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Review

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Concomitant Gastrointestinal Bleeding Prophylaxis With Dual Antiplatelet Therapy Usage

Dan Lei Zhou[a, f], Muhammad Moiz Tahir[b], Rohma Saleemi[c], Komaldeep Kaur[d], Gursimran Pal Singh Shergill[e]

Abstract

Gastrointestinal bleeding (GIB) is a critical condition that requires effective management, particularly in patients undergoing dual antiplatelet therapy (DAPT) with aspirin and clopidogrel. This literature review examines the comparative efficacy and safety of proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) in preventing GIB among these patients. PPIs have traditionally been the cornerstone for GIB prophylaxis due to their superior acid-suppressive properties and ability to promote ulcer healing. However, concerns about PPIs potentially inhibiting clopidogrel's antiplatelet activity via cytochrome P450 2C19 interactions have led to increased interest in H2RAs as an alternative. Emerging research highlights the contexts where H2RAs may be preferred, including in patients with specific cardiovascular or renal comorbidities. Recent findings also explore the role of potassium-competitive acid blockers (PCABs) as a promising alternative to PPIs. Despite conflicting data, this review underscores the need for personalized treatment strategies based on efficacy, safety, and patient-specific factors to optimize GIB prophylaxis in DAPT patients. Further large-scale studies are recommended to address gaps in the literature and refine clinical guidelines.

Keywords: Gastrointestinal bleeding; GIB prophylaxis; Dual antiplatelet therapy; Proton pump inhibitors; Cardiovascular risk

Introduction

Gastrointestinal bleeding (GIB) is a critical medical condition that necessitates prompt and effective management to prevent severe outcomes. Among the pharmacological interventions available, proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) have been widely used. This literature review aims to compare the efficacy of PPIs and H2RAs in managing GIB, discussing their mechanisms of action, and focusing on the topic of H2RA vs. PPI usage in dual antiplatelet therapy (DAPT) patients.

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[a]Paul L. Foster School of Medicine, Texas Tech Health Sciences Center, El Paso, TX 79905, USA
[b]Department of Internal Medicine, Texas Tech Health Sciences Center, El Paso, TX 79905, USA
[c]Avicenna Medical College, Lahore, Pakistan
[d]Aiken Regional Medical Center, Aiken, SC, USA
[e]Trinity West Hospital, Steubenville, OH, USA
[f]Corresponding Author: Dan Lei Zhou, Paul L. Foster School of Medicine, Texas Tech Health Sciences Center, El Paso, TX 79905, USA.
Email: danzhou@ttuhsc.edu

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Literature Review

Data related to GIB were identified through a systematic search of PubMed (October 21, 2002 to December 23, 2024) using the following search terms: H2RA, PPI, GI Bleed. Additional search terms were included for the usage of H2RA and PPIs in DAPT (aspirin and clopidogrel) patients.

Mechanisms of Action

PPIs and H2RAs both reduce gastric acid secretion but operate through different mechanisms.

PPIs, such as omeprazole and pantoprazole, irreversibly inhibit the hydrogen-potassium ATPase (H^+/K^+-ATPase) enzyme in the parietal cells of the stomach, leading to a significant and sustained reduction in gastric acid production. H^+/K^+-ATPase is a proton pump that uses energy from ATP hydrolysis to exchange intracellular H^+ with extracellular K^+, pumping hydrogen ions into the lumen of the stomach from the apical cell membrane of parietal cells.

H2RAs, including ranitidine and famotidine, are competitive antagonists of histamine H2 receptors on parietal cells. This reduces adenylyl cyclase activity, which then leads to a decrease in cyclic adenosine monophosphate (AMP) levels and protein kinase A activity, which then results in decreased phosphorylation and activation of H^+/K^+-ATPase.

Efficacy in GIB

PPIs

PPIs have been extensively studied for their role in managing upper gastrointestinal bleeding (UGIB), particularly from

peptic ulcers (PUs). Even since the 2000s, studies have shown that PPI treatment in PU bleeding have been superior to H2RAs by effectively stabilizing a clot over a bleeding ulcer, reducing bleeding and the need for surgery [1]. Furthermore, a study by Barinov et al (2014) showed that PPIs had a greater anti-inflammatory effect in modulating the reparative process and mucous/bicarbonate barrier of the marginal zone of gastric and duodenal ulcers in comparison to H2RAs [2]. Not only are PPIs effective at preventing and stopping UGIB, but they also block acid secretion from parietal cells in the stomach and promote ulcer healing. It was found that giving PPIs before endoscopy (EGD) for UGIB resulted in reduced requirement of endoscopic hemostatic treatment during EGD [3]. Long-term PPI usage has been shown to decrease the chance of UGIB occurrence [4]. PPIs have also been known as the cornerstone treatment of gastroesophageal reflux disease (GERD), where they have been deemed a safe and efficient long-term treatment [5].

Recent studies continue to support the efficacy of PPIs, which continue to be the mainstay of treatment for peptic ulcer disease (PUD). However, new research shows that potassium-competitive acid blockers (PCABs) may be an alternative to PPIs for acid suppression. One meta-analysis showed that vonoprazan was superior to PPI in *H. pylori* eradication and erosive esophagitis but not in GERD symptoms or the healing of gastric and duodenal ulcers [6]. However, some randomized controlled trials (RCTs) have shown that PCABs performed better than PPIs in GERD and had less adverse side effects, so this topic could be further explored by large-scale RCTs [7].

H2RAs

H2RAs were the first class of acid-suppressive medications used to treat PUD and associated bleeding. However, their efficacy in managing acute GIB has been less impressive compared to PPIs.

Areas where H2RAs might be preferred to PPIs included: 1) stress ulcer prophylaxis (SUP) in critically ill patients (PPIs associated with increased mortality in critical care) [8]; 2) East Asian nonsteroidal anti-inflammatory drug (NSAID)-induced ulcer prophylaxis (Japan specifically) [9]; 3) in patients with heart failure or DAPT usage [10]; and 4) chronic kidney disease (CKD)/end-stage renal disease (ESRD) patients [11] as well as cirrhotic patients with ascites [12].

This paper will focus only on the prophylaxis of GIB in DAPT (aspirin and clopidogrel) patients. Studies have shown that up to 9.2% of patients treated with DAPT experienced UGIB, which has been shown to be much higher than patients taking only aspirin alone [13]. Furthermore, GIB associated with percutaneous coronary intervention (PCI) was found to be associated with early mortality and longer hospital stays. Common causes of GIB include PUD, gastritis, vascular malformations, and diverticular bleeding. One study which retrospectively analyzed 243 patients post stent implantation on DAPT found that out of the 108 patients taking PPIs or H2RAs, none of the patients had any UGIB [14]. Therefore, UGIB in patients being treated with DAPT is preventable, but clinicians need to choose which antisecretory drug to use.

Although PPIs offer higher efficacy in the prophylaxis of GIB over H2RAs, H2RAs may be preferred in DAPT patients due to PPIs being linked to an increase in cardiovascular events. The pharmacological basis is as follows: CYP2C19 is required to transform clopidogrel into an active metabolite to prevent major cardiovascular events when given together with aspirin. PPIs competitively inhibit the CYP2C19 enzyme, resulting in decreased active clopidogrel metabolites and attenuation of the antiplatelet efficiency of clopidogrel [15].

There is an extensive history of the associations between PPI and clopidogrel use. The Food and Drug Administration (FDA) released a statement in 2009 warning about the interaction between PPIs and clopidogrel. The FDA then revised their statement to discourage the concomitant use of clopidogrel with omeprazole or esomeprazole but had insufficient information on the rest of PPIs [16]. Other regulatory agencies such as the European Medicines Agency (EMA), Medicines and Healthcare products Regulatory Agency (MHRA), and European Society of Cardiology released their own similar statements afterward. However, it was found that despite recommendations made by these regulatory authorities, physicians in the Netherlands continued to prescribe esomeprazole alongside clopidogrel usage, placing patients at risk for cardiovascular events, although at a lower rate than before advice from regulatory authorities were given [17]. The authors of this study stated that this was probably due to existing scientific doubt about the interaction between the two drugs. There had only been a few clinical trials done on the interaction between the two drugs before the FDA released their cautionary advice, none of which was conclusive.

The FDA's main evidence for their stance came from small pharmacodynamic trials, which compared unusually high doses of omeprazole (80 mg daily) to pantoprazole (80 mg daily) alongside 300 mg Plavix. The FDA then stated that omeprazole had higher CYP2C19 inhibitory activity than pantoprazole given the increase in platelet inhibition (day 5: 21% vs. 11%) respectively. However, this study did not consider other PPIs or significant clinical events and only measured the plasma concentrations of the clopidogrel active metabolite and the degree of platelet inhibition. Before the FDA released their advice, a cohort study was done which showed that PPI had increased efficacy in preventing GIB in comparison to H2RAs in patients taking DAPT (aspirin and clopidogrel) that did not report any increase in cardiovascular events [18]. A randomized trial of omeprazole vs. placebo in DAPT (aspirin and clopidogrel) users showed no statistically significant change in cardiovascular events and omeprazole showed increased efficacy in preventing GIB in comparison to placebo [19]. Furthermore, a nested case-control analysis saw that the usage of acid-suppressing drugs (PPIs, H2RAs) was increased before the occurrence of ischemic events, which could result in these drugs being a confounder in the PPI-clopidogrel interaction [20]. Overall, clinical evidence was nonconclusive or even opposed to the recommendations given by regulatory bodies.

Recent Research and Emerging Insights

H2RAs became more popular in recent years after more research was published. In 2012, a case-control study was done

on 176 patients on DAPT who were then either treated with a PPI or H2RA [21]. At 36 months follow-up, the prevalence of acute coronary syndrome (ACS) events was statistically significantly higher in the PPI group than in the H2RA group. Of note, the PPIs associated with increased risk of adverse outcomes after PCI with drug-eluting stent implantation only included omeprazole and esomeprazole. Pantoprazole and lansoprazole were found to be safer to use. In 2013, a retrospective cohort study was published where the incidence of UGIB and major adverse cardiovascular events (MACEs) was observed between 296 patients treated with H2RA and 447 patients who were not treated with H2RAs during DAPT after drug-eluting stent implantation [22]. It was found that H2RA successfully reduced UGIB compared to the control group at 1-year follow-up and that the H2RA group had a nonsignificant decreased incidence of MACE compared to the control group. In 2014, an RCT of 20 Japanese volunteers was stratified by their CYP2C19 genotypes, and it was found that famotidine did not attenuate the antiplatelet effect of clopidogrel regardless of metabolization rates [23]. A systematic review performed in 2016 that included 37 studies concluded that PPI use was associated with an increased risk of cardiovascular morbidity and all-cause morbidity but stated that further research in the area was required [24].

Conflicting information was then published in 2019, where 160 Chinese patients using DAPT were treated with either esomeprazole 40 mg/day or famotidine 40 mg/day, and their platelet reactivity was measured via adenosine diphosphate (ADP)-induced light transmittance aggregometry (LTA) and vasodilator-stimulated phosphoprotein phosphorylation-platelet reactivity index (VASP-PRI) [25]. It was found that there were no significant differences in platelet activity between the two drugs. However, this study did not look at any clinically significant adverse events as well as comparison between other PPIs of the same class, did not distinguish the genetic polymorphism of CYP2C19, and had a short follow-up period (14, 30 days). In 2023, a systematic review and meta-analysis that pooled 18 studies with a total of 173,508 patients revealed that PPIs significantly increased the risk of MACE (hazard ratio (HR): 1.15, 95% confidence interval (CI): 1.06 - 1.26, P = 0.001) over 12 months of follow-up [26]. However, there was no significant difference between net clinical adverse events or all-cause mortality between PPI or non-PPI users on DAPT with coronary heart disease (CHD).

Recently, a 2024 retrospective study looked at antisecretory agents prescribed after 23,000 Korean patients from the National Inpatient Sample during 2009 - 2020 who were started on DAPT and found that less H2RAs were being prescribed (82.5% to 25.3%) and instead more PPIs were being prescribed (4.2% to 30.7%), with PCABs found to be at 7.8% in 2020 [27]. Authors remarked that despite studies having shown that PPIs could increase the risk of cardiovascular events, PPIs were still being increasingly prescribed. However, it is important to note that this study only looked at a very specific demographic and may not be representative of prescribing behavior in the rest of the world.

Conclusion

In the management of GIB, PPIs have demonstrated superior efficacy compared to H2RAs. They are also the cornerstone of SUP and treatment of GERD. However, PCABs may be a promising new alternative for patients who tolerate PPIs poorly or are PPI-resistant. Emerging evidence suggests that H2RAs may be preferable in specific clinical scenarios. Given the potential for PPIs to inhibit CYP2C19-mediated clopidogrel activation, their use should be carefully considered in patients at high cardiovascular risk. In contrast, H2RAs provide a safer alternative without interfering with clopidogrel metabolism, making them a reasonable choice for DAPT patients with a lower risk of ulceration or GIB. Clinicians should weigh the benefits and risks of both therapies based on individual patient factors, including bleeding risk, cardiovascular status, and prior ulcer history. Future large-scale RCTs are warranted to further refine the optimal approach to GIB prophylaxis in this population.

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None to declare.

Conflict of Interest

None to declare.

Author Contributions

Dan Lei Zhou: conducted literature review and drafted manuscript. Dr. Muhammad Moiz Tahir: concept, final review, and supervising author. Rohma Saleemi: reviewer. Komaldeep Kaur: reviewer. Gursimran Pal Singh Shergill: reviewer.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

ACS: acute coronary syndrome; ADP: adenosine diphosphate; AMP: adenosine monophosphate; ATP: adenosine triphosphate; CHD: coronary heart disease; CKD: chronic kidney disease; CYP2C19: cytochrome P450 2C19; DAPT: dual antiplatelet therapy; EGD: endoscopy; EMA: European Medicines Agency; ESRD: end-stage renal disease; FDA: Food and Drug

Administration; GERD: gastroesophageal reflux disease; GI: gastrointestinal; H2RAs: histamine-2 receptor antagonists; H^+/K^+-ATPase: hydrogen-potassium ATPase; LTA: light transmittance aggregometry; MACEs: major adverse cardiovascular events; MHRA: Medicines and Healthcare products Regulatory Agency; NSAID: nonsteroidal anti-inflammatory drug; PCABs: potassium-competitive acid blockers; PCI: percutaneous coronary intervention; PPIs: proton pump inhibitors; PU: peptic ulcer; PUD: peptic ulcer disease; RCTs: randomized controlled trials; SUP: stress ulcer prophylaxis; UGIB: upper gastrointestinal bleeding; VASP-PRI: vasodilator-stimulated phosphoprotein phosphorylation-platelet reactivity index

References

1. Leontiadis GI, Sharma VK, Howden CW. Proton pump inhibitor treatment for acute peptic ulcer bleeding. Cochrane Database Syst Rev. 2006;1:CD002094. doi pubmed
2. Barinov EF, Kondratenko PG, Sulaeva ON, Zharikov SO, Radenko EE, Tverdokhleb TA. [The impact of antisecretory therapy on gastroduodenal ulcers healing after acute bleeding]. Khirurgiia (Mosk). 2014;3:15-19. pubmed
3. Kanno T, Yuan Y, Tse F, Howden CW, Moayyedi P, Leontiadis GI. Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding. Cochrane Database Syst Rev. 2022;1(1):CD005415. doi pubmed
4. Masso Gonzalez EL, Garcia Rodriguez LA. Proton pump inhibitors reduce the long-term risk of recurrent upper gastrointestinal bleeding: an observational study. Aliment Pharmacol Ther. 2008;28(5):629-637. doi pubmed
5. Pohle T, Domschke W. Results of short-and long-term medical treatment of gastroesophageal reflux disease (GERD). Langenbecks Arch Surg. 2000;385(5):317-323. doi pubmed
6. Simadibrata DM, Syam AF, Lee YY. A comparison of efficacy and safety of potassium-competitive acid blocker and proton pump inhibitor in gastric acid-related diseases: A systematic review and meta-analysis. J Gastroenterol Hepatol. 2022;37(12):2217-2228. doi pubmed
7. Shehryar M, Ahmad RU, Kareem HK, Khan L, Ashraf MF, Hassan A, Saeed S, et al. Efficacy, safety and cost-effectiveness of vonoprazan vs Proton Pump Inhibitors in reflux disorders and H. pylori eradication: A literature review. Ann Med Surg (Lond). 2022;82:104760. doi pubmed
8. Lee TC, Goodwin Wilson M, Lawandi A, McDonald EG. Proton pump inhibitors versus histamine-2 receptor antagonists likely increase mortality in critical care: an updated meta-analysis. Am J Med. 2021;134(3):e184-e188. doi pubmed
9. Nakashima S, Arai S, Mizuno Y, Yoshino K, Ando S, Nakamura Y, Sugawara K, et al. A clinical study of Japanese patients with ulcer induced by low-dose aspirin and other non-steroidal anti-inflammatory drugs. Aliment Pharmacol Ther. 2005;21(Suppl 2):60-66. doi pubmed
10. Khawaja M, Thakker J, Kherallah R, Kitakaze M, Jneid H, Angiolillo DJ, Birnbaum Y. Antacid therapy in coronary artery disease and heart failure: proton pump inhibitors vs. H(2) receptor blockers. Cardiovasc Drugs Ther. 2024;38(1):181-189. doi pubmed
11. Al-Aly Z, Maddukuri G, Xie Y. Proton pump inhibitors and the kidney: implications of current evidence for clinical practice and when and how to deprescribe. Am J Kidney Dis. 2020;75(4):497-507. doi pubmed
12. Choi EJ, Lee HJ, Kim KO, Lee SH, Eun JR, Jang BI, Kim TN. Association between acid suppressive therapy and spontaneous bacterial peritonitis in cirrhotic patients with ascites. Scand J Gastroenterol. 2011;46(5):616-620. doi pubmed
13. Yasuda H, Matsuo Y, Sato Y, Ozawa S, Ishigooka S, Yamashita M, Yamamoto H, et al. Treatment and prevention of gastrointestinal bleeding in patients receiving antiplatelet therapy. World J Crit Care Med. 2015;4(1):40-46. doi pubmed
14. Yasuda H, Yamada M, Sawada S, Endo Y, Inoue K, Asano F, Takeyama Y, et al. Upper gastrointestinal bleeding in patients receiving dual antiplatelet therapy after coronary stenting. Intern Med. 2009;48(19):1725-1730. doi pubmed
15. Sharma RK, Reddy HK, Sharma RK, Moazazi M, Elango L, Singh VN, Williams DK, et al. The interaction between clopidogrel and proton pump inhibitors (PPI): is there any clinical relevance? Clin Pharmacol. 2010;2:155-162. doi pubmed
16. Saiz LC, Alvarez J, Martinez H. Drug regulatory agencies' role in the interaction between clopidogrel and proton pump inhibitors. Am J Gastroenterol. 2011;106(7):1369-1370. doi pubmed
17. Kruik-Kolloffel WJ, van der Palen J, Kruik HJ, van Herk-Sukel MP, Movig KL. Prescription behavior for gastroprotective drugs in new users as a result of communications regarding clopidogrel - proton pump inhibitor interaction. Pharmacol Res Perspect. 2016;4(4):e00242. doi pubmed
18. Ng FH, Lam KF, Wong SY, Chang CM, Lau YK, Yuen WC, Chu WM, et al. Upper gastrointestinal bleeding in patients with aspirin and clopidogrel co-therapy. Digestion. 2008;77(3-4):173-177. doi pubmed
19. Bhatt DL, Cryer BL, Contant CF, Cohen M, Lanas A, Schnitzer TJ, Shook TL, et al. Clopidogrel with or without omeprazole in coronary artery disease. N Engl J Med. 2010;363(20):1909-1917. doi pubmed
20. Blackburn DF, Lamb DA, McLeod MM, Eurich DT. Increased use of acid-suppressing drugs before the occurrence of ischemic events: a potential source of confounding in recent observational studies. Pharmacotherapy. 2010;30(10):985-993. doi pubmed
21. Macaione F, Montaina C, Evola S, Novo G, Novo S. Impact of dual antiplatelet therapy with proton pump inhibitors on the outcome of patients with acute coronary syndrome undergoing drug-eluting stent implantation. ISRN Cardiol. 2012;2012:692761. doi pubmed
22. Yasu T, Sato N, Kurokawa Y, Saito S, Shoji M. Efficacy of H2 receptor antagonists for prevention of upper gastrointestinal bleeding during dual-antiplatelet therapy.

Int J Clin Pharmacol Ther. 2013;51(11):854-860. doi pubmed
23. Uotani T, Sugimoto M, Nishino M, Ichikawa H, Sahara S, Yamade M, Iwaizumi M, et al. Prevention of gastric mucosal injury induced by anti-platelet drugs by famotidine. J Clin Pharmacol. 2014;54(8):858-864. doi pubmed
24. Shiraev TP, Bullen A. Proton pump inhibitors and cardiovascular events: a systematic review. Heart Lung Circ. 2018;27(4):443-450. doi pubmed
25. Wu Y, Chen C, Luo Y, Yu W, Huang S, Lin D. The effect of esomeprazole vs famotidine on aspirin/clopidogrel dual therapy after percutaneous coronary intervention. Adv Clin Exp Med. 2019;28(11):1519-1524. doi pubmed
26. Luo X, Hou M, He S, Yang X, Zhang P, Zhao Y, Xing H. Efficacy and safety of concomitant use of proton pump inhibitors with aspirin-clopidogrel dual antiplatelet therapy in coronary heart disease: A systematic review and meta-analysis. Front Pharmacol. 2022;13:1021584. doi pubmed
27. Lee Y, Choi HJ, Park S, Je NK. Temporal trends in use of antisecretory agents among patients administered clopidogrel-based dual antiplatelet therapy after percutaneous coronary intervention. Pharmacoepidemiol Drug Saf. 2024;33(6):e5816. doi pubmed