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INTERACTION BETWEEN PROTON PUMP INHIBITORS AND CLOPIDOGREL

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Interaction between Proton Pump Inhibitors and Clopidogrel

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Dedication

This thesis is dedicated to my family and friends

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Abstract

Interaction between Proton Pump Inhibitors and Clopidogrel

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Introduction: Proton pump inhibitors (PPI) may impair the biotransformation of clopidogrel leading to increased major adverse cardiac events (MACE). Available studies have focused solely on patients receiving clopidogrel following a cardiac event. Given the widespread use of this combination, (about 64% in a recent study), this represents a major interaction that deserves further study. The objective of this thesis was to determine if the potential interaction between PPIs and clopidogrel leads to an increase in MACE in high-risk atherosclerotic patients receiving clopidogrel and PPIs as compared to clopidogrel alone.

Methods: We conducted a retrospective chart review of patients in the University Hospital System who received clopidogrel between January 1, 2007 and April 30, 2009. Patients were included if they were hospitalized for acute coronary syndromes, stroke/TIA, revascularization (coronary, cerebral or peripheral arteries), or aspirin

allergy. The primary outcome was the composite of myocardial infarction (MI), stroke/transient ischemic attack (TIA), coronary artery revascularization, or death (all cause) during the first year following discharge. Secondary outcomes included the composite of MI, stroke /TIA, revascularization (coronary, cerebral or peripheral arteries), or death. Bivariate analyses were conducted using Student's t test, Mann Whitney U and Chi-square tests where appropriate. Multivariate analysis was conducted to adjust for baseline differences.

Results: Overall, 1700 charts were reviewed and 572 patients met study criteria. The median follow-up was 332 days. The most common indication for clopidogrel use was coronary artery revascularization (66%). There were 201 patients in the clopidogrel with PPI group and 371 patients in the clopidogrel without PPI group. Baseline characteristics were evenly matched between both groups except for smoking, liver disease, and prior receipt of a PPI. The primary endpoint occurred in 21 patients in the clopidogrel with PPI group and 38 patients in the clopidogrel without PPI group (10% vs. 10%, p = 0.9, OR 1.02, 95% CI 0.58 – 1.80). The primary endpoint was unchanged after multivariate adjustments for baseline differences (adjusted OR 0.98, 95% CI 0.54 – 1.75). Likewise, there was no difference in the secondary endpoint (14% vs. 15%, p = 0.8, OR 1.02; 95% CI 0.58 – 1.80). The secondary endpoint was also unchanged after multivariate adjustments for baseline differences (adjusted OR 1.04, 95% CI (0.61 – 1.75)

Conclusion: Patients receiving clopidogrel with a PPI demonstrated similar rates of MACE when compared to patients receiving clopidogrel without a PPI.

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CHAPTER ONE

Introduction and Background

Atherosclerotic Coronary Heart Disease (CHD) caused about 1 in 6 deaths in the United States in 2006 thus making it the largest killer of American males and females. In 2009, the American Heart Association (AHA) estimated that approximately every 25 seconds, one person in the United States (US) suffered an acute coronary syndrome (ACS) event, with a fatal event occurring every minute.[1] AHA further estimated that there will be 785,000 new cases of ACS events in 2010 coupled with another 470,000 people experiencing a recurrent event.[1]

While CHD remains the predominant cause of death in the US, there has been a significant reduction in mortality rates over the past 30 years.[2] Impressively, the mortality rate from CHD has been halved over the past three decades. From 1980 to 2000, the age adjusted death rate from CHD in men fell from 542.9 to 266.8 deaths per 100,000.[2] In women, a similar reduction was achieved, from 263.3 to 134.4 deaths per 100,000.[2] Combined, the reductions have resulted in 341,745 fewer deaths.[2] The trend in mortality reduction has continued with an approximate 22% reduction in deaths noted between 1996 and 2006.[1]

Ford et. al. estimated that approximately 47% of the mortality reduction witnessed from 1980 to 2000 was related to improvements in medical treatment, of which antiplatelet therapy has been a major component.[2] Current guidelines for the management of atherosclerotic CHD therefore emphasize the use of antiplatelet agents for both primary and secondary prevention of cardiac related events and mortality.[3-6]

Platelets play an essential role in hemostasis and the repair of damaged endothelium. This is driven by their ability to adhere to damaged blood vessels and also accumulate at sites of injury.[7, 8] When an atherosclerotic artery plaque ruptures, it serves as a focal point for the aggregation of platelets and thrombus formation.[9] After the initial adhesion of platelets to the extracellular matrix, autocrine and paracrine mediators such as adenosine diphosphate (ADP), thrombin, epinephrine and thromboxane A_2 are released and they help increase and maintain the initial platelet response. Activated platelets also serve as a source of inflammatory mediators such as CD40 ligand, P-selectin and IL-1β.[7] While platelet activation is a normal physiologic response to endothelial injury, uncontrolled progression of the process can lead to thrombus formation, vascular occlusion, ischemia and infarction.[8]

Clopidogrel is a $P2Y_{12}$ inhibitor that blocks the interaction between ADP and platelets. It is indicated as part of a dual antiplatelet (DAT) regimen with aspirin or as an alternative antiplatelet agent to aspirin. The CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) study demonstrated the efficacy of a DAT regimen consisting of clopidogrel and aspirin in patients presenting with ACS without ST segment elevation.[10] In CURE, patients on DAT therapy had a significant 20% relative risk reduction in the combined endpoint of myocardial infarction (MI), stroke and cardiovascular (CV) death as shown in **Figure 1.1**. Furthermore, there is a consensus on the need for a prolonged DAT regimen of clopidogrel and aspirin in patients treated with coronary stents, especially after the use of drug eluting stents (DES), to prevent late in-stent thrombosis.[4]

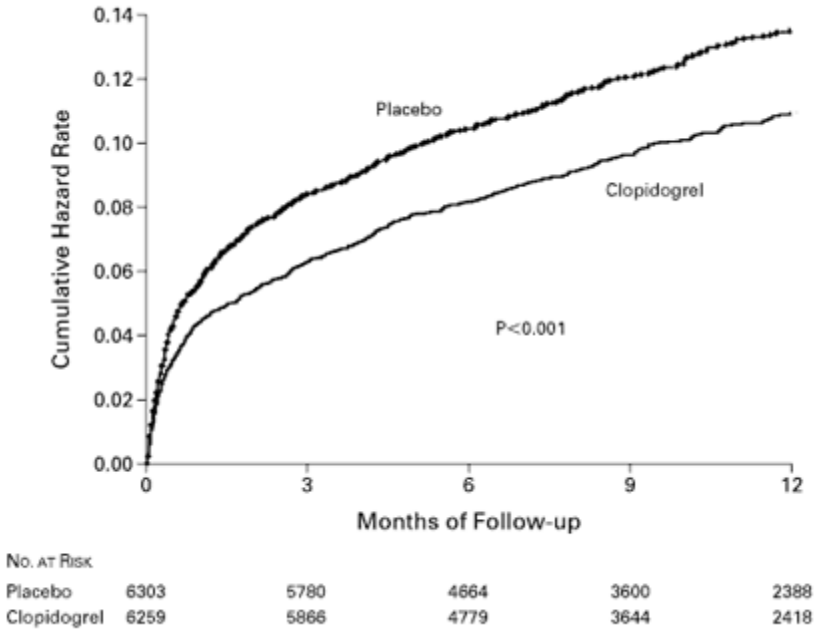


Figure 1.1: Death from CV causes, nonfatal MI or stroke in the CURE trial [10] ©2001 *Massachusetts Medical Society. All rights reserved.*

Clopidogrel, as an alternative to aspirin, reduces the combined endpoint of new ischemic stroke, new myocardial infarction (MI), and other vascular death in patients with a history of a recent MI, recent stroke, or established peripheral arterial disease. In the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) study, clopidogrel was associated with a significant relative risk reduction of 8.7% in risk of ischemic stroke, MI, or vascular death when compared to aspirin alone in patients with atherosclerosis in different vascular beds.[11] The reduction while significant in relative terms could be considered marginal in absolute terms (9.8% in the clopidogrel group vs. 10.6% in the aspirin group).[11] The reduction noted in CAPRIE must also be interpreted in the context of work done by the Antithrombotic Trialists' Collaboration (ATC) group. The ATC group conducted a meta-analysis of 287 studies to evaluate the benefits of

antiplatelet therapy in vascular disease. The study involved 135,000 patients at high risk of occlusive vascular disease who received antiplatelet therapy; mostly aspirin or control. The allocation of patients to antiplatelet therapy reduced the combined outcome of any serious vascular event by about one quarter; non-fatal MI was reduced by one third, non-fatal stroke by one quarter, and vascular mortality by one sixth. [12]

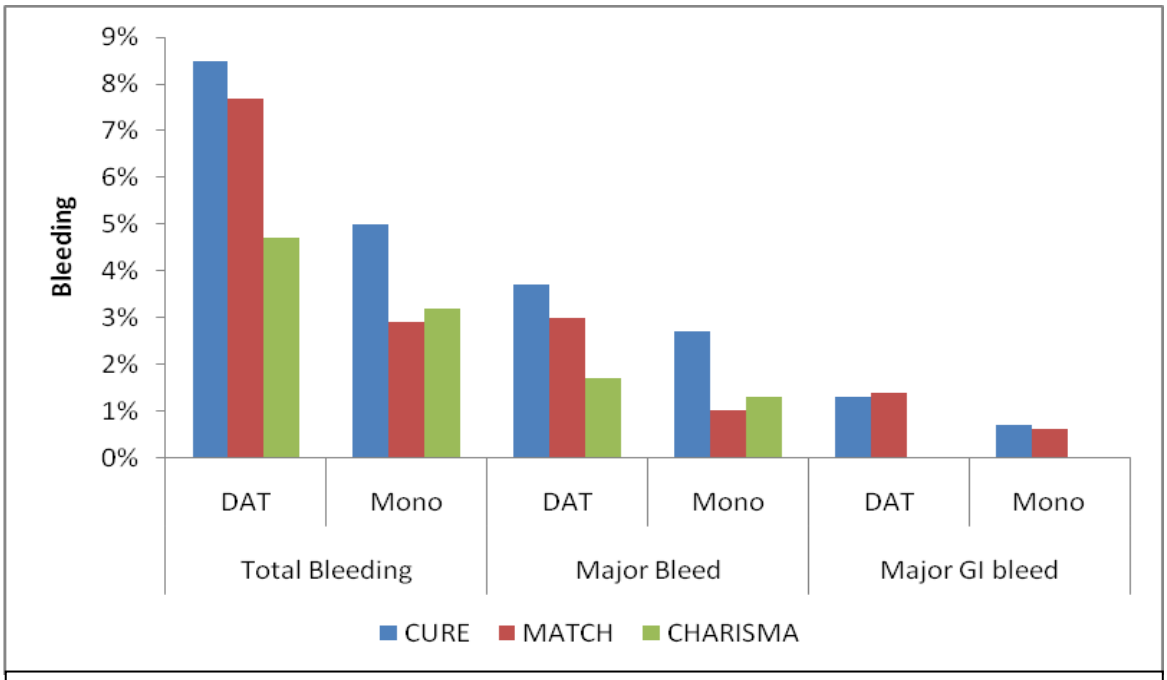
Clopidogrel use is associated with a significant bleeding risk. The gastrointestinal (GI) tract is the major site of the bleeding. In the CAPRIE study, 9.27% of patients on clopidogrel were reported to have had a bleeding episode with 1.99% representing GI bleeding, regardless of severity. The total bleeding rate was similar to that seen with aspirin therapy, although clopidogrel caused less GI bleeding (see **Table 1.1**).[11]

Table 1.1: Bleeding event rate in CAPRIE (n=19185)[11]

Type of bleeding	Clopidogrel (%)	Aspirin (%)	p-value
Any bleeding disorder			
• Any patient reporting	9.27	9.27	NS
• Severe	1.38	1.55	NS
Intracranial bleeding			
• Any patient reporting	0.35	0.49	NS
• Severe	0.31	0.43	NS
Gastrointestinal bleeding			
• Any patient reporting	1.99	2.66	<0.05
• Severe	0.49	0.71	<0.05

The overall bleeding risk, particularly the GI bleeding risk seen with clopidogrel, is further increased when it is combined with aspirin. In the CURE study, more patients in the DAT group had a major bleeding episode compared to the aspirin only group. The GI tract represented the most common site of major bleeding.[10] The increased risk of GI bleeding was further confirmed in the MATCH (Management of Atherosclerosis with

Clopidogrel in High-Risk patients) study, which compared the combination of clopidogrel and aspirin to clopidogrel alone for secondary prevention post transient ischemic attack (TIA) and/or stroke.[13] As shown in clinical trials, the increased total (and GI) bleeding risk seen with DAT is problematic for both low dose and full dose aspirin.[10, 13, 14] **Figure 1.2** illustrates the bleeding event rates reported in major trials of clopidogrel.



- CURE major bleed criteria: substantially disabling bleeding, intraocular bleeding leading to the loss of vision, or bleeding necessitating the transfusion of at least 2 units of blood
- CHARISMA GUSTO bleeding criteria: either intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention
- CHARISMA : Only severe and moderate bleeding rate reported for total bleeding
- MATCH life threatening bleeding criteria: fatal bleeding event; a drop in hemoglobin of ≥50 g/L; significant hypotension with need for inotropes [hemorrhagic shock]; symptomatic intracranial hemorrhage, or transfusion of ≥4 units of red-blood cells or equivalent amount of whole blood

Figure 1.2: Bleeding event rate in CURE,[10] CHARISMA,[14] and MATCH[13]

MECHANISM OF CLOPIDOGREL RELATED GI BLEEDING

Clopidogrel does not directly irritate the GI tract; however, its action as an antiplatelet agent leads to a disruption of the critical role played by platelets in hemostasis. Platelets play an essential role in the repair of damaged endothelium given their ability to adhere to damaged blood vessels and to accumulate at sites of injury.[7, 8] Platelets also promote the release of pro-angiogenic growth factors such as vascular endothelial growth factor, which promotes endothelial proliferation and accelerates the healing of ulcers.[15] Ultimately, the antiplatelet and anti-angiogenic effects of clopidogrel lead to impaired healing of gastric erosions or ulcers that develop as a result of other medications [commonly aspirin or other non-steroidal anti-inflammatory drugs (NSAIDS)], *Helicobacter pylori* infection, or other mechanisms.[15] The risk of GI hemorrhage is further increased in the presence of hydrochloric acid present in the stomach and duodenum.

PREVENTION OF CLOPIDOGREL RELATED GI BLEEDING

The American College of Cardiology Foundation/American College of Gastroenterologist/American Heart Association in 2008 released a clinical expert consensus document advocating for the use of proton pump inhibitors (PPI) as preferred agents for both prophylaxis and treatment of aspirin and clopidogrel associated GI injury.[15] In the consensus document, the use of DAT therapy was considered sufficient to warrant the initiation of PPIs to minimize GI bleeding. The recommendation was published as an expert consensus due to the limited evidence available for review. The recommendation for PPI use was based primarily on results from studies involving PPI

use in aspirin treated patients. The 2007 guidelines for unstable angina and non-ST elevation myocardial infarction (NSTEMI) also recommended the use of a PPI in patients with prior GI bleed who are placed on aspirin or clopidogrel or both.[5]

Recently, there have been reports of a potentially serious interaction between PPIs and clopidogrel leading to increased major adverse cardiac events (MACE).[16-18] Given the widespread use of PPI and clopidogrel, (a combination use rate of about 64% was reported in a recent study), this represents a major interaction that deserves further study.[17]

MECHANISM OF CLOPIDOGREL AND PPI INTERACTION

Clopidogrel is a pro-drug that undergoes a two-step biotransformation process into its active metabolite. When ingested, approximately 85% of the ingested dose is deactivated into the inactive carboxylic acid metabolite, SR26334, by esterases. The remaining 15% of the ingested dose is converted initially to 2-oxo-clopidogrel and finally to the active metabolite, R130964. This results in a limited amount of active metabolite being generated. This two-step biotransformation process is catalyzed by multiple cytochrome-p450 (CYP450) isotypes as shown in **Figure 1.3**.[19, 20]

The drug-drug interaction between PPIs and clopidogrel is believed to be related to CYP450 enzyme inhibition. This inhibition leads to a reduction in the amount of clopidogrel's active metabolite generated.[21] This is important as the degree of platelet inhibition by clopidogrel has been linked to the generation of its active metabolite, with more efficient generation leading to enhanced antiplatelet effect.[19, 22]

There is scant information available on the importance of individual CYP450 isotypes to the generation of the clopidogrel's active metabolite, R130964.[19, 23] Kazui et. al. investigated the contribution of individual CYP isoforms to the formation of 2-oxo-clopidogrel and R130964 using microsomes derived from β-lymphoblastoid cells expressing human CYP450 enzymes.[24] In the study, it was estimated that CYP2C19 was responsible for 45% of the generation of 2-oxo-clopidogrel and 21% of R130964. See **Table 1.2** for contribution of other CYP isotypes to clopidogrel's biotransformation. Genetic studies of patients with reduced function CYP2C19 allelles, showing increased incidence of adverse cardiac events, however, confirm the importance of CYP2C19.[25-27]

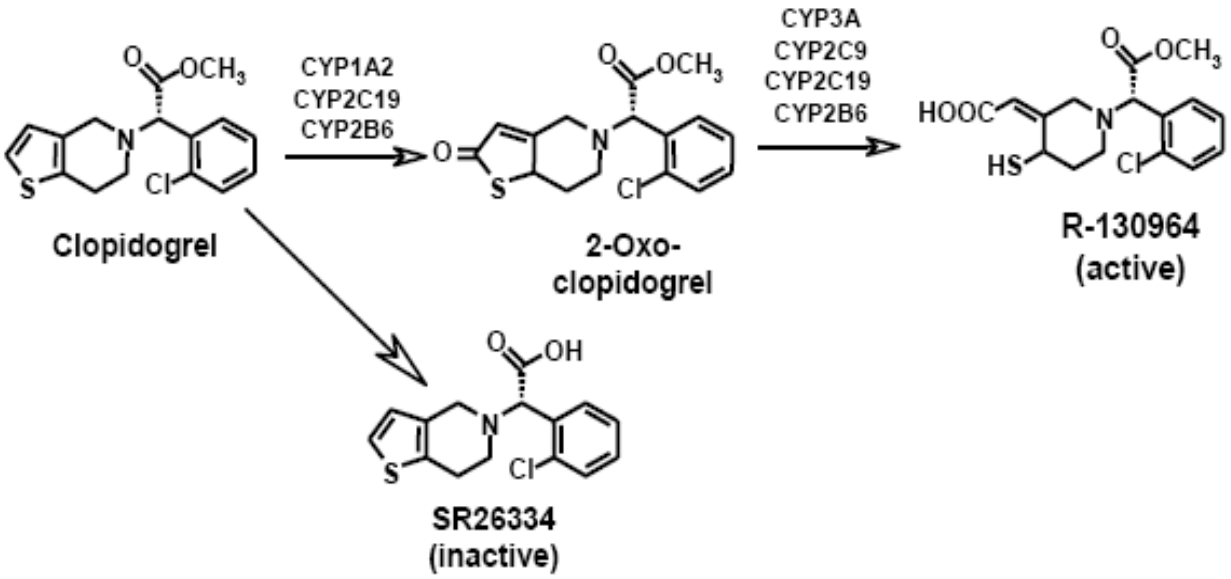


Figure 1.3: Biotransformation steps of clopidogrel. *Online supplement to Mega et. al.* [25]

Table 1.2: Estimated contribution of individual CYP isotypes in the biotransformation of clopidogrel[24]

CYP isotype	% estimated contribution to 2-oxo-clopidogrel generation[a]	% estimated contribution to R130964[b] generation[c]
1A1	ND	ND
1A2	35.8	ND
2A6	ND	ND
2B6	19.4	32.9
2C8	ND	ND
2C9	ND	6.76
2C19	44.9	20.6
2D6	ND	ND
2E1	ND	ND
3A4	ND	39.8
4A11	ND	ND

[a,c] contribution ratio determined using

$$f_{,mP450}\ (\%) = \frac{CL_{int,\ expressed\ P450}\ \text{for each P450 reaction}}{\sum CL_{int,\ expressed\ P450}}$$

where CL_{int} is the interaction ratio

[b] active metabolite of clopidogrel

ND not detected

All currently available PPIs are metabolized in the liver by CYP2C19 and CYP3A4 enzymes to varying extent. Using CY2C19 enzymes present in human liver microsomes (HLM), derived from human liver samples, it has been shown that PPIs exhibit competitive inhibition of the CYP2C19 enzyme with varying intensity in-vitro.[28] Li et. al. using HLM, demonstrated that lansoprazole had the highest inhibitory activity on CYP2C19 with K_i values of around 0.45μM, followed by omeprazole, esomeprazole, rabeprazole and then pantoprazole. The complete K_i values are listed in **Table 1.3**.

Interestingly, the thioether product formed by the non-enzymatic catalytic degradation of rabeprazole, rabeprazole thioether exhibited CYP2C19 inhibitory activity with K_i values of 2.4 μM.[28] Information on CYP2C19 inhibitory activity of dexlansoprazole, the R-enantiomer of lansoprazole, is not available yet, but is probably similar to that seen with lansoprazole.

Table 1.3: Enzyme inhibition of CYP2C19 using human liver microsomes (HLM) and recombinant CYP2C19[28]

PPI	K_i (μM)[f]		Model Inhibitor
	HLM[a]	rCYP2C19[b,e]	
omeprazole	6.2±0.8	2.4±0.05	Ticlopidine HLM =0.31±0.05 rCYP2C19 =0.68±0.04
rabeprazole	21.3±2.8 (2.4±0.1)[c]	18.8±1.3 (2.8± 0.1)[d]	
esomeprazole	8.6±1.0	7.9±0.5	
lansoprazole	0.45±0.07	0.74±0.09	
pantoprazole	69.4±9.2	15.3±1.1	
dexlansoprazole	-	-	

[a,b] marker reaction used was S-Mephenytoin 4-Hydroxylation
[c,d] rabeprazole thioether
[e] recombinant CYP2C19
[f] The lower the K_i, the stronger the inhibition

EFFECTS OF INTERACTION ON PLATELET FUNCTION

The earliest report of a possible drug interaction between clopidogrel and PPI leading to diminished response to clopidogrel was a study conducted by Gilard et. al. in 2006.[29] The study investigated the antiplatelet efficacy of clopidogrel as measured by vasodilator-stimulated phosphoprotein (VASP) phosphorylation when taken with other

commonly used medications. VASP phosphorylation provides an index of platelet reactivity to clopidogrel; a high index corresponds with poor response to clopidogrel. In the study, 105 consecutive patients receiving aspirin and clopidogrel dual therapy post-coronary angioplasty, had their platelet response analyzed for possible drug interactions between clopidogrel and statins, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, PPI or beta blockers. No significant differences in platelet reactivity were found except for PPI users, who had significantly higher VASP platelet reactivity index values than non-users [61.4 ± 23.2 (n=24) vs. 49.5±16.3 (n=81), p=0.007]. The results of this observational study were reported as a letter to the editor and served as a background for a randomized study conducted by the same investigators.

The OCLA (Omeprazole Clopidogrel Aspirin) study was a randomized double-blind placebo-controlled study that was designed to assess the influence of omeprazole on clopidogrel's efficacy as measured by VASP phosphorylation expressed as a platelet reactivity index (PRI).[16] In the trial, 124 patients undergoing coronary artery stenting received aspirin (75 mg daily) and clopidogrel (loading dose of 300mg followed by 75mg daily), and were then randomized to omeprazole (20 mg daily) or placebo for 7 days. Key exclusion criteria were previous treatment with clopidogrel or PPI, history of thrombocytopenia (platelets <150,000), or gastrointestinal ulcer. The primary outcome of the study was the PRI at day 7 in the treatment groups. At day 7, the mean PRI in the omeprazole group was significantly higher than the placebo group (51.4% vs. 39.8%, p<0.0001). A significantly greater proportion of patients were also classified as clopidogrel non-responders (PRI >50%) in the omeprazole group compared to the placebo group (60.9% vs. 26.7%, p<0.0001). The relatively short duration of the study,

lack of clinical endpoints and non-exclusion of clopidogrel non-responders at baseline were limitations of this study. However, the results cannot be entirely discounted as PRI values obtained from VASP tests have been shown to be predictive of post-procedural MACE events in patients undergoing percutaneous coronary intervention (PCI).[30]

Siller-Matula et. al. conducted a similar study in 300 patients undergoing PCI using esomeprazole and pantoprazole as the PPI agents.[31] PRI using VASP assay and ADP-induced aggregometry were assessed using blood samples obtained in the catheterization laboratory immediately after PCI. Patients were included in the analysis if they had been on clopidogrel (75mg daily) and aspirin (100mg daily) for at least 5 days before PCI. There was no statistically significant difference found in PRI between patients on pantoprazole (PRI = 50%, n=152), esomeprazole (PRI = 54%, n=74) or without PPI (PRI = 49%, n=74). This was a non-randomized study and confounders could not be entirely eliminated although the authors adjusted for several variables using a multivariable logistic regression model. Genetic information was also not available.

In a cross-sectional observational study of a 1000 patients undergoing coronary angiography on maintenance DAT with clopidogrel and aspirin for a prior PCI, Sibling et al. investigated the effects of pantoprazole (n=162), omeprazole (n=64) and esomeprazole (n=42) on ADP-induced platelet aggregation as measured using multiple electrode platelet aggregometry (MEA).[32] Platelet function testing was performed using blood samples obtained upon patient admission to the hospital. Aggregation measured by MEA was quantified as AU and area under the curve of arbitrary units (AU*min). The primary endpoint for the study was ADP-induced platelet aggregation (in AU*min) in patients with concomitant pantoprazole treatment versus patients without PPI treatment.

There was no difference in ADP-induced platelet aggregation in patients treated with pantoprazole compared to patients without PPI treatment [226.0 (150-401.5) vs. 220 (143.8-388.8) AU*min, p=0.69]. A significant increase in ADP-induced platelet aggregation was found in the omeprazole group [295.5 (193.5-571.2) AU*min].

Cuisset et al. also conducted a randomized study of PPI use in clopidogrel treated patients with similar results to those reported by Siller-Matula et. al. and Sibbling et. al..[33] The study further confirmed that not all PPIs interact with clopidogrel to the same degree. In the study, omeprazole was compared to pantoprazole in clopidogrel treated patients. The study was conducted in 104 patients who presented with a non-ST segment elevation ACS, and had undergone successful coronary stenting. The primary outcome was PRI measured using VASP at 1 month following hospital discharge. Baseline blood draw was done between 12 and 24 hours following the receipt of a loading dose of clopidogrel and aspirin (600mg clopidogrel LD and 250mg aspirin LD). Patients were randomized in a 1:1 fashion to either omeprazole 20mg or pantoprazole 20mg on a background of clopidogrel 150mg and aspirin 75mg daily. At baseline, PRI was not significantly different between omeprazole and pantoprazole treated patients (35±21% vs. 30±21%, p =0.36). However, after 1 month of PPI treatment, patients randomized to pantoprazole had a significantly better response to therapy (36±20% vs. 48±17%, p =0.007). Using PRI >50% as a marker of clopidogrel non-response, significantly more patients were classified as non-responders in the omeprazole group (44% vs. 23%, OR 2.6, 95%CI: 1.2-6.2; p=0.04).

EFFECT OF INTERACTION ON CLINICAL OUTCOMES

There have been several retrospective case-controls and cohort studies published about the interaction suggesting a clinically significant interaction exists between PPIs and clopidogrel.[17, 18, 34-36] Following the release of the OCLA study, Aetna, the insurance company, reviewed its large medical and pharmacy databases for acute MI rates in members who received clopidogrel with or without concurrent PPI therapy.[34] Members (n= 1010) were assigned into three groups based on PPI exposure: (1) those without evidence of PPI use were assigned to the control group, n=384 (2) members with less than 182 days' supply of PPI were assigned to the low PPI exposure group, n=90, and (3) members who received more than 182 days' supply of PPI were assigned to the high PPI exposure group, n=536. The 1-year MI rate increased based on exposure to PPI (1.38 % in the control vs. 3.08 % in the low exposure group vs. 5.03 % in the high exposure group). Using the MI incidence rate in the control group as the expected MI rate; there was a statistically significant difference between the control and the high exposure group. When adjusted for comorbidities (hypertension, ischemic heart disease, heart failure, hyperlipidemia and diabetes) the differences in MI rate remained significant between the control and high-exposure groups (2.60 % vs. 11.38%, $p < 0.05$). Interpretation of the results of this study, while important, is limited due to the retrospective nature of the analysis and the inherent limitations in database studies. There was also no indication of the specific PPI agent used by patients in the database.

Aubert et. al. conducted a similar retrospective medical and pharmacy claims review, also revealing a higher incidence of MACE in patients taking clopidogrel and a PPI.[35] The study was conducted using data from the Medco insurance company, as

contained in their National Medco Integrated Database. In the study, The Clopidogrel Medco Outcomes Study, 14383 patients who underwent stent placement during a one year period and were started on clopidogrel at the time of stent placement were followed for the incidence of hospitalization for stroke, MI, angina or coronary artery bypass graft (CABG) following the stent placement. In patients with no preceding cardiovascular (CV) events, the 1 year incidence of MACE was significantly higher in patients who received clopidogrel and PPI than patients who received clopidogrel alone (32.5% vs. 21.2%, adjusted OR 1.79, CI 1.62 – 1.97). The difference was greater in patients who had a prior CV event (39.8% vs. 26.2%, adjusted OR 1.86, CI 1.63 – 2.12).

Juurlink et al. conducted another study demonstrating an interaction between PPI and clopidogrel.[18] This was a population-based nested case-control study among Ontario, Canada residents aged 66 years and older. They investigated the rates of repeat hospitalization in patients who started clopidogrel following discharge for an acute MI. A cohort of patients was established that included patients who filled a prescription for clopidogrel within 3 days after hospitalization for an acute MI and were not on PPI therapy 90 days before the index date. Cases were defined as patients who died or were readmitted for a MI within 90 days of initial hospital discharge and were matched to controls based on age, receipt of PCI, date of discharge and predicted probability of short-term mortality. Extensive multivariate adjustments were made to account for baseline differences. A significant association between readmission because of MI and current use of PPI was found (adjusted OR 1.27, 95% CI 1.03–1.57). In stratified analysis based on the type of PPI used, pantoprazole use was not associated with recurrent MI when given concomitantly with clopidogrel (OR 1.02, 95% CI 0.70–1.47). The authors

further estimated that concomitant treatment with a CYP2C19-inhibiting PPI and clopidogrel following MI, was responsible for 7.4 % of readmissions due to re-infarction within 90 days (using point estimate of adjusted OR of 1.40 as an approximation of the relative risk and exposure estimate of 0.2 for any of omeprazole, lansoprazole, or rabeprazole).

Ho et al. also investigated the clinical significance of the interaction using data collected from the Veterans Health Administration (VHA) Cardiac Care Follow-up study.[17] In this retrospective cohort study of VHA hospitals, all cause mortality or rehospitalization for ACS was compared between patients who received clopidogrel with or without a PPI after hospitalization for ACS. A total of 8205 patients were identified who received clopidogrel after discharge, more than half (63.9%) were prescribed a PPI at discharge, follow-up, or both. The primary composite endpoint, death or rehospitalization for ACS, occurred more often in patients taking clopidogrel with a PPI (29.8% vs. 20.8%, adjusted OR 1.25, 95% CI 1.11–1.41). The rates of recurrent hospitalization for ACS (14.6 % vs. 6.9%, $p<0.001$), revascularization procedures (15.5% vs. 11.9%, $p<0.001$), and death (19.9 % vs. 16.6 %, $p<0.001$) were also higher among patients taking clopidogrel and a PPI. The increased rates for recurrent hospitalization for ACS and revascularization remained significant after multivariable adjustments for baseline differences; however, the rate of all-cause mortality was not significant. It is important to note, that majority of the subjects in the study received omeprazole (59.7%) while the remainder were on rabeprazole (2.9%), pantoprazole (0.4%), lansoprazole (0.2%) and a combination of more than 1 type of PPI (36.7%).

In a further analysis of the National Medco Integrated Database, Stanek et al. investigated the effect of individual PPI agents on major adverse cardiac events (MACE) in patients receiving clopidogrel post-stent placement.[36] They identified almost 17000 patients who received clopidogrel within the first month after stent placement and continued for at least 12 months. Patients were separated into a no PPI group (n=9862) and a PPI group (n=6828). Patients in the PPI group received esomeprazole (n=3257), omeprazole (n=2307), pantoprazole (n=1653), lansoprazole (n=785) or rabeprazole (n-298). Patients in the PPI cohort were older, more likely to have had a prior cardiovascular event, heart failure, diabetes and hypertension ($p<0.01$ for all). The use of PPI with clopidogrel was associated with increased MACE (25.1% vs. 17.9%, HR 1.51, 95% CI 1.39–1.64) and the effect was consistent across different sub groups. Data were adequate to stratify the incidence of MACE by use of pantoprazole (29.2%, HR 1.61 95% CI 1.44–1.81), omeprazole (25.1%, HR 1.39, 95% CI 1.22–1.57), esomeprazole (24.9%, HR 1.57, 95% CI 1.40–1.76), and lansoprazole (24.3%, HR 1.39, 95% CI 1.16–1.67). The results of this study contradict earlier mechanistic and platelet function tests conducted showing a lower likelihood of interaction between pantoprazole and clopidogrel. Even more importantly, the findings also contradict the results from the study conducted by Juurlink et. al. where pantoprazole was shown not to have any effect on 90 day rehospitalization rates for MI.

Not all studies have shown an interaction between clopidogrel and PPI. In an abstract presented at the 2008 AHA Scientific Sessions, the investigators of the CREDO (Clopidogrel for the Reduction of Events during Observation) study re-analyzed the trial data to assess the effect of PPIs on 28-day and 1-year composite endpoints in patients

receiving clopidogrel following PCI.[37] The trial was originally designed to compare the 28 day rate of MI, death, and urgent target vessel revascularization (MI/Death/UTVR) and 1 year rate of death, MI, and stroke (Death/MI/Stroke) in patients receiving clopidogrel for 1 month compared to patients receiving clopidogrel for 1 year in addition to daily aspirin. Clopidogrel reduced adverse effects at 1 year to an approximately similar degree regardless of the use of PPI. The use of a PPI was however independently associated with increased 28 day MI/Death/UTVR (HR 1.6, 95% CI 1.08–2.5) and 1 year Death/MI/Stroke (HR 1.5, 95% CI 1.1–2.1) endpoints in the overall trial population.

In another study published by Simon et al., the use of PPI also had no effect on clopidogrel's clinical effectiveness.[27] The study was designed to determine the clinical effect of genetic polymorphisms in patients taking clopidogrel following a MI. Patients carrying CYP2C19 loss-of-function alleles had a higher rate of subsequent cardiovascular events (death, nonfatal MI, and stroke) than patients without the alleles and the patients carrying two of the reduced function allele had worse outcomes compared to patients with one or none. The use of a PPI however had no statistically significant effect beyond the pharmacogenomic effect noted with carriers of the reduced function CYP2C19 alleles. Both studies, the CREDO reanalysis and the study by Simon et. al, were not designed primarily to determine the impact of PPI on clopidogrel's clinical effectiveness as such important information such as compliance and type of PPI agent used were lacking.

At the 2009 European Society of Cardiologists meeting in Barcelona, Spain, the investigators of the TRITON-TIMI 38 (Trial to assess improvement in therapeutic outcomes by optimizing platelet Inhibition with prasugrel-Thrombolysis In Myocardial

Infarction 38) trial (n=13 608), presented the results of a post-hoc analysis based on the use of PPIs.[38] The trial was designed initially to compare prasugrel to clopidogrel in patients with ACS managed invasively. In the study, 33% of the patients were on PPI at baseline with majority being on pantoprazole (n=1844) and omeprazole (n=1675). The use of PPI did not adversely affect the primary efficacy endpoint (composite cardiovascular death, myocardial infarction or stroke) of clopidogrel or prasugrel in the analysis (clopidogrel – adjusted HR 0·94, 95% CI 0·80–1·11 or prasugrel – adjusted HR 1·00, 95% CI 0·84–1·20). Given that information on use of PPI was collected at follow-up only, the investigators conducted multiple sensitivity analyses based on different time points and varying durations of follow-up with no interaction found. The results were similar in the few patients on whom genetic information was available; either with a reduced function CYP2C19 allele or the wildtype.

There are no prospective randomized control trials (RCT) assessing the clinical impact of any interaction between PPI and clopidogrel published to date. However, at the 2009 Transcatheter Cardiovascular Therapeutics (TCT) meeting, the preliminary results from COGENT-1(Clopidogrel and the Optimization of Gastrointestinal Events) were presented.[39] The COGENT-1 study was discontinued prematurely in January 2009 due to funding related problems. [40] The trial was an international, double-blind, phase 3 efficacy study designed to compare CGT-2168, a combination pill of clopidogrel 75mg and omeprazole 20mg, against clopidogrel in a randomized fashion in patients also taking aspirin. The primary outcome of the study was the efficacy of the combination pill in reducing gastrointestinal events; however a key secondary endpoint was the incidence of MACE (defined as composite cardiovascular death, non-fatal MI, CABG/PCI or ischemic

stroke) occurring in both groups. An estimated 5000 patients were to be recruited into the event driven study; at termination ~3600 patients were available for analysis with 105 adjudicated gastrointestinal (GI) events (143 GI events had been planned). Median follow-up was 133 days (maximum of 362 days) with 136 adjudicated cardiovascular events. At baseline, the majority of patients had a history of ACS or MI with no significant differences between the study groups.

There was no difference in the incidence of composite cardiovascular death, non-fatal MI, CABG/PCI or ischemic stroke between the CGT-2168 group and placebo group (HR 1.02, 95% CI 0.70–1.51), or in the MI rate between the groups (HR 0.96, 95% CI 0.59–1.56). A significant reduction in GI events was noted in the active treatment group providing the first randomized evidence of the efficacy of prophylaxis with PPI in clopidogrel treated patient (HR 0.55, 95% CI 0.36–0.85). The preliminary results presented offer some reassurance that the interaction between clopidogrel and PPI has no clinical importance however, the results have some significant limitations.

COGENT was not powered to detect a difference in the incidence of MACE and was terminated early leading to a median follow-up of just 133 days. The results of the Aetna analysis, suggest the interaction maybe more apparent in patients with high exposure to PPI (defined as >182 days). CGT-2168 was a special formulation which might not provide the same pharmacokinetics or pharmacodynamics as taking clopidogrel or omeprazole separately. Perhaps most important to note is that the results presented are preliminary and the complete methodology or results of the trial have not been presented yet.

CONCLUSION

There is strong mechanistic data to suggest an interaction exists between clopidogrel l and PPIs, particularly omeprazole, through competitive inhibition of CYP2C19. While there might be an attenuation of the antiplatelet effect of clopidogrel as measured using platelet function studies, the clinical importance is unknown. Studies conducted to assess the clinical significance have reached conflicting conclusions about the importance of the interaction on cardiovascular outcomes.

The studies available can be classified into four groups based on the source of data: (1) administrative/insurance databases; (2) post-hoc analysis of randomized studies, (3) prospective study; and (4) retrospective chart reviews. Studies using insurance or administrative databases as seen in the Aetna, Medco and Canadian studies have suggested the most risk of harm with the combination of clopidogrel and proton pump inhibitors. Post-hoc analyses of studies such as TRITON and CREDO suggest no harm. The only randomized trial to investigate the interaction showed no difference in clinical outcomes in clopidogrel treated patients who received omeprazole however; the study was terminated early due to funding issues. The preliminary results provide some reassurance that the interaction is not clinically significant.

THESIS RATIONALE

The studies completed and available for review to date have focused mainly on patients with coronary artery disease as evidenced by an ACS event, or need for coronary artery stenting. The studies have not included the full complement of patients requiring clopidogrel, most importantly excluding patients with cerebrovascular events, and symptomatic peripheral vascular disease. There is no study to our knowledge that has

included a high-risk atherosclerotic patient population similar to the current FDA approved indication for clopidogrel. The omission of such patients is an important gap in the current body of knowledge about the interaction.

CHAPTER TWO

Methodology

OBJECTIVE

The objective of this study was to determine if the pharmacodynamic drug interaction that exists between PPIs and clopidogrel led to an increase in major adverse cardiac events (MACE) in high-risk atherosclerotic patients receiving clopidogrel and PPIs as compared to clopidogrel only. MACE was defined as death, MI, stroke, transient ischemic attack (TIA) or coronary artery revascularization.

STUDY DESIGN

This single-center, retrospective, observational study was performed at the University Health System in San Antonio, Texas. The study received approval from the University of Texas Health Science Center San Antonio Institutional Review Board and the University Health System (UHS) Research Department.

STUDY PARTICIPANTS

Patients were selected if they were started on clopidogrel between January 1, 2007 and April 30, 2009 for a qualifying event with a one-year follow-up to assess for the incidence of MACE. Qualifying events were hospitalization for ACS, stroke, TIA, elective coronary artery stenting, vascular intervention (lower extremity stenting, carotid stenting and renal artery stenting), CABG, or aspirin allergy. Patients were also included if they had a qualifying event within 15 days of presentation to the UHS facility. The

timeframe was to allow for patients who might have suffered a cerebrovascular event at an outside facility but presented to the UHS rehabilitation facility. Patients were included if they had at least one follow-up visit in the medical record system of UHS. Patients were classified into two groups based on receipt of a PPI. Patients who received a PPI at any time during the one-year follow-up were classified as the clopidogrel with PPI group and patients who did not receive a PPI during the follow up group were classified as the clopidogrel without PPI group.

PPI EXPOSURE STATUS

To be classified in the PPI group, patients had to receive any of the following PPI; omeprazole, esomeprazole, lansoprazole, pantoprazole or rabeprazole. This could be a new prescription at discharge or at follow-up. Patients could also have had a previous order continued at discharge. Inpatient use of PPI without a continuing prescription did not meet criteria for inclusion in the PPI group.

DATA COLLECTION

After patient identification, an electronic chart review was conducted to collect study variables. Study variables included: age, sex, baseline conditions, baseline medications, indication for clopidogrel use, receipt of PPI and indication for PPI use. A complete list of data collection variables is available in **Appendix A**. Pharmacy records were reviewed using the UHS Clinical Inquiry system, which contains records for patients using any UHS outpatient pharmacy. Other pharmacy records were accessed

using clinic notes and the "RX writer" system which contains records of all prescriptions given to patients electronically.

CLINICAL OUTCOMES

The primary outcome of this retrospective study was the first occurrence of the composite of MI, stroke/TIA, coronary artery revascularization, or death (all cause). Information on death was derived from the Social Security Death Index available online (http://ssdi.rootsweb.ancestry.com/cgi-bin/ssdi.cgi) and when available, the patients electronic medical record. All other endpoints were derived from a review of clinic notes, admission history & physical notes, and discharge summaries. We excluded all pre-planned or staged interventions in determining if a patient had an event. This was to avoid the inclusion of known events at time of discharge as part of the study outcome. Key secondary endpoints included the first occurrence of the composite of MI, stroke/TIA, revascularization (coronary, cerebral, peripheral arteries), or death (all cause). A re-analysis of the primary endpoint based on indication for clopidogrel [coronary artery stenting, cerebrovascular accident or vascular intervention (cerebral and peripheral arteries)] was also conducted. Other prespecified secondary outcomes included (1) analysis of the primary outcome based on the total events accrued during the period of observation, (2) rehospitalization rates for ACS, (3) recurrence of the primary outcome, and (4) gastrointestinal bleeding rate. As patients could be started on a PPI at any time during the follow up period, we only included events that occurred after the initiation of the PPI. This was necessary to avoid immortal time bias.

STATISTICAL ANALYSIS

Data were analyzed using JMP 8.0 (SAS Corporation, NC). Continuous variables were reported as means and standard deviation for normally distributed data and as medians with IQR for non-normally distributed data. Dichotomous variables were reported as percentages. Comparisons were considered to be significant if the p-value was less than an *a priori* alpha level of 0.05. Comparisons of continuous variables were made with the use of the student *t* test or Mann-Whitney U test when appropriate. Dichotomous or categorical data were tested by use of the Chi-square and Fischer's Exact tests. Baseline differences were adjusted for using logistic regression models accounting for comorbidities, aspirin use at discharge, and indication for hospitalization.

Based on the results of the VA study, which demonstrated a rate of death or ACS of 29.8% among patients receiving clopidogrel with a PPI and a rate of 20.8% in patients receiving clopidogrel only, we estimated that with 800 patients, the study would have 80% power to show a 20% relative difference in MACE at one year. [18]

CHAPTER THREE

Results

A total of 1700 charts were screened for eligibility. A total of 572 patients met the inclusion criteria. There were 201 patients in the clopidogrel with PPI group and 371 patients in the clopidogrel without PPI group. The median follow-up time was 332 days (IQR, 176-380). The median follow-up time was longer in the clopidogrel without PPI group (325 days in clopidogrel with PPI group vs. 338 days in the clopidogrel without PPI group, p=0.04). The median age for patients in the study was 58 years. Patients were mostly Hispanic (62.9%) and male (60.3%). Cardiac risk factors such as hypertension (86.7%), hyperlipidemia (74.5%), and diabetes (58.9%) were highly prevalent at baseline. Established cerebrovascular disease was present in 22.7% of patients at baseline, 25.0% had a prior myocardial infarction, and 15.7% of patients had peripheral vascular disease. The proportion of patients with a prior coronary artery revascularization procedure was 40.0% (CABG was 18.9% and a prior PCI was 27.6%). The use of cardiac medications were high at baseline, 60.8% were on a statin, 60.7% were on aspirin, 53.8% were on a beta-blocker, while 52.6% of patients were on an angiotensin converting enzyme inhibitor (ACEI) and 8.4% on an angiotensin receptor blocker (ARB) at baseline.

Baseline characteristics were similar between groups (clopidogrel with PPI vs. clopidogrel without PPI), except for differences in the rate of smoking (20.4% vs. 31.8%, p=0.003), liver disease (5.0% vs. 1.6%, p=0.02), prior PPI use (66.1% vs. 1.4%, p<0.0001), and PPI use during hospitalization (73.3% vs. 27.0%, p<0.0001). Other baseline variables are shown in **Table 3.1 and Table 3.2.**

Table 3.1: Baseline characteristics

	Clopidogrel with PPI (n=201)	Clopidogrel without PPI (n=371)	P value
Age, median (IQR),y	59(51-64)	58(51-63)	0.3649
Age 65 and older (%)	45(22.4)	64 (17.3)	0.1338
Sex			0.1414
Male (%)	113(56.2)	232(62.5)	
Female (%)	88(43.7)	139(37.5)	
Ethnicity			0.5717
Hispanic (%)	124(61.7)	236(63.6)	
White (%)	45(22.4)	85(22.9)	
Black (%)	17(8.5)	20(5.4)	
Asian (%)	5(2.5)	6(1.6)	
Other (%)	10(5.0)	24(6.5)	
Hypertension (%)	179(89.1)	317(85.4)	0.2186
Diabetes (%)	121(60.2)	216(58.2)	0.6459
Hyperlipidemia (%)	158(78.6)	268(72.2)	0.0922
Smoking (%)	41(20.4)	118(31.8)	0.0031
Prior MI (%)	49(24.4)	94(25.3)	0.8001
Prior PCI (%)	64(31.8)	94(25.3)	0.0988
Prior CABG (%)	41(20.4)	67(18.1)	0.4969
CKD (%)	25(12.4)	39(10.5)	0.4885
Liver disease (%)	10(5.0)	6(1.6)	0.0240
Cerebrovascular disease (%)	41(20.4)	89(24.0)	0.3249
PVD (%)	25(12.4)	65(17.6)	0.1056
Heart Failure (%)	25(12.4)	43(11.6)	0.7656

Table 3.2: Baseline medications

	Clopidogrel with PPI (n=201)	Clopidogrel without PPI (n=371)	P value
Prior ACEI (%)	112(55.7)	189(50.9)	0.2742
Prior ARB (%)	22(10.9)	26(7.0)	0.1108
Prior Statins (%)	127(63.1)	221(59.6)	0.3969
Prior H2RA (%)	6(3.0)	10(2.7)	0.8418
Prior B-blocker (%)	118(58.7)	190(51.2)	0.0856
Prior ASA (%)	119(59.2)	228(61.4)	0.5990
81mg (%)	80(39.8)	144(38.8)	
325mg (%)	21(10.4)	49(24.4)	
Prior NSAIDs (%)	15(7.5)	34(9.2)	0.4832
Prior PPI (%)	134(66.7)	5(1.4)	<0.0001
Esomeprazole	82 (40.8)	2 (0.5)	
Lansoprazole	6 (3.0)		
Omeprazole	6 (3.0)	1 (0.4)	
Pantoprazole	40 (19.9)	2(0.5)	
Indication (%)			
GERD (%)	69 (76.7)	4(80.0)	
PUD (%)	12(13.3)		
None given (%)	9(10.0)	1(20.0)	
PPI during hospitalization (%)	148(73.3)	100(27.0)	<0.0001
ASA at discharge (%)	164(81.6)	286(77.1)	0.2055
81mg (%)	132(65.7)	216(58.2)	
325mg (%)	23(11.4)	52(25.9)	
Other (%)	1(0.5)	3(1.5)	
Statin at discharge (%)	173(86.1)	321(86.5)	0.8803
DAT at discharge (%)	164(81.6)	286(77.1)	0.2055

CLOPIDOGREL INDICATION

The study was designed to be representative of the typical use pattern of clopidogrel. The majority of patients received clopidogrel following a coronary artery revascularization event defined as either PCI (elective and ACS) or CABG (65.6% of the total study population), followed by vascular intervention, cerebrovascular accident (CVA), medically managed ACS, and aspirin allergy respectively (See **Figure 3.1**). There was no difference in the proportion of patients prescribed clopidogrel following a cardiac intervention between both groups. However, there was a statistically significant difference in patients prescribed clopidogrel following a CVA (9.0% in the clopidogrel with PPI group vs. 16.2% in the clopidogrel without PPI group, p=0.01), vascular intervention (10.9% vs. 17.3%, p=0.04) and aspirin allergy (1.5% vs. 0%, p=0.01). See **Table 3.3**

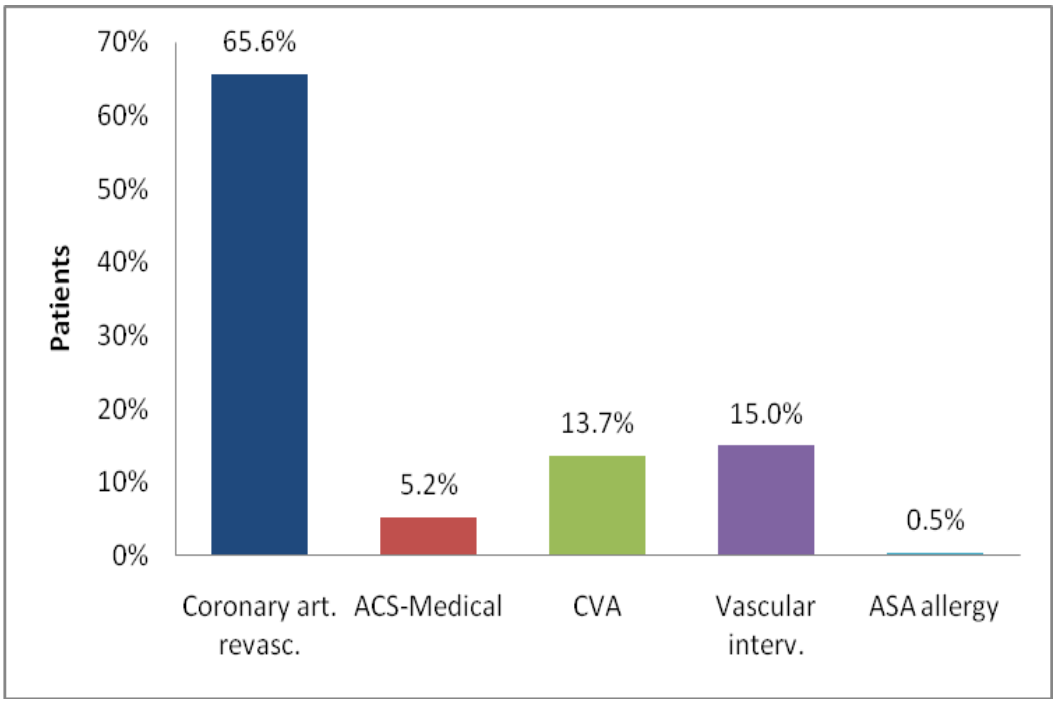


Figure 3.1: Indication for clopidogrel in overall study population

Table 3.3: Indication for clopidogrel by study groups

Indication for clopidogrel	Clopidogrel with PPI (n=201)	Clopidogrel without PPI (n=371)	P value
Coronary artery revascularization (%)	141(70.1)	234(63.1)	0.0872
ACS – PCI (%)	50(24.9)	99(26.7)	0.6371
Elective PCI (%)	61(30.3)	91(24.5)	0.1348
CABG (%)	30(14.9)	44(11.9)	0.3013
ACS – Medical (%)	17(8.5)	13(3.5)	0.0135
CVA (%)	18(9.0)	60(16.2)	0.0134
Stroke (%)	11(5.5)	38(10.2)	0.0503
TIA (%)	7(3.5)	22(5.9)	0.1899
Vascular intervention (%)[1]	22(10.9)	64(17.3)	0.0366
ASA allergy (%)	3(1.5)	-	0.0130

[1] Vascular intervention includes cerebral and peripheral arteries

PPI USE

Esomeprazole (56.2%) was the most frequently prescribed PPI in the study population followed by pantoprazole (35.3%). This reflected the UHS formulary during the study time period. Esomeprazole was the preferred outpatient PPI in the UHS formulary while pantoprazole was the preferred inpatient PPI agent. Most patients had their pre-hospitalization PPI order continued following discharge. A smaller number of patients had their PPI order started at discharge or at follow-up. The most common indication for the use of a PPI was GERD (48.3%) followed closely by patients receiving a PPI for no clear indication (42.8%). A small number of patients were prescribed a PPI

solely for GI prophylaxis (3.5%). Seventy-one percent of patients received a PPI for the entire duration of the study follow-up. See **Table 3.4 and 3.5** for details about the PPI use pattern in the study

Table 3.4: PPI use pattern

	Clopidogrel with PPI (n=201)
Indication for PPI	
GERD (%)	97(48.3)
PUD (%)	11(5.5)
GI prophylaxis (%)	7(3.5)
None given (%)	86(42.8)
PPI type	
Esomeprazole (%)	113(56.2)
Lansoprazole (%)	8(4.0)
Omeprazole (%)	9(4.5)
Pantoprazole (%)	71(35.3)
More than 1 PPI	20

Table 3.5: PPI initiation characteristics

	Total population (n=572)	Clopidogrel with PPI (n=201)
PPI started at follow-up (%)	22(3.8)	22(10.9)
PPI started at discharge (%)	57(10.0)	57(28.4)
PPI continued from baseline (%)	122(21.3)	122(60.7)
PPI active through study period (%)	144(25.2)	144(71.6)

ASPIRIN USE

The majority of patients received aspirin therapy at discharge. The receipt of aspirin therapy varied according to indication, for example, 90% in patients following coronary artery revascularization, while only 24% in patients following a stroke (See **Table 3.6)**. There was no difference in the receipt of aspirin therapy at discharge between the study groups. (81.6% in the clopidogrel with PPI group vs. 77.1% in the clopidogrel without PPI group, p=0.2).

Table 3.6: Aspirin use characteristics

Indication	Total	Clopidogrel with PPI	Clopidogrel without PPI
ACS-Medical (%)			
Yes	25(83.3)	14(82.4)	11(84.6)
No	5(16.7)	3(17.6)	2(15.4)
ACS-PCI (%)			
Yes	139(93.2)	48(96.0)	91(91.9)
No	10(6.7)	2(4.0)	8(8.1)
Elective PCI (%)			
Yes	143(94.1)	56(91.8)	87(95.6)
No	9(5.9)	5(8.2)	4(4.4)
CABG (%)			
Yes	70(94.6)	42(95.4)	28(93.3)
No	4(5.4)	2(4.5)	2(6.7)
Stroke (%)			
Yes	12(24.5)	3(27.3)	9(23.7)
No	37(75.5)	8(72.7)	29(76.3)
TIA (%)			
Yes	8(27.6)	-	8(36.3)
No	21(72.4)	7(100.0)	14(63.6)
Vascular interv. (%)			
Yes	53(61.6)	15(68.2)	38(59.4)
No	33(38.4)	7(31.8)	26(40.6)

CLINICAL OUTCOMES

The primary outcome of the first occurrence of the composite of MI, stroke/TIA, coronary artery revascularization, or death (all cause), occurred in 21 (10.4%) patients in the clopidogrel with PPI group compared to 38 (10.2%) patients in the clopidogrel without PPI group (p = 0.9, OR 1.02; 95% CI 0.58 - 1.80). There was no significant difference in the key secondary endpoint of the composite of MI, stroke, TIA, revascularization (coronary, cerebral or peripheral arteries), or death (all cause) (14.4%

vs. 15.4, p = 0.8, OR 1.02; 95% CI 0.58 -1.80) (**Figure 3.2 and Table 3.7**)**.** There was also no difference in the primary outcome when reanalyzed based on the indication for clopidogrel – coronary artery revascularization (10.6% vs. 9.8%, p = 0.8, OR 1.09; 95% CI 0.55 - 2.17), CVA (11.1% vs. 12.8 %, p= 0.6, OR 0.65; 95% CI 0.12 - 3.16) or vascular intervention (4.6% vs. 4.6 %, p = 1.00, OR 0.97; 95% CI 0.10 - 9.82).

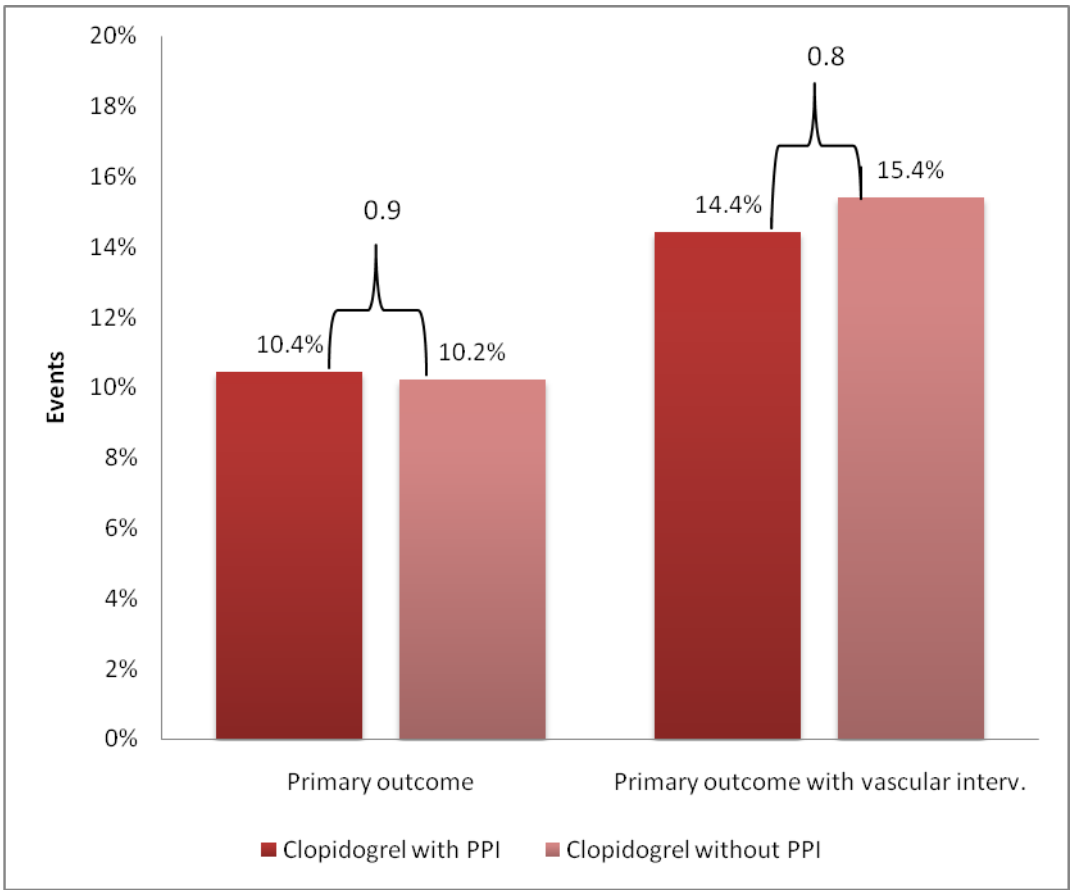


Figure 3.2: Primary outcome [MI, stroke, TIA, coronary artery revascularization, or death (all cause)] and primary with vascular intervention [MI, stroke, TIA, revascularization (coronary, cerebral or peripheral arteries) and death (all cause].

Table 3.7: One-year adverse outcomes following discharge for qualifying events

Patients	Clopidogrel with PPI (n=201)	Clopidogrel without PPI (n=370)	OR (95% CI)	P value
MI, stroke/TIA, coronary artery revascularization and death (%)	21(10.5)	38(10.2)	1.02(0.58-1.80)	0.9387
MI, stroke/TIA, revascularization (cardiac, cerebral & peripheral) and death (%)	29(14.4)	57(15.4)	0.93(0.57-1.51)	0.7643
MI (%)	5(2.5)	7(1.9)	1.33(0.42-4.2)	0.6363
Stroke/TIA (%)	3(1.5)	15(4.0)	0.36(0.10-1.26)	0.0769
Coronary artery revascularization (%)	14(7.0)	16(4.3)	1.66(0.79-3.48)	0.1823
CABG (%)	5(2.5)	5(1.4)	1.88 (0.53-6.53)	0.3318
PCI (%)	11(5.5)	14(3.8)	1.48(0.66-3.32)	0.3500
Vascular interv. (%)	9(4.5)	21(5.7)	0.78(0.35-1.74)	0.5399
Death (%)	2(1.0)	5(1.4)	0.74(0.14-3.83)	0.7097
GI bleed (%)	3(1.5)	1(0.3)	5.61(0.58-54.25)	0.1028
Rehospitalization for ACS (%)	13(6.5)	20(5.4)	1.21(0.59-2.49)	0.6009

Total Events and Recurrent Events

There was no statistically significant difference between both groups when the total events that occurred over the study period were compared, although there was a larger proportion of events in the clopidogrel with PPI group (31 events in the clopidogrel with PPI group vs. 46 events in the clopidogrel without PPI group, 15.4% vs. 12.4%, p = 0.8). A similar trend was seen in the rates for rehospitalization for ACS; there was a

larger proportion of events in the PPI with clopidogrel group although not statistically significant (18 events vs. 20 events, 9.0% vs. 5.4%, p = 0.7625) (see **Table 3.8)**. In patients with the primary outcome, there was no statistically significant increase in the rate of repeat events, although there was a larger proportion of patients with recurrence of the primary outcome in the clopidogrel with PPI group (27.3% vs. 18.4%, p = 0.4, OR 1.66, 95% CI 0.48 – 5.77).

Table 3.8: Total events occurring over 1 year following discharge for qualifying events

Events	Clopidogrel with PPI (n=201)	Clopidogrel without PPI (n=370)	P value
MI, stroke/TIA, coronary artery revascularization and death (%)	31(15.4)	46(12.4)	0.7625
MI, stroke/TIA, revascularization (cardiac, cerebral & peripheral) and death (%)	40(19.9)	77(20.8)	0.8758
MI (%)	6(3.0)	7(1.9)	0.4011
Stroke/TIA (%)	4(2.0)	15(4.1)	0.0984
Cardiac Revascularization (%)	19(9.5)	19(5.1)	0.1696
CABG (%)	5(2.5)	5(1.4)	0.3217
PCI (%)	14(7.0)	14(3.8)	0.3277
Vascular intervention (%)	9(4.5)	31(8.4)	0.5212
Rehospitalization for ACS (%)	18(9.0)	20(5.4)	0.5987

Multivariate Analysis

In multivariate analysis adjusting for co-morbidities, indication for clopidogrel use, and treatment received at discharge, the receipt of PPI was not predictive of

outcomes (adjusted OR 0.98, 95% CI 0.54 –1.75). In this model, only baseline cerebrovascular disease (CVD) was predictive of outcomes (adjusted OR 2.18, 95% CI 1.11 – 4.22). The receipt of clopidogrel for vascular interventions, was however protective in the model (adjusted OR 0.17, 95% CI 0.03 – 0.87). See **Table 3.9** for effects of over variables on the primary outcome. For the secondary outcome of the composite of MI, stroke/ TIA, revascularization (coronary, cerebral or peripheral arteries), or death the receipt of a PPI also did not predict outcomes (adjusted OR 1.04, 95% CI (0.61 – 1.75). However, baseline CVD and peripheral vascular disease (PVD) were predictive of outcomes in this model (CVD, adjusted OR 1.99, 95% CI 1.11 – 3.53 and PVD, AOR 3.92, 95 % CI 1.86 – 8.33) (See **Table 3.10**).

Table 3.9: Adjusted odds ratio for the primary outcome

Variable	Odds ratio (95% CI) for Primary Outcome
Clopidogrel with PPI	0.98 (0.54 -1.75)
Smoking	0.68 (0.32 – 1.35)
Diabetes	1.77 (0.94 – 3.46)
Hypertension	1.53 (0.55 – 5.58)
Hyperlipidemia	0.81 (0.39 – 1.75)
Prior MI	1.2 (0.61 – 2.32)
Prior PCI	0.92 (0.46 – 1.75)
Prior CABG	1.32 (0.64 – 2.56)
PVD	1.75 (0.62 – 4.48)
CKD	0.71 (0.27 – 1.62)
Cerebrovascular disease	2.18 (1.11 – 4.22)
Indication - coronary artery revasc.	0.77 (0.28 – 2.51)
Indication - CVA	0.77 (0.21 – 3.06)
Indication - vasc interv.	0.17 (0.03 – 0.87)
Statins at discharge	1.43 (0.58 – 4.06)
ASA at discharge	0.72 (0.31 – 1.75)

Table 3.10: Adjusted odds ratio for the secondary outcome of MI, stroke, TIA, revascularization (cardiac, cerebral and peripheral arteries) and death

Variable	Odds Ratio (95% CI) for Primary Outcome with Vascular Interventions
Clopidogrel with PPI	1.04 (0.61 – 1.75)
Smoking	0.81 (0.45 – 1.40)
Diabetes	1.67 (0.98 – 2.89)
Hypertension	0.69 (0.33 – 1.52)
Hyperlipidemia	0.72 (0.38 – 1.35)
Prior MI	1.51 (0.84 – 2.72)
Prior PCI	1.03 (0.56 – 1.86)
Prior CABG	1.20 (0.63 – 2.23)
PVD	3.92 (1.86 – 8.33)
CKD	0.75 (0.34 – 1.55)
Cerebrovascular disease	1.99 (1.11 – 3.53)
Indication - coronary artery revasc.	0.70 (0.27 – 2.05)
Indication - CVA	0.68 (0.20 – 2.46)
Indication - vascular intervention	0.71 (0.21 – 2.56)
Statins at discharge	1.72 (0.82 – 3.90)
ASA at discharge	0.64 (0.33 – 1.27)

CHAPTER FOUR

Discussion

In this single center observational study, the receipt of a PPI with clopidogrel did not increase major adverse cardiac outcomes compared to patients not on a PPI. To our knowledge, this is the first study to include a high risk atherosclerotic patient population similar to the current FDA indication for clopidogrel.[21] At baseline, study participants were younger with higher rates of established atherosclerotic disease (prior MI, revascularization, PVD, and stroke/TIA), and cardiac risk factors (hypertension, diabetes, and hyperlipidemia) compared to other studies.[17,18,36,39] Study participants were mostly of Hispanic ethnicity and the majority had received clopidogrel therapy following a cardiac event (revascularization or medical management of ACS). The study finding of no increase in risk is consistent with results of some other post-hoc analyses of randomized trials and single-center observational studies which have demonstrated that PPIs are not associated with adverse outcomes in patients receiving clopidogrel.[37, 38, 41, 42]

Mechanistic and pharmacodynamic studies have described a drug interaction between PPIs and clopidogrel.[16, 33] Other studies of the effects of PPI on the CYP2C19 enzyme, however, have demonstrated that PPIs inhibit CYP2C19 to varying extent leading to differing effects on clopidogrel's activity.[28, 31, 32] Siller-Matula et. al. and Sibbling et. al. demonstrated that esomeprazole and pantoprazole do not significantly affect the antiplatelet efficacy of clopidogrel as measured using platelet function tests.[31, 32] Therefore the results of our study must be viewed in light of the fact that

esomeprazole and pantoprazole were the most frequently prescribed PPI in the study. This potentially could have accounted for the lack of an interaction seen in this study.

The inclusion criteria for this study were expanded to include patients with a recent stroke, TIA, CABG or vascular intervention to better reflect the current indication and use of clopidogrel in our institution. Other studies to date have focused solely on the use of clopidogrel for secondary prevention following an ACS event or coronary artery stenting without evaluating its use for secondary prevention in patients with atherosclerosis of different vascular beds. This omission is quite important when one considers the use of clopidogrel post-stroke or TIA. Post coronary artery stenting, patients are also prescribed aspirin as part of DAT therapy, but DAT is not recommended following a stroke or TIA. This recommendation is based on results from the MATCH and CHARISMA trials.[13, 14] In both trials, the receipt of DAT was not associated with improved outcomes and was rather associated with an increased bleeding risk. The recommendation against DAT therapy post stroke or TIA is evident in our study as less than 30% of patients receiving clopidogrel were also on aspirin at discharge. Given the low rate of DAT use following a stroke or TIA, it is plausible to expect worse outcomes in patients receiving both clopidogrel and PPI due to the lack of background aspirin therapy. In a post-hoc subgroup analysis of patients included in our study following a stroke or TIA (14% of overall study population), there was no statistically significant difference in outcomes. In contrast, a larger proportion of patients with stroke or TIA who did not receive a PPI experienced the primary outcome. While the lack of an effect is reassuring, there is a need for more studies exploring this particular indication for clopidogrel.

The evidence for the benefit of clopidogrel or DAT in patients undergoing CABG surgery is mixed.[43] While there is no randomized control trial showing a benefit, it continues to be a common practice as evidenced by the results of our study. When patients receiving clopidogrel following a CABG surgery were excluded, the results were consistent with the overall results demonstrated in the trial (n=498, OR 0.97, 95% CI 0.54 – 1.76).

There are some key differences between our study and other studies that have found an increase in adverse outcomes. First, in studies with a positive outcome, patients in the clopidogrel-PPI group have been noticeably older and with more co-morbidities compared to patients receiving clopidogrel without PPI.[17, 36] While the studies adjusted for baseline differences, the uneven distribution between the groups at baseline, suggests that the receipt of a PPI could have been a marker for more severe disease. Indeed, the CREDO trial reanalysis found that receipt of PPI was independently associated with worse outcomes irrespective of clopidogrel use.[37] In our study, the groups were well balanced at baseline with comparable age and co-morbidities.

Second, insurance and administrative databases have been the main source of information used in these studies.[18, 34, 36] This is an important distinction as insurance databases are susceptible to miscoding which could potentially affect the results. Also such databases lack correlation of the coded event with the medical records from the encounter. For example, a preplanned or staged event for revascularization following a hospitalization for an ACS event could have been reported as an event although it was truly not a new event. In our study, we had access to the medical records of included patients, and were able to exclude preplanned or staged interventions.

Third, information on patients' ethnicity or racial origin has been mostly missing in the studies. In our study, the patients were mostly of Hispanic descent, which could have affected the distribution of genetic polymorphisms of the CYP2C19 enzyme. Several studies have demonstrated that patients with CYP2C19 reduced function allele have poorer outcomes and that the distribution of the reduced function allele varies by race.[25, 27, 44] While there are limited data on the prevalence of the CYP2C19 reduced function allele in patients of Hispanic descent, it is possible that it could be different from that reported for other ethnic or racial groups.[45, 46] In patients with overrepresentation of the reduced function allele of CYP2C19, there is a potential for additive reduction in the biotransformation of clopidogrel when combined with a PPI leading to poorer outcomes.

There are some limitations in our study including its limited sample size. The study was underpowered to detect a difference in outcomes; although results of positive observational studies would suggest that a trend should at least be apparent in a study population of this size, given the reported risk estimates. Also, this was a single-center study and the results might not be applicable to other centers. The impact of over-the-counter availability of omeprazole on our results cannot be discounted. Patients could potentially have been on over-the-counter omeprazole which was not reported during any subsequent hospitalization or medical contact. In addition to the aforementioned limitations, there are intrinsic limitations with observational studies which cannot be overcome even after extensive adjustments for confounders.

There is clearly a need for a larger, randomized trial to definitely answer the question of whether PPIs increase adverse outcomes in clopidogrel treated patients. Such a study should include a high-risk atherosclerotic population, genetic information about

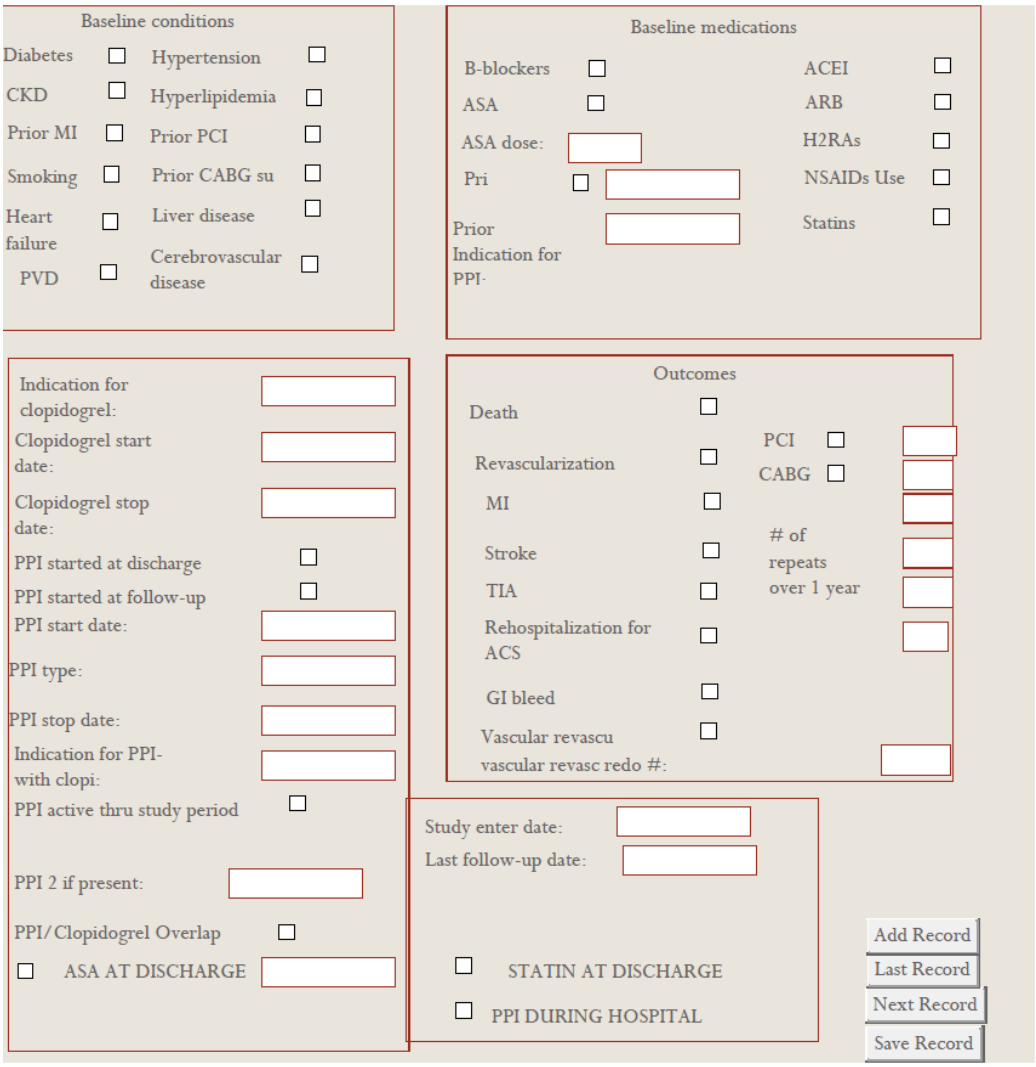
CYP2C19 status, and be of sufficient length (at least one year) to answer the study question.

Since reports of an interaction became available, a common suggestion has been that PPI use be restricted to patients with a documented indication.[47, 48] In this study, the majority of patients who ended up on concomitant clopidogrel-PPI use were on a PPI before hospitalization for the qualifying event. The most common indication for the use of PPI with clopidogrel was gastroesophageal reflux disease (48%) which was closely followed by patients receiving PPI for no clear indication (43%). The large proportion of patients on a PPI for no clear indication represents a sizeable population that could be targeted for discontinuation if concerns about the combination persist. Interestingly, the use of the combination for GI prophylaxis was quite low and only 10% of patients were started on a PPI at discharge following the initiation of clopidogrel. The receipt of a PPI did not appear to alter the incidence of GI bleeds possibly due to the patients having a baseline history of peptic ulcer disease.

In conclusion, this single-center, observational study, demonstrated similar rates of major cardiac events in patients taking clopidogrel with a PPI compared to those taking clopidogrel without a PPI. These findings are consistent with mechanistic studies that suggest esomeprazole and pantoprazole do not attenuate the antiplatelet effects of clopidogrel. There is a need for randomized controlled studies to confirm the results of this study. Until such studies are available, it is important to re-assess the need for PPIs, particularly in patients receiving them for no clear indication.

Appendix - A

DATA COLLECTION FORM



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