TITLE: Clopidogrel and Proton Pump Inhibitor Use: A Review of the Evidence on Safety

DATE: 14 March 2017

CONTEXT AND POLICY ISSUES

Clopidogrel is a thienopyridine pro-drug that is commonly prescribed in conjunction with acetylsalcylic acid (ASA), commonly known as aspirin, as dual antiplatelet therapy (DAPT) for patients who are at high risk of acute and potentially fatal cardiovascular (CV) events following percutaneous coronary intervention (PCI).[1-3] PCI involves coronary revascularization through stent implantation or coronary artery by-pass grafting (CABG).[2,3] Acute CV events associated with PCI include angina, myocardial infarction (MI), stroke, and major or minor thrombolysis in myocardial infarction (TIMI) bleeding.[1] Clopidogrel, when metabolized to its active form 2-oxo-clopidogrel, inhibits oral adenosine diphosphate (ADP)-induced platelet aggregation by blocking the $P2Y_{12}$ receptor on the surface of platelets.[4]

Proton pump inhibitors (PPIs) are commonly used to mitigate a number of adverse gastrointestinal (GI) effects that are linked to clopidogrel.[1,5] PPIs include omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole.[2] There is emerging, though uncertain, evidence suggesting that PPIs may interfere with clopidogrel metabolism, and as a result attenuate its $P2Y_{12}$ receptor-based platelet inhibition function, resulting in increased incidents or risks of acute CV events relative to clopidogrel DAPT or clopidogrel monotherapy (i.e., the use of clopidogrel without aspirin).[6-8]

Of note, the DAPT trial published in December 2014 compared the use of ASA + $P2Y_{12}$ inhibitor for 12 months versus 30 months post-PCI with stenting and found some potential clinical benefits (i.e., reduced risk of stent thrombosis and major adverse CV and cerebrovascular events) of the longer treatment duration; an increased risk of bleeding, however, was also observed.[9]

Since it may be anticipated that some patients, with lower risk of bleeding, may stay on DAPT for a longer time period post-PCI with stenting, there may be a possibility that the co-prescription of a PPI to reduce the risk of GI complications increases. Given the potential drug interaction between PPIs and clopidogrel, an assessment of the impact of this regimen on CV outcomes is needed to inform policy and clinical decisions.

Objective

The objective of this report is to assess the current evidence on the impact of PPIs on adverse events in adults being treated with clopidogrel dual antiplatelet therapy (DAPT) or monotherapy following percutaneous coronary intervention (PCI) involving stents.

RESEARCH QUESTION

1. What are the harms of proton pump inhibitors used concomitantly with clopidogrel for patients requiring antiplatelet therapy following percutaneous coronary intervention?

KEY FINDINGS

Although the findings across the studies were mixed, overall, the evidence favours clopidogrel antiplatelet therapy without PPIs. The evidence suggests that there are still some serious safety risks associated with the use of proton pump inhibitors (PPIs) with clopidogrel antiplatelet therapy (with or without aspirin) in patients following percutaneous coronary intervention (PCI) stent implantation.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, Medline via Ovid, EMBASE via Ovid, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to the main search to limit retrieval. A broader search was conducting using the health technology assessments, systematic reviews, meta-analyses filter. Both searches were limited to English language documents published between Jan 1, 2010 and Nov 21, 2016.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were assessed for inclusion. Potentially relevant studies, which met the inclusion criteria outlined in Table 1 were retrieved.

The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults requiring antiplatelet therapy following percutaneous coronary intervention with stenting
Intervention	Clopidogrel (with or without acetyl salicylic acid [ASA]) in combination with a proton pump inhibitor
Comparator	Clopidogrel (with or with ASA)

Outcomes	Stent thrombosis, urgent target vessel revascularization, major adverse cardiovascular and cerebrovascular events (including myocardial infarction, stroke, and death, bleeding (major or minor), cardiovascular death, all-cause mortality.
Study Designs	1. Systematic reviews/Meta-analyses/Health Technology Assessments 2. Randomized controlled trials 3. Non-randomized studies

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, or were duplicate publications. Studies were excluded if they involved a mixed population and results for patients with stents were not reported separately.

Critical Appraisal of Individual Studies

The included systematic reviews and meta-analyses were critically appraised using A Measurement Tool to Assess Systematic Reviews (AMSTAR),[10] and the non-randomized, cohort studies were appraised using the Scottish Intercollegiate Guideline Network (SIGN) 50 Methodology Checklist.[11] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 297 citations were identified in the literature search. Following screening of titles and abstracts, 216 citations were excluded and 81 potentially relevant reports from the electronic search were retrieved for full-text review. Three potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 61 publications were excluded for various reasons, while 23 cohort studies met the inclusion criteria for this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5: Additional References of Potential Interest.

Summary of Study Characteristics

A detailed description of individual study characteristics is provided in Table A1 of Appendix 2: Characteristics of Included Publications.

Study Design

The evidence included here was derived from 23 non-randomized, cohort studies.[2,3,6,12-31] Four of the studies were prospective,[3,16,20,22] and the remaining were retrospective.

Country of Origin

Eight of the cohort studies were conducted exclusively in the United States,[6,18,21,22,27-30] three in Japan,[17,20,24] two in China,[14,16] and one each in Austria,[25] Germany,[26] Greece,[31] Italy,[3] and Taiwan.[13] The remainder had collaborators or recruited patients in multiple European countries and the United States.[2,12,15,19,23]

Patient Population
All of the studies included adult patients who had received clopidogrel treatment following PCI involving the implantation of a drug-eluting stent (DES) or a bare metal stent (BMS).

Interventions and Comparators
All patients were on antiplatelet therapy involving clopidogrel with or without ASA (i.e., aspirin). Dosage for aspirin ranged from 75 to 100 mg per day,[15] to 100 mg per day,[3,14,16,19,20,25,26,31] 100 to 200 mg per day,[24] 200 mg per day,[17] or 325 mg per day.[30] Some studies did not report the dose of aspirin.[2,6,12,13,18,22] In five studies authors did not include information on aspirin.[21,23,27-29]

The duration and dose of clopidogrel therapy varied across the studies. The standard of practice was to treat patients with clopidogrel for thirty days,[26] one month for BMS and one year for DES,[25] at least three months for BMS and one year for DES,[17] six or twenty-four months,[15] for six months,[19] at least six months,[30] for one year irrespective of stent,[2,3,14,22,27,28,31] or for one year or more.[6,24] Halfway through one study that spanned four years, the length of clopidogrel treatment changed from 30 days for patients treated with BMS and six months for those treated with DES to 12 months for all patients.[18] The remaining studies did not comment on duration of treatment.[13,16,20,21,23,29] Clopidogrel was typically given at a dose of 75 mg per day.[2,3,14-17,19,20,25,26,28,31] In one study clopidogrel was given at either 75 mg per day or 150 mg per day at the physician's discretion,[27] and in another at 50 to 75 mg per day.[24] The remaining studies did not report on clopidogrel dosage.[6,12,13,18,22,30]

In the intervention arm, patients received prescriptions of a single PPI. PPIs (i.e., omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole) were prescribed at the physician's discretion primarily for patients with a history of upper GI conditions including ulcer (i.e., *H.pylori* positive), bleeding, heartburn or epigastric pain.[16,20] Other indications for prescribing PPIs were concomitant use of a nonsteroidal anti-inflammatory drug, steroid, anticoagulant, or other antiplatelet agents.[20] The proportions of patients who received specific PPIs varied. In ten studies more than 75% of patients received prescriptions for specific PPIs as follows: lansoprazole,[15,17] omeprazole,[14,16,23,31] pantoprazole,[25,26] and rabeprazole.[24,28] One study focused exclusively on rabeprazole[24] while two focused exclusively on omeprazole.[16,31] All but four of the remaining studies prescribed at least three PPIs. Those four studies did not specify the types of PPIs prescribed and the proportions of patients to which each was prescribed.[6,12,13,18]

Outcomes
Outcomes were measured at various intervals from 30 days,[26] 6 months,[16,22] 9 months,[18] 12 months,[2,3,13,14,17,21,23-25,27,29-31] 18 months,[20] 24 months,[6,12,15] 36 months,[19] and 50 months.[28]

Outcomes were reported either as the incidence or risk of cardiac-related or gastrointestinal (GI)-related events. Risks were reported as unadjusted or adjusted hazard ratios[2,6,12-15,22,23,25,26,30,31] or odds ratios[28] following Cox regression analyses or propensity-score matching.

Cardiac-related outcomes were composite major adverse cardiac events (MACE) ,[2,3,6,8,12,14,15,17-25,27,28,30,31] all-cause mortality,[3,6,8,14,15,17,18,22,23,25,26,28,30] CV mortality,[6,8,12,15,19,20,24,25,31] non-cardiac mortality,[6] MI,[6,8,12,14,15,17-20,22,26,27] re-hospitalization for non-fatal MI,[31] re-admission for acute MI (AMI),[29] unstable angina,[27] stent thrombosis (ST),[3,6,8,12,14,15,17,19,22,24-26,30,31] revascularization (including but not limited to target lesion revascularization [TLR] and target vessel revascularization [TVR]), [12-14,17-19,22-24,27,28,30,31] heart failure,[17] stroke,[8,17] acute coronary syndromes (ACS),[13] re-hospitalization for ACS,[25] major or minor thrombolysis in myocardial

infarction (TIMI) bleeding,[3,8,12,15,22,26] and clinically relevant bleeding.[6] Definitions for cardiac outcomes varied across studies, with some amount of overlap. MACE, for example, was defined as a composite of a variety of cardiac events as follows:

- All-cause mortality, non-fatal MI, ST, TVR, TLR, and coronary artery by-pass graft (CABG)[14]
- All-cause mortality, MI, and cerebrovascular accident[15]
- All-cause mortality and MI[17]
- All-cause mortality, MI, ST, and TVR[22,30]
- All-cause mortality, MI, ACS requiring hospitalization, and non-fatal stroke[3]
- All-cause mortality, non-fatal MI, and revascularization[18,23]
- All-cause mortality, ACS requiring hospitalization, and ST[25]
- CV mortality, spontaneous MI, definite or probable ST, and TLR[12]
- CV mortality, MI, and ischemia-driven TLR[6]
- CV mortality, non-fatal MI, and TVR[19]
- CV mortality, non-fatal MI, and ischemic stroke[20]
- CV mortality, MI, ischemic stroke, ST, and TLR[2]
- CV mortality, AMI, and non-fatal or fatal stroke[21]
- CV mortality and non-fatal MI requiring hospitalization[31]
- CV mortality, ACS, ST, and TLR[24]
- CV mortality, ACS, MI, unstable angina, stroke or transient ischemic attack requiring hospitalization, and coronary revascularization[27]

Similarly, multiple definitions were used for other clinical outcomes. One study defined CV mortality as "death from MI, congestive heart failure, or documented sudden cardiac death".[20] In another study, MI was defined as "typical symptoms with an elevated level of cardiac enzymes (i.e., troponin I, troponin T or creatine phosphokinase) above the upper limit of normal or typical ST-segment changes in the electrocardiogram at the time of symptom development".[19] Another study specified that the increase of creatine kinase-MB value had to be "three or more times the upper limit of normal" for a diagnosis of MI.[25] Yet another study defined spontaneous MI in less specific terms "as myocardial ischemia measured by cardiac biomarkers confirmed clinically or by electrocardiography".[12] ACS was defined as MI or unstable angina[27] or angina pectoris at rest and elevated troponin I levels.[25] In one study, diagnosis of ischemic stroke required clinical and radiological evidence of stroke without intracranial hemorrhage.[20] The Academic Research Consortium criteria described definite ST as the "occurrence of an ACS with either angiographic or pathological confirmation of thrombosis".[26] TLR was defined as any repeat intervention (percutaneous or surgical bypass) for the target lesion and further classified as clinically indicated or not.[12] Bleeding was classified using the Bleeding Academic Research consortium (BARC),[12] Thrombolysis in Myocardial Infarction (TIMI) criteria, or a combination of the TIMI critiera, a Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) criteria, the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) criteria for major bleeding, and any post-discharge bleeding requiring medical attention.[6]

GI-related outcomes were primarily bleeding but could also include symptoms of heartburn, epigastric pain, hematemesis, or melena, and confirmed by endoscopic examination with obvious findings of ulcer or erosion.[17,20,24,27] One study excluded esophageal lesions, atrophic gastritis, and malignancies from the definition of GI outcomes.[20]

Summary of Critical Appraisal

A detailed summary of the strengths and limitations of the cohort studies is provided in Table A2 in Appendix 3: Critical Appraisal of Included Publications.

The cohort studies had more limitations than strengths. In terms of limitations, there was extensive variation in patient characteristics, verification of treatment compliance, and study follow-up periods. The indications for stent implantation ranged from ACS[18] and angina,[2,3,26] to carotid stenosis[16] and chronic ischemic heart disease.[18] Six studies may have been underpowered to adequately detect a statistical difference between patient cohorts.[16,24,25,28,30,31]

A minority of the studies enrolled groups with matching patient characteristics.[3,17,18,21,26,30,31] Due to the retrospective nature of most studies, patient characteristics were generally not comparable between study groups. Patients treated with PPI were more often older,[6,13,15,19,20,22] female,[6,13,15,19,22,25] hypertensive,[6] with diabetic,[2,6,19] had peripheral arterial disease,[6] had chronic kidney disease[2,6], had an established CV disease or ACS,[6,13,15,22-25] had GI disorders,[14,19] at a higher bleeding risk,[15] had worse renal function,[15] had cancer and liver disease,[13] or had previous heart failure.[13,23] Further, non-PPI users were more likely to have a history of MI,[14] impaired left ventricular ejection fraction,[14] or diabetes,[25] and had taken more aspirin,[13] angiotensin-converting-enzyme (ACE) inhibitors,[13,14] calcium channel blockers,[14] or lipid-lowering agents.[13] Adjustment for potentially confounding factors through Cox regression analysis did not change the conclusion from the comparative results for the most part, suggesting that there may be unknown confounding factors.[15]

Compliance with administered drugs was verified in a minority of studies through prescription claims databases and patient reports.[2,12-15,20,22,27,30,31] In five of these studies, compliance was verified through patients self-reporting on DAPT.[12,15,22,30,31] One study collected information on clopidogrel compliance but not on aspirin compliance.[30] Seven studies specified that PPI or DAPT compliance, duration, interruption, and discontinuation information was not collected.[6,12-14,18,26,29] Without verifying compliance the period over which patients received treatment remains unknown. Furthermore, types of PPIs administered and the proportions of patients who received each PPI varied across studies. In addition, self-medication with PPIs and other gastroprotective medication bought over-the-counter was not monitored.[12,13,18,21-23,27] Evidence of blinding when determining incidences of outcomes was present in three studies.[6,12,14] Although definitions for adverse outcomes were provided, the method of assessment of treatment was not disclosed in most studies.

Results were primarily reported 12 months following stent implantation. There was, however, a wide range of study periods. The shortest study period was 30 days,[26] while the longest was 50 months.[28]
The strengths of the studies included addressing appropriate and explicit questions and outcomes measured, and accounting for known confounders in the data analysis. All but four studies reported confidence intervals around estimates of hazard ratios and odds ratios.[16,19,20,24] All but one study provided a measure (*P* value) of statistical significance of differences in incidences of clinical outcomes between study groups.[16]

Summary of Findings

A detailed description of the study findings is provided in Table A3 in Appendix 4: Main Study Findings and Author's Conclusions.

What are the harms of proton pump inhibitors used concomitantly with clopidogrel for patients requiring antiplatelet therapy following percutaneous coronary intervention?

The findings on the impact of PPI on safety outcomes were mixed. Some studies found that PPIs increased some adverse events yet their impact on other adverse events was not statistically significant.

Cardiovascular events

One set of results using incidence rates, unadjusted hazard ratios and odds ratios suggested that PPIs led to statistically increased risk of MACE,[6,12,14,18,19,23,27,28,30] all-cause mortality,[6,18,23,26,30] CV mortality,[6] non-cardiac mortality,[6] MI,[19,27] re-admission for AMI,[29] unstable angina,[27] stroke,[27] ST,[14] revascularization,[12,18,23,27] heart failure,[17] ACS with Limus-eluting stents,[13] major TIMI bleeding,[26] and clinically relevant bleeding.[6]

Another set of results suggested that PPIs do not have a statistically significant impact on the incidence of MACE,[2,3,15,17,20-22,24,25,31] all-cause mortality,[3,14,15,17,22,25,28] CV mortality,[12,15,19,20,24,25,31] MI,[6,12,14,15,17,18,20,22,26] re-hospitalization for non-fatal MI,[31] stroke,[17] ST,[3,6,12,15,17,19,22,24-26,30,31] revascularization, [13,14,17,19,22,24,28,30,31] re-hospitalization for ACS,[25] ACS with Paclitaxel-eluting stents,[13] and major or minor TIMI bleeding.[3,12,15,22] Cox regression adjustments for HR did not change the findings except in one study where the differences in MACE lost statistical significance.[19]

GI events

Without providing data, one study reported that omeprazole lead to a statistically significant decrease in incidence of GI bleeding.[16] The study provided no primary data other than proportions of GI bleeding in a population of 64 patients of whom 11% were lost to follow-up without an explanation.[16] Results from a second study indicated that PPIs were associated with statistically significant increase in incidence of GI bleeding,[27] while three studies found that the differences in incidence or risk of GI bleeding or GI events were not statistically significant.[17,20,24]

Patients with co-morbidities (type II diabetes mellitus)

One of the cohort studies in which PPIs increased incidence and risk of ACS enrolled only patients with type II diabetes.[13] Specifically, patients with Limus-eluting stents were affected. For patients treated with Paclitaxel-eluting stents, PPI use trended toward an increase in ACS, but the difference was not statistically significant.

Limitations

The main limitation of the body of evidence is that 19 of the 23 primary studies were retrospective; therefore establishing clear evidence of an association between exposure and outcome was challenging. Four of the primary studies were prospective.[3,16,20,22] Study cohorts were generally selected with PPIs offered to patients with a history of GI conditions at the discretion of physicians.[16,20] As well, authors acknowledged that residual confounding may have remained after regression analyses due to unmeasured or unknown confounding factors.[3,6,12,14,15,21-23,25,27,30] An example of a residual confounding factor may be the use of second-generation DES which is associated with a reduction in ST relative to the use of older stents.[6]

Another important limitation is that studies used a variety of definitions for safety outcomes and evaluated patients under varying treatment regimen, and after a range of follow-up periods. Some studies measured incidences of re-hospitalization for outcomes[29,31] but did not specifically

state whether all patients who survived these conditions were re-hospitalized. The majority of studies reported on outcomes 12 months following stenting.[2,3,13,14,17,21,23-25,27,29-31] Others reported outcomes at 30 days,[26] 6 months,[16,22] 9 months,[18] 18 months,[20] 24 months,[6,12,15] 36 months,[19] and 48 months.[28] At 24 months, PPIs (primarily lansoprazole) had a non-significant trend toward increasing safety outcomes in one study,[15] but led to higher adjusted risk for MACE,[6,12] all-cause mortality,[6] CV mortality,[6] TLR[12] and clinically-relevant bleeding.[6] At 36 months, PPIs led to an increase in MI and MACE.[19] Moreover, PPIs were associated with a higher risk of MACE after 48 months.[28] Another way in which studies varied was in compliance to treatment. Although patients were generally on lifetime treatment of aspirin, approximately 70% of patients complied with the treatment in one of the studies,[13] In another study, 86.4% of patients were on aspirin and only 45% on clopidogrel at follow-up.[2] Without matching definitions for clinical outcomes treatment duration, follow-up periods, and rates of compliance, a comparison of findings across the studies presented a great challenge.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Based on the current evidence from 23 cohort studies, there are still some serious safety risks associated with the use of PPIs in patients following PCI stent implantation. Overall, the evidence favours clopidogrel antiplatelet therapy without PPIs.

Caution should be taken when interpreting the results of this report as findings may not be applicable to the entire population in which the use of $P2Y_{12}$ reimbursement may be considered. The report was limited to findings involving patients who had received PCI stent implantation exclusively, treatment duration varied widely, and none of the studies were conducted in Canada.

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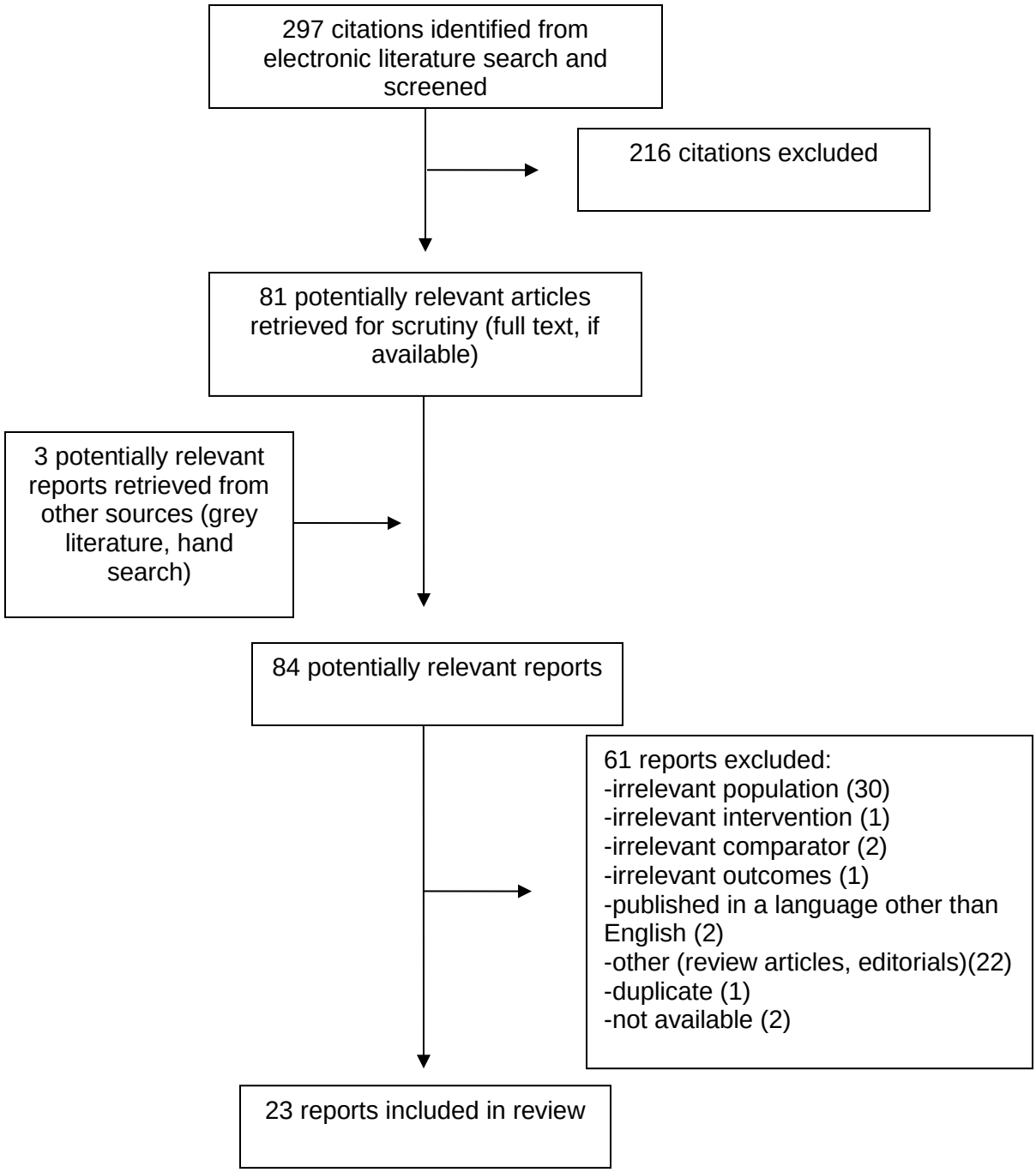
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Cohort Studies

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
Chandrasekhar, 2016,[12] United States, United Kingdom, Italy, Germany, France	Retrospective, 24 months	n=4635 patients who underwent PCI stent implantation between July 1 2009 and December 2 2010; mean age 64.4±11.4 years; 26.1% female; enrolled in the PARIS registry	Clopidogrel +aspirin +PPI (n=1062) PPI: OME, PAN, LAN, ESO, and RAB Duration of tx: 12 months	Clopidogrel +aspirin (n=3573)	MACE, CV mortality, spontaneous MI, TLR, definite or probable ST, major bleeding, minor bleeding
Gargiulo, 2016,[15] Switzerland, Italy, The Netherlands, Belgium	Retrospective, 24 months	n=1970 patients tx'd with PCI stent implantation; date range NR; mean age 69.3 years; 23.3% female	Clopidogrel 75 mg/day +aspirin 75 to 100 mg/day +PPI (n=738) PPI: ESO (NR), LAN (90.9%), OME (1.5%), PAN (7.6%), and RAB (NR) Duration of tx: 6 months or 24 months	Clopidogrel 75 mg/day +aspirin 75 to 100 mg/day (n=1232)	MACE, all-cause mortality, CV mortality, MI, ST, major bleeding, minor bleeding
Hsieh, 2015,[13] Taiwan	Retrospective cohort, 12 months	n=8856 patients with type II diabetes tx'd with DES implantation between January 1, 2007 and December 31, 2010; mean age 73.5 years; 34.3% female; had ≥ 1	Clopidogrel +PPI (n=949); approximately 70% on aspirin PP: NR Duration of tx: NR	Clopidogrel (n=8,856); approximately 71% on aspirin	Revascularization, ACS

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
		prescription for a hypoglycemic agent during a 1-year period prior to the first stent placement; reported in the National Health Insurance Research Database			
Weisz, 2015,[6] United States	Retrospective cohort from the ADAPT-DES study, 24 months	n= 8582 patients with CAD and successful placement of one or more DES between January 7, 2008, and September 16, 2010; average age 63.6 years; 25.9% female	Clopidogrel +aspirin+ PPI (n=2697) PPI: NR Duration of clopidogrel tx: ≥ 12 months	Clopidogrel +aspirin (n=5885)	MACE, all-cause mortality, MI, definite or probable ST, clinically relevant bleeding
Zou, 2014,[14] China	Retrospective cohort, 12 months	n=7653 patients tx'd with DES between October 1, 2005 and September 30, 2010; average age 66.1 years; 26.4% female	Clopidogrel 75 mg/day +aspirin 100 mg/day +PPI (n=6188) for median of 40 days (range 6 to 301) PPI: ESO (3.1%), OME (90.3%), PAN (6.6%) Duration of tx: 12 months	Clopidogrel 75 mg/day +aspirin 100 mg/day (n=1465)	MACE, all-cause mortality, non-fatal MI, definite ST, TVR, TLR, CABG

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
Ma, 2013,[16] China	Prospective cohort, 6 months	n=64 patients with carotid stenoses tx'd with carotid stenting between January 2009 and March 2011; average age = 55.16 ± 8.38 years; 32% female	Clopidogrel 75 mg/day +enteric-coated aspirin 100 mg/day+ PPI (n=26); *H pylori* positive or history of gastric conditions PPI: OME 20 mg/day	Clopidogrel 75 mg/day +enteric-coated aspirin 100 mg/day (n=31)	GI bleeding
Aihara, 2012,[17] Japan	Retrospective cohort, 12 months	n=1887 patients tx'd with PCI stenting between February 2006 and August 2009; mean age 68.6 years; 25% female; enrolled in the Ibaraki Cardiac Assessment Study registry	Clopidogrel 75 mg/day +aspirin 200 mg/day +PPI (n=1068) PPI: LAN (77.7%), OME (17.8%), RAB (4.5%) Duration of tx: 12 months for DES, 3 months for BMS	Clopidogrel 75 mg/day +aspirin 200 mg/day (n=819)	MACE, all-cause mortality, MI, stroke, ST, coronary revascularization, GI bleeding
Burkard, 2012,[19] Switzerland and The Netherlands	Retrospective cohort, 3 years	n=801 patients with STEMI, ACS or angina; tx'd with PCI randomly assigned to two DES and 1 BMS; dates NR; mean age 63.7 years; 22% female; enrolled in BASKET trial	Clopidogrel 75 mg/day +aspirin 100 mg/day +PPI (n=109) PPI: ESO (51%), LAN (7%), OME (17%), PAN (25%) Duration of tx: 6 months	Clopidogrel 75 mg/day +aspirin 100 mg/day (n=692)	MACE, CV mortality, non-fatal MI, ST, TVR

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
Ching, 2012,[18] United States	Retrospective cohort, 9 months	n=3,287 patients tx'd with PCI stenting at the Hartford Hospital Cardiac Catheterization Laboratory from January 1, 2004 to November 20, 2008; 2,575 had ACS and 712 had chronic ischemic heart disease; average age 63.3 years; 32% female	Clopidogrel +aspirin +PPI (n=1128) PPI : ESO (11%), LAN (28.5%), OME (25.3%), PAN (33.9%), RAB (1.3%) Duration of tx: 6 months for DES, and 30 days for BMS	Clopidogrel +aspirin (n=2159)	MACE, all-cause mortality, non-fatal MI, ST, TVR
Chitose, 2012,[20] Japan	Prospective cohort, 18 months	n=1,270* patients tx'd with PCI stent implantation between June 2008 and March 2009; average age 69.3 years; 28% female; enrolled in the Kumamoto Intervention Conference Study registry * Only 630 patients were tx'd with clopidogrel	Clopidogrel 75 mg/day or ticlopidine 200 mg/day +aspirin 100 mg/day +PPI (n=331) PPI: LAN, OME, RAB Duration of tx: NR	Clopidogrel 75 mg/day or ticlopidine 200 mg/day+ aspirin 100 mg/day (n=939)	MACE, CV mortality (from MI, congestive heart failure, documented sudden cardiac death), non-fatal MI, ischemic stroke, GI event
Schmidt, 2012,[2] Denmark, United States	Retrospective cohort, 12 months	n=13,001 patients with STEMI (n=3790), non-STEMI or unstable angina pectoris (n=3987), and stable angina	Clopidogrel 75 mg/day +aspirin +PPI (n=1,600) PPI: ESO, LAN, OME, PAN, RAB	Clopidogrel 75 mg/day +aspirin (n=10,259)	MACE

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
		pectoris (n=4876); tx'd with stent implantation between January 1, 2002 and June 30, 2005; median age 64 years; 28% female; enrolled in the Western Denmark Heart Registry	Duration of tx: ≤ 12 months		
Banerjee, 2011,[23] United States and Germany	Retrospective cohort, 12 months	n=4,545 patients following coronary stent implantation between January 2003 to December 2008; average age 64 years; 1.7% female; enrolled in Veterans Affairs Pharmacy Benefits Management and the National Patient Care databases Full cohort of 23,300 followed up to 6 years	Clopidogrel +PPI (n=867) PPI: ESO, LAN, OME (88.9%), PAN, RAB Duration of tx; NR	Clopidogrel (n=3,678)	MACE, mortality, MI, repeat revascularization
Harjai, 2011,[22] United States	Prospective cohort, 6 months	n=2,653 patients with PCI involving coronary stenting (95.3%) between July 2001 and December 2007; average age	Clopidogrel +aspirin +PPI (n=751) PPI: ESO, OME, others NR Duration of	Clopidogrel +aspirin (n=1,902)	MACE, mortality, MI, ST, TVR, major or minor bleeding

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
		64.6 years; 31% female; enrolled in the Guthrie PCI Registry	tx: 1 to 12 months		
Rossini, 2011,[3] Italy	Prospective cohort, 12 months	n=1,328 patients with stable angina, unstable angina, and AMI; tx'd with PCI DES implantation; average age 63.9 years; 23.7% female	Clopidogrel 75 mg/day +aspirin 100 mg/day +PPI (n=1158) PPI: LAN (74%), OME (11%), PAN (15%) Duration of tx: 12 months	Clopidogrel 75 mg/day +aspirin 100 mg/day (n=170)	MACE, all-cause mortality, ST, major bleeding, minor bleeding
Evanchan, 2010,[29] United States	Retrospective cohort, 12 months	n=5,794 patients with AMI; tx'd with stent implantation between January 2003 and January 2008; average age 63 years; % female NR	Clopidogrel +PPI (n=1,369) PPI: ESO (46%), LAN (2%), OME (10%), PAN (42%) Duration of tx: NR	Clopidogrel (n=4,425)	Readmission for AMI
Gupta, 2010,[28] United States	Retrospective cohort, 48 months	n=315 patients tx'd with stent implantation between January 2003 and August 2004; average age 61.9 years; % female NR; enrolled at the John L. Mcllelan Veterans Health Administration Hospital	Clopidogrel 75 mg/day +PPI (n=72) PPI: LAN (7%), OME (15%), RAB (78%) Duration of tx: ≥ 12 months	Clopidogrel 75 mg/day (n=243)	MACE, mortality, TLR, TVF

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
Kreutz, 2010,[27] United States	Retrospective cohort, 12 months	n=16,690 patients ≥ 18 years old following PCI stent implantation between October 1, 2005 and September 30, 2006; average age 66.1 years; 31% female	Clopidogrel 75 or 150 mg/day +PPI (n=6,828) PPI: ESO (48%), LAN (11%), OME (34%), PAN (24%) Authors excluded RAB (4%) from analysis Duration of tx: 12 months	Clopidogrel 75 or 150 mg/day (n=9,862)	MACE, CV mortality, MI, unstable angina, stroke or ischemic attack, coronary revascularization, GI bleeding
Ray, 2010,[21] United States	Retrospective cohort, 12 months	n=13,966 patients enrolled on MEDICAID and hospitalized with AMI, coronary artery revascularization, or unstable angina pectoris; tx'd with PCI stenting between January 1, 1999 and December 31, 2005; out of 20,596-patient cohort (average age 60 years, 25.8% female)	Clopidogrel +PPI (n=5,254) PPI: OME (9%), PAN (62%), others (29%) Duration of tx: NR	Clopidogrel (n=8,712)	MACE, serious gastroduodenal bleeding
Sarafoff, 2010,[26] Germany	Retrospective cohort, 30 days	n=3,338 patients with AMI or angina; tx'd with DES implantation between July 2002 and December 2006; average age	Clopidogrel 75 mg/day +aspirin 200 mg/day +PPI (n=698) PPI: ESO (17%), LAN (0.3%), OME	Clopidogrel 75 mg/day +aspirin 200 mg/day (n=2,640)	All-cause mortality, MI, ST (definite), major bleeding

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
		66.8 years; 24% female	(38%), PAN (77%), RAB (0.1%) Duration of tx: 30 days		
Tentzeris, 2010,[25] Austria	Retrospective cohort, 12 months	n=1210 patients following PCI stent implantation between January 2003 and December 2006; mean age 64.3 years; 31% female	Clopidogrel 75 mg/day +aspirin 100 mg/day +PPI (n=691) PPI: ESO (14%), LAN (3.8%), OME (4.5%), PAN (76%), RAB (1.6%) Duration of tx: 12 months for DES, and 1 month for BMS	Clopidogrel 75 mg/day +aspirin 100 mg/day (n=519)	MACE, all-cause mortality, CV mortality, rehospitalization for ACS, ST (definite)
Yasu, 2010,[24] Japan	Retrospective cohort, 12 months	n=302 patients who underwent PCI DES implantation between June 2006 and March 2009; mean age 67.9 years	Clopidogrel 50-75 mg/day +aspirin 100-200 mg/day +PPI (n=103) PPI: RAB Duration of tx: ≥ 12 months	Clopidogrel 50-75 mg/day +aspirin 100-200 mg/day (n=199)	MACE, CV mortality, ST, TLR, GI bleeding
Zairis, 2010,[31] Greece	Retrospective, 12 months	n=588 patients with stable angina or ACS; tx'd with PCI stent implantation between April 2003 and January 2005;	Clopidogrel 75 mg/day +aspirin 100 mg/day +PPI (n=340) PPI: OME Duration of	Clopidogrel 75 mg/day +aspirin 100 mg/day (n=248)	MACE, CV mortality, Re-hospitalization for non-fatal MI, ST, revascularization

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
		average age 61.9 years; 17.8% female	tx: 7 days to 12 months		
Gaglia, 2010,[30] United States	Retrospective, 12 months	n=820 patients with angina and AMI; tx'd with PCI DES implantation between April 2003 and April 2006; average age 64 years; 37% female	Clopidogrel +aspirin 325 mg/day +PPI (n=318) PPI: ESO (58.2%), LAN (12.9%), OME (12.9%), PAN (11.0%), RAB (5%) Duration of tx: ≥ 6 months	Clopidogrel +aspirin 325 mg/day (n=502)	MACE, all-cause mortality, MI, TVR, ST

ACS = acute coronary syndrome; ADAPT-DES = Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents; AMI = acute MI; BASKET = BAsel Stent Kosten Effektivita¨ts Trial; BMS = bare metal stent; CABG = coronary artery by-pass graft; CAD = coronary artery disease; CV = cardiovascular; DES = drug-eluting stent implantation; ESO = esomeprazole; GI = gastrointestinal; H2RA = H2 antagonist receptor; LAN = lansoprazole; MA = meta-analysis; MACE = major adverse cardiovascular events; MI = myocardial infarction; NSTE-ACS = non-ST-segment elevated acute coronary syndrome; OME = omeprazole; PAN = pantoprazole; PARIS = Patterns of Non-Adherence to Dual Antiplatelet Therapy in Stented Patients; PCI = percutaneous coronary intervention; PPI = proton pump inhibitors; RAB = rabeprazole; RCT(s) = randomized controlled trial(s); ST = stent thrombosis; TIMI = thrombolysis in MI; NR = not reported; TLR = target lesion revascularization; TVF = target volume failure; TVR = target vessel revascularization; tx = treat/treatment/therapy

APPENDIX 3: Critical Appraisal of Included Publications

Table A2: Strengths and Limitations of the Included Cohort Studies using the Sign 50 Methodology Checklist[11]

Strengths	Limitations
Chandrasekhar, 2016[12]	
Reporting	
• The study addressed an appropriate and clearly focused question • The likelihood that some eligible subjects might have the outcome at the time of enrolment was assessed and taken into account in the analysis	• The two groups being studied were selected from similar source populations but the differences in characteristics were statistically significant
Assessment	
• The outcomes were explicit • The assessment of outcome was made blind to exposure status	• Evidence from other sources was not used to demonstrate that the method of outcome assessment was valid and reliable • Exposure level or prognostic factor was not assessed more than once
Confounding	
• The main potential confounders were identified	• The main confounders were not taken into account in the design and analysis
Statistical analysis	
• Confidence intervals were provided	• None
Summary	
The study was acceptable in minimizing the risk of bias or confounding. Taking into account clinical considerations, the evaluation of the methodology used, and the statistical power of the study, there was clear evidence of an association between exposure and outcome. The results of this study directly applicable to the patient group targeted in this report. PPI results in higher adjusted 2-year risk of combined CV mortality, spontaneous MI, definite or probably ST, and TLR; however the impact on GI bleeding was not reported.	
Garguilo, 2016[15]	
Reporting	
• The study addressed an appropriate and clearly focused question • The likelihood that some eligible subjects might have the outcome at the time of enrolment was assessed and taken into account in the analysis	• The two groups being studied were selected from similar source populations but the differences in characteristics were statistically significant
Assessment	
• The outcomes were explicit	• The assessors of outcomes were not blind to exposure status. • There was no recognition that knowledge of exposure status could have influenced the assessment of outcome • Evidence from other sources was not used to

Table A2: Strengths and Limitations of the Included Cohort Studies using the Sign 50 Methodology Checklist[11]	
Strengths	**Limitations**
	demonstrate that the method of outcome assessment was valid and reliable • Exposure level or prognostic factor was not assessed more than once
Confounding	
• The main potential confounders were identified	• The main confounders were not taken into account in the design and analysis
Statistical analysis	
• Confidence intervals were provided	• None
Summary	
The study was acceptable in minimizing the risk of bias or confounding. Taking into account clinical considerations, the evaluation of the methodology used, and the statistical power of the study, there was no clear evidence of an association between exposure and outcome. The results of this study were directly applicable to the patient group targeted in this report. PPI does not statistically affect CV outcomes	
Hsieh, 2015[13]	
Reporting	
• The study addressed an appropriate and clearly focused question • The likelihood that some eligible subjects might have the outcome at the time of enrolment was assessed and taken into account in the analysis	• The two groups being studied were selected from similar source populations but the differences in characteristics were statistically significant
Assessment	
• The outcomes were explicit	• The assessors of outcomes were not blind to exposure status. • There was no recognition that knowledge of exposure status could have influenced the assessment of outcome • Evidence from other sources was not used to demonstrate that the method of outcome assessment was valid and reliable • Exposure level or prognostic factor was not assessed more than once
Confounding	
• The main potential confounders were identified	• The main confounders were not taken into account in the design and analysis
Statistical analysis	
• Confidence intervals were provided	• None
Summary	
The study was acceptable in minimizing the risk of bias or confounding. Taking into account clinical considerations, the evaluation of the methodology used, and the statistical power of the study, there was no clear evidence of an association between exposure and outcome. The results of this study were directly applicable to diabetic patients who were a subset of the patient group targeted in this	

Table A2: Strengths and Limitations of the Included Cohort Studies using the Sign 50 Methodology Checklist[11]	
Strengths	**Limitations**
report. Patients with type II diabetes and a history of ACS, were at a higher risk of repeat ACS if treated with Limus-eluting stents.	
Weisz, 2015[6]	
Reporting	
• The study addressed an appropriate and clearly focused question • The likelihood that some eligible subjects might have the outcome at the time of enrolment was assessed and taken into account in the analysis	• The two groups being studied were selected from similar source populations but the differences in characteristics were statistically significant
Assessment	
• The outcomes were explicit • The assessors of outcomes were blind to exposure status.	• Evidence from other sources was not used to demonstrate that the method of outcome assessment was valid and reliable • Exposure level or prognostic factor was not assessed more than once
Confounding	
• The main potential confounders were identified	• The main confounders were not taken into account in the design and analysis
Statistical analysis	
• Confidence intervals were provided	• None
Summary	
The study was acceptable in minimizing the risk of bias or confounding. Taking into account clinical considerations, the evaluation of the methodology used, and the statistical power of the study, there was no clear evidence of an association between exposure and outcome. The results of this study were directly applicable to the patient group targeted in this report. Patients treated with DES and on DAPT for at least 1 year were at a higher risk of composite CV mortality, MI, and ischemia-driven TLR, and of all-cause mortality, CV mortality, and clinically relevant bleeding, individually	
Zou, 2014[14]	
Reporting	
• The study addressed an appropriate and explicit question • The likelihood that some eligible subjects might have the outcome at the time of enrolment was assessed and taken into account in the analysis	• The two groups being studied were selected from similar source populations but the differences in characteristics were statistically significant
Assessment	
• The outcomes were explicit • The assessors of outcomes were blind to exposure status.	• Evidence from other sources was not used to demonstrate that the method of outcome assessment was not valid and reliable • Exposure level or prognostic factor was assessed more than once

Table A2: Strengths and Limitations of the Included Cohort Studies using the Sign 50 Methodology Checklist[11]	
Strengths	**Limitations**
Confounding	
• The main potential confounders were identified	• The main confounders were not taken into account in the design and analysis
Statistical analysis	
• Confidence intervals were provided	• None
Summary	
The study was acceptable in minimizing the risk of bias or confounding. Taking into account clinical considerations, the evaluation of the methodology used, and the statistical power of the study, there was no clear evidence of an association between exposure and outcome. The results of this study were directly applicable to the patient group targeted in this report. PPIs (specifically omeprazole) may be associated with an increased risk of MACE and ST.	
Ma, 2013[16]	
Reporting	
• The study addressed an appropriate and explicit question	• It was not possible to ascertain whether the two groups being studied were selected from similar source populations • It was not possible to ascertain the likelihood that some eligible subjects might have the outcome at the time of enrolment and whether it was assessed and taken into account in the analysis • 11% of patients were lost to follow-up • Those lost to follow-up were not compared to others
Assessment	
• None	• The outcomes were not clearly defined • It was not possible to ascertain whether the assessment of outcomes was made blind to exposure status • Evidence from other sources was not used to demonstrate that the method of outcome assessment was valid and reliable • Exposure level or prognostic factor was not assessed more than once
Confounding	
• None	• The main confounders were not identified nor taken into account in the design and analysis
Statistical analysis	
• None	• Confidence intervals were not provided
Summary	
The study was not acceptable in minimizing the risk of bias or confounding. Taking into account clinical considerations, the evaluation of the methodology used, and the statistical power of the study, there was no clear evidence of an association between exposure and outcome. The results of this study were directly applicable to the patient group targeted in this report. There was insufficient data to make a meaningful conclusion on the impact of PPIs.	

Table A2: Strengths and Limitations of the Included Cohort Studies using the Sign 50 Methodology Checklist[11]

Strengths	Limitations
Aihara, 2012[17]	
Reporting	
• The study addresses an appropriate and explicit question • The two groups being studied were selected from source populations that were comparable in all respects other than the factor under investigation • The likelihood that some eligible subjects might have the outcome at the time of enrolment was assessed and taken into account in the analysis.	• None
Assessment	
• The outcomes were explicit • There was some recognition that knowledge of exposure status could have influenced the assessment of outcomes	• The assessment of outcomes was not made blind to exposure status • It was not possible to ascertain whether the method of assessment of exposure was reliable • Evidence from other sources was not used to demonstrate that the method of outcome assessment was valid and reliable • Exposure level or prognostic factor was not assessed more than once
Confounding	
• The main confounders were identified and taken into account in the design and analysis	• None
Statistical analysis	
• Confidence intervals were provided	• None
Summary	
The study was acceptable in minimizing the risk of bias or confounding. Taking into account clinical considerations, the evaluation of the methodology used, and the statistical power of the study, there is no clear evidence of an association between exposure and outcome. The results of this study are directly applicable to the patient group targeted in this report. PPI appears to increase heart failure but is not associated with higher risk of other adverse events.	
Burkard, 2012[19]	
Reporting	
• The study addresses an appropriate and explicit question • The likelihood that some eligible subjects might have the outcome at the time of enrolment was assessed and taken into account in the analysis.	• The two groups being studied were selected from similar source populations but the differences in characteristics were statistically significant

Table A2: Strengths and Limitations of the Included Cohort Studies using the Sign 50 Methodology Checklist[11]	
Strengths	**Limitations**
Assessment	
• The outcomes were explicit	• It was not possible to ascertain whether the assessment of outcomes was made blind to exposure status • There was no recognition that knowledge of exposure status could have influenced the assessment of outcomes • It was not possible to ascertain whether the method of assessment of exposure was reliable • Evidence from other sources was not used to demonstrate that the method of outcome assessment was valid and reliable • Exposure level or prognostic factor was not assessed more than once
Confounding	
• The main confounders were identified and taken into account in the design and analysis	• None
Statistical analysis	
• None	• Confidence intervals were not provided
Summary	
The study was not acceptable in minimizing the risk of bias or confounding. Taking into account clinical considerations, the evaluation of the methodology used, and the statistical power of the study, there is no clear evidence of an association between exposure and outcome. The results of this study are directly applicable to the patient group targeted in this report. PPI is associated with increases in MACE, CV mortality, MI, ST, and TVR but the statistical significance remains only for MI after propensity-score matching.	
Ching, 2012[18]	
Reporting	
• The study addresses an appropriate and explicit • The two groups being studied were selected from source populations that were comparable in all respects other than the factor under investigation • The likelihood that some eligible subjects might have the outcome at the time of enrolment was assessed and taken into account in the analysis.	• None • 8% of patients were lost to follow-up • Patients who were lost to follow-up were not compared with others who completed treatment
Assessment	
• The outcomes were explicit • There was some recognition that knowledge of exposure status could	• It is not possible to ascertain whether the assessment of outcomes was made blind to exposure status • It was not possible to ascertain whether the method of

Table A2: Strengths and Limitations of the Included Cohort Studies using the Sign 50 Methodology Checklist[11]	
Strengths	**Limitations**
have influenced the assessment of outcomes	assessment of exposure was reliable • Evidence from other sources was not used to demonstrate that the method of outcome assessment was valid and reliable • Exposure level or prognostic factor was not assessed more than once
Confounding	
• The main confounders were identified and taken into account in the design and analysis	• None
Statistical analysis	
• Confidence intervals were provided	• None
Summary	
The study was acceptable in minimizing the risk of bias or confounding. Taking into account clinical considerations, the evaluation of the methodology used, and the statistical power of the study, there is no clear evidence of an association between exposure and outcome. The results of this study are directly applicable to the patient group targeted in this report. PPI is associated with a statistically significant increase in MACE, all-cause mortality, and TVR and a trending increase in MI	
Chitose, 2012[20]	
Reporting	
• The study addresses an appropriate and explicit question • The two groups being studied were selected from source populations that were comparable in all respects other than the factor under investigation • The likelihood that some eligible subjects might have the outcome at the time of enrolment was assessed and taken into account in the analysis.	• None
Assessment	
• The outcomes were explicit • There was some recognition that knowledge of exposure status could have influenced the assessment of outcomes	• The assessment of outcomes was not made blind to exposure status • It was not possible to ascertain whether the method of assessment of exposure was reliable • Evidence from other sources was not used to demonstrate that the method of outcome assessment was valid and reliable • Exposure level or prognostic factor was not assessed more than once
Confounding	
• The main confounders were	• None

Table A2: Strengths and Limitations of the Included Cohort Studies using the Sign 50 Methodology Checklist[11]	
Strengths	**Limitations**
identified and taken into account in the design and analysis	
Statistical analysis	
• None	• Confidence intervals were not provided
Summary	
The study was acceptable in minimizing the risk of bias or confounding. Taking into account clinical considerations, the evaluation of the methodology used, and the statistical power of the study, there is no clear evidence of an association between exposure and outcome. The results of this study are directly applicable to the patient group targeted in this report. PPI had no impact on adverse cardiac or GI events.	
Schmidt, 2012[2]	
Reporting	
• The study addresses an appropriate and explicit question • The likelihood that some eligible subjects might have the outcome at the time of enrolment was assessed and taken into account in the analysis.	• None • It was not possible to ascertain whether the two groups being studied were selected from source populations
Assessment	
• The outcomes were explicit	• It was not possible to ascertain whether the assessment of outcomes was made blind to exposure status • There was no recognition that knowledge of exposure status could have influenced the assessment of outcomes • It was not possible to ascertain whether the method of assessment of exposure was reliable • Evidence from other sources was not used to demonstrate that the method of outcome assessment was valid and reliable • Exposure level or prognostic factor was not assessed more than once
Confounding	
• The main confounders were identified and taken into account in the design and analysis	• None
Statistical analysis	
• Confidence intervals were provided	• None
Summary	
The study was not acceptable in minimizing the risk of bias or confounding. Taking into account clinical considerations, the evaluation of the methodology used, and the statistical power of the study, there is no clear evidence of an association between exposure and outcome. The results of this study are directly applicable to the patient group targeted in this report. PPI led to an increase in MACE although only 45% of patients were confirmed to have completed the tx plan after 12 months	

Table A2: Strengths and Limitations of the Included Cohort Studies using the Sign 50 Methodology Checklist[11]	
Strengths	**Limitations**
Banerjee, 2011[23]	
Reporting	
• The study addresses an appropriate and explicit question • The likelihood that some eligible subjects might have the outcome at the time of enrolment was assessed and taken into account in the analysis.	• None • It was not possible to ascertain whether the two groups being studied were selected from source populations
Assessment	
• The outcomes were explicit	• It was not possible to ascertain whether the assessment of outcomes was made blind to exposure status • There was no recognition that knowledge of exposure status could have influenced the assessment of outcomes • It was not possible to ascertain whether the method of assessment of exposure was reliable • Evidence from other sources was not used to demonstrate that the method of outcome assessment was valid and reliable • Exposure level or prognostic factor was not assessed more than once
Confounding	
• The main confounders were identified and taken into account in the design and analysis	• None
Statistical analysis	
• Confidence intervals were provided	• None
Summary	
The study was not acceptable in minimizing the risk of bias or confounding. Taking into account clinical considerations, the evaluation of the methodology used, and the statistical power of the study, there is no clear evidence of an association between exposure and outcome. The results of this study are directly applicable to the patient group targeted in this report. PPI led to an increase in MACE and all-cause mortality after 12 months of tx.	
Harjai, 2011[22]	
Reporting	
• The study addresses an appropriate and explicit question	• None • The two groups being studied were selected from similar source populations but the differences in characteristics were statistically significant • The likelihood that some eligible subjects might have the outcome at the time of enrolment was not assessed nor taken into account in the analysis
Assessment	

Table A2: Strengths and Limitations of the Included Cohort Studies using the Sign 50 Methodology Checklist[11]	
Strengths	**Limitations**
• The outcomes were clearly defined • There was some recognition that knowledge of exposure status could have influenced the assessment of outcomes	• The assessment of outcomes was not made blind to exposure status • It was not possible to ascertain whether the method of assessment of exposure was reliable • Evidence from other sources was not used to demonstrate that the method of outcome assessment was valid and reliable • Exposure level or prognostic factor was not assessed more than once
Confounding	
• The main confounders were identified and taken into account in the design and analysis	• None
Statistical analysis	
• Confidence intervals were provided	• None
Summary	
The study was acceptable in minimizing the risk of bias or confounding. Taking into account clinical considerations, the evaluation of the methodology used, and the statistical power of the study, there is no clear evidence of an association between exposure and outcome. The results of this study are directly applicable to the patient group targeted in this report. PPI had no statistically significant impact on adverse CV outcomes.	
Rossini, 2011[3]	
Reporting	
• The study addresses an appropriate and explicit question • The two groups being studied were selected from source populations that were comparable in all respects other than the factor under investigation • The likelihood that some eligible subjects might have the outcome at the time of enrolment was assessed and taken into account in the analysis.	• None
Assessment	
• The outcomes were explicit	• The assessment of outcomes was not made blind to exposure status • There was no recognition that knowledge of exposure status could have influenced the assessment of outcomes • It was not possible to ascertain whether the method of assessment of exposure was reliable • Evidence from other sources was not used to demonstrate that the method of outcome assessment

Table A2: Strengths and Limitations of the Included Cohort Studies using the Sign 50 Methodology Checklist[11]	
Strengths	**Limitations**
	was valid and reliable • Exposure level or prognostic factor was not assessed more than once
Confounding	
• The main confounders were identified and taken into account in the design and analysis	• None
Statistical analysis	
• Confidence intervals were provided	• None
Summary	
The study was acceptable in minimizing the risk of bias or confounding. Taking into account clinical considerations, the evaluation of the methodology used, and the statistical power of the study, there is no clear evidence of an association between exposure and outcome. The results of this study are directly applicable to the patient group targeted in this report. PPI had no statistically significant impact on adverse CV outcomes.	
Evanchan, 2010[29]	
Reporting	
• The study addresses an appropriate and clearly focused question • The likelihood that some eligible subjects might have the outcome at the time of enrolment was assessed and taken into account in the analysis.	• It was not possible to ascertain whether the two groups being studied were selected from source populations that were comparable in all respects other than the factor under investigation
Assessment	
• The outcomes were explicit	• It was not possible to ascertain whether the assessment of outcomes was made blind to exposure status • There was no recognition that knowledge of exposure status could have influenced the assessment of outcomes • It was not possible to ascertain whether the method of assessment of exposure was reliable • Evidence from other sources was used not to demonstrate that the method of outcome assessment was valid and reliable • Exposure level or prognostic factor was not assessed more than once
Confounding	
• None	• The main confounders were identified but they were not taken into account in the design and analysis
Statistical analysis	
• Confidence intervals were provided	• None
Summary	
The study was not acceptable in minimizing the risk of bias or confounding. Taking into account	

Table A2: Strengths and Limitations of the Included Cohort Studies using the Sign 50 Methodology Checklist[11]	
Strengths	**Limitations**
clinical considerations, the evaluation of the methodology used, and the statistical power of the study, there is no clear evidence of an association between exposure and outcome. The results of this study are directly applicable to the patient group targeted in this report. PPI is associated with an increase in the risk of readmission for AMI.	
Gupta, 2010[28]	
Reporting	
• The study addresses an appropriate and explicit question • The likelihood that some eligible subjects might have the outcome at the time of enrolment was assessed and taken into account in the analysis.	• The two groups being studied were selected from similar source populations but the differences in characteristics were statistically significant
Assessment	
• The outcomes were explicit • There was some recognition that knowledge of exposure status could have influenced the assessment of outcomes	• The assessment of outcomes was not made blind to exposure status • It was not possible to ascertain whether the method of assessment of exposure was reliable • Evidence from other sources was not used to demonstrate that the method of outcome assessment was valid and reliable • Exposure level or prognostic factor was not assessed more than once
Confounding	
• The main confounders were identified and taken into account in the design and analysis	• None
Statistical analysis	
• Confidence intervals were provided	• None
Summary	
The study was acceptable in minimizing the risk of bias or confounding. Taking into account clinical considerations, the evaluation of the methodology used, and the statistical power of the study, there is no clear evidence of an association between exposure and outcome. The results of this study are directly applicable to the patient group targeted in this report. Based on information from a small group of patients, PPI led to a statistically significant increase in composite MACE but not its individual components	
Kreutz, 2010[27]	
Reporting	
• The study addresses an appropriate and explicit question • The likelihood that some eligible subjects might have the outcome at the time of enrolment was assessed and taken into account in the analysis.	• The two groups being studied were selected from source populations but it was not possible to ascertain whether they were comparable in all respects other than the factor under investigation

Table A2: Strengths and Limitations of the Included Cohort Studies using the Sign 50 Methodology Checklist[11]	
Strengths	**Limitations**
Assessment	
• The outcomes were explicit	• The assessment of outcomes was not made blind to exposure status • There was no recognition that knowledge of exposure status could have influenced the assessment of outcomes • It was not possible to ascertain whether the method of assessment of exposure was reliable • Evidence from other sources was not used to demonstrate that the method of outcome assessment was valid and reliable • Exposure level or prognostic factor was not assessed more than once
Confounding	
• The main confounders were identified and taken into account in the design and analysis	• None
Statistical analysis	
• Confidence intervals were provided	• None
Summary	
The study was acceptable in minimizing the risk of bias or confounding. Taking into account clinical considerations, the evaluation of the methodology used, and the statistical power of the study, there is no clear evidence of an association between exposure and outcome. The results of this study are directly applicable to the patient group targeted in this report. PPI was associated with a statistically significant increase in MACE, MI, unstable angina, stroke or ischemic attack, coronary revascularization and GI bleeding.	
Ray, 2010[21]	
Reporting	
• The study addresses an appropriate and explicit question • The two groups being studied were selected from source populations that were comparable in all respects other than the factor under investigation • The likelihood that some eligible subjects might have the outcome at the time of enrolment was assessed and taken into account in the analysis.	• None
Assessment	
• The outcomes were explicit	• It was not possible to ascertain whether the assessment of outcomes was made blind to exposure status • There was no recognition that knowledge of exposure

Table A2: Strengths and Limitations of the Included Cohort Studies using the Sign 50 Methodology Checklist[11]	
Strengths	**Limitations**
	status could have influenced the assessment of outcomes • It was not possible to ascertain whether the method of assessment of exposure was reliable • Evidence from other sources was not used to demonstrate that the method of outcome assessment was valid and reliable • Exposure level or prognostic factor was not assessed more than once
Confounding	
• The main confounders were identified and taken into account in the design and analysis	• None
Statistical analysis	
• Confidence intervals were provided	• None
Summary	
The study was acceptable in minimizing the risk of bias or confounding. Taking into account clinical considerations, the evaluation of the methodology used, and the statistical power of the study, there is no clear evidence of an association between exposure and outcome. The results of this study are directly applicable to the patient group targeted in this report. PPI is not associated with statistically significant changes in serious CV events or gastroduodenal bleeding	
Saraffof, 2010[26]	
Reporting	
• The study addresses an appropriate and explicit question • The two groups being studied were selected from source populations that were comparable in all respects other than the factor under investigation • The likelihood that some eligible subjects might have the outcome at the time of enrolment was assessed and taken into account in the analysis.	• None
Assessment	
• The outcomes were explicit	• The assessment of outcomes was not made blind to exposure status • There was no recognition that knowledge of exposure status could have influenced the assessment of outcomes • It was not possible to ascertain whether the method of assessment of exposure was reliable • Evidence from other sources was not used to demonstrate that the method of outcome assessment

Table A2: Strengths and Limitations of the Included Cohort Studies using the Sign 50 Methodology Checklist[11]	
Strengths	**Limitations**
	was valid and reliable • Exposure level or prognostic factor was not assessed more than once
Confounding	
• The main confounders were identified and taken into account in the design and analysis	• None
Statistical analysis	
• Confidence intervals were provided	• None
Summary	
The study was acceptable in minimizing the risk of bias or confounding. Taking into account clinical considerations, the evaluation of the methodology used, and the statistical power of the study, there is no clear evidence of an association between exposure and outcome. The results of this study are directly applicable to the patient group targeted in this report. PPIs are associated with a statistically significant increase in mortality.	
Tentzeris, 2010[25]	
Reporting	
• The study addresses an appropriate and explicit question • The two groups being studied were selected from source populations that were comparable in all respects other than the factor under investigation • The likelihood that some eligible subjects might have the outcome at the time of enrolment was assessed and taken into account in the analysis.	• None
Assessment	
• The outcomes were explicit	• The assessment of outcomes was not made blind to exposure status • There was no recognition that knowledge of exposure status could have influenced the assessment of outcomes • It was not possible to ascertain whether the method of assessment of exposure was reliable • Evidence from other sources was used to demonstrate that the method of outcome assessment was valid and reliable • Exposure level or prognostic factor was assessed more than once
Confounding	
• The main confounders were identified and taken into account in	• None

Table A2: Strengths and Limitations of the Included Cohort Studies using the Sign 50 Methodology Checklist[11]	
Strengths	**Limitations**
the design and analysis	
Statistical analysis	
• Confidence intervals were provided	• None
Summary	
The study was acceptable in minimizing the risk of bias or confounding. Taking into account clinical considerations, the evaluation of the methodology used, and the statistical power of the study, there is no clear evidence of an association between exposure and outcome. The results of this study are directly applicable to the patient group targeted in this report. PPIs were not associated with an increased risk of clinical outcome parameters	
Yasu, 2010[24]	
Reporting	
• The study addresses an appropriate and explicit question • The two groups being studied were selected from source populations that were comparable in all respects other than the factor under investigation • The likelihood that some eligible subjects might have the outcome at the time of enrolment was assessed and taken into account in the analysis.	• 3.6% of patients were lost to follow-up • Patients lost to follow-up were not compared with others
Assessment	
• The outcomes were explicit	• The assessment of outcomes was not made blind to exposure status • There was no recognition that knowledge of exposure status could have influenced the assessment of outcomes • It was not possible to ascertain whether the method of assessment of exposure was reliable • Evidence from other sources was used to demonstrate that the method of outcome assessment was valid and reliable • Exposure level or prognostic factor was assessed more than once
Confounding	
• The main confounders were identified and taken into account in the design and analysis	• None
Statistical analysis	
• None	• Confidence intervals were not provided
Summary	
The study was acceptable in minimizing the risk of bias or confounding. Taking into account clinical considerations, the evaluation of the methodology used, and the statistical power of the study, there	

Table A2: Strengths and Limitations of the Included Cohort Studies using the Sign 50 Methodology Checklist[11]

Strengths	Limitations
is no clear evidence of an association between exposure and outcome. The results of this study are directly applicable to the patient group targeted in this report. PPI had no statistically significant impact on adverse CV or GI events.	
Zairis, 2010[31]	
Reporting	
• The study addresses an appropriate and explicit question • The two groups being studied were selected from source populations that were comparable in all respects other than the factor under investigation • The likelihood that some eligible subjects might have the outcome at the time of enrolment was assessed and taken into account in the analysis.	• None
Assessment	
• The outcomes were explicit	• The assessment of outcomes was not made blind to exposure status • There was no recognition that knowledge of exposure status could have influenced the assessment of outcomes • It was not possible to ascertain whether the method of assessment of exposure was reliable • Evidence from other sources was used to demonstrate that the method of outcome assessment was valid and reliable • Exposure level or prognostic factor was assessed more than once
Confounding	
• The main confounders were identified and taken into account in the design and analysis	• None
Statistical analysis	
• Confidence intervals were provided	• None
Summary	
The study was acceptable in minimizing the risk of bias or confounding. Taking into account clinical considerations, the evaluation of the methodology used, and the statistical power of the study, there is no clear evidence of an association between exposure and outcome. The results of this study are directly applicable to the patient group targeted in this report. Omeprazole had no statistically significant impact on MACE and its components.	
Gaglia, 2010[30]	
Reporting	
• The study addresses an appropriate	• None

Table A2: Strengths and Limitations of the Included Cohort Studies using the Sign 50 Methodology Checklist[11]	
Strengths	**Limitations**
and explicit question • The two groups being studied were selected from source populations that were comparable in all respects other than the factor under investigation • The likelihood that some eligible subjects might have the outcome at the time of enrolment was assessed and taken into account in the analysis.	
Assessment	
• The outcomes were explicit	• It was not possible to ascertain whether the assessment of outcomes was made blind to exposure status • There was no recognition that knowledge of exposure status could have influenced the assessment of outcomes • It was not possible to ascertain whether the method of assessment of exposure was reliable • Evidence from other sources was used to demonstrate that the method of outcome assessment was valid and reliable • Exposure level or prognostic factor was assessed more than once
Confounding	
• The main confounders were identified and taken into account in the design and analysis	• None
Statistical analysis	
• Confidence intervals were provided	• None
Summary	
The study was acceptable in minimizing the risk of bias or confounding. Taking into account clinical considerations, the evaluation of the methodology used, and the statistical power of the study, there is no clear evidence of an association between exposure and outcome. The results of this study are directly applicable to the patient group targeted in this report. PPI is not associated with an increase in MACE but not its components	

CV = cardiovascular events; GI = gastrointestinal; MACE = major adverse cardiovascular events; PPI = proton pump inhibitors; tx = treatment

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A3: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
Chandrasekhar, 2016[12]	
*PPI (n=1062) vs no-PPI (n=3573) @ 24 months** MACE: 13.8% vs 10.2%, *P*=0.0012; adjusted HR=1.28 (CI 1.05 to 1.56)* CV mortality: 5.6% vs 4.3%, *P*=0.0579; adjusted HR=1.26 (CI 0.97 to 1.64) Spontaneous MI: 3.9% vs 3.5%, *P*=0.5460; adjusted HR=1.19 (CI 0.83 to 1.71) TLR: 9.1% vs 6.3%, *P*=0.0016; adjusted HR=1.33 (CI 1.04 to 1.71) ST: 1.9% vs 1.2%, *P*=0.1095; adjusted HR=1.35 (CI 0.78 to 2.34) Major bleeding: 1.9% vs 2.2%, *P*=0.60; adjusted HR=NR Minor bleeding: 1.5% vs 1.5%, *P*=0.91; adjusted HR=NR * Values reported in abstract differ from values reported within the body of the article. Excluded net adverse cardiac events from this report	• "Clopidogrel treated PCI patients discharged on PPI represent a higher risk group with a significantly greater adjusted 2-year risk of MACE and net adverse cardiac events outcomes driven by higher TLR compared to non-PPI users, without a difference in bleeding."[12] Page 9
Gargiulo, 2016[15]	
*PPI (n=738) vs no-PPI (n=1232) @ 6 months or 24 months** MACE: 11.5% vs 9.2%, *P*=0.094; HR=1.272 (CI 0.960 to 1.685) All-cause mortality: 7.2% vs 6.2%, *P*=0.433; HR=1.150 (CI 0.811 to 1.632) CV mortality: 3.9% vs 3.6%, *P*=0.688; HR=1.101 (CI 0.689 to 1.759) MI: 4.3% vs 3.9%, *P*=0.633; HR=1.115 (CI 0.713 to 1.744) ST: 5.0% vs 3.8%, *P*=0.207; HR=1.320 (CI 0.858 to 2.030) Major bleeding: 1.5% vs 0.9%, *P*=0.224; HR=1.679 (CI 0.728 to 3.873) Minor bleeding: 1.4% vs 08%, *P*=0.246; HR=1.680 (CI 0.699 to 4.036) 50% of patients were on DAPT for only six months*	• "Overall, PPI use was not associated with an increased risk of CV events in all-comer patients undergoing PCI and receiving DAPT. Our findings do not support the need to avoid concomitant use of PPIs and DAPT with aspirin plus clopidogrel, when clinically indicated."[15] Page 101
Hsieh, 2015[13]	
Patients with Limus-eluting stents *PPI (n=670) vs no-PPI (n=5933) @ 12 months*	• "If a diabetic patient is at low risk of GI tract bleeding, it is best to avoid or decrease the

Table A3: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
Revascularization: 18.96% vs 19.62%, *P*=NR; adjusted HR=0.90 (CI 0.75 to 1.09) ACS: 13.73% vs 8.98%, *P*=NR; adjusted HR=1.55 (CI 1.11 to 2.16)* Patients with Paclitaxel-eluting stents *PPI (n=279) vs no-PPI (n=2923) @ 12 months* Revascularization: 20.79% vs 20.15%, *P*=NR; adjusted HR=1.00 (CI 0.76 to 1.31) ACS: 14.7% vs 10.06%, *P*=NR; adjusted HR=1.31 CI (0.78 to 2.19)* * Adjusted HR was reported only for patients with a history of ACS	dosage of PPIs used in combination with clopidogrel, as the risk of negative interaction is greater than the risk of GI tract bleeding."[13] Page 11
Weisz, 2015[6]	
*PPI (n=2162) vs non-PPI (n=6419) @ 24 months** MACE: 11.6% vs 8.7%, *P*=0.0002 ; adjusted HR=1.21 (CI 1.04 to1.40), *P*=0.02 All-cause mortality: 5.4% vs 3.3%, *P*<0.0001; adjusted HR=1.28 (CI 1.00 to 1.63), *P*=0.051 CV mortality: 2.9% vs 1.8%, *P*=0.007; adjusted HR=NR Non-CV mortality: 2.1% vs 1.3%, *P*=0.005; adjusted HR=NR MI: 3.9% vs 3.2%, *P*=0.12; adjusted HR=NR ST (definite or probable): 1.24% vs 0.94%, *P*=0.22; adjusted HR=NR TVR: 0.22% vs 0.19%, *P*=0.73; adjusted HR=1.27 (CI 1.09 to 1.49), *P*=0.0027 Clinically relevant bleeding: 7.1% vs 6.0%, *P*=0.049; adjusted HR=1.03 (CI 0.84 to 1.26), *P*=0.76 * Excluded outcomes reported in-hospital	• "…in patients treated with aspirin and clopidogrel after successful DES implantation in the large-scale, prospective ADAPT-DES study, the concomitant administration of a PPI was associated with […] an increased rate of MACE occurring during 2-year follow-up. Additional studies are warranted to determine the risk-benefit ratio of PPI use in patients with DES in whom clopidogrel is used to inhibit the $P2Y_{12}$ platelet receptor".[6] Page 6
Zou, 2014[14]	
*PPI (n=6188) vs no-PPI (n=1465) @ 12 months** MACE: 13.9% vs 10.6%; HR=1.36 (CI 1.14 to 1.64), *P*=0.001 All-cause mortality: 3.6% vs 4.3%; HR=0.83 (CI 0.62 to 1.11), *P*=0.214 MI (non-fatal): 1.1% vs 0.6%; HR=1.82 (CI 0.91 to 3.66), *P*=0.68 ST: 1.0% vs 0.4%; HR=2.50 (CI 1.08 to 5.79), *P*=0.015 TVR: 6.9% vs 5.6%; HR=1.25 (CI 0.98 to 1.59)	• "PPI users had a higher incidence of [MACE] than non-PPI users… However, concomitant use of clopidogrel and a PPI was not associated with an increased risk for developing MI, cardiovascular death, TVR…"[14] Page 4

Table A3: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
P=0.066 TLR: 5.5% vs 4.9%; HR=1.12 (0.87 to 1.46), *P*=0.371 CABG outcome was not included in this report	
Ma, 2013[16]	
*PPI (n=26) vs no-PPI (n=31) @ 6 months** GI bleeding: 3.8% vs 22.6%, *P*=NR; HR=NR * 7 patients were lost to f/u without explanation	• "…patients with carotid artery stent placement who were receiving DAPT had a significant reduction in gastrointestinal bleeding with omeprazole use as compared without omeprazole"[16] Page 139
Aihara, 2012[17]	
*PPI (n=1068) vs no-PPI (n=819) @ 12 months** MACE: 4.6% vs 4.6%, *P*=0.77; adjusted HR=0.64 (CI 0.36 to 1.14), *P*=0.13* All-cause mortality: 3.4% vs 3.4%, *P*=0.82; adjusted HR=0.74 (CI 0.39 to 1.42), *P*=0.36 MI: 1.1% vs 2.0%, *P*=0.26; adjusted HR=0.30 (CI 0.08 to 1.11), *P*=0.07 Stroke: 2.4% vs 1.2%, *P*=0.11; adjusted HR=1.60 (CI 0.70 to 3.96), *P*=0.27 Heart failure: 6.7% vs 2.4%, *P*=0.0003; adjusted HR=3.19 (CI 1.44 to 8.45), *P*=0.0031 ST: 1.3% vs 0.5%, *P*=0.06; adjusted HR=0.91 (CI 0.26 to 3.61), *P*=0.89 Coronary revascularization: 16.5% vs 12.6%, *P*=0.09; adjusted HR=0.81 (CI 0.59 to 1.12), *P*=0.20 GI bleeding: 1.1% vs 2.0%, *P*=0.10; adjusted HR=0.36 (CI 0.14 to 0.85), *P*=0.019 * Adjusted HR was reported for non-PPI vs PPI patients	• "Concomitant therapy of a PPI and clopidogrel after coronary stenting was not associated with a higher risk of adverse outcomes"[17] Page 7
Burkard, 2012[19]	
*PPI (n=109) vs no-PPI (n=692) @ 36 months** MACE: 30.3% vs 20.8%, *P*=0.027 CV mortality: 9.2% vs 7.4%, *P*=0.51 MI (non-fatal): 14.7% vs 7.4%, *P*=0.01; adjusted HR=1.88 (CI 1.05 to 3.37), *P*=0.034 ST: 11.0% vs 8.1%, *P*=0.31 TVR: 20.1% vs 15.3%, *P*=0.2 * Adjusted HR was not reported for MACE, CV mortality, ST, and TVR	• "…in this real-world PCI population, the combination of PPIs and clopidogrel was associated with a doubling of MI rates at 3 years. Even after adjustment for confounding factors, PPI use remained an independent predictor of outcome emphasizing the clinical importance of this drug-drug interaction in our all-comer daily practice CV population"[19] Page 262

Table A3: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
Ching, 2012[18]	
*PPI (n=1128) vs no-PPI (n=2159) @ 9 months** MACE: 7.1% vs 3.5%, *P*<0.001; adjusted HR=1.70 (CI 1.20 to 2.41), *P*=0.003 All-cause mortality: 3.0% vs 1.1%, *P*<0.001; adjusted HR=1.79 (CI 1.03 to 3.12), *P*=0.038 MI: 1.1% vs 0.6%, *P*=0.135; adjusted HR=NR ST: Event rate too low to infer statistical significance TVR: 3.8% vs 2.1%, *P*=0.005; adjusted HR=1.75 (CI 1.12 to 2.72), *P*=0.014 * 8% of patients were lost to f/u without explanation.	• Concomitant use of PPIs and clopidogrel among post-PCI patients was associated with significantly increased rates of combined MACE, all-cause mortality, and TVR…"[18] Page 210
Chitose, 2012[20]	
Patients on clopidogrel alone *PPI (n=187) vs no-PPI (n=443) @ 18 months* MACE: 3.7% vs 3.6%, *P*=0.75 CV mortality: 2.1% vs 1.1%, *P*=0.28 MI (non-fatal): 0.5% vs 0.6%, *P*=0.97 Stroke: 1.1% vs 1.8%, *P*=0.60 GI event: 0% vs 2.0%, *P*=0.06 Patients on either clopidogrel or ticlopidine *PPI (n=331) vs no-PPI (n=939) @ 18 months* MACE: 3.3% vs 3.4%, *P*=0.58 CV mortality: 1.5% vs 1.2%, *P*=0.43 MI (non-fatal): 0.9% vs 0.5%, *P*=0.24 Stroke: 0.9% vs 1.7%, *P*=0.51 GI event: 0.3% vs 1.8%, *P*=0.08	• "…PPIs had no increased risk of adverse clinical events after stent implantation."[20] Page 77
Schmidt, 2012[2]	
PPI (n=1,600) vs no-PPI (n=10,259) @ 12 months MACE: 8.6% vs 6.6%; adjusted HR=1.40 (CI 1.17 to 1.68), *P*=0.19 * 86.4% of patients were on aspirin; 45% were on clopidogrel at follow-up	• "Use of PPIs individually or as a class did not modify the protective effect of clopidogrel substantially. However, PPIs use was associated with an increased rate of MACE itself, particularly among longer-term users."[2] Page 171-171
Banerjee, 2011[23]	
PPI (n=867) vs no-PPI (n=3,678) @ 12 months MACE: 73.9% vs 68.9%, HR=1.18 (CI 1.05 to 1.31), *P*=NR Mortality: 26.8% vs 21.4%, HR=1.37 (CI 1.03 to 1.82), *P*=NR Repeat revascularization: 49.5% vs 44.1%,	• "In the post-PCI period, the hazards of mortality and MACE were significantly elevated with concomitant PPI use…"[23] Page 876

Table A3: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
HR=1.11 (CI 0.95 to 1.29), *P*=NR * Did not include combined mortality and MI outcome in this report	
Harjai, 2011[22]	
*PPI (n=707) vs no-PPI (n=1,897) @ 6 months** MACE: adjusted HR=0.89 (CI 0.63 to 1.27), *P*=0.40 Mortality: adjusted HR=0.95 (CI 0.56 to 1.63), *P*=0.86 MI: adjusted HR=1.04 (CI 0.64 to 1.69), *P*=0.89 ST: adjusted HR=1.32 (CI 0.67 to 2.58), *P*=0.42 TVR: adjusted HR=0.74 (CI 0.42 to 1.29), *P*=0.28 Major or minor bleeding: adjusted HR=0.67 (CI 0.31 to 1.47), *P*=0.32 * Did not include net adverse clinical events, combined mortality and MI, and TIMI in this report. Forty nine patients were lost to f/u. Analysis involving propensity-score matched pairs was not included	• "We found that use of PPI agents in conjunction with clopidogrel and aspirin was not associated with worse CV outcomes after PCI."[22] Page 167
Rossini, 2011[3]	
PPI (n=1158) vs no-PPI (n=170) @ 12 months MACE: 7.5% vs 5.0%, *P*=0.27; adjusted HR=1.54 (CI 0.60 to 4.02), *P*=0.382 All-cause mortality: 2.1% vs 3.1%, *P*=0.39; adjusted HR=0.97 (CI 0.28 to 3.31), *P*=0.961 ST: 2.2% vs 1.2%, *P*=0.56; adjusted HR=1.01 (CI 0.23 to 4.47), *P*=0.998 Major bleeding: 3.3% vs 2.4%, *P*=0.52; adjusted HR=1.51 (CI 0.40 to 5.03), *P*=0.500 Minor bleeding: 5.4% vs 5.3%, *P*=0.97; adjusted HR=0.89 (CI 0.41 to 1.92), *P*=0.765	• "… concomitant use of clopidogrel and PPI was not associated with an increased risk of MACE, death, and ST. Of note, no significant clinical interaction between PPIs and clopidogrel was found […] except for [patients] with chronic kidney disease."[3] Page 202
Evanchan, 2010[29]	
PPI (n=1,369) vs no-PPI (n=4,425) @ 12 months Readmission for AMI: 26% vs 16%, *P*=NR; adjusted OR 1.78 (CI 1.55 to 2.07), *P*=NR	• "… findings suggest that concomitant therapy with clopidogrel and PPIs, particularly pantoprazole and esomeprazole, may increase the risk of recurrent AMI within 1 year."[29] Page 171
Gupta, 2010[28]	
PPI (n=72) vs no-PPI (n=243) @ 48 months MACE: 56% vs 38%, *P*=0.025; adjusted OR=1.95 (CI 1.09 to 3.49) Mortality: 19% vs 14%, *P*=0.66; adjusted	• "… concomitant use of clopidogrel and PPIs among patients following percutaneous coronary revascularization is associated with higher risk of CV events compared to patients who are

Table A3: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
OR=1.20 (CI 0.53 to 2.70) TLR: 29% vs 22%, *P*=0.18; adjusted OR=1.57 (CI 0.80 to 3.03) TVF: 42% vs 29%, *P*=0.18; adjusted OR=1.51 (CI 0.82 to 2.77)	discharged on clopidogrel alone."[28] Page 1968
Kreutz, 2010[27]	
PPI (n=6,828) vs no-PPI (n=9,862) @ 12 months MACE: 25% vs 17.9%; adjusted HR=1.51 (CI 1.39 to 1.64), *P*<0.0001 CV mortality: 0.3% vs 0.2%; adjusted HR=1.10 (0.51 to 2.40), *P*=0.8041 MI: 7.0% vs 4.8%; adjusted HR=1.63 (1.40 to 1.90), *P*<0.0001 Unstable angina: 12.3% vs 6.6%; adjusted HR=1.86 (1.64 to 2.11), *P*<0.0001 Stroke or ischemic attack: 2.1% vs 1.1%; adjusted HR=1.48 (1.08 to 2.01) *P*=0.0135 Coronary revascularization: 16.2% vs 13.3%; adjusted HR=1.35 (1.22 to 1.50), *P*<0.0001 GI bleeding: 1.0% vs 0.08%, *P*<0.001	• "…concomitant use of a PPI with clopidogrel after coronary stent placement is associated with an increased risk of subsequent hospitalization for a MACE over 12 months."[27] Page 795
Ray, 2010[21]	
*PPI (n=5254, PY=7688) vs no-PPI (n=8712, PY=9621) @ 12 months** MACE: HR=0.94 (CI 0.69 to 1.29), *P*=NR Gastroduodenal bleeding: 8.2% vs 12.2%; adjusted HR=0.50 (CI 0.39 to 0.65) * Excluded patients tx'd without stents	• "Concurrent PPI use was not associated with a statistically significant increased risk of serious cardiovascular disease, either for the entire cohort or for patients having a PCI with stenting."[21] Page 7
Sarafoff, 2010[26]	
PPI (n=698) vs no-PPI (n=2,640) 30 days All-cause mortality: 2.6% vs 0.9%; HR=3.0 (CI 1.6 to 5.5), *P*<0.001; adjusted HR=2.2 (CI 1.1 to 4.3), *P*=0.02 MI: 3.0% vs 2.0%, HR=1.5 (CI 0.9 to 2.5), *P*=0.11; adjusted HR=1.3 (CI 0.8 to 2.3), *P*=0.30 ST (definite or probably): 1.4% vs 0.8%, HR=1.9 (CI 0.9 to 4.1), *P*=0.09; adjusted HR=1.5 (CI 0.7 to 3.5), *P*=0.29 Major bleeding: 2.7% vs 0.7%, HR=4.0 (CI 2.1 to 7.7), *P*<0.001; adjusted HR=3.3 (CI 1.7 to 6.7), *P*<0.001	• "Concomitant tx with a PPI in patients receiving DAPT after drug-eluting coronary stents is not an independent predictor of ST. Mortality rates were higher in patients tx'd with PPIs but as these patients were at a higher risk at baseline, confounding is likely."[26] Page 631
Tentzeris, 2010[25]	
PPI (n=691) vs no-PPI (n=519) @ 12 months MACE: 3.3% vs 2.7%; HR=1.14 (CI 0.59 to 2.21) *P*=0.70	• "…long-term administration of PPIs together with DAPT was not associated with an increased risk of clinical outcome

Table A3: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
All-cause mortality: 2.2% vs 2.1%, HR=0.92 (CI 0.42 to 1.99), *P*=0.82; adjusted HR=0.78 (CI 0.34 to 1.76), *P*=0.54 CV mortality: 1.2% vs 1.9%; HR=0.54 (CI 0.21 to 1.38) *P*=0.19; adjusted HR=0.54 (CI 0.21 to 1.38), *P*=0.19 ACS (re-hospitalization): 0.9% vs 0.6%, HR=1.42 (CI 0.36 to 5.7), *P*=0.61; adjusted HR=1.28 (CI 0.29 to 5.7), *P*=0.75 ST (definite): 0.9% vs 0.4%, *P*=0.41; HR=2.19 (CI 0.44 to 10.87), *P*=0.33; adjusted HR=2.56(CI 0.49 to 13.2), *P*=0.26	parameters…"[25] Page 1216
Yasu, 2010[24]	
*PPI (n=103) vs no-PPI (n=188) @ 12 months** MACE: 8.7% vs 6.9%; HR=1.28 (CI 0.54 to 3.00), *P*=0.56 CV mortality: 0% vs 1.1%, *P*=NR; HR=NR ST: 1.0% vs 0.5%, *P*=NR; HR=NR TLR: 6.8% vs 5.3%, *P*=NR; HR=NR *PPI (n=103) vs no-PPI (n=199) @ 12 months* GI bleeding: 3.9% vs 8.0%, *P*=0.17; adjusted HR=0.47 (CI 0.15 to 1.42), *P*=0.18 * Rabeprazole was temporarily used in 11 patients in the no-PPI group therefore these patients were excluded from the analyses except for GI bleeding	• "…in patients receiving DAPT after DES implantation, the clinical effect of rabeprazole to prevent GI bleeding is limited. The additional administration of rabeprazole in these patients does not increase the incidence of MACE including ST."[24] Page 1748
Zairis, 2010[31]	
*PPI (n=340) vs no-PPI (n=248) @ 12 months** MACE: 10% vs 9.7%; HR=1.1 (CI 0.6 to 1.8), *P*=0.89 CV mortality: 3.5% vs 3.2%; HR=1.1 (CI 0.4 to 2.7), *P*=0.84 MI (non-fatal, re-hospitalization): 6.5% vs 6.5%; HR=1 (CI 0.5 to 1.9), *P*=0.99 ST: 8.8% vs 8.5%; HR=1.1 (CI 0.7 to 1.8) Revascularization: 9.4% vs 8.9%; HR=1 (CI 0.6 to 1.9), *P*=0.82 * HR values were not specified as adjusted but patient groups were matched and differences were reported following Cox regression analysis	• "…treatment with omeprazole had no impact on the clinical effectiveness of clopidogrel drug tx during the first year after successful coronary stenting. While firm conclusions cannot be drawn due to the observational and retrospective design of the present study, it does provide preliminary evidence on little or no clinical relevance of the proposed omeprazole-clopidogrel interaction. Higher-powered studies are necessary to confirm that omeprazole has no clinical effect on patients concomitantly taking clopidogrel."[31] Page e57
Gaglia, 2010[30]	
PPI (n=318) vs no-PPI (n=502) @ 12 months (univariate survival analysis)	• "…PPI…was significantly associated with MACE at one year. This relation remained significant

Table A3: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
MACE: 13.8% vs 8.0%; HR=1.8 (CI 1.2 to 2.7), *P*=0.009; adjusted HR=1.8 (CI 1.1 to 2.7) *P*=0.01 All-cause mortality: 4.7% vs 1.8%, *P*=0.02; HR=NR ST: 0.9% vs 0.6%, *P*=0.68; HR=NR TVR: 9.2% vs 6.0%, *P*=0.08; HR=NR	after adjustment for traditional cardiac risk factors, as well as for baseline hematocrit and clopidogrel compliance."[30] Page 835

CABG = coronary artery by-pass graft; CI = confidence interval; CV = cardiovascular; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; F/u = follow up; GI = gastrointestinal; HR = hazard ratio; OR = odds ratio; TLR = target lesion revascularization; TVF = target vessel failure; TVR = target vessel revascularization; MACE = major adverse cardiovascular events; MI = myocardial infarction; NR = not reported; PPI = proton pump inhibitor; PY = patient year; ST = stent thrombosis; TIMI = thrombolysis in MI

APPENDIX 5: Additional References of Potential Interest

Updated mini-review

Juel J, Pareek M, Jensen SE. The clopidogrel-PPI interaction: An updated mini-review. Current Vascular Pharmacology. 2014;12(5):751-7

Reviews involving a single database

Lin E, Padmanabhan R, Moonis M. Antiplatelet agents and proton pump inhibitors - personalizing treatment. Pharmacogenomics and Personalized Medicine. 2010;3(1):101-9

Liu TJ, Jackevicius CA. Drug interaction between clopidogrel and proton pump inhibitors. Pharmacotherapy. 2010;30(3):275-89

Tran M, Tafreshi J, Pai RG. Combination of clopidogrel and proton pump inhibitors: Implications for clinicians. Journal of Cardiovascular Pharmacology and Therapeutics. 2010;15(4):326-37

Weber ZA, Rodgers PT. The clinical significance of the interaction between proton pump inhibitors and clopidogrel. J Pharm Technol. 2010;26(1):22-6

Mistry S, Trivedi H, Parmar D, Dalvi P, Jiyo C. Impact of proton pump inhibitors on efficacy of clopidogrel: Review of evidence. Indian J Pharmacol. 2011;43(2):183-6

Meta-analysis without quality assessment performed on included studies

Serbin MA, Guzauskas GF, Veenstra DL. Clopidogrel-Proton pump inhibitor Drug-Drug Interaction and Risk of Adverse Clinical Outcomes Among PCI-Treated ACS Patients: A Meta-analysis. J Manag Care Spec Pharm. 2016 Aug;22(8):939-47