

REVIEW

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Proton Pump Inhibitors and the Prevention of Recurrent GI Bleed in Patients Treated with Clopidogrel

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Abstract: Clopidogrel is an antiplatelet agent indicated in the management of atherothrombotic conditions. Bleeding is a predictable adverse event associated with antiplatelet agents. While non-ulcerogenic; a major site of bleeding with clopidogrel is the gastrointestinal (GI) tract. The risk of GI bleeding with clopidogrel monotherapy is generally low; however, it increases with the presence of other risk factors such as aspirin use, advanced age, prior GI bleed, non-steroidal anti-inflammatory drugs, steroids and anticoagulants. In patients with a prior GI bleed, the risk of recurrence is high and strategies to prophylactically mitigate the risk should be implemented. In this review, evidence supporting the use of proton pump inhibitors to reduce the risk of recurrent GI bleed is discussed. Recommendations on an appropriate regimen to diminish the risk are provided.

Keywords: clopidogrel, proton pump inhibitors, GI bleeding, antiplatelet

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Indication and Benefit

Clopidogrel is a P2Y₁₂ receptor antagonist which blocks the interaction between adenosine diphosphate (ADP) and platelets.¹ It binds irreversibly to P2Y₁₂ leading to inhibition of ADP induced platelet activation and aggregation. On the basis of studies such as CAPRIE and CURE, clopidogrel is indicated for use in patients presenting with acute coronary syndromes (ACS) and for secondary prevention in patients with a history of myocardial infarction (MI), stroke or peripheral artery disease (PAD).¹ In the pivotal CAPRIE (Clopidogrel versus Aspirin in patients at Risk of Ischemic Events) study, clopidogrel was compared to aspirin in 19185 patients with recent ischemic stroke, recent MI or PAD over a 2 year time period. For the primary composite endpoint of ischemic stroke, MI or vascular death, patients treated with clopidogrel had an annual risk of 5.3% compared to 5.8% in aspirin treated patients (RR, 0.91; 95% CI, 0.3–16.5).²

The CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) study compared the combination of aspirin and clopidogrel to aspirin alone in patients presenting with ACS without ST segment elevation. Dual antiplatelet therapy (DAPT) with clopidogrel and aspirin was associated with a significant 20% relative risk reduction in the combined endpoint of MI, stroke and cardiovascular (CV) death over a 12 month study period (9.3% vs. 11.4%, 95% CI, 0.72–0.90).³ Given its robust evidence base, clopidogrel is recommended first line by professional organizations for multiple atherothrombotic conditions, including MI.^{4,5}

Risk of GI Bleeding

As an antiplatelet agent, bleeding is a predictable adverse event associated with the use of clopidogrel. The overall bleeding rate associated with clopidogrel monotherapy is comparable to that seen in aspirin treated patients. In the CAPRIE study, any bleeding disorder was reported in 9.27% of patients receiving clopidogrel compared to 9.28% of patients receiving aspirin.² A major site of bleeding, as seen in the CAPRIE study, is the gastrointestinal tract (GI) with GI bleeding reported in 1.99% of patients on clopidogrel compared to 2.66% in aspirin treated patient ($P < 0.05$).

Fork et al conducted a gastroscopic study of 36 healthy volunteers exposed to clopidogrel 75 mg

daily or aspirin 325 mg daily for 8 days to determine the GI toxicity of clopidogrel using the modified Lanza score.⁶ The modified Lanza score assigns points based on the severity of mucosal lesions, with higher scores signifying more GI damage. The modified Lanza score of patients exposed to clopidogrel was unchanged from baseline to study completion (0 vs. 0) whereas the score rose significantly in patients exposed to aspirin (0 vs. 7.5; $P < 0.001$). In contrast to aspirin, clopidogrel is not a direct mucosal irritant as demonstrated in the study by Fork et al, nonetheless it is still associated with GI hemorrhage. The exact mechanism of clopidogrel induced GI bleeding is unknown, but is thought to primarily be due to its antiplatelet effects.⁷

Platelets play a crucial role in achieving hemostasis through their ability to adhere to the site of injury to form platelet plugs and also release pro-angiogenic growth factors that promote healing.^{7,8} Clopidogrel therefore can impair healing and enhance bleeding from ulcers formed due to other medications (such as NSAIDs, aspirin), hydrochloric acid or other mechanisms.⁷ In the CURE trial, DAPT with clopidogrel and aspirin was associated with almost double the rate of major GI bleeds compared to aspirin monotherapy (1.3% vs. 0.7%).³

Risk of Recurrent GI Bleeding

A history of GI bleed is a strong predictor of having a recurrent GI bleed. In a prospective case-control study of patients with upper GI bleeds, the most important clinical risk factor for recurrence was a previous history of GI bleed. It was associated with an almost fourfold increase in the risk of an upper GI bleed in patients admitted for an acute upper GI bleed (OR, 3.7; 95% CI, 1.2–11; $P = 0.01$).⁹

Given its non-ulcerogenic properties, there was considerable interest in using clopidogrel as an alternative to aspirin in patients with prior GI bleed to lessen the chance of a recurrence. Chan et al conducted a study comparing clopidogrel to the combination of aspirin and esomeprazole for prevention of recurrent GI bleeds.¹⁰ In the study, 320 patients who initially presented with an acute GI bleed with endoscopic evidence of ulcer healing were randomized to clopidogrel daily or aspirin 80 mg daily plus esomeprazole 20 mg twice daily for 12 months. The primary endpoint of endoscopically



proven recurrent ulcer bleeding was seen in 8.6% of patients randomized to clopidogrel compared to 0.7% in patients randomized to aspirin plus esomeprazole (95% CI, 3.4–12.4; $P = 0.001$). In 10 of the 14 patients with recurrent bleeding, the ulcer recurred at the site of previous ulceration. The results from this study provide further evidence of the increased risk of recurrent GI bleeds in clopidogrel treated patients and the need for preventive strategies to prevent initial and recurrent GI bleeds.

Risk of Early Termination of Clopidogrel Therapy

Clearly there is an increased risk of recurrent bleeding with continued clopidogrel therapy; however, the risk must be balanced with the risk of early termination of clopidogrel therapy or denial of therapy in patients with a definite indication. Premature discontinuation of thienopyridines, such as clopidogrel, has been identified as a key risk factor for stent thrombosis, often a fatal condition, in patients receiving drug eluting stents (DES).¹¹ In a prospective observational cohort study of 2229 consecutive patients who underwent DES placement, 1.3% of patients had a stent thrombosis with a case fatality rate of 45%. Premature discontinuation of antiplatelet therapy was identified as the most significant predictor of stent thrombosis (HR, 89.78; 95% CI, 29.9–269.6; $P < 0.001$).

There is also evidence of benefit for prolonged clopidogrel therapy in certain patient populations. For example, in the CREDO study, 2116 patients undergoing elective PCI were randomized into two groups to assess for the rate of major adverse cardiac events (MACE): clopidogrel 300 mg loading dose followed by 75 mg daily for 1 year or placebo loading dose with clopidogrel 75 mg daily for 28 days on background aspirin therapy.¹² The co-primary outcomes were assessed at 2 different time points: day 28 and at 12 months. At day 28, there was a non-significant trend towards benefit in patients pretreated with clopidogrel loading dose for the outcome of death, MI or urgent target vessel revascularization (UTVR) (6.8% vs. 8.3%; 95% CI, -14.2–41.8; $P = 0.23$) with clear benefit for prolonged treatment with clopidogrel at 1 year compared to 28 days for the outcome of death, MI and stroke (8.5% vs. 11.5%; 95% CI, 3.9–44.4; $P = 0.02$).

Due to the potential for increased or recurrent MACE in patients who have their clopidogrel therapy interrupted, there is a need to develop strategies to prevent recurrent GI bleeds.

PPIs to Prevent GI Bleeding

A potential strategy for preventing GI bleeding is suppression of gastric acid production to promote healing and stabilize thrombi.⁷ Available options for gastric acid suppressive therapy are predominantly histamine H₂ receptor antagonists (H2RA) or proton pump inhibitors (PPI). H2RAs competitively inhibit histamine mediated gastric acid secretion whereas proton pump inhibitors suppress gastric acid secretion irrespective of stimulus. PPIs inhibit basal and stimulated gastric acid secretion by covalently binding to the H⁺, K⁺ adenosine triphosphatase (ATPase) enzyme at the secretory surface of gastric parietal cells.¹³ Other options such as misoprostol or sucralfate have not been well studied in patients taking clopidogrel. The vast majority of data supporting the use of gastric acid suppressive therapy to reduce the GI risk of clopidogrel comes from retrospective data.

Mixed results exist regarding the protective effect of H2RAs in patients on clopidogrel. Ng et al conducted a cohort study of 987 patients prescribed the combination of aspirin and clopidogrel. The investigators found that the use of H2RAs (OR, 0.43; 95% CI, 0.18–0.91) and PPIs (OR, 0.04; 95% CI, 0.002–0.21) each reduced the risk of UGIB when compared to the control group.¹⁴ Another retrospective study evaluating the use of antisecretory agents on the risk of ulcer bleeding associated with ticlopidine or clopidogrel came to a different conclusion. The study evaluated the effect of nitrates, H2RAs or PPI on the risk of GI bleeding in patients on NSAIDs, aspirin, and ticlopidine or clopidogrel separately. Patients in the NSAID or aspirin group experienced a statistically significant reduction in upper GI bleeding with the use of PPIs, H2RAs, and nitrates whereas in the clopidogrel/ticlopidine group only the use of PPIs achieved a statistically significant decrease in GI bleeding (adjusted RR, 0.19; 95% CI, 0.07–0.49).¹⁵

PPIs provide more potent and prolonged acid suppression and have emerged as preferred agents for the management of ulcerative disease.¹⁶ Few studies have examined the benefits of PPIs in reducing the GI bleeding risk associated with clopidogrel therapy.

Table 1

Trial	Design	Sample size (N)	Intervention studied (N)	Primary endpoint	Results	Comments
Ng et al ¹⁴	Retrospective, cohort study of patients receiving aspirin and clopidogrel	987	H2RA (287) PPI (213) Control (487)	Upper GI bleeding	H2RA vs. control 0.43 (0.18–0.91) PPI vs. control OR 0.04 (0.002–0.21)	43 patients (4.4%) had a prior history of GI bleed which was identified as an independent risk factor for recurrent bleed in the study
Lanas et al ¹⁵	Retrospective case-control of patients receiving NSAIDs, aspirin, antiplatelets or anticoagulants	Cases: 2777 with confirmed GI bleeds Controls: 5532 <i>Antiplatelet subgroup (clopidogrel/ticlopidine)</i> Cases: 107 Control: 81	H2RAs PPIs Nitrates	Upper GI bleeding	<i>Antiplatelet subgroup:</i> H2RA vs. control 0.83 (0.20–3.51) PPI vs. control RR 0.19 (0.07–0.49) Nitrates vs. control 0.88 (0.34–2.28)	
Ray et al ¹⁷	Retrospective, cohort study of patients receiving clopidogrel after hospitalization for CAD	20596	PPI (7593) No PPI	Hospitalization due to gastroduodenal bleeding	PPI vs. control 0.5 (0.39–0.65)	Pantoprazole was the most commonly used PPI (62% of cases). There was a higher rate of previous GI bleed in the no PPI group (4.9% vs. 1.4%, $P < 0.001$)
Lunistra et al ¹⁸	Retrospective, cohort study of patients on aspirin and clopidogrel with additional risk factors for bleeding	347 (with 115 having additional risk factor for bleeding)	PPI Overall: 128 <i>In patients with additional risk factor</i> : 60 No PPI	Major bleed	Patients with additional risk factor: PPI : 1.7% vs. no PPI 11.1%; $P = 0.05$	Risk factor for GI bleeds defined as: age > 70, previous GI Ulcer, previous aspirin or NSAID related bleed and DAPT Major bleeds: bleeds resulting in death, requiring transfusion or readmission
COGENT ¹⁹	Prospective, placebo controlled RCT of patients receiving aspirin and clopidogrel following cardiac stenting	3761	PPI (1876) No PPI (1876)	GI endpoint: composite of overt or occult bleeding, symptomatic gastroduodenal ulcers or erosions, obstruction or perforation	PPI vs. no PPI : 0.34 (0.18–0.63) Overt upper GI bleeds 0.1 (0.0–0.3)	Study terminated early



Hsaio et al ²⁰	Retrospective cohort study of patients with history of hospitalization for GI complications before initiation of antiplatelet therapy	2626	PPI (590) No PPI (2036)	Major GI complication (peptic ulcer, bleeding and perforation)	PPI vs. no PPI: Unadjusted : 1.15 (0.95–1.40)	Result unchanged after adjustments using propensity score
Hsu et al ²¹	Randomized control study of patients with previous history of peptic ulcer on clopidogrel	165	PPI (83) No PPI (82)	Occurrence of gastric and/or duodenal ulcers	PPI vs. no PPI 1.2% vs. 11.0%; <i>P</i> = 0.009 Upper GI bleed: 0 in PPI group vs. 1 in no PPI group; <i>P</i> = NS	Primary endpoint determined by endoscopy

Ray et al, in the largest retrospective cohort study published to date, evaluated 20 596 patients hospitalized for MI, coronary artery revascularization, or unstable angina from the Tennessee Medicaid database.¹⁷ Two patient groups were identified: those receiving clopidogrel concurrently with a PPI (*n* = 7593) and those without a PPI (*n* = 13003). The study objective was to evaluate the effect of concurrent PPI use on risk of hospitalizations due to gastroduodenal bleeding and serious CV disease (fatal or nonfatal MI, stroke, or other CV death). Serious GI bleeding was identified by diagnostic procedure codes compatible with bleeding at gastroduodenal site upon hospital admission. The authors found that the utilization of a PPI in patients concurrently using clopidogrel decreased the relative risk of hospitalization for a gastroduodenal bleed by 50% (HR, 0.5; 95% CI, 0.39–0.65) while having no impact on cardiovascular disease outcomes (HR, 0.99; 95% CI, 0.82–1.19).

Another retrospective cohort trial conducted by Luinstra et al in Australia suggested that the use of PPIs was most beneficial for preventing bleeds in patients on DAPT with at least one of the following risk factors: age > 70, previous GI ulcer, previous aspirin or non-steroidal anti-inflammatory drug-related bleed and dual antiplatelet therapy (aspirin and clopidogrel).¹⁸ Compared to patients on DAPT with ≥1 additional risk factor and not receiving acid suppressive therapy, the addition of a PPI decreased the likelihood of developing a major bleed (1.7% vs. 11.1%; *P* = 0.05). No major bleeds were reported in the clopidogrel monotherapy group, so the addition of a PPI was not detected to be beneficial in these patients. This retrospective analysis used a broad definition of major bleed (bleeds resulting in death, requiring a blood transfusion or readmission to the hospital) and did not differentiate between gastrointestinal bleeding and other bleeding sites.

The COGENT study was the first prospective, randomized trial to evaluate the use of PPIs in patients receiving clopidogrel.¹⁹ In the study, 3761 patients on background therapy with aspirin were randomized into two groups: clopidogrel with omeprazole (*n* = 1876) or clopidogrel alone (*n* = 1885) with median follow-up of 106 days (IQR 55–166 days). The primary GI efficacy endpoint evaluated was a composite endpoint of upper GI clinical events. This extensive composite endpoint consisted of: overt bleeding



of gastroduodenal origin, overt upper GI bleeding of unknown origin, bleeding of presumed occult gastrointestinal origin with a documented decrease in hemoglobin ≥ 2 g/dL or hematocrit $\geq 10\%$ from the baseline value, symptomatic uncomplicated gastroduodenal ulcer, persistent pain of presumed gastrointestinal origin with a duration of three days or more and with ≥ 5 gastroduodenal erosions, obstruction, or perforation. The primary GI endpoint was significantly reduced in the omeprazole group from 2.9% to 1.1% compared to clopidogrel alone at 180 days (HR, 0.34; 95% CI, 0.18–0.63; $P < 0.001$). More specifically, overt GI bleeding was reduced from 0.6% to 0.1% (HR, 0.12, $P = 0.03$) in the omeprazole group.

In 2008, the American College of Cardiology Foundation (ACCF), the American College of Gastroenterology (ACG), and the American Heart Association (AHA) published a consensus document providing expert recommendations regarding the reduction of GI risks associated with antiplatelet therapy and NSAID use.⁷ The consensus document recognized the increased GI risk associated with the use of antiplatelet agents and NSAIDs particularly GI bleeding. Their expert recommendation was to utilize PPIs in patients at risk for developing GI bleeds while taking DAPT. Several patient risk factors were identified including *Helicobacter pylori* infection, advanced age, prior GI bleed and concurrent use of anticoagulants, steroids or NSAIDs. As the number of risk factors present increases, the risk of an adverse GI event also increases.

PPIs to Prevent Recurrent GI Bleed

A prior history of a GI bleed increases the risk of a recurrent event as discussed earlier; therefore it is important that strategies to prophylactically reduce the risk are implemented. Few studies have evaluated the role of PPIs in reducing the risk of recurrent GI events. Hsiao et al conducted a population based retrospective study using data derived from the Taiwan National Health Insurance Database to evaluate the risk of recurrent GI complications in 2626 patients with a history of hospitalization for gastrointestinal complications (bleeding, peptic ulcer or perforation) prior to the initiation of clopidogrel.²⁰ Outcomes were derived using ICD-9 codes with adjustments made for confounders. A PPI was utilized in 590 patients (22%)

with no risk reduction in recurrent GI complications requiring hospitalization between the PPI and no PPI group (HR 1.08; 95% CI, 0.89–1.33).

Lanas et al evaluated 2777 patients hospitalized with an UGIB confirmed through endoscopy compared to 5532 controls.¹⁵ As discussed earlier, PPI use was associated with a reduction in recurrent upper GI bleed among patients receiving clopidogrel (RR 0.19, 95% CI, 0.07–0.49). The authors noted that 19% ($n = 528$) of the cases and 4.9% ($n = 269$) of the controls had a history of bleeding ulcers; however this stratification was not done in the results, making it difficult to determine if PPIs had an effect on recurrent ulceration.

An international, single-site, prospective, randomized open-label trial evaluating the use of a PPI (esomeprazole) to decrease recurrent GI events associated with clopidogrel therapy was recently published.²¹ In the study, 165 patients were randomized in a 1:1 design to either esomeprazole 20 mg daily before breakfast plus clopidogrel 75 mg daily at bedtime or clopidogrel alone for six months. Patients had to have a history of peptic ulcer (defined as endoscopy showing ≥ 5 mm ulcer diameter) and atherosclerosis (defined as ischemic heart disease or stroke). The authors performed an initial endoscopy at baseline to ensure patients did not have a peptic ulcer upon the start of the trial. Notably, patients taking aspirin were excluded from the trial as well as those who received any PPI within two weeks of the initial endoscopy.

The primary objective was to evaluate the effects of esomeprazole therapy on prevention of a recurrent gastric or duodenal ulcer defined as ≥ 5 mm diameter mucosal break on endoscopy. To identify the incidence of the primary outcome, an endoscopy was conducted at the end of the six month treatment period and also whenever severe GI symptoms (persistent dyspepsia, severe epigastric pain, hematemesis, and melena) occurred. At baseline, a history of ulcer bleeding was reported in 36% of the esomeprazole group and in 31% of the clopidogrel alone group. There was a statistically significant reduction in the incidence of peptic ulcers in patients taking esomeprazole compared to clopidogrel alone (1.2% vs. 11%; 95% CI, 0.02–0.17; $P = 0.009$). However, 31 asymptomatic patients (approximately 9% in each arm) refused a follow-up endoscopy and were subsequently reported as having no recurrent ulcers. Upper GI bleeding occurred in one patient in the clopidogrel alone group



compared with none reported in the esomeprazole group (95% CI, -0.01–0.04).

PPI-Clopidogrel Interaction

A possible concern with the use of PPIs is their reported interaction with clopidogrel. The prescribing information for clopidogrel was updated in 2009 to include a warning information on the pharmacokinetic and pharmacodynamic interaction between PPIs, particularly omeprazole, and clopidogrel.¹ Clopidogrel is a pro-drug which undergoes activation into its active metabolite via multiple CYP450 enzymes.¹ One of the CYP isoenzymes involved in its activation cascade is CYP2C19 which is inhibited by PPIs in varying degrees.^{1,22,23} Using platelet function studies, a pharmacodynamic interaction between PPIs (mainly omeprazole) and clopidogrel has been demonstrated by several investigators.^{24–28} In the studies, patients receiving PPI consistently had lower platelet inhibition on clopidogrel.

There is a pharmacokinetic and pharmacodynamic interaction between PPIs and clopidogrel; however, the clinical significance of the interaction is questionable. Multiple retrospective analyses of clinical trial data, insurance database and registry data have reached disparate conclusions on the significance of the interaction on clinical outcomes.^{29–33} In a retrospective analysis of 8205 Veterans Health Administration (VHA) hospital patients discharged following hospitalization for ACS, the receipt of a PPI was associated with an increase in the composite endpoint of death or rehospitalization for ACS in patients who received clopidogrel at discharge (29.8% vs. 20.8%, adjusted OR 1.25, 95% CI, 1.11–1.41).³⁴

The lone randomized study available for review is the COGENT study discussed earlier, which also evaluated the effect of omeprazole on cardiovascular outcomes in clopidogrel treated patients.¹⁹ In COGENT, there was no difference noted in the incidence of the co-primary composite cardiovascular endpoint of CV death, nonfatal MI, coronary revascularization between both groups (4.9% in the omeprazole group vs. 4.9% in the placebo group, HR 0.99; 95% CI, 0.68 to 1.44; $P = 0.96$). See Table 1 for more details on studies discussed.

Conclusion

There is a risk of GI bleed with the use of clopidogrel monotherapy and this risk increases with the

addition of aspirin, which is frequently co-indicated in clopidogrel treated patients. In patients with a prior GI bleed, the risk of a recurrent event is high and strategies to prophylactically reduce this risk must be considered. Presence of other risk factors such as advanced age, concomitant use of NSAIDs, anticoagulants and corticosteroids further amplify the risk. Avoidance of clopidogrel is rarely an option given the effectiveness of clopidogrel in reducing MACE in indicated patients. Additionally, there are inherent risks to premature discontinuation of clopidogrel as highlighted earlier, underlining the need for an effective strategy to prevent GI events.

Evidence for strategies to reduce the risk of a recurrent event in clopidogrel treated patients are limited and focused on acid suppression therapy utilizing PPIs. There is a paucity of high level, randomized data to guide selection of appropriate therapy. The evidence base supporting the role of PPIs is mainly from retrospective, registry and insurance database derived studies and also from studies in aspirin treated patients.^{10,35} Therefore, the data must be interpreted with caution, as retrospective data is highly susceptible to bias and confounding. There is undoubtedly a need for more randomized control trials evaluating this subject given the efficacy associated with clopidogrel and the recent availability of even more potent antiplatelet agents such as prasugrel and ticagrelor.

Patients initiated on clopidogrel should be evaluated for the presence of risk factors for GI bleeds at the start of therapy. Initiation of a PPI is recommended in all patients with a prior GI bleed. The risk of an interaction between PPIs and clopidogrel has not been conclusively determined; therefore, it is reasonable to consider pantoprazole as the PPI of choice for recurrent GI bleeding prophylaxis, as it has been demonstrated to be the least likely to interact with clopidogrel.²⁶

Disclosures

Authors have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed



patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

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