). Some studies have suggested that PPI types differ in their ability to inhibit CYP2C19; however findings reported have been inconsistent and warrant further investigation (Amin et al. 2017). Following warnings issued by US FDA and other regulatory bodies to avoid concomitant treatment except in high risk patients in 2009, numerous epidemiological studies have been performed to assess the potential for adverse cardiovascular effects of combined treatment relative to treatment on clopidogrel only; findings have been inconclusive regarding the clinical significance of the interaction.

In this study, we assess the association between combined treatment of clopidogrel and PPIs and the risk of a myocardial infarction (MI) and other adverse events (stroke, death from all causes) in a large cohort of US patients that received clopidogrel treatment following an MI.

4.2 METHODS

4.2.1 DATA SOURCE

We used the Cerner Health Facts® database to select a retrospective cohort of patients that were hospitalized for an MI and treated with clopidogrel. Health Facts® consists of electronic medical records (EMRs) that include time-stamped information on admissions, discharges, diagnoses, hospital procedures, drug prescriptions and laboratory tests. Over 500 US hospitals contributed data for over 69 million unique patients from January 1, 2000 to December 31, 2016. Health Facts® complies with Health Insurance Portability and Accountability Act and contains only de-identified information. The study protocol was approved by the Ottawa Health Science Network Research Ethics Board at The Ottawa Hospital, Canada.

4.2.2 COHORT SELECTION

We identified a cohort of patients that were hospitalized for an MI between January 1, 2001 and December 31, 2015. All inpatients and emergency department patients hospitalized with a first MI, received clopidogrel during their hospitalization and were discharged alive were eligible for cohort entry (n= 95,562). Only the first qualifying encounter for each patient was considered. International Classification of Diseases (ICD) codes (ICD-9: 410.xx excluding 410.x2 and ICD-10 I21x) in the principal or secondary position (Kim et al. 2017) indicated in the patients' records were used to identify those admitted with an MI. Patients between 18 and 89 years of age at the time of hospitalization with complete age, sex and ethnicity data were eligible for inclusion, to allow for matching between cases and controls. Patients that had received clopidogrel or had an MI in the year 2000 were excluded (n=85). Patients that received prasugrel or ticagrelor in addition to clopidogrel during the qualifying hospitalization were excluded to avoid having patients that are likely to switch antiplatelets (n=79). Patients with a length of stay of less than three days during their first MI hospitalization were also excluded (n= 37,394) (Figure 4-1). Restricting cohort entry to patients with a minimum of 3-day was important for data on covariates. The rationale behind this decision is that a 3-day stay ensures patients will receive chronic medications as pharmacy orders in the hospital; as such, we can use pharmacy orders data within Health Facts to collect information on chronic medication use at baseline. The length of stay restriction of three days is reported to have a high positive predictive value when used with the primary and secondary positions for MI diagnosis (Kiyota et al. 2004). The date of hospital discharge of the qualifying encounter served as the date of cohort entry for each patient. Further, patients with adjacent encounters that occurred within 24 hours were combined into one encounter having the earlier admission date and the later discharge date of the two encounters. This could happen in two cases: 1) the patient was admitted to one hospital for MI and then transferred to another hospital; or 2) the patient was admitted to ER for an MI and was later admitted as an inpatient at the same hospital. The type of MI experienced by the patient (STEMI, NSTEMI or unspecified) was also identified.

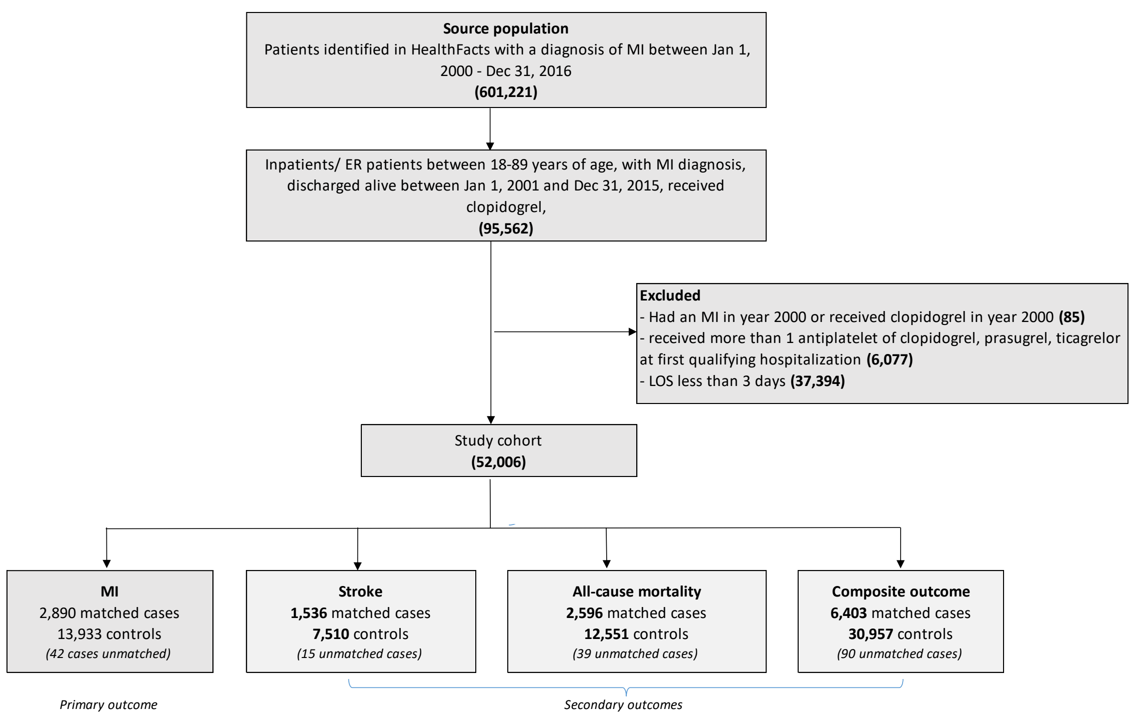

FIGURE 4- 1. SELECTION OF STUDY COHORT AND CASES FROM HEALTH FACTS®.

4.2.3 CASE DEFINITION AND CONTROL SELECTION

PRIMARY OUTCOME

MI cases were selected from the cohort such that a patient was hospitalised with an MI within one year of the discharge date their cohort entry hospitalization. MI cases had to have an ICD code for MI in the principal or secondary position and length of hospitalization at least 3 days (unless the patient died during the hospital encounter). Each case was assigned an index date corresponding to the date of hospitalization of the second MI.

Controls were selected using incidence density sampling. For each case, a risk set of potential controls was constructed. Candidate controls had the same sex (male/female), same ethnicity (Caucasian, African American, other), and similar age as the corresponding case (± 3 years). In addition, the controls had to have entered the cohort within 30 days of the matched case's cohort entry date. Matching on cohort entry was used to ensure cases and matched controls were treated in accordance with similar treatment guidelines which changed over time due to FDA warnings regarding the potential interaction between PPIs and clopidogrel. Up to five controls were randomly selected for each case within each risk set. The risk set sampling methods employed here allow for a patient to serve a control for multiple cases. Further, cases can act as controls for multiple cases until they experience the outcome (Etminan 2004). Cases that could not be matched to at least one control were excluded from the analysis. Similar sampling approaches have been used in recent pharmacoepidemiologic studies (Juurlink et al. 2009; Tascilar et al. 2016) and have been shown to provide consistent risk estimates in nested case control analyses (Lubin and Gail 1984; Lubin 1986; Robins et al. 1986; Wang et al. 2009).

SECONDARY OUTCOMES

The secondary outcomes assessed were stroke, all-cause mortality, and the composite outcome (stroke, MI and all-cause mortality). Cases for secondary outcomes were selected using a similar approach as for MI case selection. Patients that were admitted to the hospital within one year of cohort entry and had an ICD code for stroke as the primary diagnosis were identified as stroke cases. Patients who we readmitted during the one-year post cohort entry for any reason and had a discharge disposition of death were identified as cases for the all-cause mortality endpoint. For the composite outcome, patients that experienced any one of MI, stroke or death from any cause were considered cases. Only the earliest event after cohort entry event was considered among patients that experienced more the one event. The date of admission for a case event was designated as the index date and only the first eligible readmission was considered for each patient in the cohort. Up to 5 controls were matched to each case using the methods outlined above for the primary outcome. Each outcome was analysed separately.

4.2.4 MEDICATION EXPOSURE ASSESSMENT

Exposure to medications was assessed using the hospital pharmacy orders available in Health Facts®. Patients were selected such that they received clopidogrel during their first hospitalization for MI. As the guidelines by the ACA/AHA recommend a duration of dual antiplatelet therapy for 12 months for most patients (Levine et al. 2016), patients that received clopidogrel during their hospitalization for MI were assumed to have maintained treatment for 12 months after initiation. For the key exposure variable, PPI, patients were classified as exposed or unexposed based on whether or not they had received any type of PPI during their first hospitalization that qualified for cohort entry. The type of PPI that the patient received during hospitalization was identified for subgroup analyses. The PPI exposure status was considered constant for each patient for 12 months post cohort entry or until the patient became a case, whichever occurred earlier. We also assessed the use of medications that are associated with either the exposure or the outcome, and were selected based on a review of similar studies in the literature and clinical expert opinion. Patients records were searched to determine whether they an order for each medication was dispensed during the first hospitalization that lead to cohort entry. All patients in the cohort were classified as exposed to a specific medication if their medication records included a valid order for that medication; otherwise they were classified as unexposed.

4.2.5 COMORBIDITIES AND CARDIOVASCULAR PROCEDURES

Comorbidities were assessed for each patient the electronic diagnoses records. We determined whether each patient had an ICD diagnosis code for any of the 30 comorbidities of the Quan Elixhauser Comorbidity Measures (ECM) (Quan et al. 2005) (originally developed by Elixhauser, Steiner, and Harris (1998)). The use of ECM index was recently validated in Health Facts® and was demonstrated to be a good predictor of in-hospital mortality with 1 year of follow-up (Fortin et al. 2017a; Fortin et al. 2017b). Patients that had a diagnosis for a condition during any encounter within the year preceding cohort entry were assumed to have the condition. We computed a comorbidity score based on a modified ECM defined as the sum of all the conditions a patient has (of the 30 ECM conditions) minus the sum of ten conditions that are related to the exposure or outcome. The latter group consists of the following: congestive heart failure, cardiac arrhythmia, valvular disease, pulmonary circulation disorders, peripheral vascular disorders, hypertension, diabetes with complications, peptic ulcer disease, coagulopathy and blood loss anemia list them. Each of these diseases was included as an individual covariate in the regression models described below.

In addition, patients that had undergone any coronary revascularization (coronary artery bypass grafting (CABG), PCI, or carotid revascularization (carotid endarterectomy, stenting, angioplasty or atherectomy, or carotid bypass) procedures were identified.

4.3 STATISTICAL METHODS

4.3.1 PRIMARY ANALYSIS

Baseline characteristics for the cases and controls for each outcome of interest at 12 months post cohort entry were compared. The means and standard deviations of continuous variables were reported; the Mann-Whitney U test was used to evaluate the significance of the difference between the cases and controls if the variable was not normally distributed (based on the Shapiro Wilk test). For categorical variables, we reported the corresponding frequencies and percentages and made comparisons using the chi-square test.

We used conditional logistic regression to estimate the adjusted odds ratio (aOR) and 95% confidence interval (CI) of hospital readmission for a second MI for PPIs users compared to non-users. The odds ratios were assessed at three, six and 12 months following cohort entry. Models were further adjusted for additional variables selected based on prior studies and expert clinical opinion, including variables reflecting demographics, comorbidities, use of comedications, prior cardiovascular procedures, and hospital characteristics. The comorbidity score (described above) was included as a continuous variable and the ten individual comorbidities were included as separate covariates in the regression model. The year of cohort entry, the length of hospital stay of first MI encounter as well as select characteristics of the admitting hospital (acute status, number of beds, presence of diagnostic catheterization lab, teaching facility) were tested for inclusion in the model; variables that resulted in at least 10% relative increase in the adjusted ORs were included in the regression model (Greenland 1989). Findings for the primary outcome were stratified by age at time of cohort entry (18-64 years; 65-79 years; 80-89 years), and by the type of PPI that the patient received at cohort entry. All statistical analyses were completed using SAS software, version 9.4 (SAS Institute Inc, Cary, NC).

SENSITIVITY ANALYSES

The ORs for PPI use vs nonuse were compared with the ORs for H2 receptor antagonists (H2RAs) use vs nonuse for the primary outcome. H2RAs were assumed to act as a negative control exposure since they have similar indications to PPIs and have not been reported to interact with clopidogrel or to be associated with major adverse cardiovascular outcomes. We also performed a sensitivity analysis using laboratory results in Health Facts® for troponin, the biomarker for cardiac injury. We restricted the MI patients identified for cohort entry and selected as MI cases to those with a high cardiac troponin value (≥0.04 ng/ml for cardiac troponin I (cTn I) and ≥ 0.01 for cardiac troponin T (cTn T)), in addition to the case definition used in the main analyses.

4.3.2 SECONDARY OUTCOMES

For each of the secondary outcomes of stroke, in-hospital mortality, and the composite endpoint adjusted ORs evaluating PPI use vs nonuse were estimated at 3-, 6-, and 12-month post cohort entry using the methods described above.

4.4 RESULTS

4.4.1 PRIMARY OUTCOME

We identified a cohort of 52,006 patients that had been hospitalized for a first MI in Health Facts®, received clopidogrel during that hospital encounter, and were discharged alive (Figure 4-1). More than half of the cohort (56.3%) received PPIs in addition to clopidogrel during their first hospitalization for an MI. The mean age of the cohort was 67.8 years (standard deviation SD = 12.9 years). The majority of patients were of Caucasian ethnicity (82.1%) and male (59.3%). Forty percent of the cohort was covered through Medicare, while 15.8% had private insurance. Medicaid beneficiaries comprised 6.3% of the cohort and 33.4% had missing or unknown health insurance provider in the database (Table 4-1). A detailed description of the study cohort is presented in the Supplemental Material (Table S4-2).

We identified 2,932 cases hospitalized for an MI within 12 months of cohort entry. Of these, 2,890 cases were matched to 13,933 controls. Forty-two cases could not be matched to at least one control and were excluded from the analysis: these cases were mainly of non-Caucasian ethnicity (90%), females (60%) and were generally under 50 years old or over 80 years old. Table 2 presents detailed demographic and clinical characteristics of the matched MI cases and controls included in the analysis. The proportion of females and mean age of patients were not significantly different between cases and controls. However, there was a notable difference in the mean Elixhauser comorbidity weighted index: 15.2 for cases and 10.8 for controls. Cases were more likely than controls to smoke (23.7% vs 17.8%) and to be obese (21.1% vs 14.8%). Cases were also more likely to have experienced a non-ST-elevation MI (NSTEMI) (70.8% vs 59.6%) and to have been diagnosed with congestive heart failure (63.1% vs 41.0%), diabetes

TABLE 4- 1. CHARACTERISTICS OF THE STUDY COHORT (N=52,006).

Characteristic	Percent
Age (years)*	67.8 (12.9)
Comorbidity score*	4.3 (2.8)
Sex	
Male	59.3%
Female	40.7%
Ethnicity	
Caucasian	82.1%
African American	13.3%
Other	4.6%
Health insurance status	
Medicare	39.8%
Medicaid	6.3%
Uninsured	4.7%
Private	15.8%
Missing/unknown	33.4%
Census Region	
Midwest	13.0%
Northeast	46.6%
South	31.5%
West	9.0%

* Mean (standard deviation) are reported.
ACE: angiotensin converting enzyme; CABG: coronary artery bypass grafting; CCBs: calcium channel blockers; GPR: glycoprotein IIb/IIIa receptor; H2RA: H2 receptor antagonist; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; PPI: proton pump inhibitor; STEMI: ST-elevation myocardial infarction.

(21.5% vs 10.8%), hypertension (22.9% vs 10.5%), and peptic ulcer disease (2.3% vs 1.1%) among other diseases, when compared to the controls. Further, cases were more likely to receive PPIs (58.8% vs 54.6%), aspirin, loop diuretics, calcium channel blockers (CCBs), beta blockers and antihyperglycemic agents. On the other hand, controls were more likely to have been hospitalized at hospitals in urban regions relative to cases.

TABLE 4- 2. STUDY SAMPLE DESCRIPTION FOR MI AT 12 MONTHS FOLLOW-UP.

		Cases N=2,890		Controls N=13,933		p-value
		No.	%	No.	%	
Age (years)*†		70.2	(12.1)	70.4	(11.7)	0.4
LOS at cohort entry (days)*‡		8.3	(7.3)	8.0	(7.7)	0.1
Comorbidity score*		5.9	(3.0)	4.0	(2.8)	<0.0001
Sex†	Females	1,262	43.6	6,029	43.3	0.7
Ethnicity†	African American	418	14.5	1,855	13.3	<0.0001
	Caucasian	2,348	81.2	11,690	83.9	
	Other	126	4.4	394	2.8	
Health insurance status‡	Medicare	1,422	49.2	6,799	48.8	<0.0001
	Medicaid	200	7.0	853	6.1	
	Private	412	14.3	1,560	11.2	
	Uninsured	119	4.1	492	3.5	
	Missing/unknown	737	25.5	4,229	30.4	
Census Region	Midwest	320	11.1	2,086	15.0	<0.0001
	Northeast	1,563	54.1	7,314	52.5	
	South	789	27.3	3,347	24.0	
	West	218	7.5	1,186	8.5	
Obesity‡		611	21.1	2,066	14.8	<0.0001
Smoking		686	23.7	2,480	17.8	<0.0001
MI Type	NSTEMI	2,047	70.8	8,306	59.6	<0.0001
	STEMI	396	13.7	2,969	21.3	
	Unspecified	447	15.5	2,658	19.1	
CV procedures	PCI stent	1,394	48.2	7,171	51.5	<0.01
	CABG	170	5.9	982	7.1	0.02
	Carotid revascularization	49	1.7	234	1.7	1.0
Comedications	Aspirin	1,465	50.7	5,501	39.5	<0.0001
	ACE inhibitors	1,673	57.9	8,217	59.0	0.3
	Beta blockers	2,669	92.4	12,469	89.5	<0.0001
	CCBs	1,023	35.4	4,422	31.7	<0.0001
	Direct vasodilators	751	26.0	3,330	23.9	0.02
	Loop diuretics	1,784	61.7	7,591	54.5	<0.0001
	Potassium diuretics	257	8.9	1,068	7.7	0.03
	Thiazide diuretics	285	9.9	1,324	9.5	0.6
	Fibrates	103	3. 6	455	3.3	0.4
	Statins	2,590	89.6	12,453	89.4	0.7
	GPR antagonists	537	18.6	3,421	24.6	<0.0001
	Warfarin	377	13.0	2,147	15.4	<0.01
	Antihyperglycemics	508	17.6	2,099	15.1	<0.001
	Lytics	81	2.8	368	2.6	0.6
	PPIs	1,700	58.8	7,601	54.6	<0.0001
	H2RAs	714	24.7	3,850	27.6	<0.01
Comorbidities	Congestive heart failure	1,820	63.1	5,682	41.0	<0.0001
	Cardiac arrhythmia	1,398	48.5	5,648	40.7	<0.0001
	Valvular disease	871	30.2	2,674	19.3	<0.0001
	Pulmonary circulation disorders	359	12.5	986	7.1	<0.0001
	Peripheral vascular disorders	793	27.5	2,037	14.7	<0.0001
	Hypertension	659	22.9	1,452	10.5	<0.0001
	Diabetes complicated	620	21.5	1,493	10.8	<0.0001
	Peptic ulcer disease	67	2.3	156	1.1	<0.0001
	Coagulopathy	243	8.4	815	5.9	<0.0001
	Blood loss anemia	77	2.7	181	1.3	<0.0001
Hospital characteristics	Hospital with full catheterization lab	2,178	75.4	11,221	80.6	<0.0001
	Acute care hospital‡	2,883	99.8	13,930	100.0	<0.0001

	Cases N=2,890		Controls N=13,933		p-value
	No.	%	No.	%	
Hospital in urban location	2,178	75.4	11,940	85.7	<0.0001
Bed size 200-500‡	1,142	39.5	7,497	53.8	
Bed size <200‡	456	15.8	1,460	10.5	<0.0001
Bed size >500‡	1,290	44.7	4,973	35.7	

* Mean (standard deviation) are reported; comparison made using Mann Whitney U test.
† Matching variable.
‡Variable not included in regression models.
ACE: angiotensin converting enzyme; CABG: coronary artery bypass grafting; CCBs: calcium channel blockers; GPR: glycoprotein IIb/IIIa receptor; H2RA: H2 receptor antagonist; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; PPI: proton pump inhibitor; STEMI: ST-elevation myocardial infarction;

Conditional logistic regression performed on the matched MI cases and controls in the primary analyses were adjusted for all the variables in Table 4-3, excluding matching variables (age, sex, and ethnicity) and length of stay, health insurance status, acute status of hospital and hospital bed size. The latter group of variables were excluded based on empirical testing, as their inclusion had an insignificant impact (less than 10% relative change) on the adjusted OR. The health insurance status was not included in the model due approximately 30% of the study sample having *missing* or *unknown* health insurance status.

The adjusted OR for experiencing an MI at 12 months post cohort entry for patients that received concomitant clopidogrel-PPI treatment compared to those that received clopidogrel without a PPI was 1.05 (95% CI: 0.96-1.15). Similar aORs were found at 3 and 6 months post cohort entry (Figure 4-2). Referring to the negative control, H2RAs, the aOR at 12 months follow-up was slightly lower also showing no statistical significance aOR 0.93 (95% CI: 0.84-1.04). Similar patterns were observed at three and six months follow-up periods.

Adjusted ORs were stratified by age group. Findings suggest a positive association in the 80-89 year old age group (aOR =1.26 (95% CI: 1.05-1.51), but not in the younger age groups (Figure 4-3). In contrast, a protective effect was estimated for H2RA use among the 18-64 years age group.

Similar findings were observed for the 3 months and 6 months follow-up periods (Supplemental Material, Table S4-3).

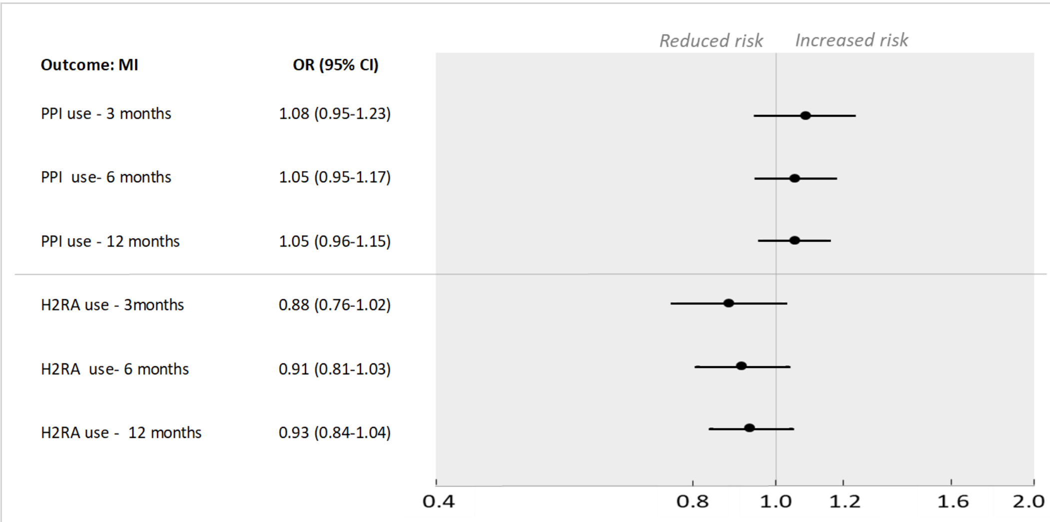

FIGURE 4- 2. ADJUSTED ORS FOR RISK OF MI RECURRENCE WITH PPI USE (VS NONUSE) OR H2RA USE (VS NONUSE) AMONG CLOPIDOGREL USERS AT 3, 6 AND 12-MONTHS FOLLOW-UP.

Subgroup analyses were performed by type of PPI the patient received during the cohort-qualifying hospitalization. The adjusted OR for receiving omeprazole suggested a protective effect for recurrent MI (OR =0.52, 95% CI: 0.40-0.68), whereas the OR for receiving lansoprazole suggested an increased risk of recurrent MI (OR 4.14, 95% CI: 2.73-6.27). In interpreting these findings, it is important to keep in mind the relatively low number of MI events among patients receiving either lansoprazole (N=57) and omeprazole (N=85) and the low prevalence of exposure to either of these PPIs among controls (0.4% for lansoprazole and 4.4 for omeprazole). Sample size calculations suggest that the subgroup analyses lack sufficient power to detect the observed ORs and are therefore may not be meaningful. Detailed findings on this analysis are discussed in the Supplemental Material (Table S4-4).

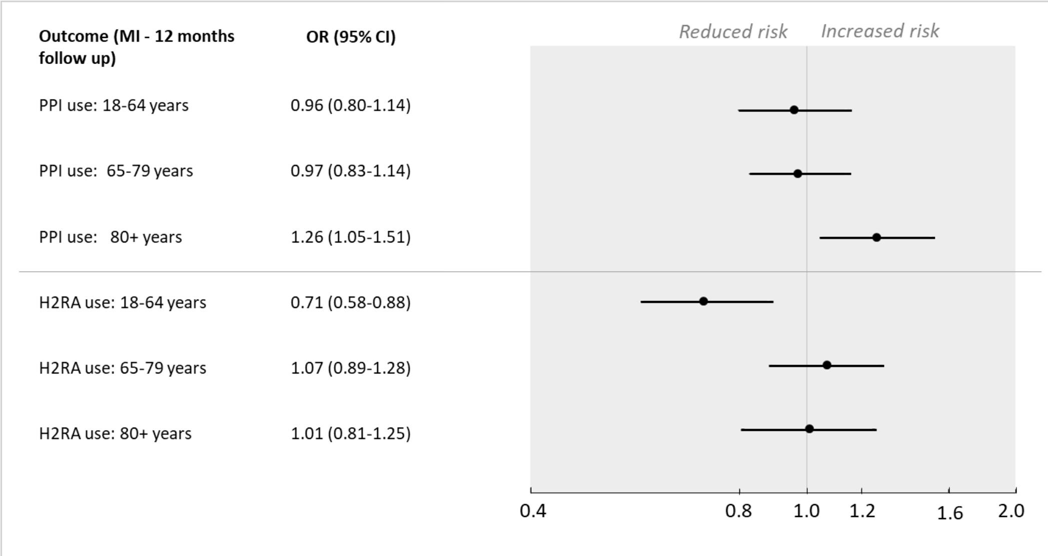

FIGURE 4- 3. ADJUSTED ORS FOR PPI USE (VS NONUSE) OR H2RA USE (VS NONUSE) AND MI RECURRENCE AMONG CLOPIDOGREL USERS AT 12 MONTHS POST COHORT ENTRY, STRATIFIED BY AGE.

A sensitivity analysis showed no notable change in the adjusted ORs when the study cohort and MI cases were restricted to patient with high values for cardiac troponin. The number of MI cases and controls analysed was 1,108 and 5,130, respectively. The aOR was 1.06 (95% CI: 0.91-1.24) at 12 months post cohort entry, similar to the odds ratio obtained for the primary analysis but with wider confidence intervals as a result of smaller sample size. A comparable aOR to the primary analyses was also obtained for H2RA use (aOR 0.93 (95% CI: 0.77-1.12).

4.4.2 SECONDARY OUTCOMES

A total of 1,551 stroke cases and 2,635 in-hospital mortality cases were identified within 12 months of cohort entry, of which 1,536 and 2,596 cases were matched to 7,510 and 12,551 controls, respectively. For the composite outcome, a total of 6,493 cases were identified within the same period, of which 6,403 cases were matched to 30,957 controls (Figure 4-1).

Adjusted ORs for PPI use vs nonuse at 12-months follow-up were elevated, but not statistically significant, for all-cause mortality (OR 1.04, 95% CI: 0.95-1.15) and the composite endpoint (OR 1.04, 95% CI: 0.98-1.11). A slightly lower OR was obtained for the stroke outcome (OR 0.96, 95% CI: 0.85-1.08). Detailed description of the study sample analysed for each of the secondary outcomes, the aORs at the remaining follow-up periods as well as the corresponding ORs for H2RA use vs nonuse can be found in the Supplemental Material (Tables S4-5, S4-6 and S4-7).

4.5 DISCUSSION

Since the first reports of a potential interaction between the clopidogrel and PPIs (Gilard et al. 2006; Gilard et al. 2008), many observational studies have investigated the potential clinical impact among patients receiving concomitant treatment with both drugs and have arrived at inconsistent findings. In the present case control study, we analysed EMRs that represent real-world data over a 17-year period for a cohort of patients that initiated clopidogrel treatment after experiencing an MI. Overall, findings do not support an association between the concomitant use of clopidogrel and PPIs and an increased risk for MI readmission, or for stroke, all-cause mortality, and the composite endpoint.

Based on the biological interaction reported between PPIs and clopidogrel, PPIs have the potential to compete for the active site of the CYP2C19, the enzyme mainly responsible for converting clopidogrel into its active form. It is hypothesized clopidogrel's antiplatelet activity is attenuated by way of competitive inhibition, potentially putting the patients taking both medications at an increased risk of a cardiovascular event relative to clopidogrel-treated patients not receiving PPIs. Findings from this study however do not provide evidence of an association between combined treatment and any of the clinical endpoints assessed. Our findings may indicate that although a biological interaction does occur, it may not translate into significant adverse effects among the majority of ACS study cohort.

Although findings do not support an association between combined treatment recurrences of an MI, we did report an increased risk of MI recurrence may be present among patients 80+ years of age: patients in this age group that received a PPI appeared to be more susceptible to experiencing a second MI compared to patients not receiving PPI (OR 1.26, 95% CI: 1.05-1.51). There may be several explanations for why this association was not observed in the younger age groups. First, this patient population is likely to be on multiple medications in addition to PPIs due to the increased number of comorbidities that occur with age (Hajjar et al. 2007; Kantor et al. 2015), and may therefore more susceptible to experiencing drug-drug interactions (Maher et al. 2014). Moreover, a study by Doan et al. (2013) reported that the risk of CYP-medicated drug-drug interactions is high among elderly patients with polypharmacy (defined as five medications or more), with the risk increasing with the number of medications the patient is receiving. PPIs are one of many drugs metabolized by the CYP pathway. Another possibility may be that clopidogrel-PPI interaction demonstrated in mechanistic studies may in be clinically meaningful only among the elderly. Specifically, it may be that the elderly patients over 80 years of age are more vulnerable to adverse drug events due to metabolic and physiologic changes that come with increased age. For example, clearance of drugs metabolized by the liver decreases in the elderly by as much as 30-40%, possibly as a result of reduced liver mass and hepatic flood flow (Pennsylvania Patient Safety Authority 2005). In addition, PPIs were added to the Beers list in 2015, advising against the use of PPIs for more than 8 weeks among elderly patients except among high risk patients (American Geriatric Association 2015). These guidelines were put in place due to strong evidence associating PPI use with Clostridium difficile infection, bone loss and fractures.

Our findings are consistent with prior studies that have reported a lack of an association between concomitant treatment and an increased risk for an MI relative to treatment with clopidogrel alone (O'Donoghue et al. 2009; Rassen et al. 2009; Charlot et al. 2010; Sarafoff et al. 2010; Zairis et al. 2010; Harjai et al. 2011; Simon et al. 2011; Valkhoff et al. 2011; Aihara et al. 2012; Douglas et al. 2012; Zou et al. 2014). This finding supports the idea that although mechanistic studies show that PPIs have the potential to attenuate the pharmacodynamic effects of clopidogrel, it is possible that this does not translate into adverse clinical outcomes.

O'Donoghue et al. (2009) reported a significantly lower inhibition of platelet aggregation among patients on combined treatment relative to patients on clopidogrel alone. These same authors reported findings performed post-hoc analysis of the TRITON-TIMI 38 trial and did not detect an association between PPI use and the composite endpoint of cardiovascular mortality, MI or stroke among clopidogrel users. The authors speculate that despite the attenuation of the antiplatelet effect of clopidogrel in vitro, the effect may be insufficient to lead to an increased risk of adverse clinical events. A similar situation exists in the literature focusing on possible interactions between atorvastatin and clopidogrel which are frequently co-prescribed to heart disease patients. Atorvastatin is extensity metabolized by CYP3A4, which has been hypothesized to competitively inhibit the activation of clopidogrel since CYP3A4 is has a role in activating clopidogrel. The attenuation of the antiplatelet effect of clopidogrel by atorvastatin was reported in a study measuring platelet aggregation ex-vivo in 2003 (Lau et al. 2003). However, studies assessing clinical impact of the potential interaction found no effect on mortality, MI or stroke among patients treated with both drugs (Saw et al. 2003; Wienbergen et al. 2003).

Various studies have reported positive associations between PPIs and adverse cardiovascular events, but have attributed the observed findings to unmeasured confounders (Rassen et al. 2009; Charlot et al. 2010; Stockl et al. 2010; Mahabaleshwarkar et al. 2013). In this study, we matched the cases to controls on important characteristics and included an extensive list of variables including comedications and comorbidities, to adjust for possible confounders that may affect the exposure or the outcome. Of note is the inclusion of the comorbidity index, which was based on the Elixhauser Comorbidity Measures. Conditions related to the outcome or exposure were removed and put directly into the regression model. We also included smoking status of patients referred from the presence of ICD codes for tobacco use (ICD9 305.1; ICD-10: F17.x and Z72.0). Smoking is a well-documented risk factor for MI (Teo et al. 2006). Additionally, smoking may be associated with PPI use, as smokers are at increased risk of developing peptic ulcers and may therefore be more likely to receive PPIs (Eastwood 1988).

H2RAs as negative control

Odds ratios reflecting the risk of adverse cardiovascular outcomes among patients taking H2RAs were presented, effectively representing a negative control group. Negative controls can be used in epidemiology to detect confounding and selection bias in the observed associations where the role of the control is to essentially “produce a condition that cannot involve the hypothesized causal mechanism, but is very likely to involve the same sources of bias that may have been present in the original association” (Lipsitch et al. 2010). H2RAs have similar indications to PPIs, although PPIs are more effective in treating GI bleeding in patients receiving antiplatelet agents (Scott et al. 2014); however, the biological mechanism hypothesized to exist between PPIs, clopidogrel and adverse cardiovascular events does not apply to H2RAs. In this case, if a positive association between H2RA use and MI is estimated from the same model used to assess the PPI-MI association, it would indicate bias in the PPI-MI associations. The opposite is also true, in that if a null association is obtained between H2RAs and MI in the same model used to assess the PPI-MI association, this would indicate that the association between PPIs and MI is unbiased (assuming that H2RAs are the negative control) (Lipsitch et al. 2010). In this study, adjusted ORs for H2RAs were evaluated for every outcome and were comparable to the OR for PPIs, suggesting that potential confounders that could significantly impact the findings may have been adequately controlled for. In fact, H2RAs as a negative control have been used in the literature to confirm the opposite scenario. In a Canadian study, Juurlink et al. (2013) reported a two-fold higher risk of MI recurrence in both elderly patients that had initiated PPIs (compared to no PPIs) as well as in patients that had initiated H2RAs (compared to no H2RAS). Since H2RAs have no known causal link to MIs, the authors dismissed the presence of an association and interpreted their findings due to bias or confounding. Similar interpretations of findings were reported by Goodman et al. (2012) and Charlot et al. (2010). Moreover, given the absence of an RCT where PPI exposure is randomized among patients, Kwok and Loke (2010) suggested the conduct of an RCT where H2RAs can serve as an appropriate control exposure among clopidogrel treated patients.

4.5.1 LIMITATIONS

The use of EMRs collected for purposes other than epidemiological research, while providing large sample sizes, introduces some limitations. Drug exposure was assessed at the time of admission for a first MI and was assumed to be constant during the 12-month follow-up period or until the patient experience an outcome of interest (whichever occurred first). During follow-up, we did not have information on patients' adherence to the medication regimen they received at cohort entry, including whether they had switched between difference antiplatelet agents, discontinued any of the drugs or initiated new medications. These factors could not be accounted for in the analysis and could potentially bias the results. However, although switching between antiplatelet agents is possible, a large multicenter study reported that 76.2% of patients that were discharged on DAPT did not switch to another antiplatelet during the first 12 months following initiation (Bueno et al. 2017). To minimize the potential for including patients that are likely to switch antiplatelet agents, we excluded patients that had received more than one of three common antiplatelets (clopidogrel, prasugrel and ticagrelor) during their first hospitalization.

Further, information on the use of over the counter drugs was not available for use in our analyses. As PPIs and aspirin are available without prescription in the US, which may result in exposure misclassification for these medications. It is possible for patients that received PPIs during hospitalization to discontinue it at a later time, or for patients that had not received PPIs to initiate it post cohort entry. This type of misclassification – if nondifferential and corresponds to a dichotomous exposure - has the potential to bias results towards the null, and would be expected to more pronounced with time since exposure assessment (at cohort entry in this study) (Rothman 2002; Schneeweiss 2010). Findings from this study do not indicate that the ORs moved towards the null with increasing follow-up periods from 3 months to 1 year. This may suggest, that if misclassification of exposure is present there is no indication that it introduces significant bias to our findings.

The potential for misclassification of outcome also exists as the cohort entry eligibility and the identification of MI cases was based on ICD diagnosis codes. However, findings from the sensitivity analyses show that the ORs were similar when the MI definition was made more stringent by adding the condition of positive cardiac troponin level confirming the diagnosis. Another limitation is that Health Facts® does not capture potential cases admitted to health facilities not reporting to Cerner, as well as deaths that occur outside hospitals. We had also intended to assess risk of PPI exposure with cardiovascular mortality among the cohort but were unable to do so as we did not have information on the cause of death of deceased cases.

Finally, there were variables used in the analysis which had missing data. Patients with missing information on ethnicity (2.67%), gender (0.15%) and age (0.80%) were excluded from cohort entry. The proportions of these observations that are missing are small and their exclusion is not likely to bias our findings. Further, approximately 30% of the cohort had missing or unknown values for health insurance status, a variable that can serve as an indicator of socioeconomic status. We decided not to include this variable in the regression model and performed a sensitivity analysis by assessing the effect of this variable when included or excluded from the models. Results show that incorporation of health insurance status did not have a notable effect on the odds ratios, where the percent change in odds ratios was between 1.25% and 1.05%

compared to results excluding the variable. This was consistent across all four outcomes at the three follow-up periods assessed (Supplemental Material, Table S4-9).

4.5.2 STRENGTHS

The current study has many strengths including a large and geographically diverse cohort of US patients from over 500 health centers and covering the 2000-2016 period. The cohort was selected from health records of over 69 million US patients residing across all census regions of the United States. The Health Facts® database is rich in real-world clinical information that allowed us to adjust the findings for many potential confounders. In particular, the reported ORs were adjusted for smoking and obesity; smoking was included as a separate dichotomous covariate and obesity was included in the comorbidity score. Both variables are not commonly captured in administrative databases and have been reported as limitations in similar prior studies (van Boxel et al. 2010; Charlot et al. 2010; Stockl et al. 2010; Schmidt et al. 2012; Mahabaleshwarkar et al. 2013). Further, the large study sample further allowed us to stratify the findings by age groups and perform sensitivity analyses using laboratory data.

4.5.3 CONCLUSION

Findings from this case control study nested in a large retrospective cohort of patients that had experienced an MI and received clopidogrel do not provide evidence of an association between PPI use and MI, stroke or all-cause mortality compared to non-use of PPIs. An increased risk for MI was detected among patients between 80 and 89 years, which may represent an increased susceptibility or may be a result of unmeasured confounding. Odds ratios for PPI use vs non-use were similar in magnitude to those of H2RA use vs non-use. In summary, our findings are consistent with numerous prior studies that have reported a lack of an association on the highly debated topic of concomitant clopidogrel-PPI treatment. Although there is a potential for a biological interaction between clopidogrel and PPIs this interaction likely does not lead to detectable adverse clinical effects.

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SUPPLEMENTAL MATERIAL S4

Additional material referenced in the main article is included in this section, including relevant International classification of disease (ICD) codes for diagnoses, detailed characteristics of the study cohort, detailed comparison of the cases and controls corresponding to the secondary outcomes, and sensitivity analyses.

ICD CODES

ICD diagnosis codes used in the present are listed in Table S4-1. These codes were used to identify patients that had experienced a myocardial infarction for entry into the study cohort, cases for the myocardial infarction and stroke outcomes as we as the type of myocardial infarction.

TABLE S4- 1. ICD CODES FOR MI, MI TYPE AND STROKE.

Myocardial infarction	ICD 9: 410.xx excluding 410.x2 ICD 10: I21.x
MI type	NSTEMI ICD 9: 410.71 , 410.7 ; ICD 10: I21.4 , I22.2 STEMI ICD 9: 410.1 , 410.11 , 410.2 , 410.21, 410.3 , 410.31 , 410.4 , 410.41, 410.5, 410.51 , 410.6, 410.61, 410.8, 410.81, 410.9, 410.91; ICD 10: I21.0, I21.01, I21.02, I21.09, I21.1, I21.11, I21.19, I21.2, I21.21, I21.29, I21.3, I22.0, I22.1, I22.8, I22.9 Unspecified ICD 9: 410; ICD 10: I21, I22
Stroke	ICD 9: 430.xx, 431.xx, 432,xx, 433.xx, 434.xx, 436.xx ICD 10: I60.x, I61.x, I62.x, I63.x, I65.x, I66.x

ADDITIONAL RESULTS

Detailed cohort characteristics

The study cohort included patients that experienced the first MI documented in Health Facts® and received clopidogrel during their hospital encounter for the MI. Detailed description of cohort characteristics are presented in Table S4-2.

TABLE S4- 2. DETAILED DESCRIPTION OF STUDY COHORT.

Variable	Class	Cohort (N=52,006)
Age (years)*		67.8 (12.9)
LOS at cohort entry (days)*		8.3 (7.9)
Comorbidity score*		4.3 (2.8)
Sex	Females	40.7
Ethnicity	African American	13.3
	Caucasian	82.1
	Other	4.6
Health insurance status	Medicare	39.8
	Medicaid	6.3
	Private	15.8
	Uninsured	4.7
	Missing/unknown	33.4
Census Region	Midwest	13.0
	Northeast	46.6
	South	31.5
	West	9.0
Obesity		16.3
Smoking		23.8
MI Type	NSTEMI	60.6
	STEMI	20.9
	Unspecified	18.4
CV procedures	PCI stent	58.8
	CABG	9.8
	Carotid revascularization	1.6
Comedications	Aspirin	47.8
	ACE inhibitors	60.9
	Beta blockers	91.4
	CCBs	31.3
	Direct vasodilators	22.5
	Loop diuretics	53.1
	Potassium diuretics	8.3
	Thiazide diuretics	9.7
	Fibrates	3.6
	Statins	89.9
	GPR antagonists	27.7
	Warfarin	13.5
	Antihyperglycemics	14.5
	Lytics	3.5
	PPIs	56.3
	H2RAs	26.6

Variable	Class	Cohort (N=52,006)
Comorbidities	Congestive Heart Failure	42.9
	Cardiac Arrhythmia	41.6
	Valvular Disease	21.5
	Pulmonary Circulation Disorders	7.9
	Peripheral Vascular Disorders	16.6
	Hypertension Combined	10.7
	Diabetes Complicated	11.6
	Peptic Ulcer Disease excluding bleeding	1.4
	Coagulopathy	6.7
	Blood Loss Anemia	1.7
Hospital characteristics	Hospital with full catheterization lab	80.0
	Unknown status of catheterization lab	16.8
	Acute care hospital	99.8
	Urban hospital location	85.1
	Bed size 200-500	41.9
	Bed size <200	16.7
	Bed size >500	41.3

*Mean and standard deviation are reported
ACE: angiotensin converting enzyme; CABG: coronary artery bypass grafting; CCBs: calcium channel blockers; GPR: glycoprotein IIb/IIIa receptor; H2RA: H2 receptor antagonist; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; PPI: proton pump inhibitor; STEMI: ST-elevation myocardial infarction;

Findings stratified by age

Odds ratios stratified by age group for the risk of recurrent MI among PPI users vs non-users that were reported in the study are presented in Table S-4 alongside corresponding ORs for H2RA use vs nonuse. In the 65-79 years age group we see that ORs are similar for PPI use vs nonuse and H2RA use vs nonuse. In the 80-89 years age group, positive associations are reported. Possible reasons for this association are provided in the paper. A protective effective is seen among the 18-64 year age group with H2RA use; this observation requires further investigation.

TABLE S4- 3. ADJUSTED ORS BETWEEN PPI USE AND H2RA USE WITH MI AT THREE AND SIX MONTHS POST COHORT ENTRY, STRATIFIED BY AGE GROUP.

	Age group	OR (95% CI)	
		3 months	6 months
PPI use	18-64	1.05 (0.81-1.34)	0.93 (0.75-1.15)
	65-79	1.01 (0.80-1.27)	0.96 (0.80-1.15)
	80-89	1.29 (1.01-1.64)	1.30 (1.06-1.61)
H2RA use	18-64	0.65 (0.48-0.87)	0.69 (0.54-0.87)
	65-79	0.95 (0.73-1.24)	1.03 (0.84-1.28)
	80-89	0.98 (0.73-1.32)	1.01 (0.79-1.30)

Findings stratified by PPI type

There were large differences in the proportion of study sample that had received each of the PPIs: 37.7% pantoprazole, 8.6% esomeprazole, 4.2% omeprazole, and 0.7% lansoprazole. Four percent of the study sample received more than one type of PPI. The remaining 44.7% of the sample did not receive PPIs.

To examine differences in the risk of MI by PPI type, the odds ratios were calculated for individual PPIs. Odds ratios obtained were significantly different between PPI types and ranged from 0.52 (95% CI 0.40-0.68) for omeprazole to 4.14 (95% CI: 2.73-6.27) for lansoprazole. The effect estimates are not as expected; omeprazole has been reported to have the strongest inhibiting potential of clopidogrel's activity (Scott et al. 2014). The number of events (MI cases) was low for lansoprazole (56 cases) and omeprazole (84 cases). Similarly, the ORs for receiving more than one PPI type suggests a protective effect (OR = 0.71 (95% CI: 0.56-0.91) and was based on 102 MI cases.

To investigate the apparently anomalous ORs obtained for lansoprazole and omeprazole, we compared the characteristics listed in Table 4-2 of the cases that received either of these PPIs lansoprazole (N=56) and omeprazole (N=84) with the rest of the study sample. The cases were, in general, sicker than the rest of the study sample. However, this observation is true for all of the cases compared to the controls. Therefore, we could not attribute the observed ORs to selection bias in this case.

We further looked into the prevalence of exposure to these medications among the study sample (cases and controls) for the MI outcome. The prevalence was 4.2% for omeprazole and substantially lower for lansoprazole (0.7%). Using sample size calculations, we determined for a case control study to detect ORs of these magnitudes, at least 860 and 337 cases are required to detect the ORs observed for omeprazole and lansoprazole, respectively (calculations based OpenEpi version 3, using the Kelsey formula, where power = 80%, controls/case ratio = 5 and alpha = 5%) (The OpenEpi Project 2007).

Given that the current study contained substantially lower number of MI cases that were exposed to omeprazole and lansoprazole, the observed odds ratio are not likely meaningful representations of the true association. Similarly, to detect the OR obtained for receiving more than one type of PPI, the case control study would require at least 2254 MI cases.

TABLE S4- 4. ADJUSTED ODDS RATIOS FOR MI STRATIFIED BY TYPE OF PPI AT 12 MONTHS FOLLOW-UP.

Exposure	OR	95% CI	MI Cases[1]
PPIs			
Esomeprazole	0.96	(0.80-1.60)	231
Lansoprazole	4.14	(2.73-6.27)	56
Omeprazole	0.52	(0.40-0.68)	84
Pantoprazole	1.14	(1.03-1.27)	1227
>1 type of PPI	0.71	(0.56-0.91)	102
H2RAs	0.95	(0.85-1.05)	714

[1]Represents the number of MI cases included in each exposure group.

Comparisons of cases and controls for secondary outcomes

Odds ratios were calculated for three secondary outcomes assessing the risk among PPI users relative to PPI nonusers: 1) stroke, 2) all-cause mortality and 3) composite endpoint of MI, stroke and all-cause mortality. The same statistical analyses used for the primary analyses were used for these outcomes. Detailed characteristics of the cases and controls for each secondary outcome are presented in Table S-5 to Table S-7.

Odds ratios at the three follow-up periods assessed are presented in Table S-8 along with the corresponding risk estimates for H2RA use vs nonuse. Adjusted odds ratios for all-cause mortality were positive in the range of 1.04-1.13 at the three follow-up periods assessed but did not reach statistical significance. They were also slightly higher than the corresponding odds ratios for H2RA, which were also not statistically significant. Similar trends were observed for the composite endpoint and the stroke endpoint, although the point estimates for stroke less than 1, in the range of 0.92-0.96. The slightly lower estimates for H2RAs across all outcomes may suggest that either 1) H2RAs are an imperfect negative control although they have similar indications for PPIs; thus, PPIs may still be preferred in patients that have a higher baseline risk for the outcomes which would introduce confounding from unmeasured sources or 2) PPIs are in fact associated with a modest risk of the outcomes when combined with clopidogrel, although the risk does result in clinical significance.

Prior studies that have assessed the risk of all-cause mortality among patients with ACS have generally reported a lack of association with concomitant clopidogrel-PPI treatment (Ho 2009; Juurlink et al. 2009; O'Donoghue et al. 2009; Rassen et al. 2009; Gaspar et al. 2010; Simon et al. 2011; Aihara et al. 2012; Ortolani et al. 2012), while positive associations have also been reported (van Boxel et al. 2010; Douglas et al. 2012; Goodman et al. 2012; Mahabaleshwarkar et al. 2013).

For stroke, observational studies have reported a lack of association generally among ACS patients (van Boxel et al. 2010; Ray et al. 2010; Simon et al. 2011; Aihara et al. 2012; Mahabaleshwarkar et al. 2013). Charlot et al. (2010) reported a positive association but contributed it to unmeasured confounding.

TABLE S4- 5. DETAILED DESCRIPTION OF STROKE CASES AND CONTROLS AT 12 MONTHS FOLLOW-UP.

		Cases N=1,356		Controls N=7,510		p-value
		No.	%	No.	%	
Age (years) *†		70.4	(11.0)	70.5	(10.8)	0.93
LOS at cohort entry (days) *‡		9.5	(9.0)	7.9	(7.2)	<0.0001
Comorbidity score *		5.2	(2.9)	4.2	(2.9)	<0.0001
Sex†	Females	693	45.1	3,380	45.0	0.94
Ethnicity†	African American	229	14.9	1,053	14.0	0.26
	Caucasian	1,258	81.9	6,262	83.4	
	Other	49	3.2	195	2.6	
Health insurance status‡	Medicaid	94	6.1	472	6.3	0.07
	Medicare	769	50.1	3,913	52.1	
	Private	211	13.7	834	11.1	
	Uninsured	53	3.5	258	3.4	
	Other/missing	409	26.6	2,033	27.1	
Census Region	Midwest	239	15.6	1,234	16.4	<.0001
	Northeast	646	42.1	3,719	49.5	
	South	509	33.1	1,904	25.4	
	West	142	9.2	653	8.7	
Obesity‡		297	19.3	1,166	15.5	<0.001
Smoking		374	24.4	1,407	18.7	<.0001
MI Type	NSTEMI	1,032	67.2	4,495	59.9	<.0001
	STEMI	199	13.0	1,474	19.6	
	Unspecified	305	19.9	1,541	20.5	
CV procedures	PCI/stent	755	49.2	3,923	52.2	0.03
	CABG	140	9.1	513	6.8	<0.01
	Carotid revascularization	45	2.9	125	1.7	<0.001
Comedications	Aspirin	653	42.5	2,693	35.9	<.0001
	ACE inhibitors	914	59.5	4,251	56.6	0.04
	Beta blockers	1,400	91.2	6,786	90.4	0.34
	CCBs	606	39.5	2,433	32.4	<.0001
	Direct vasodilators	464	30.2	1,872	24.9	<.0001
	Loop diuretics	860	56.0	4,223	56.2	0.86
	Potassium diuretics	118	7.7	623	8.3	0.42
	Thiazide diuretics	187	12.2	750	10.0	0.01
	Fibrates	72	4.7	298	4.0	0.19
	Statins	1,388	90.4	6,792	90.4	0.93
	GPR antagonists	244	15.9	1,741	23.2	<.0001
	Warfarin	287	18.7	1,120	14.9	<0.001
	Antihyperglycemics	248	16.2	1,077	14.3	0.07
	Lytics	67	4.4	213	2.8	<0.01
	PPIs	879	57.2	4,146	55.2	0.15
	H2RAs	399	26.0	2,078	27.7	0.18
Comorbidities	Congestive heart failure	739	48.3	3,192	42.7	<.0001
	Cardiac arrhythmia	691	45.2	3,089	41.3	0.01
	Valvular disease	406	26.5	1,377	18.4	<.0001
	Pulmonary circulation disorders	155	10.1	552	7.4	<0.001
	Peripheral vascular disorders	455	29.7	1,175	15.7	<.0001
	Hypertension	276	18.0	831	11.1	<.0001
	Diabetes (complicated)	239	15.6	866	11.6	<.0001
	Peptic ulcer disease (excluding bleeding)	28	1.8	94	1.3	0.08
	Coagulopathy	135	8.8	482	6.4	<0.001
	Blood loss anemia	23	1.5	100	1.3	0.61

		Cases N=1,356		Controls N=7,510		p-value
		No.	%	No.	%	
Hospital characteristics	Hospital with full catheterization lab	1,280	83.3	5,805	77.3	<.0001
	Unknown status catheterization lab	182	11.9	1,594	21.2	
	Acute care hospital‡	1,531	99.7	7,510	100.0	<.0001
	Hospital in urban location	1,327	86.4	6,222	82.9	<0.001
	Bed size 200-500‡	675	44.0	4,230	56.3	<.0001
	Bed size <200‡	265	17.3	882	11.8	
	Bed size >500‡	595	38.8	2,396	31.9	

* Mean (standard deviation) are reported; comparison made using Mann Whitney U test.
† Matching variable.
‡Variable not included in regression models.
ACE: angiotensin converting enzyme; CABG: coronary artery bypass grafting; CCBs: calcium channel blockers; GPR: glycoprotein IIb/IIIa receptor; H2RA: H2 receptor antagonist; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; PPI: proton pump inhibitor; STEMI: ST-elevation myocardial infarction;

TABLE S4- 6. DETAILED DESCRIPTION ALL-CAUSE MORTALITY CASES AND CONTROLS AT 12 MONTHS FOLLOW-UP.

		Cases N=2,596		Controls N=12,551		p-value
		No.	%	No.	%	
Age (years)*†		73.6 (10.7)		73.6 (10.5)		0.50
LOS at cohort entry (days)*‡		10.4 (10.2)		8.1 (7.5)		<0.0001
Comorbidity score*		6.11 (3.0)		4.18 (2.8)		<0.0001
Sex†	Females	1,139	43.9	5447	43.4	0.66
Ethnicity†	African American	460	17.7	2,081	16.6	
	Caucasian	2,036	78.4	10,164	81	<0.0001
	Other	100	3.9	306	2.4	
Health insurance status‡	Medicaid	138	5.3	631	5.0	
	Medicare	1,442	55.6	6,913	55.1	
	Private	260	10.0	1,178	9.4	0.48
	Uninsured	74	2.9	335	2.7	
	Other/missing	682	26.3	3,494	27.8	
Census Region	Midwest	368	14.2	1,820	14.5	
	Northeast	1,195	46.0	6,566	52.3	<0.0001
	South	813	31.3	3,103	24.7	
	West	220	8.5	1,062	8.5	
Obesity‡		377	14.5	1,755	14.0	0.47
Smoking		460	17.7	1,875	14.9	<0.001
MI Type	NSTEMI	1,821	70.2	7,847	62.5	
	STEMI	290	11.2	2,492	19.9	<0.0001
	Unspecified	485	18.7	2,212	17.6	
CV procedures	PCI stent	1,040	40.1	6,571	52.4	<0.0001
	CABG	99	3.8	875	7.0	<.0001
	Carotid revascularization	34	1.3	173	1.4	0.78
Comedications	Aspirin	1,124	43.3	4,988	39.7	<0.001
	ACE inhibitors	1,346	51.9	7,233	57.6	<0.0001
	Beta blockers	2,328	89.7	11,388	90.7	0.09

		Cases N=2,596		Controls N=12,551		p-value
		No.	%	No.	%	
	CCBs	926	35.7	4,271	34	0.11
	Direct vasodilators	574	22.1	3,007	24	0.04
	Loop diuretics	1,849	71.2	6,966	55.5	<0.0001
	Potassium diuretics	256	9.9	1,001	8.0	<0.01
	Thiazide diuretics	250	9.6	1,282	10.2	0.37
	Fibrates	75	2.9	427	3.4	0.18
	Statins	2,341	90.2	11,299	90	0.81
	GPR antagonists	371	14.3	2,811	22.4	<0.0001
	Warfarin	431	16.6	1,954	15.6	0.19
	Antihyperglycemics	355	13.7	1,940	15.5	0.02
	Lytics	135	5.2	358	2.9	<0.0001
	PPIs	1,593	61.4	7,019	55.9	<0.0001
	H2RAs	636	24.5	3,333	26.6	0.03
Comorbidities	Congestive heart failure	1,792	69.1	5,386	43.1	<0.0001
	Cardiac arrhythmia	1,359	52.4	5,315	42.5	<0.0001
	Valvular disease	784	30.2	2,628	21.0	<0.0001
	Pulmonary circulation disorders	407	15.7	931	7.4	<0.0001
	Peripheral vascular disorders	754	29.1	2,024	16.2	<0.0001
	Hypertension	518	20	1,446	11.6	<0.0001
	Diabetes (complicated)	499	19.2	1,315	10.5	<0.0001
	Peptic ulcer disease	51	2.0	151	1.2	<0.01
	Coagulopathy	265	10.2	808	6.5	<0.0001
	Blood loss anemia	73	2.8	172	1.4	<0.0001
Hospital characteristics	Hospital with full catheterization lab	2,113	81.4	10,144	80.8	<0.0001
	Unknown status catheterization lab	357	13.8	2,222	17.7	
	Acute care hospital‡	2,591	99.8	12,548	100	<0.001
	Hospital in urban location	411	15.8	1,800	14.34	0.05
	Bed size 200-500‡	1,203	46.3	6,748	53.8	
	Bed size <200‡	485	18.7	1,410	11.2	<0.001
	Bed size >500‡	908	35.0	4,392	35.0	

* Mean (standard deviation) are reported; comparison made using Mann Whitney U test.
† Matching variable.
‡Variable not included in regression models.
ACE: angiotensin converting enzyme; CABG: coronary artery bypass grafting; CCBs: calcium channel blockers; GPR: glycoprotein IIb/IIIa receptor; H2RA: H2 receptor antagonist; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; PPI: proton pump inhibitor; STEMI: ST-elevation myocardial infarction;

TABLE S4- 7. DETAILED DESCRIPTION OF COMPOSITE ENDPOINT CASES AND CONTROLS AT 12 MONTHS FOLLOW-UP.

		Cases N=6,403		Controls N=30,957		p-value
		No.	%	No.	%	
Age (years)*†		71.3 (11.5)		71.4 (11.2)		0.97
LOS at cohort entry (days)*‡		9.3 (8.9)		7.9 (7.3)		<0.0001
Comorbidity score*		5.8 (3.0)		4.1 (2.8)		<0.0001
Sex†	Females	2,804	43.8	13,458	43.5	0.64
Ethnicity†	African American	989	15.5	4,412	14.3	<.0001
	Caucasian	5,168	80.7	25,746	83.2	
	Other	246	3.8	799	2.6	
	Medicaid	401	6.3	1,764	5.7	<.0001

		Cases N=6,403		Controls N=30,957		p-value
		No.	%	No.	%	
Health insurance status‡	Medicare	3,295	51.5	15,857	51.2	
	Private	806	12.6	3,329	10.8	
	Uninsured	228	3.6	1,014	3.3	
	Other/missing	1,673	26.1	8,993	29.1	
Census Region	Midwest	850	13.3	4,642	15.0	<.0001
	Northeast	3,084	48.2	16,042	51.8	
	South	1,935	30.2	7,611	24.6	
	West	534	8.3	2,662	8.6	
Obesity‡		1,189	18.6	4,563	14.7	<.0001
Smoking		1,404	21.9	5,296	17.1	<.0001
MI Type	NSTEMI	4,439	69.3	18,642	60.2	<.0001
	STEMI	822	12.8	6,415	20.7	
	Unspecified	1,142	17.8	5,900	19.1	
CV procedures	PCI stent	2,939	45.9	16,175	52.3	<.0001
	CABG	392	6.1	2,158	7.0	0.01
	Carotid revascularization	122	1.9	483	1.6	0.05
Comedications	Aspirin	2,947	46	11,911	38.5	<.0001
	ACE inhibitors	3,602	56.3	17,999	58.1	0.01
	Beta blockers	5,827	91.0	27,841	89.9	0.01
	CCBs	2,314	36.1	10,086	32.6	<.0001
	Direct vasodilators	1,664	26.0	7,451	24.1	<0.01
	Loop diuretics	4,075	63.6	17,013	55.0	<.0001
	Potassium diuretics	576	9.0	2,454	7.9	<0.01
	Thiazide diuretics	653	10.2	3,034	9.8	0.33
	Fibrates	227	3.6	1,067	3.5	0.69
	Statins	5,784	90.3	27,744	89.6	0.09
	GPR antagonists	1,077	16.8	7,339	23.7	<.0001
	Warfarin	997	15.6	4,744	15.3	0.62
	Antihyperglycemics	1,021	16.0	4,579	14.8	0.02
	Lytics	263	4.1	859	2.8	<.0001
	PPIs	3,818	59.6	17,010	55.0	<.0001
	H2RAs	1,615	25.2	8,430	27.2	<0.01
Comorbidities	Congestive heart failure	3,919	61.4	12,820	41.6	<.0001
	Cardiac arrhythmia	3,126	48.9	6,071	41.4	<.0001
	Valvular disease	1,862	29.2	6,071	19.7	<.0001
	Pulmonary circulation disorders	825	12.9	2,254	7.3	<.0001
	Peripheral vascular disorders	1,808	28.3	4,665	15.1	<.0001
	Hypertension	1,315	20.6	3,341	10.8	<.0001
	Diabetes (complicated)	1,224	19.2	3,281	10.6	<.0001
	Peptic ulcer disease	132	2.1	338	1.1	<.0001
	Coagulopathy	583	9.1	1,888	6.1	<.0001
	Blood loss anemia	157	2.5	407	1.3	<.0001
Hospital characteristics	Hospital with full catheterization lab	5,049	78.9	24,773	80.0	<.0001
	Unknown status catheterization lab	1,077	16.8	5,767	18.6	
	Acute care hospital‡	6,386	99.7	30,952	100.0	<.0001
	Hospital in urban location	5,185	81	26,360	85.2	<.0001
	Bed size 200-500‡	2,718	42.5	16,734	54.1	<.0001
	Bed size <200‡	1,104	17.3	3,430	11.1	
	Bed size >500‡	2,578	40.3	10,786	34.9	

* Mean (standard deviation) are reported; comparison made using Mann Whitney U test.
† Matching variable.
‡Variable not included in regression models.

ACE: angiotensin converting enzyme; CABG: coronary artery bypass grafting; CCBs: calcium channel blockers; GPR: glycoprotein IIb/IIIa receptor; H2RA: H2 receptor antagonist; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; PPI: proton pump inhibitor; STEMI: ST-elevation myocardial infarction;

TABLE S4- 8. ADJUSTED ORS OF PPI USE OR H2RA USE WITH THE SECONDARY OUTCOMES AT THREE FOLLOW-UP PERIODS.

Outcome	3 months		6 months		12 months	
	OR	95% CI	OR	95% CI	OR	95% CI
In-hospital mortality						
PPI	1.13	(0.98-1.29)	1.10	(0.98-1.24)	1.05	(0.94-1.15)
H2RA	1.04	(0.90-1.21)	1.00	(0.88-1.14)	0.93	(0.83-1.04)
Stroke						
PPI	0.92	(0.77-1.1)	0.96	(0.82-1.11)	0.96	(0.85-1.09)
H2RA	0.82	(0.67-1.01)	0.83	(0.70-0.99)	0.82	(0.71-0.95)
Composite outcome						
PPI	1.07	(0.99-1.16)	1.06	(0.99-1.14)	1.04	(0.98-1.11)
H2RA	0.94	(0.85-1.03)	0.94	(0.87-1.02)	0.92	(0.86-0.98)

Sensitivity analysis for health insurance status

The health insurance status of patients was not included in the logistic regression models used to estimate the odds ratios for recurrent MI, since one third of the patients had missing or unknown values for this categorical variable. Table S-8 presents findings of a sensitivity analysis showing the ORs when including this variable (categories: Medicare, Medicaid, private, uninsured, other, unknown/missing) and when excluding this variable from the analyses. This analysis indicates that removing the health insurance status of patients had minimal impact on the findings reported in this study.

TABLE S4- 9. PERCENT CHANGE IN THE ADJUSTED ODDS RATIOS FOR STUDY OUTCOMES (PPI USE VS NONUSE) WHEN INCLUDING AND EXCLUDING THE "HEALTH INSURANCE STATUS" VARIABLE IN THE REGRESSION MODELS.

Outcome	Regression model	3 months		6 months		12 months	
		OR	% change*	OR	% change*	OR	% change*
Myocardial infarction							
	With health insurance variable	1.089	0.37%	1.051	1.06%	1.057	0.86%
	Without health insurance variable	1.085		1.04		1.048	
All-cause mortality							
	With health insurance variable	1.132	0.62%	1.11	0.54%	1.046	0.48%
	Without health insurance variable	1.125		1.104		1.041	
Stroke							
	With health insurance variable	0.910	-0.87%	0.95	-1.04%	0.949	-0.52%
	Without health insurance variable	0.918		0.96		0.954	
Composite outcome							
	With health insurance variable	1.077	0.28%	1.067	0.38%	1.045	0.29%
	Without health insurance variable	1.074		1.063		1.042	

*Calculated as: $(OR_{\text{with variable}} - OR_{\text{without variable}})/(OR_{\text{without variable}})$ x100

CHAPTER 5

ADVERSE CARDIOVASCULAR EVENTS FOLLOWING MYOCARDIAL INFARCTION IN PATIENTS RECEIVING PROTON PUMP INHIBITORS WITH TICAGRELOR OR PRASUGREL

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PREFACE

The current chapter consists of the fourth manuscript from this thesis. Using similar methods to the previous study presented in Chapter 4, I assess the associations between concomitant use of PPIs and two other antiplatelet agents (ticagrelor and prasugrel) with adverse cardiovascular events, by analysing data from Health Facts®. Although there are no prior reports of adverse events related to the concomitant treatment of PPIs with ticagrelor or prasugrel, this study was essential in the context of the thesis objectives in order to allow the comparison of findings with those I reported in the previous chapter.

Contributions

I designed the study, performed the analysis and wrote the first draft of the manuscript with guidance from my supervisors. My supervisors and thesis advisory committee provided feedback and suggestions on all aspects of the study design, statistical analyses, and interpretation of findings during our regular meetings and provided suggestions for revisions on the manuscript. Ms Nisrine Haddad contributed to various aspects of the analyses and interpretation of findings as well as revising the draft manuscript. Dr Yannick Fortin contributed to the computation of the Quan Elixhauser Comorbidity Measures index for the statistical analysis, interpreting the findings, and reviewing the manuscript.

Ethical approval

Ethical approval for this study was obtained from the Ottawa Health Science Network Research Ethics Board at the Ottawa Hospital, Ottawa, Canada (Appendix A).

ADVERSE CARDIOVASCULAR EVENTS FOLLOWING MYOCARDIAL INFARCTION IN PATIENTS RECEIVING PROTON PUMP INHIBITORS WITH TICAGRELOR OR PRASUGREL

ABSTRACT

Although numerous studies have examined the potential association between proton pump inhibitor (PPI) use and adverse cardiovascular events in patients receiving clopidogrel, a P2Y12 receptor inhibitor, only a few studies have focused on the safety of PPI use concomitantly with other P2Y12 receptor inhibitors. In this article, we assessed the association between PPI use and cardiovascular endpoints in ticagrelor users and prasugrel users. Using the Cerner Corporation Health Facts® database of electronic health records, we selected two cohorts of patients that were hospitalized for a myocardial infarction (MI), one comprised of prasugrel users, and the other of ticagrelor users. Using a nested case-control study, we estimated odds ratios (ORs) for the association between PPI use vs nonuse and rehospitalisation for a second MI, the primary outcome, as well as three secondary outcomes: stroke, all-cause mortality, and a composite endpoint comprised of MI, stroke or death. Cases identified for each outcome within one year of the first MI encounter were matched to five controls based on age, sex, ethnicity and cohort entry using risk set sampling. ORs were adjusted for comorbidities and comedications. Adjusted ORs for PPI use vs non-use were 1.04 (95% CI: 0.67-1.61) among prasugrel users and 0.96 (95% CI: 0.69-1.33) among ticagrelor users. Results for the secondary outcomes showed no statistically significant associations with PPI use. Findings from our study are consistent with findings in the literature and suggest

no association between concomitant PPI use with ticagrelor or prasugrel and adverse cardiovascular events in patients with a history or a prior MI.

5.1 INTRODUCTION

Current clinical practice guidelines recommend dual antiplatelet therapy (DAPT) comprised of aspirin and a P2Y12 receptor inhibitor for patients with acute coronary syndrome (Amsterdam et al. 2014). Proton pump inhibitors (PPIs) are commonly prescribed in combination with DAPT to offer protection against gastrointestinal bleeding (Bhatt et al. 2008). In 2009, the US Food and Drug Administration (FDA) issued warnings discouraging treatment with clopidogrel and PPIs due to a potential drug-drug interaction that may attenuate clopidogrel's antiplatelet efficacy (FDA 2009a; FDA 2009b). Numerous epidemiological studies have subsequently assessed whether the potential drug-drug interaction between clopidogrel and PPIs puts patients receiving both drugs at increased risk for adverse cardiovascular event relative to patients not receiving a PPI. Findings to date, mainly from observational studies, have produced conflicting results.

The antiplatelet agents - prasugrel, ticagrelor and clopidogrel - are metabolized differently in the human body. Clopidogrel, available in the US since 1997, is a prodrug that requires bioactivation in the liver by the CYP pathway. The interaction with PPIs is based on the fact that PPIs are metabolized by the CYP pathway and can competitively inhibit the activation of clopidogrel (Scott, Obeng, et al. 2014). Prasugrel and ticagrelor are also P2Y12 receptor inhibitors and were approved by the FDA in 2009 and 2011, respectively. Although both are currently unavailable in generic form their use has been increasing in the US among patients with acute coronary syndrome (ACS) (Farhat et al. in press). To date, few studies have assessed the association between cardiovascular events and concomitant treatment of either of these two novel antiplatelet agents with PPIs (Kubisz 2018). Two post-hoc analyses of the in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) trial (O'Donoghue et al. 2009) and the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRIOLOGY-ACS) trial (Nicolau et al. 2015) reported no association between PPI use and the risk of the composite endpoint of MI, stroke or cardiovascular death among patients treated with prasugrel or clopidogrel. On the other hand, findings from the post-hoc analysis of the Study of Platelet Inhibition and Patient Outcomes (PLATO) trial showed an elevated risk of the composite endpoint of MI and cardiovascular death in patients treated with PPIs in combination with either clopidogrel or ticagrelor (Goodman et al. 2012); however, no associations were reported for the endpoints when assessed individually.

Given that the possibility for PPIs to interact with and adversely affect the platelet inhibition abilities of P2Y12 receptor inhibitors - an association that remains poorly investigated - we conducted case control analyses nested among two cohorts (prasugrel users and ticagrelor users) of patients co-administered PPIs and one of these two antiplatelet agents. Our objective was to assess the associations between PPI use and adverse cardiovascular endpoints in patients receiving either ticagrelor or prasugrel using electronic medical records from a large US database.

5.2 METHODS

5.2.1 DATA SOURCE

Data were abstracted from the Cerner Health Facts® database, which consists of electronic medical records with information on hospital admissions, diagnoses, hospital procedures, medication orders and laboratory tests. The Health Facts® dataset used contains information for over 69 million unique US patients from January 1, 2000 to December 31, 2016. Over 500 hospitals from all US census regions report to Health Facts®. The database complies with Health Insurance Portability and Accountability Act and contains only de-identified patient data. The protocol for the current study was approved by the Ottawa Health Science Network Research Ethics Board at the Ottawa Hospital, Canada.

5.2.2 COHORT SELECTION

Two cohorts satisfying the eligibility criteria were selected from Health Facts®: 1) prasugrel users and 2) ticagrelor users. The methods used for the selection of the cohort, cases and controls are detailed in our previous work (Chapter 4). Briefly, patients eligible for cohort entry: 1) had been admitted to the hospital as an inpatient or to the emergency room for a first MI; 2) received prasugrel or ticagrelor during their hospitalization; 3) had complete age (18-89 years), sex, and ethnicity data; and 4) were discharged alive before December 31, 2015 (Figure 5-1). Principal or secondary diagnoses based on recorded International Classification of Diseases (ICD) codes (ICD-9: 410.xx excluding 410.x2 and ICD-10 I21x) where used to identify patients admitted with an MI (Kim et al. 2017). To ensure that the medications dispensed in the hospital are representative of the patients' chronic medication use, we excluded patients that had a length of stay less than three days. For patients that were first admitted to the ER then became inpatients (at the same or different medical institutions), the length of stay was calculated as the total number of days of adjacent encounters. The date of hospital discharge of the qualifying encounter served as the date of cohort entry for each patient.

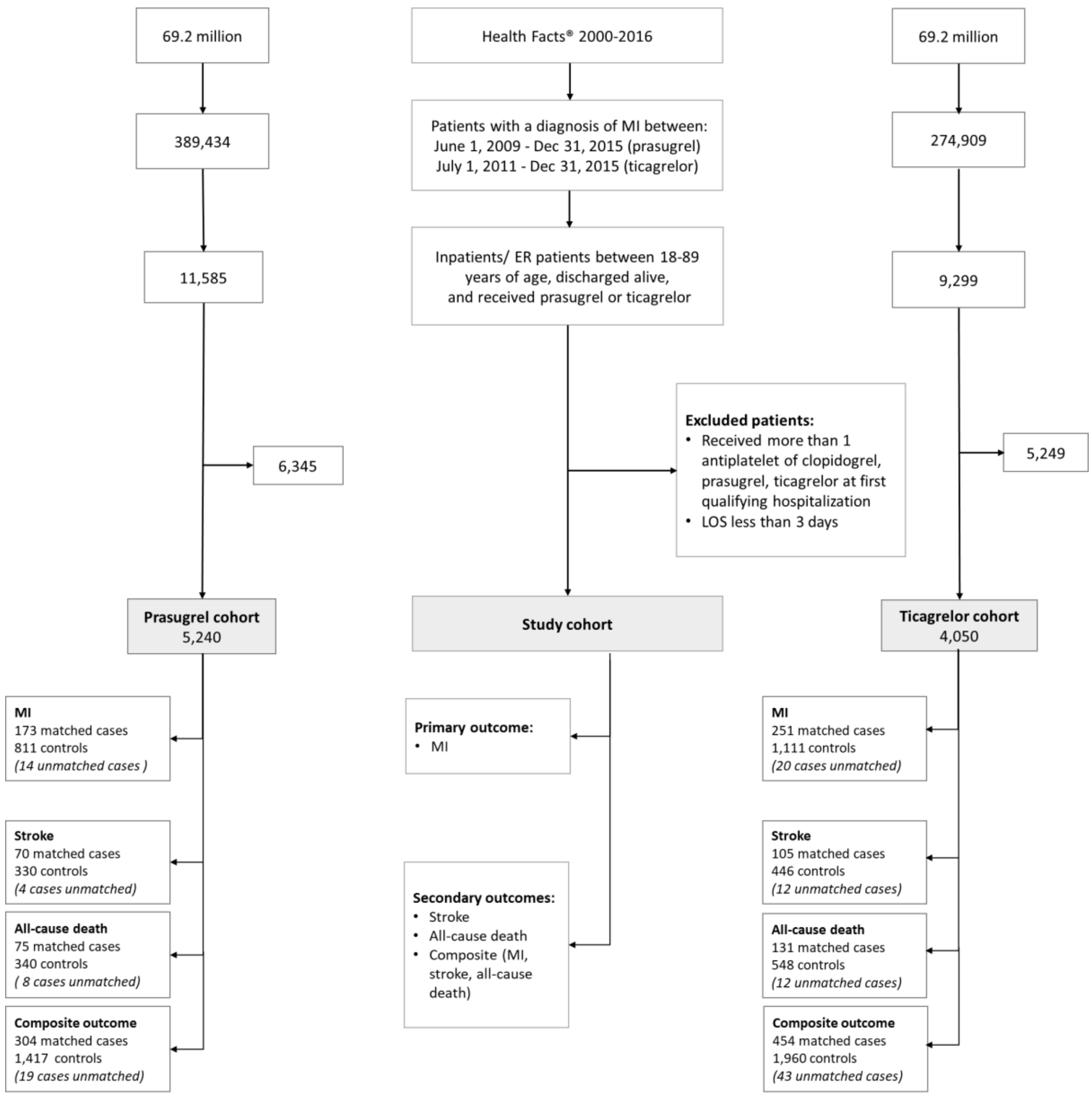

FIGURE 5- 1. SELECTION OF THE STUDY COHORTS, CASES, AND CONTROLS FROM HEALTH FACTS®.

5.2.3 CASE DEFINITION AND CONTROLS SELECTION

The primary outcome was hospitalization for a second MI. Patients that experienced a second MI within one year of the discharge date of their cohort entry hospitalization were selected as cases. MI cases were defined using the same ICD codes in the first or secondary position used to define an MI for cohort entry. The length of stay had to be at least 3 days unless the patient died during the hospital encounter. The date of hospitalization for the second MI served as the index date for the case.

Secondary outcomes included hospitalization for a stroke, in-hospital death from any cause, and the composite of MI, stroke or all-cause mortality, within one year of cohort entry. ICD-9 and ICD-10 codes corresponding to a stroke diagnosis in the primary position were used to identify stroke patients (Supplementary Material, Table S5-1). Cases for the all-cause mortality endpoint were selected if death was recorded in the EHR discharge disposition field in any hospital encounters during the 12-month study follow-up period. The date of readmission was designated as the index date and only the first eligible readmission was considered. Each outcome was analysed separately. For the composite endpoint, patients that experienced the first of either one of these outcomes were considered cases.

For each case, up to five controls were randomly selected using incidence density sampling. Controls were matched to cases on sex (male/female), ethnicity (Caucasian, African American, other), age (± 3 years), and cohort entry date (± 30 days). In this sampling approach, a patient could act as a control for multiple cases until they experience the outcome. In addition, a case could serve as a control before its index date (Etminan 2004). This approach has been shown to be valid and to yield consistent risk estimates in nested case control analyses (Lubin and Gail

1984; Lubin 1986; Robins et al. 1986; Wang et al. 2009). In instances where a case could not be matched to at least one control, the case was excluded from the analysis.

5.2.4 MEDICATION EXPOSURE ASSESSMENT

Medication orders dispensed during hospital encounters are available in Health Facts® and were used to determine exposure of patients to various medications. All patients received either prasugrel or ticagrelor during their first hospitalization for MI. Patients were assumed to have been put on the treatment for 12 months as per current guidelines (Bhatt et al. 2008). Patients were classified as exposed or unexposed to PPIs based on whether or not they had received any type of PPI during the hospitalisation qualifying them for cohort entry. PPI exposure status was considered constant for each patient for 1-year post cohort entry or until the patient becomes a case, whichever occurred at an earlier date. The use of select chronic medications was identified based on the medications dispensed during the first hospitalization that lead to cohort entry (Table 5-2). Medications, other than clopidogrel and PPIs, were selected based on a review of similar studies in addition to clinical expert opinion. All patients in the cohort were classified as exposed to a specific medication if their medication records included an order with a valid dispensing status for that medication; otherwise they were classified as unexposed.

5.2.5 COMORBIDITIES AND CARDIOVASCULAR PROCEDURES

We assessed patient comorbidities from the diagnoses records of patients. Using diagnoses codes, we identified whether patients had been diagnosed with any of the 30 conditions of the Quan Elixhauser Comorbidity Measures (ECM) (Quan et al. 2005). The use of Quan ECM index was recently validated in HealthFacts® and was demonstrated to be a good predictor of in-hospital mortality and in-hospital mortality with 1 year of follow-up (Fortin et al. 2017a; Fortin et al. 2017b). Each patient's records were searched for the presence of diagnosis codes corresponding to 30 conditions of the ECM. We assumed the presence of a disease if a patient had been diagnosed with that condition during any encounter within the 1 year prior to cohort entry. We further computed a comorbidity score by modifying the Quan ECM index to represent the sum of all of the conditions a patient has been diagnosed with (of the 30 ECM comorbidities) but excluding the following ten conditions: congestive heart failure, cardiac arrhythmia, valvular disease, pulmonary circulation disorders, peripheral vascular disorders, hypertension, diabetes with complications, peptic ulcer disease, coagulopathy and blood loss anemia list them. The latter comorbidities were excluded from the calculation of the comorbidity score and included as individual covariates.

We also assessed whether cohort patients had undergone any of several cardiovascular procedures including coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI) or carotid revascularization (carotid endarterectomy, stenting, angioplasty or atherectomy, or carotid bypass).

5.2.6 STATISTICAL ANALYSES

We compared the baseline characteristics of MI cases and controls in each cohort. For continuous variables, we reported the mean and standard deviations and used the Mann-Whitney U test to evaluate the significance of differences between the study groups for variable not normally distributed (based on the Shapiro Wilk test). We reported categorical variables as frequencies and percentages, with comparisons made using the chi-square test.

We estimated the adjusted odds ratio (aOR) and 95% confidence interval of hospital readmission for a second MI for PPI users vs non-users by conditional logistic regression. Covariates adjusted for in the regression models were based on similar prior studies and expert clinical opinion. Covariates included demographic variables, comorbidities, comedications, prior cardiovascular procedures and hospital characteristics. Adjusted ORs were estimated for each of the secondary outcomes using the same method as for the primary outcome. We used the SAS software (SAS Institute Inc, Cary, NC), version 9.4, for all statistical analyses.

SENSITIVITY ANALYSES

We performed a sensitivity analysis by assessing the adjusted ORs for receiving H2 receptor antagonists (H2RAs) with the outcomes of interest using the same statistical models described above. H2RAs are gastric acid suppressive drugs that have similar indication to PPIs but have no known interaction with antiplatelet agents. Observed ORs were compared with those corresponding to PPI use for each outcome. No associations are expected to be observed between H2RA use and the outcomes and can thus serve as a negative control exposure.

5.3 RESULTS

The final study cohorts of prasugrel and ticagrelor users were comprised of 5,240 and 4,050 patients, respectively. Baseline characteristics of these cohorts assessed at the time of cohort entry are summarized in Table 5-1. Patients in both cohorts were predominantly Caucasian, were frequently males, and were more likely to have been hospitalized at acute care teaching hospitals located in urban areas. The mean age was higher among ticagrelor users (65.0 years) compared to prasugrel users (58.9 years), likely because the latter drug is contraindicated in patients over 75 years. In both cohorts, more than 40% had visited hospitals in the South census region and more than two thirds were enrolled in Medicare or private health insurance.

TABLE 5- 1. DESCRIPTION OF THE STUDY COHORTS.

	Prasugrel users N=5,240	Ticagrelor users N=4,050
Age[ǂ] (years)	58.9 (11.0)	65.0 (12.4)
Comorbidity score[ǂ]	1.9 (1.8)	2.8 (1.9)
Sex		
Males	73.1%	62.3%
Females	26.9%	37.7%
Ethnicity		
Caucasian	81.0%	77.1%
African American	12.5%	16.8%
Other	6.5%	6.1%
Health insurance status		
Private	34.3%	22.7%
Medicare	27.0%	45.2%
Medicaid	9.4%	9.1%
Uninsured	8.8%	5.2%
Other/missing	20.7%	18.0%
Census Region		
Midwest	9.6%	15.2%
Northeast	26.4%	32.8%
South	48.0%	41.4%
West	16.1%	10.6%
Location of hospital		
Rural	10.9%	23.0%
Urban	89.1%	77.0%

[ǂ] Mean and standard deviation

For the primary outcome, MI, we matched 173 cases to 811 controls among prasugrel users, and 251 cases to 1,111 controls among ticagrelor users. Baseline characteristics are compared for these cases and controls in Table 5-2. Cases had a higher comorbidity score compared to controls suggesting higher comorbidity. Cases were also more likely to be obese and to have been diagnosed with the diseases listed in Table 5-2. Detailed comparisons of cases and controls for the secondary outcomes are found in Supplemental Material (Tables S5-3, S5-4 and S5-6).

TABLE 5- 2. DESCRIPTION OF MI CASES AND CONTROLS AMONG THE TWO COHORTS.

	Prasugrel users			Ticagrelor users		
	Cases (%) N=173	Controls (%) N=811	p-value	Cases (%) N=251	Controls (%) N=1,111	p-value
Age (years)*†	58.8 (10.5)	58.7 (9.6)	0.89	65.6 (11.5)	66.0 (10.8)	0.79
LOS at cohort entry (days)*‡	5.2 (5.7)	4.4 (5.3)	<0.01	7.2 (5.7)	7.3 (8.2)	0.1
Comorbidity score *	3.1 (2.2)	1.6 (1.7)	<0.0001	3.3 (2.1)	2.7 (1.9)	<0.001
Male†	112 (64.74%)	537 (66.21%)	0.71	154 (61.4%)	707 (63.6%)	0.51
Ethnicity†						
African American	32 (18.5%)	130 (16.0%)	0.69	37 (14.7%)	108 (9.7%)	0.01
Caucasian	135 (78.0%)	656 (80.9%)		209 (83.3%)	995 (89.6%)	
Other	6 (3.5%)	25 (3.1%)		5 (2.0%)	9 (0.8%)	
Health insurance status‡						
Medicare	57 (33.0%)	222 (27.4%)	<0.01	23 (9.2%)	103 (9.3%)	<0.001
Medicaid	24 (13.9%)	69 (8.5%)		133 (53.0%)	458 (41.2%)	
Private	52 (30.1%)	226 (27.9%)		29 (11.6%)	253 (22.8%)	
Uninsured	9 (5.2%)	43 (5.3%)		53 (21.1%)	238 (21.4%)	
Missing/unknown	31 (17.9%)	251 (31.0%)		13 (5.2%)	60 (5.4%)	
US Census Region						
Midwest	14 (8.1%)	104 (12.8%)	0.01	30 (12.0%)	184 (16.6%)	0.17
Northeast	70 (40.5%)	347 (42.8%)		116 (46.2%)	446 (40.1%)	
South	74 (42.8%)	248 (30.6%)		75 (29.9%)	357 (32.1%)	
West	15 (8.7%)	112 (13.8%)		30 (12.0%)	125 (11.3%)	
Obesity‡	65 (37.6%)	152 (18.7%)	<0.0001	74 (29.5%)	249 (22.4%)	0.02
Smoking	76 (43.9%)	226 (27.9%)	<0.0001	75 (29.9%)	305 (27.5%)	0.43
MI Type						
NSTEMI	65 (37.6%)	235 (29%)	0.08	118 (47%)	450 (40.5%)	0.16
STEMI	56 (32.4%)	309 (38.1%)		59 (23.5%)	293 (26.4%)	
Unspecified	52 (30.1%)	267 (32.9%)		74 (29.5%)	369 (33.2%)	
Cardiovascular procedures						
PCI/stent	117 (67.6%)	443 (54.6%)	<0.01	148 (59.0%)	596 (53.6%)	0.12
CABG	1 (0.6%)	7 (0.9%)	0.7	7 (2.8%)	36 (3.2%)	0.71
Carotid revascularization	4 (2.3%)	27 (3.3%)	0.49	18 (7.2%)	98 (8.8%)	0.4
Comedications						
Aspirin	54 (31.2%)	187 (23.1%)	0.02	107 (42.6%)	355 (32%)	<0.001
ACE inhibitors	97 (56.1%)	485 (59.8%)	0.36	160 (63.7%)	712 (64.1%)	0.93
Beta blockers	144 (83.2%)	734 (90.5%)	<0.01	231 (92.0%)	1018 (91.6%)	0.8
CCBS	40 (23.1%)	184 (22.7%)	0.91	62 (24.7%)	297 (26.7%)	0.51
Direct vasodilators	29 (16.8%)	110 (13.6%)	0.27	66 (26.3%)	260 (23.4%)	0.33
Loop diuretics	67 (38.7%)	186 (22.9%)	<0.0001	128 (51%)	492 (44.3%)	0.05
Potassium diuretics	12 (6.9%)	45 (5.6%)	0.48	27 (10.8%)	59 (5.3%)	<0.001
Thiazide diuretics	9 (5.2%)	43 (5.3%)	0.96	17 (6.8%)	77 (6.9%)	0.93
Fibrates	9 (5.2%)	22 (2.7%)	0.09	9 (3.6%)	23 (2.1%)	0.15
Statins	148 (85.6%)	728 (89.8%)	0.11	240 (95.6%)	1070 (96.3%)	0.65
GPR antagonists	52 (30.1%)	328 (40.4%)	0.01	54 (21.5%)	289 (26.0%)	0.14
Warfarin	11 (6.4%)	31 (3.8%)	0.13	31 (12.4%)	100 (9.0%)	0.1
Antihyperglycemics	13 (7.5%)	87 (10.7%)	0.20	29 (11.6%)	111 (10.0%)	0.46
Lytics	4 (2.3%)	10 (1.2%)	0.28	3 (1.2%)	30 (2.7%)	0.16
PPIs	84 (48.6%)	328 (40.4%)	0.05	128 (51.0%)	576 (51.8%)	0.82
H2RA	38 (22.0%)	175 (21.6%)	0.91	63 (25.1%)	293 (26.4%)	0.68
Comorbidities						
Congestive heart failure	71 (41.0%)	124 (15.3%)	<0.0001	128 (51.0%)	436 (39.2%)	<0.001
Cardiac arrhythmia	68 (39.3%)	203 (25.0%)	<0.001	119 (47.4%)	462 (41.6%)	0.09
Valvular disease	18 (10.4%)	37 (4.6%)	<0.01	52 (20.7%)	153 (13.8%)	0.01

	Prasugrel users			Ticagrelor users		
	Cases (%) N=173	Controls (%) N=811	p-value	Cases (%) N=251	Controls (%) N=1,111	p-value
Pulmonary circulation disorders	12 (7.0%)	19 (2.3%)	<0.01	18 (7.2%)	60 (5.4%)	0.28
Peripheral vascular disorders	33 (19.1%)	51 (6.3%)	<0.0001	42 (16.7%)	137 (12.3%)	0.06
Hypertension	21 (12.1%)	34 (4.2%)	<0.0001	46 (18.3%)	89 (8.0%)	<.0001
Diabetes (complicated)	28 (16.2%)	49 (6.0%)	0.59	51 (20.3%)	126 (11.3%)	0.61
Peptic ulcer disease	1 (0.6%)	1 (0.1%)	0.23	7 (2.8%)	19 (1.7%)	0.26
Coagulopathy	9 (5.2%)	14 (1.7%)	<0.01	20 (8.0%)	44 (4.0%)	0.01
Blood loss anemia	0 (0%)	3 (0.4%)	0.423	8 (3.2%)	8 (0.7%)	<0.001
Hospital characteristics						
Full catheterization lab	144 (83.2%)	658 (81.1%)	0.76	165 (65.7%)	745 (67.1%)	0.85
No full catheterization lab	2 (1.2%)	8 (1%)		11 (4.4%)	41 (3.7%)	
Unknown	27 (15.6%)	145 (17.9%)		75 (29.9%)	326 (29.3%)	
Acute status‡	172 (99.4%)	807 (99.5%)	0.89	249 (99.2%)	1098 (98.8%)	0.54
Urban location	156 (90.2%)	692 (85.3%)	0.09	161 (64.1%)	848 (76.3%)	<0.001
Bed size 200-500‡	75 (43.4%)	510 (62.9%)	<.0001	71 (28.3%)	464 (41.8%)	<0.001
Bed size <200‡	40 (23.1%)	123 (15.2%)		48 (19.1%)	228 (20.5%)	
Bed size >500‡	58 (33.5%)	178 (21.9%)		132 (52.6%)	420 (37.8%)	

* Mean (standard deviation) are reported; comparison made using Mann Whitney U test.
† Matching variable.
‡Variable not included in regression models.
ACE: angiotensin converting enzyme; CABG: coronary artery bypass grafting; CCBs: calcium channel blockers; GPR: glycoprotein IIb/IIIa receptor; H2RA: H2 receptor antagonist; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; PPI: proton pump inhibitor; STEMI: ST-elevation myocardial infarction;

The ORs estimated for the four outcomes in each of the two cohorts were adjusted for all variables in Table 5-2 except for matching variables (sex, age, cohort entry and ethnicity) and the variables that were not significant in the model based on empirical testing (length of stay, health insurance status, acute status of hospital and hospital bed size). Obesity was represented in the comorbidity score and thus not included in as an individual covariate.

For prasugrel, ORs for the MI endpoint suggest a lack of association for concomitant PPI treatment versus no PPIs (adjusted OR 1.04, 95% CI 0.67-1.61). Adjusted ORs for the secondary outcomes also suggest a lack of association for combined PPI treatment with prasugrel. Similarly, there is no association between receiving PPIs in combination with ticagrelor and experiencing an MI (adjusted OR 0.96; 95% CI: 0.69-1.33) or experiencing either of the secondary endpoints (Figure 5-2).

Wide confidence intervals were observed around the odds ratios point estimates, due to the relatively small number cases in each analysis. The point estimates were similar in magnitude between the two cohorts, except for stroke among prasugrel users, where the point estimate was 0.52 among prasugrel users and 1.24 among ticagrelor users. Both ORs however, did not reach statistical significance.

In the sensitivity analysis, adjusted ORs for H2RA use vs nonuse association with MI were 0.84 (95% CI: 0.58-1.22) among ticagrelor users and 1.15 (95% CI: 0.71 - 1.89) among prasugrel users. Similar ORs were obtained for the secondary outcomes, suggesting a lack of association with H2RA use (Supplemental Material, Table S5-6).

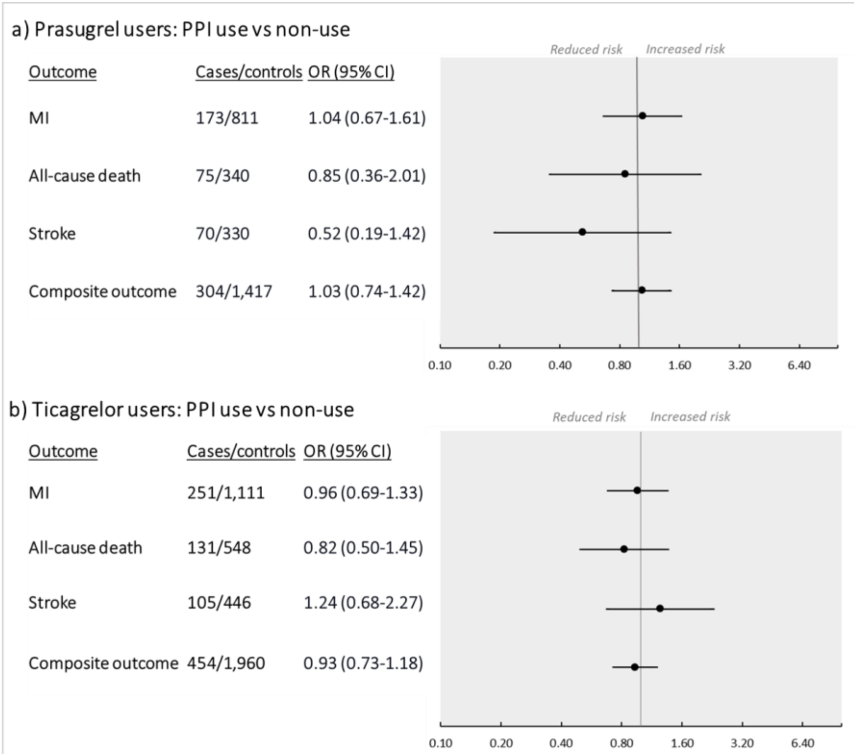

FIGURE 5- 2. ADJUSTED ORS FOR THE RISK OF ADVERSE CARDIOVASCULAR EVENTS AMONG ASSOCIATED WITH PPI USE AMONG A) PRASUGREL USERS AND B) TICAGRELOR USERS.

5.4 DISCUSSION

In this study, we used electronic health records of patients that had experienced an MI in over 500 US hospitals to investigate the risk of adverse cardiovascular events associated with PPI use in prasugrel users and in ticagrelor users. Our findings suggest the lack of association with the outcomes assessed: MI, stroke, death from any cause, or the composite endpoint of these three individual outcomes.

Our findings are in agreement with prior observational studies that have assessed clinical endpoints and have reported similar findings among ticagrelor users (Yan et al. 2016; Hoedemaker et al. 2018) and prasugrel users in a post hoc-analysis of the TRITON-TIMI 38 trial

(O'Donoghue et al. 2009). Goodman et al. (2012) reported a positive association (adjusted hazards ratio (aHR) 1.24, 95% CI: 1.07–1.45) between PPIs and the composite outcome (cardiovascular death, MI or stroke) among ACS patients receiving ticagrelor based on a post-hoc analysis of the PLATO trial. However, they also reported a lack of association for the individual outcomes. The authors dismissed the possibility of a causal association and attributed the elevated risk they identified to confounding by indication. Their conclusion was based on the observation of higher event rates among patients treated with a PPI which were independent of receiving an antiplatelet.

Studies on platelet reactivity have also been performed on these two antiplatelet agents. Storey et al. (2010) reported that there was no difference in platelet reactivity among patients receiving ticagrelor with or without PPIs. Similarly, no difference in platelet reactivity or platelet inhibition was reported among patients that received prasugrel with or without PPIs (Nicolau et al. 2015) and specifically lansoprazole (Collet et al. 2014).

Such studies have led to many observational studies since 2009 assessing cardiovascular endpoints that have arrived at inconclusive findings regarding the clinical significance of the interaction between PPIs and clopidogrel. Previously, we performed a case control study nested within a cohort a clopidogrel users by using the same data source and statistical analyses as the present study (Chapter 4). We reported no association between concomitant clopidogrel and PPI treatment and adverse cardiovascular events (MI, stroke, all-cause death and composite endpoint of the prior three outcomes). Our findings supported prior findings that suggest a lack of a statistically significant clinical impact, despite the presence of a drug-drug interaction at the biological level.

Prasugrel and ticagrelor, which are the focus of the main study, have key differences in their metabolism in the human body compared to clopidogrel that support a lack of an interaction with PPIs. In the case of clopidogrel, the biological mechanism for a drug-drug interaction between PPIs and clopidogrel is the competitive inhibition of the hepatic enzymes involved in the metabolism of both drugs. CYP2C19 is a major contributor to the transformation of clopidogrel to its active form in the human body is largely dependent on the CYP2C19 pathway ((Kurihara et al. 2005) in (Farid et al. 2010)), making it prone to interact with other drugs requiring this pathway (Scott, Owusu Obeng, et al. 2014). Prasugrel requires hepatic metabolism to transform it to its active form (Baron et al. 2014); however, CYP2C19 has a relatively small contribution and is not predominant in the bioactivation process (Scott, Owusu Obeng, et al. 2014; Nicolau et al. 2015). Further, a large proportion of prasugrel is believed to be activated by intestinal CYP3A enzymes (Farid et al. 2010). Ticagrelor, on the other hand, is a direct acting drug that does not require bioactivation in the body. Hence, the potential for PPIs to interact with both prasugrel and ticagrelor is low compared with clopidogrel (Scott, Owusu Obeng, et al. 2014; Kubisz 2018) and interactions of these antiplatelets with PPIs have not been reported (Kubisz 2018).

5.4.1 LIMITATIONS

This study is subject to several limitations that should be acknowledged. The number of cases identified for the individual outcomes was relatively small, leading to wide confidence intervals around the estimated ORs. This was likely due to low prevalence of use of prasugrel or ticagrelor, as they are relatively recent drugs not yet available in generic form. Patient exposure to drugs, including PPIs and antiplatelets, was assessed at the time of cohort entry, which may have changed during the 1-year follow-up. There is the possibility that patients may have switched medications, stopped treatment, or initiated new treatments. Although this is possible, a prior study has suggested the majority of patients (76.2%) that initiate DAPT treatment following discharge from hospital do not switch antiplatelet agents during the first year after initiation (Bueno et al. 2017). Findings had the potential for bias from misclassification of exposure, as we had no information on adherence and thus could not take this into account in the analysis. Further, we may have missed the total events that occurred among the cohort patients up as we did not have information on patients that may have experienced an event and received treatment at a hospital that does not report to Cerner. Finally, the relatively low number of cases for each outcome did not allow us to stratify the findings by age group, PPI type or shorter follow up periods.

5.4.2 STRENGTHS

Strengths of the current analyses are the use of real-world data from a diverse cohort of US patients from more than 500 US health centers located in all of the census regions. This database is rich in clinical information collected from real-world settings, which allowed the inclusion of numerous covariates in the regression models. Particularly, we had information on obesity and smoking, both of which are important risk factors for cardiovascular disease and are commonly missing from studies based on insurance claims databases.

5.4.3 CONCLUSION

Overall, the findings presented in this paper add to the limited literature on potential adverse effects associated with the use of PPIs with antiplatelets other than clopidogrel. Our results, based on our analysis of electronic health records from US hospitals, do not show an increased risk of MI, stroke or all-cause death with concomitant treatment of PPIs among prasugrel or ticagrelor users in patients with a history or a prior MI.

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SUPPLEMENTAL MATERIAL S5

Additional material referenced in the main article is included in this section, including relevant International classification of disease (ICD) codes for diagnoses, detailed characteristics of the two study cohorts, and detailed comparison of the cases and controls corresponding to the secondary outcomes.

ICD CODES

ICD diagnosis codes used in the present are listed in Table S5-1. These codes were used to identify patients that had experienced a myocardial infarction for entry into the study cohort, cases for the myocardial infarction and stroke outcomes as we as the type of myocardial infarction.

TABLE S5-1. INTERNATIONAL CLASSIFICATION OF DISEASE (ICD) CODES FOR MI, MI TYPE AND STROKE.

Myocardial infarction	*ICD 9*: 410.xx excluding 410.x2 *ICD 10*: I21.x
Type of myocardial infarction	NSTEMI (non-ST-elevation myocardial infarction) *ICD 9*: 410.71 , 410.7 ; *ICD 10*: I21.4 , I22.2 STEMI (ST-elevation myocardial infarction) ICD 9: 410.1 , 410.11 , 410.2 , 410.21, 410.3 , 410.31 , 410.4 , 410.41, 410.5, 410.51 , 410.6, 410.61, 410.8, 410.81, 410.9, 410.91; *ICD 10:* I21.0, I21.01, I21.02, I21.09, I21.1, I21.11, I21.19, I21.2, I21.21, I21.29, I21.3, I22.0, I22.1, I22.8, I22.9 Unspecified ICD 9: 410; ICD 10: I21, I22
Stroke	ICD 9: 430.xx, 431.xx, 432,xx, 433.xx, 434.xx, 436.xx ICD 10: I60.x, I61.x, I62.x, I63.x, I65.x, I66.x

ADDITIONAL RESULTS

Detailed cohort characteristics

The two study cohorts included patients that were hospitalized for a first MI (documented in Health Facts®) and received either prasugrel or ticagrelor. A detailed description of the cohorts' characteristics is presented in Table S5-2.

TABLE S5-2. DETAILED DESCRIPTION OF THE TWO STUDY COHORTS.

	Prasugrel users	Ticagrelor users
Number of patients	5,240	4,050
Age[ǂ] (years)	58.9 (11.0)	65.0 (12.4)
Comorbidity score [ǂ]	1.9 (1.8)	2.8 (1.9)
LOS at cohort entry [ǂ] *(days)*	6.02 (6.0)	7.2 (7.5)
Sex		
Males	73.11%	62.3%
Females	26.89%	37.7%
Ethnicity		
Caucasian	81%	77.1%
African American	12.53%	16.8%
Other	6.47%	6.1%
Health insurance status		
Private	34.3%	22.7%
Medicare	27.0%	45.2%
Medicaid	9.4%	9.1%
Uninsured	8.8%	5.2%
Other/missing	20.7%	18.0%
US Census Region		
Midwest	9.6%	15.2%
Northeast	26.4%	32.8%
South	48.0%	41.4%
West	16.1%	10.6%
Teaching status of hospital		
Teaching facility	60.7%	64.9%
Non-teaching facility	25.1%	19.3%
Unknown	14.1%	15.8%
Full catheterization lab		
No	6.4%	5.5%
Yes	78.1	71.5%
Unknown	15.5%	23.0%
Hospital care		
Acute care	99.2%	98.8%
Non-acute care	0.8%	1.2%
Location of hospital		
Rural	10.9%	23.0%
Urban	89.1%	77.0%
Size of hospital (number of beds)		
<200	24.9%	21.6%
200-500	45.7%	41.3%
>500	29.4%	37.1%

† Mean and standard deviation reported.
LOS: length of stay.

Comparisons of cases and controls for secondary outcomes

Cases and controls were identified at 12 months post cohort entry were identified from the study cohorts for three secondary outcomes. Detailed description of the cases and controls are presented in Tables S5-3, S5-4 and S5-5 for stroke, death from all causes and the composite of myocardial infarction, stroke and death from all causes, respectively.

TABLE S5-3. DESCRIPTION OF CASES AND CONTROLS FOR THE STROKE OUTCOME IN THE TWO STUDY COHORTS.

	Prasugrel users			Ticagrelor users		
	Cases (%) N=70	Controls (%) N=330	p-value	Cases (%) N=105	Controls (%) N=446	p-value
Age (years) *†	63.4 (10.8)	62.6 (9.7)	0.65	68.3 (10.6)	69.0 (9.7)	0.65
LOS at cohort entry (days) *‡	6.4 (8.9)	4.6 (4.6)	0.31	9.8 (11.3)	7.1 (7.9)	<0.01
Comorbidity score*	2.8 (1.8)	1.8 (1.9)	<0.001	3.7 (1.8)	2.8 (1.9)	<0.001
Male†	70%	70.6%	0.92	54.3%	58.1%	0.48
Ethnicity†						
African American	11.4%	10.3%	0.56	16.2%	10.5%	0.13
Caucasian	85.7%	88.5%	0.11	80%	87.4%	
Other	2.9%	1.2%		3.8%	2%	
Health insurance status ‡						
Medicare	40%	35.5%	0.92	62.9%	53.6%	<0.001
Medicaid	12.9%	7.9%		15.2%	4.9%	
Private	17.1%	25.5%		10.5%	16.6%	
Uninsured	8.6%	3.6%		3.8%	2.9%	
Missing/unknown	21.4%	27.6%		7.6%	22%	
US Census region						
Midwest	8.6%	19.1%	<0.001	24.8%	15%	<0.001
Northeast	12.9%	43.0%		18.1%	43.7%	
South	64.3%	31.5%		47.6%	32.3%	
West	14.3%	6.4%		9.5%	9%	
Obesity‡	30%	17.9%	0.02	29.5%	20%	0.03
Smoking	37.1%	25.8%	0.05	36.2%	24%	0.01
MI type						
NSTEMI	42.9%	31.2%	0.16	58.1%	41.7%	<0.01
STEMI	25.7%	29.1%		21%	24.4%	
Unspecified	31.4%	39.7%		21%	33.9%	
Cardiovascular procedures						
PCI/stent	60%	48.5%	0.08	71.4%	50.5%	<0.001
CABG	1.4%	2.1%	0.71	8.6%	1.6%	<0.001
Carotid revascularization	4.3%	3%	0.59	6.7%	4.3%	0.3
Comedications						
Aspirin	12.9%	15.5%	0.58	28.6%	37.4%	0.09
ACE inhibitors	62.9%	59.1%	0.56	58.1%	62.8%	0.37
Beta blockers	87.1%	91.5%	0.25	93.3%	93.5%	0.95
CCBS	27.1%	20%	0.18	40%	26%	<0.01

	Prasugrel users			Ticagrelor users		
	Cases (%) N=70	Controls (%) N=330	p-value	Cases (%) N=105	Controls (%) N=446	p-value
Direct vasodilators	22.9%	14.2%	0.07	29.5%	25.3%	0.38
Loop diuretics	38.6%	26.4%	0.04	49.5%	47.5%	0.71
Potassium diuretics	4.3%	5.5%	0.69	7.6%	7.4%	0.94
Thiazide diuretics	15.7%	5.2%	<0.01	11.4%	5.6%	0.03
Fibrates	2.9%	1.5%	0.44	6.7%	1.8%	0.01
Statins	88.6%	95.2%	0.04	98.1%	92.8%	0.04
GPR antagonists	38.6%	38.5%	0.99	23.8%	23.5%	0.95
Warfarin	8.6%	4.9%	0.21	11.4%	8.1%	0.27
Antihyperglycemics	5.7%	10.9%	0.19	17.1%	10.1%	0.04
Lytics	2.9%	1.5%	0.44	5.7%	2.9%	0.16
PPIs	50%	40%	0.12	61%	56.1%	0.36
H2RA	20%	21.5%	0.78	31.4%	21.5%	0.03
Comorbidities						
Congestive heart failure	28.6%	17%	0.02	45.7%	41.9%	0.5
Cardiac arrhythmia	38.6%	22.4%	<0.01	51.4%	41%	0.06
Valvular disease	18.6%	6.4%	<0.001	24.8%	18.2%	0.13
Pulmonary circulation disorders	7.1%	2.7%	0.07	2.9%	8.1%	0.04
Peripheral vascular disorders	20%	7.6%	<0.01	35.2%	16.4%	<.001
Hypertension	11.4%	4.9%	0.04	17.1%	11.9%	0.15
Diabetes (complicated)	17.1%	7%	0.82	18.1%	13%	0.34
Peptic ulcer disease	1.4%	0%	0.03	1.9%	1.8%	0.94
Coagulopathy	7.1%	2.1%	0.03	4.8%	4.7%	0.99
Blood loss anemia	0%	0.3%	0.64	0%	0.9%	0.33
Hospital characteristics						
With full cath. lab	84.3%	65.5%	<0.01	83.8%	65%	<0.001
Without full cath. lab	1.4%	1.2%		2.9%	3.4%	
Unknown	14.3%	33.3%		13.3%	31.6%	
Acute status‡	100%	100 %		100%	99.8%	0.63
Non-acute status ‡	0%	0%		0%	0.2%	
Urban location	90.0%	77.0%	0.01	87.6%	75.1%	0.01
Rural location	10.0%	23.0%		12.4%	24.9%	
Bed size 200-500‡	35.7%	66.4%	<0.001	38.1%	43.1%	0.36
Bed size <200‡	28.6%	18.5%		23.8%	17.9%	
Bed size >500‡	35.7%	14.9%		38.1%	39%	

* Mean (standard deviation) are reported; comparison made using Mann Whitney U test.
† Matching variable.
‡Variable not included in regression models.
ACE: angiotensin converting enzyme; CABG: coronary artery bypass grafting; cath lab: catheterization lab; CCBs: calcium channel blockers; ECM: Elixhauser comorbidity measures; GPR: glycoprotein IIb/IIIa receptor; H2RA: H2 receptor antagonist; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; PPI: proton pump inhibitor; STEMI: ST-elevation myocardial infarction;

TABLE S5-4. DESCRIPTION OF THE CASES AND CONTROLS FOR THE ALL-CAUSE MORTALITY OUTCOME IN THE TWO COHORTS.

	Prasugrel users			Ticagrelor users		
	Cases (%) N=75	Controls (%) N=330	p-value	Cases (%) N=131	Controls (%) N=548	p-value
Age (years)* †	63.3 (10.3)	63.0 (9.6)	0.66	71.3 (10.6)	71.4 (9.5)	0.81
LOS at cohort entry (days)* ‡	7.3 (7.7)	4.1 (3.3)	<0.0001	9.8 (8.4)	7.1 (6.0)	<0.0001
Comorbidity index score*	3.6 (2.1)	2.0 (1.8)	<0.0001	4.1 (2.1)	2.8 (1.8)	<0.0001
Male†	65.3%	66.5%	0.85	64.9%	65.2%	0.96
Ethnicity†						
African American	24%	19.7%	0.35	25.2%	16.2%	0.02
Caucasian	69.3%	76.5%		74.8%	84%	
Other	6.7%	3.8%		0%	0%	
Health insurance status‡						
Medicare	60%	45%	0.06	70.2%	59.3%	0.08
Medicaid	5.3%	7.1%		8.4%	6.6%	
Private	16%	25%		7.6%	13.9%	
Uninsured	5.3%	2.4%		2.3%	2.9%	
Missing/unknown	13.3%	20.6%		11.5%	17.3%	
US Census region						
Midwest	8.0%	12.7 %	0.04	13.7%	15.9%	0.05
Northeast	24.0%	37.7%		29%	37.2%	
South	56.0%	40.6%		48.9%	35.8%	
West	12.0%	9.1%		8.4%	11.1%	
Obesity‡	34.7%	20.3%	0.01	32.1%	20.8%	0.01
Smoking	28%	28.2%	0.97	24.4%	22.8%	0.69
MI type						
NSTEMI	52.0%	35.6 %	<0.01	54.2%	44%	0.1
STEMI	16.0%	35.6%		16.8%	21.9%	
Unspecified	32.0%	28.8%		29%	34.1%	
Cardiovascular procedures						
PCI/stent	56%	60%	0.52	61.8%	57.9%	0.41
CABG	0%	1.2%	0.35	2.3%	1.8%	0.73
Carotid revascularization	2.7%	2.1%	0.74	4.6%	5.5%	0.68
Comedications						
Aspirin	25.3%	24.7%	0.91	32.1%	32.9%	0.86
ACE inhibitors	49.3%	56.2%	0.28	48.1%	64.8%	<0.001
Beta blockers	86.7%	92.1%	0.14	92.4%	93.6%	0.61
CCBS	26.7%	22.7%	0.46	24.4%	31.4%	0.12
Direct vasodilators	21.3%	16.5%	0.31	26%	29%	0.49
Loop diuretics	61.3%	26.5%	<.0001	70.2%	51.1%	<.0001
Potassium diuretics	6.7%	3.8%	0.27	16.8%	7.7%	<0.01
Thiazide diuretics	5.3%	6.8%	0.65	11.5%	7.7%	0.16
Fibrates	6.7%	2.4%	0.05	4.6%	2%	0.09
Statins	88%	92.1%	0.26	97.7%	95.1%	0.19
GPR antagonists	29.3%	37.4%	0.19	27.5%	22.5%	0.22
Warfarin	9.3%	3.5%	0.03	18.3%	8.9%	<0.01
Antihyperglycemics	10.7%	10.9%	0.96	13.7%	11.3%	0.44
Lytics	8%	1.2%	<0.001	5.3%	2.7%	0.13
PPIs	54.7%	41.2%	0.03	55.7%	54.2%	0.75
H2RA	22.7%	25.6%	0.6	29%	26.5%	0.55
Comorbidities						
Congestive heart failure	61.3%	19.1%	<.0001	71%	44.7%	<.0001
Cardiac arrhythmia	38.7%	24.7%	0.01	59.5%	44.3%	<0.01

	Prasugrel users			Ticagrelor users		
	Cases (%) N=75	Controls (%) N=330	p-value	Cases (%) N=131	Controls (%) N=548	p-value
Valvular disease	9.3%	7.4%	0.56	27.5%	16.2%	<0.01
Pulmonary circulation disorders	6.7%	3.2%	0.16	9.9%	5.5%	0.08
Peripheral vascular disorders	29.3%	9.7%	<.0001	32.8%	17.9%	<0.001
Hypertension	17.3%	5.9%	<0.001	25.2%	11.7%	<.0001
Diabetes (complicated)	21.3%	8.2%	0.04	22.1%	12.6%	0.49
Peptic ulcer disease	1.3%	0.6%	0.49	3.1%	2.7%	0.84
Coagulopathy	2.7%	3.2%	0.8	12.2%	4.9%	<0.01
Blood loss anemia	4.0%	0.6%	0.01	2.3%	0.9%	0.1892
Hospital characteristics						
With full cath. lab	6.7%	1.2 %	<0.01	78.6%	69.5%	0.06
Without full cath. lab	77.3%	72.9%		4.6%	3.7%	
Unknown	16.0%	25.9%		16.8%	26.8%	
Acute status‡	100%	100%		100%	98.9%	0.23
Non-acute status ‡	0%	0%		0%	1.1%	
Urban location	90.8%	77.3	0.01	78.6%	76.1%	0.54
Rural location	9.3%	22.7		21.4%	23.9%	
Bed size 200-500‡	34.7%	57.6	<0.01	35.1%	41.2%	0.33
Bed size <200‡	29.3%	6.1		19.9%	20.4%	
Bed size >500‡	34.7%	24.1		45%	38.3%	

* Mean (standard deviation) are reported; comparison made using Mann Whitney U test.
† Matching variable.
‡Variable not included in regression models.
ACE: angiotensin converting enzyme; CABG: coronary artery bypass grafting; cath lab: catheterization lab; CCBs: calcium channel blockers; ECM: Elixhauser comorbidity measures; GPR: glycoprotein IIb/IIIa receptor; H2RA: H2 receptor antagonist; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; PPI: proton pump inhibitor; STEMI: ST-elevation myocardial infarction;

TABLE S5-5. DESCRIPTION OF THE CASES AND CONTROLS FOR THE COMPOSITE ENDPOINT IN THE STUDY COHORTS.

	Prasugrel users			Ticagrelor users		
	Cases (%) N=304	Controls (%) N=1,417	p-value	Cases (%) N=454	Controls (%) N=1,961	p-value
Age (years)*†	60.8 (10.7)	60.4 (9.8)	0.53	67.7 (11.3)	67.9 (10.6)	0.94
LOS at cohort entry (days)*‡	5.9 (7.0)	4.4 (4.8)	<0.0001	8.4 (8.1)	7.2 (7.6)	<0.0001
Comorbidity index score*	3.1 (2.1)	1.7 (1.7)	<0.0001	3.5 (2.1)	2.7 (1.9)	<0.0001
Male†	66.1%	67.3%	0.7	61.2%	63.6%	0.36
Ethnicity†						
African American	17.8%	15.3%	0.25	16.5%	10.5%	<0.001
Caucasian	78%	81.7%		81.5%	88.6%	
Other	4.3%	3.0%		2.0%	1.0%	
Health insurance status ‡						
Medicare	39.8%	32.3%	<0.001	59%	47.6%	<0.0001
Medicaid	11.5%	8.1%		10.3%	7.6%	
Private	24.7%	26.8%		15.6%	18.7%	
Uninsured	6.3%	4.6%		4.2%	4.3%	
Missing/unknown	17.8%	28.2%		10.8%	21.8%	
US Census region						
Midwest	8.2%	14.3 %	<0.0001	15.4%	15.8%	0.41
Northeast	31.3%	41.5%		36.3%	40%	
South	50.0%	32.9%		37.4%	33.6%	
West	10.5%	11.4%		10.8%	10.7%	
Obesity‡	34.5%	18.7%	<0.0001	30.2%	21.3%	<.0001
Smoking	38.5%	27.7%	<0.001	29.7%	25.2%	0.04
MI type						
NSTEMI	40.5%	30.4 %	<0.01	51.1%	41.4%	<0.01
STEMI	27.6%	36.0%		21.4%	24.9%	
Unspecified	31.9%	33.6%		27.5%	33.7%	
Cardiovascular procedures						
PCI/stent	63.2%	54.6%	0.01	61.7%	54.6%	0.01
CABG	0.7%	1.3%	0.37	4.2%	2.8%	0.12
Carotid revascularization	2.6%	3.1%	0.66	6.4%	7%	0.62
Comedications						
Aspirin	26%	21.2%	0.07	36.3%	33%	0.17
ACE inhibitors	56.6%	58.8%	0.48	58.8%	64.4%	0.03
Beta blockers	84.5%	91%	<0.001	92.3%	92.3%	0.98
CCBS	23.7%	21.9%	0.49	27.8%	27.4%	0.86
Direct vasodilators	19.1%	14.4%	0.04	26.9%	24.2%	0.24
Loop diuretics	43.4%	23.6%	<0.0001	55.3%	46.4%	<0.001
Potassium diuretics	6.3%	5.2%	0.44	11.2%	6.4%	<0.001
Thiazide diuretics	7.6%	5.6%	0.18	8.8%	6.7%	0.12
Fibrates	5.3%	2.4%	0.01	4.6%	2.1%	<0.01
Statins	86.8%	91.8%	0.01	96.9%	95.5%	0.15
GPR antagonists	32.2%	39.7%	0.01	23.4%	25.1%	0.44
Warfarin	7.6%	3.7%	<0.01	13.2%	8.5%	<0.01
Antihyperglycemics	7.9%	10.5%	0.17	13%	10.4%	0.11
Lytics	3.6%	1.4%	0.01	3.5%	2.5%	0.2
PPIs	50.3%	40.4%	<0.0001	54%	52.6%	0.59
H2RA	21.4%	21.7%	0.89	27.8%	25.3%	0.28
Comorbidities						
Congestive heart failure	42.1%	15.7%	<0.0001	53.3%	40.9%	<.0001
Cardiac arrhythmia	40.1%	24.6%	<0.0001	51.1%	41.5%	<0.001
Valvular disease	12.2%	5.2%	<0.0001	22.9%	15.2%	<0.0001

	Prasugrel users			Ticagrelor users		
	Cases (%) N=304	Controls (%) N=1,417	p-value	Cases (%) N=454	Controls (%) N=1,961	p-value
Pulmonary circulation disorders	6.6%	2.4%		6.6%	5.9%	0.55
Peripheral vascular disorders	21.4%	7%	<0.0001	24.5%	13.8%	<0.0001
Hypertension	13.2%	4.7%	<0.0001	19.2%	9.4%	<0.0001
Diabetes (complicated)	17.8%	6.6%	0.23	19.6%	11.8%	0.61
Peptic ulcer disease	1%	0.2%	0.04	2.4%	1.9%	0.46
Coagulopathy	4.9%	2.1%	<0.0001	8.2%	4.1%	<0.001
Blood loss anemia	1.0%	0.4%	0.22	1.8%	0.9%	0.1163
Hospital characteristics						
With full cath. lab	82.2%	75.7 %	<0.01	66.5%	72.3%	66.45
Without full cath. lab	2.6%	1.2%		3.7%	4.2%	
Unknown	15.1%	23.2%		29.8%	23.6%	
Acute status‡	99.7%	99.7%	0.89	100.0%	99.6%	98.93
Non-acute status‡	0.3%	0. 3%		0%	0.4%	
Urban location	90.1%	81.9 %	<0.001	76.0%	72.9%	76.03
Rural location	9.9%	18.1%		24.0%	27.1%	
Bed size 200-500‡	39.5%	20.8%	<0.0001	42.0%	32.4%	42.02
Bed size <200‡	25.6%	4.25%		20.5%	19.6%	
Bed size >500‡	34.8%	62.2%		37.5%	48.0%	

* Mean (standard deviation) are reported; comparison made using Mann Whitney U test.
† Matching variable.
‡Variable not included in regression models.
ACE: angiotensin converting enzyme; CABG: coronary artery bypass grafting; cath lab: catheterization lab; CCBs: calcium channel blockers; ECM: Elixhauser comorbidity measures; GPR: glycoprotein IIb/IIIa receptor; H2RA: H2 receptor antagonist; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; PPI: proton pump inhibitor; STEMI: ST-elevation myocardial infarction;

Sensitivity analyses

Effect estimates assessing the association between H2RA use and each of the study outcomes were compared to those for PPI use in the two study cohorts. Adjusted ORs were similar for both exposures and suggested a lack of association with either outcome (Table S5-6).

TABLE S5-6. ADJUSTED ODDS RATIOS (ORS) AND 95% CONFIDENCE INTERVALS (CI) FOR H2RA USE VS NON-USE AT 12 MONTHS POST COHORT ENTRY.

	Ticagrelor users OR (95% CI)	Prasugrel users OR (95% CI)
MI	0.84 (0.58 - 1.22)	1.15 (0.71 - 1.89)
Stroke	1.30 (0.66 - 2.53)	0.50 (0.16 - 1.54)
All-cause mortality	1.07 (0.62 - 1.85)	0.50 (0.17 - 1.45)
Composite	0.93 (0.72 - 1.21)	0.81 (0.56 - 1.17)

CHAPTER 6

GENERAL DISCUSSION

In the previous chapters, I presented four studies that comprise my PhD thesis research with the overall objective of gaining a better understanding of the potential clinical impact of the much-debated drug-drug-interaction between clopidogrel and PPIs. The first study (Chapter 2) was a systematic review and meta-analysis that summarized published findings on the risk of adverse cardiovascular events associated with PPI use, alone or in combination with clopidogrel or with other antiplatelet agents. Although several recent systematic reviews have summarized findings related to the concomitant use of clopidogrel and PPIs, the broader scope of my review allowed the inclusion of studies that had assessed the potential harms of PPIs independent of clopidogrel. The review of evidence from the latter group of studies was essential to address the thesis research question, as recent reports have suggested mechanisms in which PPIs may independently affect cardiovascular health (Böger and Zoccali 2003; Ghebremariam et al. 2013; Rochette et al. 2013).

The second study (Chapter 3) examined the patterns of concomitant clopidogrel-PPI treatment in response to US FDA warnings issued in 2009 and 2010. This study demonstrated that in US inpatient settings, patterns of combined clopidogrel-PPI treatment changed after the warnings in a manner consistent with the clinical practice recommendations made by the FDA. In this chapter, I also noted that many events that followed the FDA communications - revised treatment guidelines, label changes, and the availability of new drugs or generic forms of existing drugs - likely contributed to the observed trends. This analysis further indicated that in 2016, 14% of inpatients with ACS received clopidogrel in addition to PPIs, despite the introduction of newer and more potent antiplatelet agents. The continued popularity of clopidogrel among ACS patients provided additional motivation from a public health perspective to better understand the harms potentially associated with concomitant treatment.

In Chapter 4, I presented a case-control analysis assessing the risk of adverse cardiovascular events with concomitant therapy, where the statistical analysis controlled for as many relevant covariates as possible, given the information available in Health Facts®. The findings suggested no increased risk, except in patients between 80 and 89 years old.

Finally, in Chapter 5, I presented additional case-control analyses assessing the risk of adverse clinical events in association with the concomitant treatment of PPIs with either ticagrelor or prasugrel. The findings of this study, also suggestive of a lack of association, allowed the direct comparison with findings reported in Chapter 4. As the systematic review highlighted the scarcity of studies in the literature that examined clinical effects of other antiplatelet agents in combination with PPIs, this last study serves as a contribution to filling this important knowledge gap.

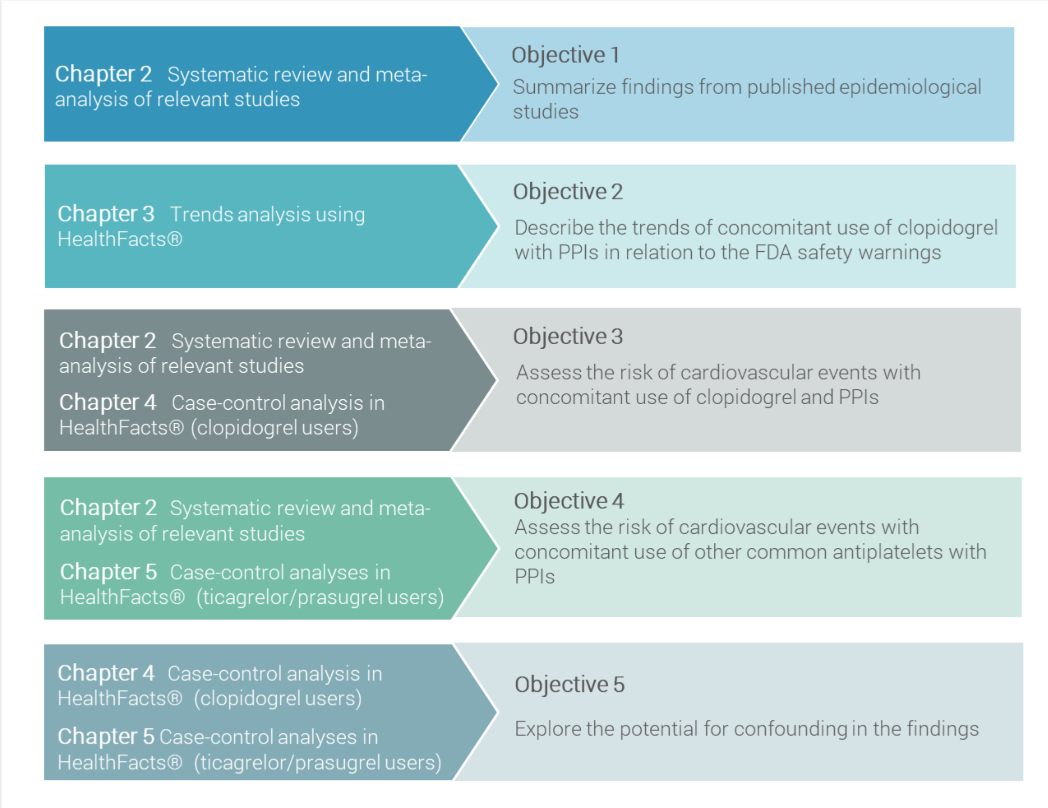

FIGURE 6- 1. RELATIONSHIP BETWEEN THE RESEARCH OBJECTIVES AND THE INDIVIDUAL STUDIES PRESENTED IN THIS THESIS.

The objectives of this PhD thesis were addressed in the four studies completed. As illustrated in Figure 6-1, the first two objectives were directly answered from Chapters 2 and 3, respectively. Objectives 3, 4, and 5 were addressed by integrating findings from Chapters 2, 4 and 5.

In the current chapter, I discuss some of the methodological considerations of the analytical studies presented in this thesis (Section 6.1) and then describe how the findings presented meet the thesis objectives. More specifically, I elaborate on how the findings can provide answers to the following questions:

- Is there an association between concomitant PPI-clopidogrel treatment and adverse cardiovascular events?

- Is there an association between concomitant use of PPIs with other agents and adverse cardiovascular events?
- What can we conclude about the potential for confounding in the findings from the case-control analyses of Health Facts®?
- Was a there a decline in the combined use of clopidogrel and PPIs after the FDA safety communications were issued in 2009 and 2010?

6.1 METHODOLOGICAL ASPECTS OF THE ANALYTICAL STUDIES

6.1.1 STUDY DESIGN

In Chapters 4 and 5, I presented two nested case-control studies that examined the association of PPI use vs nonuse among clopidogrel users and ticagrelor or prasugrel users, respectively. Case-control designs have been used in prior studies to examine similar associations. For example, ten percent of Group B studies included in the systematic review (Chapter 2) were based on case-control analyses. As discussed below there were several reasons for my choice of a case-control rather than a cohort study design.

First, prior work has shown that the odds ratios obtained from nested case-control analyses where the controls are randomly selected from the risk set of each case are comparable to the risk estimates obtained from a cohort analysis (Liddell et al. 1977; Breslow et al. 1983; Lubin and Gail 1984)

Second, in nested case-control studies, information corresponding to a subset of the cohort is analysed. This subset contains all the cases identified from the cohort and their corresponding controls. On the other hand, in a cohort study, information on all cohort members is collected and analysed. This analytical aspect makes nested case-control analyses much less computationally demanding, particularly when dealing with large samples commonly found in electronic health records. With current technological advancements, computers have the power to handle extremely large datasets. However, in our experience with the Health Facts® database, substantially longer periods of time are required for the analysis of large datasets compared to smaller datasets. Health Facts® is a large and complex database comprised of many data tables that house detailed clinical data for over 69 million unique patients. When performing analytical studies in this database – similar to the analyses presented in this thesis – several large tables are linked to obtain patients' complete clinical information. We have found this to be a resource intensive process when using the statistical software SAS.

Given the complexity and nature of the Health Facts® database, we found it preferable to conduct case-control analyses on a subset of the identified ACS cohort, so that it can be more efficiently analysed while providing risk estimates comparable to those obtained from the analysis of the full cohort.

The steps followed when conducting the nested case-control analyses were based on the those outlined in the *Textbook of Pharmacoepidemiology* (Strom et al. 2013), which involve:

1) definition of the cohort;
2) selection of all cases in the cohort (all patients that experience an outcome of interest);

3) creation of a risk-set for each case (all eligible controls for the case); and

4) the random selection of controls from each risk-set.

We also ensured that controls were sampled in a manner that 1) allowed cases to act as controls so long as they have not had an event of interest and 2) a patient can act as a control for multiple cases (Strom et al. 2013).

6.1.2 COVARIATE SELECTION

Several strategies are available when selecting covariates to include in the regression models that compute risk estimates. Greenland (1989) describes two methods that are commonly used in health research: 1) stepwise regression (backward deletion or forward selection), where selection or elimination of candidate variables is based on a significance criterion, and 2) the change-in-estimate method, in which candidate variables are selected based on their impact on the effect estimates. Greenland (1989) further notes that the change-in-estimate approach performs better than the stepwise regression method, where the latter approach may lack power to detect true confounders.

Integrating prior knowledge of potential confounders of the exposure-outcome association is also very useful in selecting covariate for inclusion into the statistical models. For example, covariates that are known to be confounders of the exposure-outcome association can be forced into models (Greenland 1989). Heinze et al (2018) suggest the use of directed acyclic graphs (DAGs) when using background information to guide covariate selection. The careful use of DAGs allows the identification of a set of variables that are sufficient to control for confounding through adjustment (Greenland et al. 1999). This ensures that confounders are included in the model while variables that are considered colliders and mediators are excluded. Although the use of DAGs is increasing in epidemiological research, their use is greatly dependent on empirical knowledge and speculative hypotheses which may sometimes be based on incorrect knowledge or erroneous hypotheses (Tu and Greenwood 2012).

In the studies presented in this thesis, the selection of covariates included in the statistical models was based on a combination of methods, namely 1) a priori selection of variables based on a review of the literature, 2) expert opinion, and 3) empirical selection based on the change-in-estimate criterion. The detailed examination of the studies included in the systematic review (Chapter 2) allowed us to identify important confounders that have been included in prior studies. Further, the consultation of a cardiologist provided the opportunity to identify further confounders that we may have missed. Finally, the change-in-effect criteria was used to empirically select various demographic variables and hospital characteristics. In the latter approach, variables that resulted in a change of ten percent or more in the odds ratio were selected for inclusion in the statistical regression model (Greenland 1989).

6.2 RISK OF ADVERSE CARDIOVASCULAR EVENTS WITH CONCOMITANT TREATMENT OF PPIS AND CLOPIDOGREL

The risk of adverse cardiovascular events associated with the combined treatment of clopidogrel and PPIs was examined using two approaches: 1) a systematic review and meta-analysis (Chapter 2) and 2) a case-control analysis of an EMR database (Chapter 4). The detailed review presented in Chapter 2 demonstrated that the link between combined clopidogrel-PPI treatment and cardiovascular events has been studied extensively since 2009 (referred to as Group B studies in Chapter 2). In fact, fifty relevant studies were included in the review, 38 of which reported adjusted effect estimates that were pooled in the meta-analyses. As clopidogrel is used for the treatment of ACS, all patients in the reviewed studies had some form of ACS such as a history of MI, stent placement, or PCI. Aside from the three RCTs (Tables 2-4 and 2-6), the included studies were observational in design and predominantly based on the analyses of large databases of medical claims data, prescription data, registries, or electronic medical records. The studies pooled together displayed varying degrees of heterogeneity in the effect estimates, as indicated by the I^2 statistic that ranged between no heterogeneity (I^2=0%) to substantial heterogeneity (I^2=88%) among certain subgroups of studies (Figure 2-6). The observed heterogeneity is likely due to differences in the studied populations, study designs and statistical methods employed. As mentioned earlier, findings on concomitant clopidogrel-PPI treatment have been inconsistent; therefore, it was expected to observe reported effect estimates that either showed no association or significant positive associations with adverse cardiovascular endpoints. When individual effect estimates were combined, the pooled risk ratios (RR) (presented in Chapter 2) were positive and statistically significant; statistical significance of the pooled RRs, however, was only observed for the all-cause mortality and MI outcomes. The findings presented demonstrated that when studies were grouped by separating the post-hoc analyses of RCTs and studies that used propensity scores (PS) matching from the remaining observational, a common pattern was observed in the pooled estimates for MI, all-cause mortality and cardiovascular mortality: the RRs obtained were attenuated and no longer statistically significant in the post-hoc analyses and studies that used PS matching in their analyses, compared to the remaining observational studies. In Chapter 2, I cited two prior systematic reviews had employed similar subgroup analyses and reported similar patterns in the findings (Kwok and Loke 2010; Cardoso et al. 2015). The motivation for this subgrouping was to group studies that generally follow strict protocols for outcome and exposure ascertainment (post-hoc analyses of RCTs) and observational studies that provide better balance between observed covariates among the study groups which may reduce selection bias (PS matched studies) (Morgan 2017). As observational studies can be subject to inherent to bias from unmeasured confounders, this observation was viewed as support for a lack of an association between combined treatment and adverse cardiovascular events, and as an indication that reported positive associations in the literature may be in fact due to confounding bias.

In Chapter 4, I presented an original observational study that I carried out to assess the association using the Health Facts® database provided by Cerner Corporation. This large database of electronic health records covers a 17-year period (2000-2016) and is rich with clinical information for over 69 million patients distributed across the four US census regions. The case-control study (Chapter 4) was nested within a cohort of patients that had experienced an MI and received clopidogrel. The cohort identified was similar to the cohorts analysed in many of the studies included in the systematic review; this allowed meaningful comparisons of our findings with prior findings. Considering the observation made above, suggesting that reported elevated risks may be due to confounding bias, the statistical logistic regression models developed to estimate the adjusted odds ratios adjusted for numerous potential confounders. In addition to the list of a priori selected variables based on the review of the relevant literature, I also relied on clinical expert opinion to identify additional key variables that may be associated with both the exposure and the outcome and for which the corresponding data was available in Health Facts®. The clinical expert identified ten conditions from the 30 conditions included in the Elixhauser comorbidity index that are related to the exposure and the outcome. The ten diseases were included as individual covariates in the regression model. The sum of the remaining 20 conditions represented a comorbidity score and was included as one continuous variable in the model. Moreover, empirical testing was used for assessing additional potential covariates for inclusion in the logistic regression models. Through Health Facts®, information on smoking and obesity was available. Smoking was included in the model as an individual covariate, while obesity was one of the 20 conditions represented in the comorbidity score. Both of these variables, which are known to be associated with cardiovascular outcomes, were not generally adjusted for in prior studies (Table 2-5).

Findings from the case-control study presented in Chapter 4 include ORs for concomitant PPI-clopidogrel use that suggest a lack of association with the outcomes assessed at three, six, and 12 months after patients had a first MI. To assess the validity of the observed associations for PPI-use, the observed ORs corresponding to H2RA use, derived from the same statistical models, were examined. H2RAs, as explained in Chapter 4, can serve as a negative control exposure since they do not inhibit CYP2C19 (Juurlink et al. 2009). As such, I expected [and observed] a lack of association with adverse events with H2RA-use vs non-use in clopidogrel treated patients. On the other hand, the observation of an elevated risk for H2RA-use vs non-use may suggest the presence of residual confounding rather than a true association, because neither current knowledge of underlying biological mechanisms nor prior reports support an association between H2RAs and adverse cardiovascular events. As the reported findings showed a lack of association with H2RA use, this may suggest the statistical analyses - which adjusted for numerous covariates - had adequately controlled for residual confounding. Extending the assumption of adequate management of confounding further allows us to conclude that ORs obtained for PPI-use vs non-use among clopidogrel users were subject to minimal confounding bias from unmeasured variables. However, an elevated risk was observed in elderly patients 80 to 89 years of age. In the Discussion section of Chapter 4, I indicated that this observation may represent a true elevated risk due to increased susceptibility to drug-drug interactions, polypharmacy, or reduced hepatic clearance in this age group. Alternatively, the possibility of observing this finding as a result of bias from unmeasured confounders cannot be dismissed (discussed in section 6.3).

In Chapter 4, findings further stratified by PPI type were presented. Prior studies have suggested that different PPIs are metabolized by CYP pathway to varying extents. Specifically, omeprazole and esomeprazole have been reported to be strong inhibitors of clopidogrel's activation process due to their strong dependence on the CYP pathway. Conversely, pantoprazole, lansoprazole and rabeprazole are classified weak inhibitors of clopidogrel. However, findings on clinical endpoints reported in the literature have been inconsistent, suggesting this topic requires further investigation. The OR stratified by PPI type, reported in Chapter 4, showed unexpected associations: an elevated MI risk for lansoprazole use (adjusted OR 4.14; 95% CI: 2.73-6.27), and a protective effect for omeprazole use (adjusted OR 0.52; 95% CI: 0.40-0.68). As discussed in Chapter 4 (Supplemental Material S4-B), given the relatively low exposure for either of these PPIs among controls, the analysis had insufficient power to detect the associations reported.

Although the associations examined in Chapter 4 have been extensively studied over the last decade, the clinical significance of the potential association remains relevant today as clopidogrel and PPIs are commonly coprescribed to ACS patients. Findings from the case-control analysis add to the literature results that are in support of a lack of association from a relatively large and diverse cohort using statistical analyses that include a wide range of covariates.

6.3 RISK OF ADVERSE CARDIOVASCULAR EVENTS OF PPIS COMBINED WITH PRASUGREL AND TICAGRELOR

The systematic review presented in Chapter 2 demonstrated that relatively few studies had reported on the risk of cardiovascular events associated with the concomitant use of PPIs with antiplatelet agents other than clopidogrel (referred to as Group C studies in Chapter 2). Two observational studies concluded a lack of association between PPI use and ticagrelor (Goodman et al. 2012) and prasugrel (O'Donoghue et al. 2009), while a third study reported an elevated risk with the use of PPIs and aspirin but acknowledged the need for further investigation (Charlot et al. 2011). Pooling across studies in this group was not feasible due in Chapter 2 due to the low number of studies reporting on the same outcome and same exposure group. Therefore, the findings were summarized in tabular form (Table 2-8).

Given the clear gap in the literature, the case-control analyses assessing the risk of PPI use in combination with either prasugrel or ticagrelor (Chapter 5) was helpful in two important ways: firstly, this analysis contributes to filling this critical gap in the literature, and second, to compare the findings with those observed in Chapter 3 where the risk of concomitant clopidogrel-PPI use was assessed.

As described in Chapter 5, the choice of prasugrel and ticagrelor was, driven by their dependency on the CYP2C19 pathways to exhibit an antiplatelet effect in the human body. Prasugrel has a lower dependency on CYP2C19 pathway for activation, while ticagrelor is taken in its active form and does not require activation in the body. In contrast to clopidogrel, a reduced dependency on CYP2C19 activation and the lack of prior reports suggesting potential interactions, the concomitant use of PPIs with prasugrel or ticagrelor is not expected to be associated with an increased risk of cardiovascular events. Therefore, the hypothesis was that if elevated risks are observed in the study presented in Chapter 5 for either of the outcomes assessed, they may be attributed to residual confounding. Findings across the four outcomes assessed in Chapter 5, suggested null associations for both antiplatelets at 12 months post cohort entry. The relatively small sample sizes in the study, however, precluded subgroup analyses by age, PPI type, or shorter follow up periods. As a result, I could not assess whether the elderly patients were particularly susceptible to elevated risk -an observation that was noted with clopidogrel in Chapter 4.

6.4 POTENTIAL FOR CONFOUNDING OF FINDINGS

Findings from pharmacoepidemiologic studies, such as the study presented in Chapter 4, need to be interpreted cautiously. They are generally subject to residual confounding caused by imbalances in covariates between users and nonusers of the exposure of interest. The main objective of Chapter 4 was to assess the risk of adverse events in clopidogrel users exposed to PPIs compared to clopidogrel users not exposed to PPIs. Since Health Facts® reflects real-world data collected in the process of patients receiving medical care at hospitals, the use of PPIs was not randomized among patients. Rather, the choice to receive a PPI or not was largely at the discretion of the treating physician, likely influenced by a combination of factors -including but not limited to- the physician's preference, hospital protocols, patient's comorbidities, severity of disease and prognosis.

The potential for residual confounding to bias results is commonly acknowledged as a limitation in studies similar to the Chapter 4 study. To illustrate this point, I refer to studies that were included in the systematic review and had investigated the risk of concomitant clopidogrel-PPI treatment (referred to as Group B studies in Chapter 2). The findings reported in this group of studies can be classified into two broad categories as shown in Figure 6-2. The first category comprised of studies that reported statistically insignificant effects and consequently concluded a lack of association (for example studies by Tentzeris et al. (2010) and Simon et al. (2011)). The second category of studies are those that reported statistically significant effect estimates. The studies in the latter category could be further categorized into the following two categories, based on the authors' interpretation of their findings: a) studies whose authors viewed their findings as support of a causal association and suggested the avoidance of concomitant treatment (Burkard et al. 2010; Kreutz et al. 2010); and b) studies whose authors discussed the likelihood that their findings are confounded due to unmeasured variables or by means of sensitivity analyses (Charlot et al. 2010; Goodman et al. 2012).

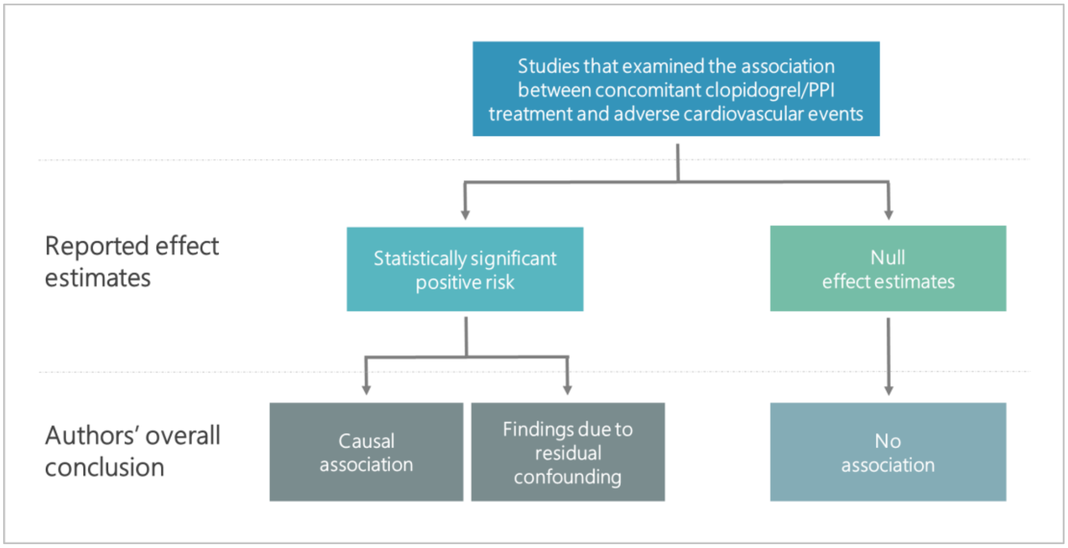

FIGURE 6- 2. SUMMARY OF THE CONLCUSIONS ARRIVED AT BY THE AUTHORS OF THE GROUP B STUDIES REVIEWED IN CHAPTER 2.

In order to explore the potential for confounding bias in our findings corresponding to concomitant clopidogrel-PPI treatment, the observed ORs from Chapter 4 were compared with: 1) ORs corresponding to H2RA use with clopidogrel from the same study; and 2) ORs corresponding to concomitant use of PPIs with prasugrel or ticagrelor (from Chapter 5). The selection of H2RAs, prasugrel and ticagrelor (as shown in Figure 6-3) was discussed previously and was largely driven by the lack of reported mechanisms that suggest drug-drug interactions. Hence, I assumed that an observation of null associations in the ORs corresponding to the use of these three drugs can be considered an indication that the management of confounding from unmeasured sources was achieved to a large extent.

The rationale for using H2RAs and the antiplatelet agents as negative control exposure drugs is described in (Hennessy et al. 2016). In a typical drug-drug interaction, the affected drug is called the *object* drug, while the affecting drug is called the *precipitant* drug. As such, clopidogrel can be viewed as the object drug while PPIs as the precipitant drug. Hennessey et al (2016) explain how the use of negative control exposure drugs, as is used in the context of the present analyses, can aid in the interpretation of observed risk estimates. A negative control precipitant drug (for example H2RAs) are drugs that have similar indications as the precipitant drug under study (PPIs), but are not believed to interact with the object drug. Similarly, a negative control object drug (for example ticagrelor) is a drug that has similar indications as the object drug but there has no known pharmacological interactions with the precipitant drug (Figure 6-3).

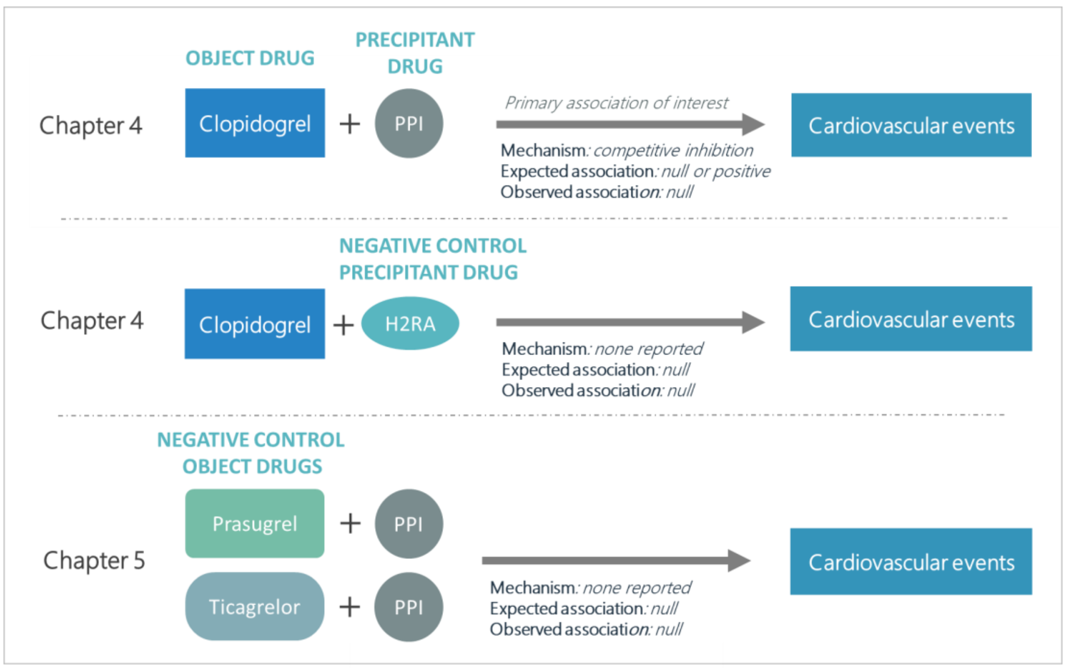

FIGURE 6- 3. ILLUSTRATION OF THE ASSOCIATIONS ASSESSED IN CHAPTERS 4 AND 5.

The findings from Chapter 4 suggest a lack of association for PPI use in combination with clopidogrel for the four outcomes assessed: MI (recurrent), stroke, all-cause mortality, and a composite of these three endpoints. We further reported null effect estimates across the four outcomes of interest for 1) H2RA use in combination with clopidogrel (Chapter 4); and 2) PPI use in combination with either prasugrel or ticagrelor (Chapter 5). Therefore, assuming that the null effects for the associations involving H2RAs, prasugrel and ticagrelor reflect adequate control for confounding from unmeasured variables in the logistic regression models, we can infer that the observed ORs for concomitant clopidogrel-PPI treatment are not significantly biased by confounding.

H2RAs, in this sense, serve as a negative control exposure. Both negative control exposures and negative control outcomes, are commonly used in biological laboratory experiments and, as Lipsitch et al. (2010) explain, should be applied more extensively in epidemiological studies to detect confounding from unmeasured variables. Lipsitch et al (2010) further state that “the essential purpose of a negative control is to reproduce a condition that cannot involve the hypothesized causal mechanism but is very likely to involve the same sources of bias that may have been present in the original association”. The use of H2RAs as a negative control is not new in the context of PPIs. In Chapter 4, I highlighted how prior studies have based their conclusions of the validity of their findings (relevant to clopidogrel-PPI treatment) on comparisons with corresponding findings for H2RA use in combination with clopidogrel.

Although null associations are generally reported in Chapter 4, an elevated risk for MI was observed (adjusted OR 1.26; 95% CI 1.05-1.51) in the elderly (80-89 years). In the Discussion of Chapter 4, I indicated that this observation may represent a true elevated risk due to increased susceptibility to drug-drug interactions, polypharmacy, and reduced hepatic clearance this age group. Nevertheless, there is the potential for the observation to a result of unmeasured confounding. To investigate this possibility, I estimated the strength of the confounder (or combination of confounders) required to elevate the risk from the null association (1.00) to the observed association (1.26). Using methods provided by Schneeweiss (2006), the confounder would need to have a strong association (at least three-fold) with each of the exposure (PPI) and the disease outcome (MI) to result in the observed OR of 1.26 (Figure 6-4).

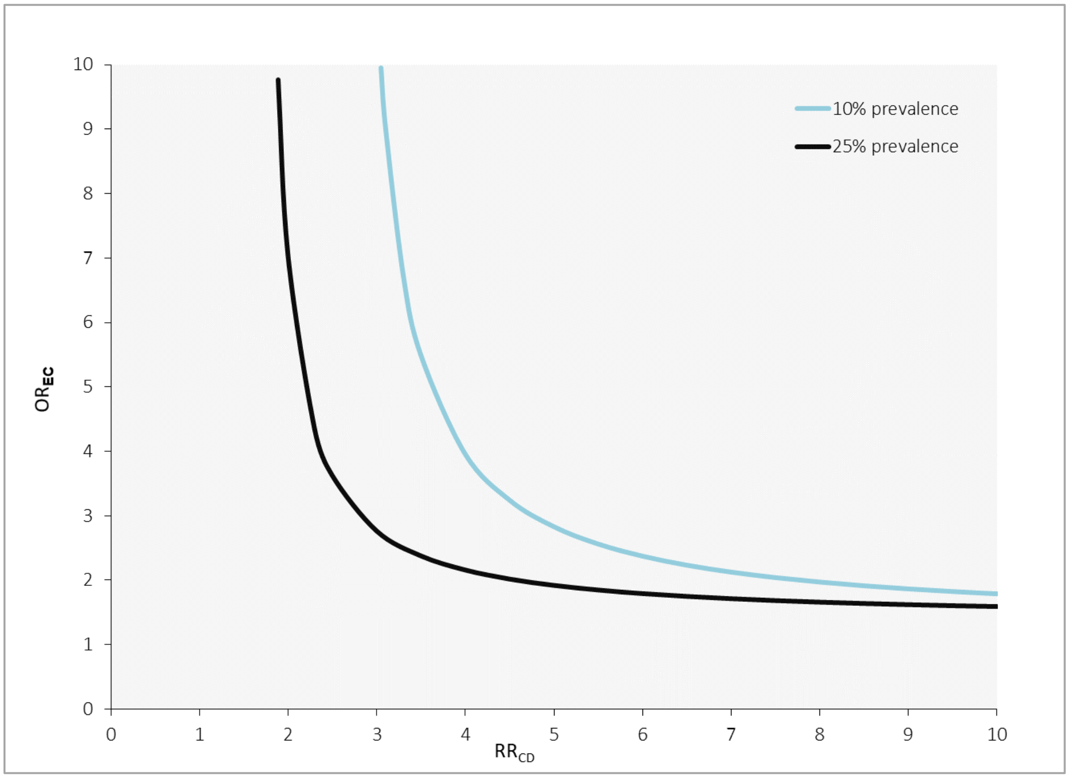

FIGURE 6- 4. SIZE OF CONFOUNDER NEEDED TO EXPLAIN THE INCREASE OF RISK FROM 1.00 TO 1.26.

RRCD : ASSOCIATION BETWEEN CONFOUNDER AND DISEASE OUTCOME; OREC : ASSOCIATION BETWEEN DRUG USE AND CONFOUNDER.

6.5 RELATIONSHIP BETWEEN THE BIOLOGICAL DRUG-DRUG INTERACTION BETWEEN AND CORRESPONDING CLINICAL EFFECTS

The presence of a pharmacological interaction between clopidogrel and PPIs has been demonstrated in several studies that have assessed platelet aggregation (Small et al. 2008; Yun et al. 2010; Zhang et al. 2010; Angiolillo et al. 2011). In light of the findings presented in the previous chapters, a question that readily comes to mind is: how can a demonstrated drug-drug interaction not lead to clinical effects?

Many authors have previously contemplated this question and provided possible explanations. For example, Focks et al. (2013) noted "there is no one-to-one translation of impaired ex vivo platelet inhibition into adverse clinical outcome" and suggested the need for well-designed randomized trials to assess the potential clinical impact. Moreover, Siller-Matula et al. (2009) provided a list of alternative explanations for this observation, which can be summarized as follows:

- other isoenzymes, in addition to CYP2C19, may be involved in the bioactivation of clopidogrel;
- the degree of competitive inhibition caused by PPIs varies by type; omeprazole is a strong inhibitor, while pantoprazole is a weak inhibitor;
- evidence from ex vivo assessments "miss acuity and comparability" such that the relevant cut-off levels for reduced platelet inhibition of clopidogrel to translate into a clinical impact have not been properly defined; and
- reported [positive] associations are may be a result of confounding bias.

The reasons given above are all possible explanations for the inconsistent findings reported between pharmacokinetic and pharmacodynamic studies on the one hand, and the findings of many epidemiologic studies on the other hand. It is possible that a combination of the factors above may be involved as well.

Moreover, in Chapter 4, I discussed a similar scenario involving clopidogrel and atorvastatin. Atorvastatin is a statin frequently co-administered with clopidogrel to heart disease patients. It is extensively metabolized by CYP3A4, the enzyme involved in the metabolism of numerous medications including clopidogrel. Similar to the case of PPIs, ex vivo studies reported a reduced antiplatelet effect of clopidogrel in the presence of atorvastatin due to competitive inhibition of CYP3A4 (Lau et al. 2003). However, subsequent studies that assessed the clinical impact of the potential interaction reported a lack of association with mortality, MI or stroke among patients treated with both drugs (Saw et al. 2003; Wienbergen et al. 2003). The events described in this paragraph and those of clopidogrel and PPIs have many similarities. Although the case of atorvastatin does not provide support of a lack of a clinical impact for the interaction between clopidogrel and PPIs, it does, however, serve as an example of how it is possible for surrogate endpoints from laboratory studies to not necessarily translate into adverse clinical endpoints.

Finally, the presence of an underlying biological mechanisms that explains the association between and exposure and an outcome represents one of the nine Bradford Hill criteria (Hill 1965) for assessing causality. In the case of clopidogrel and PPIs, a clear mechanism involving competitive inhibition is known. However, the knowledge of this biological mechanism alone is insufficient to suggest that there should be an association between the use of both drugs and adverse clinical effects:

> *"None of my nine viewpoints can be indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental*

question -is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?" (Hill 1965).

6.6 TRENDS OF CONCOMITANT TREATMENT WITH PPIS AND CLOPIDOGREL IN RESPONSE TO THE FDA SAFETY WARNINGS (OBJECTIVE 2)

Chapter 3 is a trends analysis with the main objective of examining the rates of concomitant use of clopidogrel and PPIs in relation to the FDA safety warnings issued in 2009. Using Health Facts®, the proportion of inpatients hospitalized for ACS that were co-administered clopidogrel and PPIs was computed. Rates for each quarter-year over the study period were standardized (for sex, race and census region) to the US population based on data from the 2010 US census. The following three main observations were made in relation to the FDA warnings issued in 2009 and 2010: 1) concomitant treatment did in fact decline during this period; 2) during this period, there was a marked [temporary] increase in the use of H2RAs in combination with clopidogrel; and 3) clopidogrel was preferentially co-administered with PPIs that are considered weak inhibitors of the clopidogrel's bioactivation compared to the PPIs that are strong inhibitors. Recognizing other events that occurred following the FDA safety communications that may contributed to the observed trends in drug use, the findings suggest that clinical practice recommendations were followed in inpatient settings.

Another important observation made from this study, though not directly related to the study objective, was that clopidogrel remains one of the most prescribed antiplatelet agents, compared to the newer and more potent P2Y12 antagonists, ticagrelor and prasugrel. Standardized rates estimate that, in the last quarter of 2016, 14% of inpatients with an ACS diagnosis were co-administered clopidogrel and PPIs, compared to 3% and 7% of inpatients that received PPIs with prasugrel or ticagrelor, respectively. The large proportion of patients that continue to receive both drugs concomitantly highlights the importance of achieving a clear understanding of the potentially associated adverse effects.

6.7 STRENGTHS AND LIMITATIONS

The individual studies presented in this thesis have several strengths and limitations that were acknowledged and discussed in detail in the respective chapters. In this section, I discuss the general strengths and limitations of using Health Facts® to carry out pharmacoepidemiologic studies that investigated the clinical impact of the clopidogrel-PPI drug interaction.

6.7.1 STRENGTHS

The use of Health Facts® allowed the examination of associations between drug-exposure and clinical endpoints in a large and geographically diverse cohort of US patients that received medical care at one [or more] of the 500 health facilities that report to Cerner Corporation. Compared to collection of primary data, I had access to a wealth of longitudinal health records at a relatively low cost. Further, the cohorts selected for the studies in Chapters 4 and 5 comprised all patients in the database that fit the eligibility criteria, including patient groups that are commonly under-represented in RCTs, such older patients, frail patients or those with severe health conditions. Therefore, an advantage of using Health Facts® for this investigation is that the findings apply to the wide range of antiplatelet users (clopidogrel, prasugrel and ticagrelor) that are typically found in real-world settings.

Electronic medical records contain detailed clinical information that are typically not found in insurance claims databases (Schneeweiss and Avorn 2005). By using Health Facts®, I had access to detailed clinical data that enabled me to adjust the computed odds ratio to numerous clinical variables that may confound the associations assessed. For example, medication data allowed us the extraction of select chronic medications that were dispensed to patients during hospitalization, detailed diagnoses data provided information on all relevant diseases that may confound our findings, in addition to a list of 20 conditions used to compute a comorbidity score. Moreover, data on revascularization procedures performed was used for covariates in regression models as well laboratory tests results for cardiac troponin measures (used for sensitivity analysis).

Finally, the two case-control studies (Chapter 4 and 5) were both based on cohorts selected from Health Facts® and both had similar statistical analyses, which allowed the direct comparison of the findings. As a whole, the two studies provided effects estimates for the risk of combining PPIs with three antiplatelet agents, where only clopidogrel is suspected of interacting with PPIs through a known underlying biological mechanism.

6.7.2 LIMITATIONS

The analytic studies presented also have several limitations common to pharmacoepidemiologic studies based on large databases in general. First, there is the potential for information bias arising from misclassification of the exposures and outcomes of interest. In Health Facts®, diagnoses (in the form of ICD codes) made at each patient encounter are assigned by a medical records coder retrospective to the encounter. The use of ICD codes has not been validated in

Health Facts® specifically; however, the definitions used for clinical endpoints were based on select ICD codes that have been validated and shown to have high positive predictive values in US health care settings. The use of validated codes may reduce misclassification bias, but the potential for this bias remains and should be acknowledged. On the other hand, the potential for misclassification of exposure may be of greater concern in the completed studies. Patients in the study cohorts were assumed to have continued treatment on the same antiplatelet for 12 months after their cohort entry hospitalization. I noted in Chapter 4 that the 12-month assumption is based on treatment guidelines (Levine et al. 2016), and that the majority of patients discharged on an antiplatelet generally do not switch to a different antiplatelet during the one year after hospital discharge (Bueno et al. 2017). Nevertheless, the possibility for misclassification of exposure is present given that patients may have discontinued treatment, initiated a new treatment or simply not adhered to their medications. It is also possible that some patients received over-the-counter PPIs that I did not have any information on. Such misclassification of a dichotomous exposure - if nondifferential - has the potential to bias results towards the null and would be more pronounced with longer follow-up periods (time since exposure assessment) (Schneeweiss 2010).

Another limitation is the possibility that Health Facts® may not capture all clinical events of interest experienced by the study sample analysed. Although a large number of hospital report data to Cerner, it is possible that certain patients had experienced an MI or stroke and visited hospitals that are not included in Health Facts. In analyses of mortality as the outcome of interest, only deaths that occurred in the hospital were captured. These limitations may lead to underestimation of effects. Furthermore, the risk of cardiovascular mortality was not assessed -

although initially specified in the study protocol- because Health Facts does not include the cause of death for death events. Many database studies link their data to national mortality data to obtain the cause of death; this was not possible in the completed studies.

Lastly, I had to deal with missing data for some of the variables included in the analyses. Patients with missing demographics (age, sex and ethnicity) were excluded from the cohort as these variables were necessary for matching case to controls. This is not expected introduce any notable bias to the findings since the proportion of patients missing these variables did not exceed five percent of the cohort. Health insurance status was also noted to be missing for approximately 30% of the cohort (Chapter 4). Since 30% is substantial, patients with missing values for this variable were not excluded. Instead I performed a sensitivity analysis, which suggested minute differences in the ORs of statistical models that included or excluded the health insurance variable (Table S4-9).

6.8 CONCLUSIONS AND FUTURE DIRECTIONS

Findings of analytical studies presented in this thesis provide an excellent example on the secondary use of electronic medical records for pharmacoepidemiologic research. In the investigation of the clinical impacts of concomitant treatment of clopidogrel and PPIs, I analysed data covering a large and diverse sample of US patients that was collected from real-world clinical care settings. The findings to do not support an association of concomitant treatment with MI, stroke, death from all-causes or the composite endpoint of these three outcomes within one year of experiencing a first MI. We did, however, report an elevated risk among patients 80-89 years old, suggesting that this patient population may be more susceptible to the clinical manifestations of the underlying biological interaction. Although the findings do not serve as definitive evidence of a lack of an association, they represent valuable contributions to the literature that may be considered when weighing the evidence from similar studies.

Future work that may provide further insight into this topic would be to 1) assess the potential association in a large cohort of elderly patients (over 80) to confirm the elevated risk reported in our study, and to identify risk factors; 2) take into account non-prescription use of PPIs, given that some types of PPIs are available over-the-counter in the US; and 3) repeat the study investigating concomitant treatment of PPIs and other antiplatelet agents on a larger sample to allow stratification of findings by PPI type and age.

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APPENDICES

APPENDIX A ETHICS APPROVAL

Ethics approval from the Ottawa Health Science Network Research Ethics Board for the research protocol comprising the four studies of this thesis. Appendix A contains the following related documents:

- Approval of the initial protocol (February 9, 2016)
- Renewal (January 25, 2017 and January 17, 2018)
- Approval of revised protocol (June 6, 2018)

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Institut de recherche de l'Hôpital d'Ottawa

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INSTITUT DE CARDIOLOGIE DE L'UNIVERSITÉ D'OTTAWA

Ottawa Health Science Network Research Ethics Board/ Conseil d'éthique de la recherche du Réseau de science de la santé d'Ottawa

Civic Box 411 725 Parkdale Avenue, Ottawa, Ontario K1Y 4E9 613-798-5555 ext. 14902 Fax : 613-761-4311
http://www.ohri.ca/ohsn-reb

February 9, 2016

Ms. Nawal Farhat
McLaughlin Centre for Population Health Risk Assessment
Faculty of Medicine
University of Ottawa
850 Peter Morand Crescent, Room 124
Ottawa, Ontario, Canada K1G 3Z7

Dear Ms. Farhat:

Re: Protocol #	**20160046-01H**	**Investigating the risk of adverse cardiovascular events associated with concomitant proton pump inhibitor and clopidogrel treatment**
Protocol approval valid until -		**February 8, 2017**

I am pleased to inform you that your Application for Chart Review underwent expedited review by the Ottawa Health Science Network Research Ethics Board (OHSN-REB), and is approved. No changes, amendments or addenda may be made to the protocol without the OHSN-REB's review and approval.

Approval is for the following:
- Proposal dated December 2015

If the study is to continue beyond the expiry date noted above, a Renewal Form should be submitted to the OHSN-REB approximately six weeks prior to the current expiry date. If the study has been completed by this date, a Termination Report should be submitted.

The Ottawa Health Science Network Research Ethics Board (OHSN-REB) was created by the merger of both the Ottawa Hospital Research Ethics Board (OHREB) and the Human Research Ethics Board (HREB) for meetings held at the University of Ottawa Heart Institute.

OHSN-REB complies with the membership requirements and operates in compliance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; the International Conference on Harmonization - Good Clinical Practice: Consolidated Guideline, and the provisions of the Personal Health Information Protection Act 2004.

Yours sincerely,

Raphael Saginur, M.D.
Chairperson
Ottawa Health Science Network Research Ethics Board

/kd

Ottawa Health Science Network Research Ethics Board/ Conseil d'éthique de la recherche du Réseau de science de la santé d'Ottawa

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January 25, 2017

Ms. Nawal Farhat
McLaughlin Centre for Population Health Risk Assessment
Faculty of Medicine
University of Ottawa
850 Peter Morand Crescent, Room 124
Ottawa, Ontario, Canada K1G 3Z7

Dear Ms. Farhat:

RE: Protocol# - 20160046-01H **Investigating the risk of adverse cardiovascular events associated with concomitant proton pump inhibitor and clopidogrel treatment**

Renewal Expiry Date - February 8, 2018

I am pleased to inform you that your Annual Renewal Request was reviewed by the Ottawa Health Science Network Research Ethics Board (OHSN-REB) and is approved. No changes, amendments or addenda may be made in the protocol without the OHSN-REB's review and approval.

Renewal is valid for a period of one year. Approximately one month prior to that time, a single renewal form should be sent to the REB office.

The OHSN-REB complies with the membership requirements and operates in compliance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; the International Conference on Harmonization - Good Clinical Practice: Consolidated Guideline and the provisions of the Personal Health Information Protection Act 2004.

Yours sincerely,

Chairperson
Ottawa Health Science Network Research Ethics Board

/kd

Ottawa Hospital Research Institute
Institut de recherche de l'Hôpital d'Ottawa

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January 17, 2018

Ms. Nawal Farhat
McLaughlin Centre for Population Health Risk Assessment
Faculty of Medicine
University of Ottawa
850 Peter Morand Crescent, Room 124
Ottawa, Ontario, Canada K1G 3Z7

Dear Ms. Farhat:

RE: Protocol# - 20160046-01H **Investigating the risk of adverse cardiovascular events associated with concomitant proton pump inhibitor and clopidogrel treatment**

Renewal Expiry Date - January 16, 2019

I am pleased to inform you that your Annual Renewal Request was reviewed by the Ottawa Health Science Network Research Ethics Board (OHSN-REB) and is approved. No changes, amendments or addenda may be made in the protocol without the OHSN-REB's review and approval.

This renewal is approved as of: January 17, 2018.

The projected date of study completion has been extended to December 31, 2018.

Renewal is valid for a period of one year. If the study is to continue beyond the expiry date noted above, a Renewal Form should be submitted to the REB, in hardcopy. All Annual Renewal Reports, regardless of review type (i.e., full board or delegated), must now be submitted according to the full board meeting submission deadlines AND at least 30 days prior to the expiry date of the study to prevent a lapse in approval. If the study is completed by this date, a Termination Report should be submitted.

The OHSN-REB complies with the membership requirements and operates in compliance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; the International Conference on Harmonization - Good Clinical Practice: Consolidated Guideline; and the provisions of the Personal Health Information Protection Act 2004.

Yours sincerely,

Vice-Chairperson
Ottawa Health Science Network Research Ethics Board

MV/ag

Ottawa Hospital Research Institute
Institut de recherche de l'Hôpital d'Ottawa

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June 6, 2018

Ms. Nawal Farhat
McLaughlin Centre for Population Health Risk Assessment
Faculty of Medicine
University of Ottawa
850 Peter Morand Crescent, Room 124
Ottawa, Ontario, Canada K1G 3Z7

Dear Ms. Farhat:

Re: Protocol # 20160046-01H Investigating the risk of adverse cardiovascular events associated with concomitant proton pump inhibitor and clopidogrel treatment

Thank you for your email of June 4, 2018.

The following documents are approved:
- Protocol Amendment Report dated December 19, 2017
- Revised Protocol dated January 2018

Date of approval: June 6, 2018

The projected date of study completion has been extended to December 31, 2018.

Ethical approval remains in effect until January 16, 2019. If the study is to continue beyond the expiry date, a Renewal Form should be submitted to the REB, in hardcopy. All Annual Renewal Reports, regardless of review type (i.e., full board or delegated), must now be submitted according to the full board meeting submission deadlines AND at least 30 days prior to the expiry date of the study to prevent a lapse in approval. If the study is completed by this date, a Termination Report should be submitted.

The OHSN-REB complies with the membership requirements and operates in compliance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; the International Conference on Harmonization - Good Clinical Practice: Consolidated Guideline and the provisions of the Personal Health Information Protection Act 2004.

Yours sincerely,

Chairperson
Ottawa Health Science Network Research Ethics Board
RS/kd

APPENDIX B STATUS OF SUBMISSIONS TO JOURNALS

The manuscript presented in Chapter 2 was published in the European Journal of Clinical Pharmacology:

> Farhat N, Haddad N, Crispo J, Birkett N, McNair D, Momoli F, Wen S-W, Mattison DR, Krewski D. 2019. Trends in concomitant clopidogrel and proton pump inhibitor treatment among ACS inpatients, 2000–2016. Eur. J. Clin. Pharmacol. 75:227–235. doi:10.1007/s00228-018-2564-8.

The systematic review and meta-analysis presented in Chapter 3 was accepted for publication in Critical Reviews of Toxicology.

Critical Reviews in Toxicology - Decision on Manuscript ID BTXC-2018-0039.R1

6 messages

Mon, Feb 11, 2019 at 7:30 PM

11-Feb-2019

Dear Dr Farhat:

Ref: Systematic review and meta-analysis of adverse cardiovascular events associated with proton pump inhibitors used alone or in combination with antiplatelet agents

It was a pleasure to receive your revised manuscript and, especially, to note the careful attention you gave to the reviewers comments. In my opinion, the manuscript has been improved and will be a valuable contribution to the literature. Hence, I am pleased to accept your paper in its current form which will now be forwarded to the publisher for copy editing and typesetting.

You will receive proofs for checking, and instructions for transfer of copyright in due course.

The publisher also requests that proofs are checked and returned within 48 hours of receipt.

Thank you for your contribution to Critical Reviews in Toxicology and we look forward to receiving further submissions from you.

Sincerely,

Roger O. McClellan
Editor-in-Chief, Critical Reviews in Toxicology