Original Research

GASTROENTEROLOGY

Association between proton pump inhibitors and anti-coagulants for a better prevention of gastrointestinal bleeding

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Abstract

Background and aim. Gastrointestinal bleeding (GIB) is one of the most common medical emergencies. Proton pump inhibitors (PPI) are among the most widely used drugs in gastroenterology to treat various types of acid-related disorders. We aim to investigate the safety of proton pump inhibitors (PPIs) when used concurrently with anticoagulants in patients with upper and lower gastrointestinal bleeding (GIB) and assess the risk of hospitalization, GIB, and mortality in patients receiving this combined treatment.

Methods. A retrospective multicenter study was conducted at two tertiary care hospitals. Patients were selected according to inclusion and exclusion criteria. Demographic data, vital signs, medical history, physical examinations, comorbid conditions, medications, laboratory investigations, endoscopy findings, management, and complications were retrieved from the medical records of all participants.

Data obtained from all patients' medical records were reviewed. Endoscopic findings and management of the bleeding site were collected according to the presenting symptoms. Statistical analyses were performed using IBM SPSS version 25.0 software.

Results. Our results revealed a significant increase in acute GIB risk with the number of concurrent anticoagulants used, particularly in patients not using PPIs. Those using four anticoagulants along with PPIs had a lower likelihood of acute GIB at 6.3% ($P = 0.0001$). Patients taking two or three anticoagulants also experienced reduced GIB risk when PPIs were added ($P \leq 0.05$). Age played a role, with a statistically significant difference between PPI users and non-users, especially in the 31-40 age group, where PPI users had a higher incidence of GIB (69.80%) compared to non-users (30.20%) ($P < 0.05$). Comparing patients on anticoagulants with or without PPIs, the study found a lower risk of hospitalization (adjusted hazard ratio, AHR: 1.02; 95% CI: 0.92-1.57) and mortality (AHR: 1.00; 95% CI: 0.84-1.11) in those using Rivaroxaban and PPIs concurrently. By contrast, patients using Rivaroxaban alone without PPIs faced an increased risk of hospitalization (AHR: 1.15; 95% CI: 0.98-2.35) and mortality (AHR: 1.12; 95% CI: 0.90-1.37).

Conclusions. Combining PPIs with anticoagulant drugs reduced the risk of GIB, hospitalization, and mortality, particularly in older adults, thereby mitigating potential complications.

Keywords: gastrointestinal bleeding, proton pump inhibitors, anticoagulants, geriatric, acid release

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Introduction

Proton pump inhibitors (PPI) are widely used to treat various acid disorders such as gastroesophageal reflux syndrome (GERD), upper gastrointestinal bleeding (UGIB), certain subtypes of dyspepsia, peptic ulcers, and erosive esophagitis (ERD) [1-5]. Although PPIs effectively suppress gastric acid production in the stomach and proximal duodenum, their acid-neutralizing effect diminishes in the more distal sections of the gastrointestinal tract [6].

Gastrointestinal bleeding (GIB) refers to bleeding of any part of the gastrointestinal tract (GIT), including upper gastrointestinal bleeding (UGB) which originates from the esophagus, stomach, or duodenum and lower gastrointestinal bleeding (LGIB) which originates from the large or small intestine [7]. In a recent local study, GIB represented 8.8% of all bleeding cases presented to the emergency department (ED). About 37% of patients were observed with one-time GIB, while the majority bled several times [8]. Whereas the prevalence of lower GIB appears to increase with age, upper GIB rates have shown a decline, potentially attributed to interventions such as PPI therapy [9]. Nonetheless, GIB may cause major and extensive bleeding that leads to eventual death [10].

According to some studies, PPI reduces the incidence of acute GIB in some anticoagulant users by up to 40% [11]. Literature comparing patients using PPI and histamine-II receptor blockers as prophylaxis for stress ulcers showed an increased mortality rate during hospitalization (23.8%) and GIB (8.9%) in the PPI group compared to the histamine-II receptor blockers group [12].

Despite the common use of PPI and the significant morbidity and mortality of GIB, few published studies show the extent of their association. Existing studies have highlighted the lack of evidence-based guidelines for PPI use in large patient populations, particularly in the context of concomitant anticoagulant therapy [13]. This knowledge gap is especially pronounced in Saudi Arabia, where data on the safety and efficacy of PPI and anticoagulant co-therapy for GIB are scarce. This study aimed to examine the safety of PPIs in patients with a history of both upper and lower GIB who were also receiving anticoagulant therapy. In addition, we examined the risk of hospitalization, GIB, and mortality among patients receiving anticoagulants and PPIs concurrently.

We hypothesize that the use of PPIs in conjunction with anticoagulants reduces the risk of GIB, hospitalization, and mortality. Additionally, we hypothesize that patients receiving anticoagulants without PPIs may experience higher rates of GIB, leading to worse clinical outcomes.

Methods

Study design, setting, and sample size

This multicenter, retrospective cohort study was conducted at two tertiary care hospitals, King Abdulaziz Medical City and King Fahad Medical City, Riyadh, Kingdom of Saudi Arabia, from January 2010 to January 2020. The study included a total of 760 cases, and data were collected using a convenience sampling technique. The sample size was calculated using the Rao Soft calculator based on an anticipated effect size and the prevalence of gastrointestinal bleeding (GIB) among the population.

Inclusion/exclusion criteria

The study included reported cases of gastrointestinal bleeding (GIB) among patients of both genders, aged over eighteen years, who visited the emergency department of either of the two hospitals due to GIB or developed GIB during hospitalization within the study period. All patients with confirmed GIB, irrespective of the underlying cause, comorbidities, bleeding location, or concomitant medications, were eligible for inclusion. Exclusion criteria were strictly adhered to and included cases with incomplete medical records lacking essential information, as well as cases where endoscopy reports were unavailable. Given the retrospective nature of the study, informed consent was not required, but efforts were made to ensure the reliability of data by adhering to standardized medical record documentation protocols.

Data collection

Data collection was carefully structured to minimize biases that may arise from the retrospective design. Two independent researchers collected data from all enrolled cases using Microsoft Excel 2016. To ensure data accuracy and consistency, a senior researcher regularly reviewed the collected data and resolved any discrepancies between the two independent reviewers. Comprehensive data were extracted from each patient's medical records, including demographics, vital signs, medical history, physical examinations, comorbidities, medication profiles (including PPI, NSAIDs, anti-platelet drugs, and anticoagulants administration), laboratory investigations (such as blood glucose test, lipid profile, complete blood count, and coagulation test), radiological investigations, endoscopy findings (esophagogastroduodenoscopy [EGD], endoscopy capsule, and colonoscopy), cause and stage of liver disease, management, and complications.

Efforts were made to minimize bias related to missing or incomplete data by performing quality checks on the data extracted from the hospital's electronic medical records (EMRs), which are regularly updated and audited to ensure accuracy. To further ensure the robustness of the data, variables were cross-verified with multiple entries in the medical records where possible.

Statistical analysis

The data were analyzed using SPSS (Statistical Package for Social Sciences) version 25.0. Given the diversity of variables collected, we employed both descriptive and inferential statistical methods. For

continuous variables such as age and lab values, mean and standard deviation were calculated. For categorical variables like the presence or absence of certain medications (PPI, anticoagulants, etc.), frequency and percentage were calculated. To justify the selection of statistical tests, the t-test was chosen for continuous variables due to its robustness in comparing mean differences between two independent groups (e.g., patients using PPI vs. non-PPI users). For categorical variables, the chi-square test was used to compare proportions, as it is a well-suited method for analyzing the association between categorical variables in large datasets like ours. Additionally, logistic regression was employed to assess the individual contribution of risk factors (such as the use of PPIs, NSAIDs, and anticoagulants) on key outcomes like GIB recurrence, hospitalization, and mortality. This method allowed us to control for potential confounders and to provide an adjusted hazard ratio (AHR) with a 95% confidence interval, thus allowing for a more nuanced analysis of how these factors independently affected patient outcomes. The decision to use logistic regression was based on its ability to handle multiple covariates simultaneously, making it particularly useful in retrospective cohort studies where many variables may interact. In response to concerns about potential biases introduced by the retrospective nature of the study, we acknowledge that retrospective designs inherently carry risks of selection bias and information bias. However, we mitigated these biases by utilizing a standardized data extraction process and performing regular reviews to ensure data accuracy. Furthermore, as data were collected from hospital EMRs, which were subjected to routine audits, we believe that this would minimize the potential risk of data errors or inconsistencies. A p-value of less than 0.05 was considered statistically significant ($P < 0.05$), as per standard statistical conventions, ensuring that the likelihood of Type I errors (false positives) remained acceptably low.

Results

Our study included 760 patients (mean age ± SD: 62.69 ± 17.81 years) with a history of GIB. Out of those, 642 were from the National Guard Hospital and 118 from King Fahad Medical City. The majority were male (n = 467, 61.4%), Arab constituted 99.2%, and 97% were residents of Riyadh City. Additional demographic data revealed that 3.7% were smokers, 1.3% reported alcohol consumption, and 86.1% were married. These findings provide a representative demographic profile of the population studied, with most patients having risk factors commonly associated with GIB. Regarding medical history, 13.7% of patients had a history of esophageal varices, 6.2% had peptic ulcers, and 2.4% had portal vein thrombosis (PVT). The most prevalent comorbidities were hypertension (54.1%) and diabetes mellitus (51.2%), conditions which are known to potentially exacerbate the risk of GIB. Additionally, ischemic heart disease (18.2%), chronic liver disease (12.4%), and chronic pulmonary disease (4.6%) were present among the patients. The high prevalence of these comorbidities suggests a complex health profile that could influence the clinical management of GIB, including the decision to prescribe acid-suppressing therapy.

PPI use was reported in 48.9% of patients, highlighting its widespread use for either prophylactic or therapeutic purposes for acid-related conditions (Table I).

Table I. Demographic and clinical characteristics of the study population.

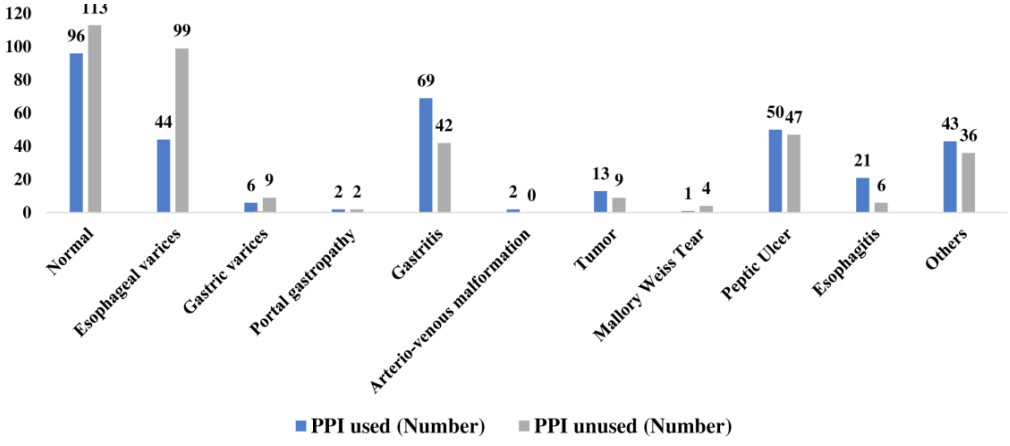
Characteristics	All Patients N (%)	Proton Pump Inhibitors	
		Used N (%)	Unused N (%)
Gender			
Male	467 (61.4)	207 (44.3)	260 (55.7)
Female	293 (38.6)	145 (49.5)	148 (50.5)
Marital status			
Married	652 (85.8)	323 (49.5)	329 (50.5)
Single	69 (9.1)	16 (23.2)	53 (76.8)
Unknown	39 (5.1)	13 (33.3)	26 (66.7)
Risk Factors			
Esophageal varices	104 (13.7)	34 (32.7)	70 (67.3)
Peptic ulcer	47 (6.2)	23 (49)	24 (51)
Portal vein thrombosis	18 (2.4)	5 (27.8)	13 (72.2)
Comorbidities			
Hypertension	411 (54.1)	255 (62)	156 (38)
Diabetes	389 (51.2)	222 (57)	167 (43)
Ischemic heart disease	138 (18.2)	97 (70.3)	41 (29.7)
Chronic liver disease	94 (12.4)	32 (34)	62 (66)
Chronic pulmonary disease	35 (4.6)	17 (48.6)	18 (51.4)

We examined the impact of PPI administration on GIB in conjunction with various anticoagulants. Our findings revealed that in patients who take anticoagulants without concurrent PPI, there was a significant increase in the risk of acute GI bleeding with the increase in the number of anticoagulants used. Patients who used 4 anticoagulants and PPI simultaneously were less likely to have acute GI bleeding, constituting 6.3% (P = 0.0001). Reduced GI bleeding was also reported in patients using two and three anti-coagulants, as a significant difference was observed among both groups upon the addition of PPIs (P <0.05) (Table II).

Of all GIB cases, 54.8% of PPI users experienced upper GIB, while 44.1% had lower GIB. Endoscopic findings for upper GIB included esophageal varices (143/760, 18.8%), gastritis (110/760, 14.5%), peptic ulcer (97/760, 12.8%), esophagitis (26/760, 3.4%), benign tumors (22/760, 2.9%), gastric varices (15/760, 2%), portal hypertensive gastropathy (4/760, 0.5%), esophageal (Mallory-Weiss) tear (3/760, 0.4%), arteriovenous malformation (1/760, 0.1%), and other causes (78/760, 10.3%). Endoscopy was negative for 209/760 (27.5%) patients. Lower GIB bleeding from the total cases used for PPI accounted for 47.2%, including hemorrhoids in 163/760 (21.4%), polyps 84/760 (11.1%), diverticular disease 67/760 (8.8%), ulcers 58/760 (7.6%), benign tumors 27/760 (3.6%), malignant tumors 19/760 (2.5%), angiodysplasia 13/760 (1.7%), and colonic/rectal varices 5/760 (0.7%), while the other causes 37/760 (4.9%). Endoscopy was negative in 160/760 (21.1%) (Figures 1 and 2).

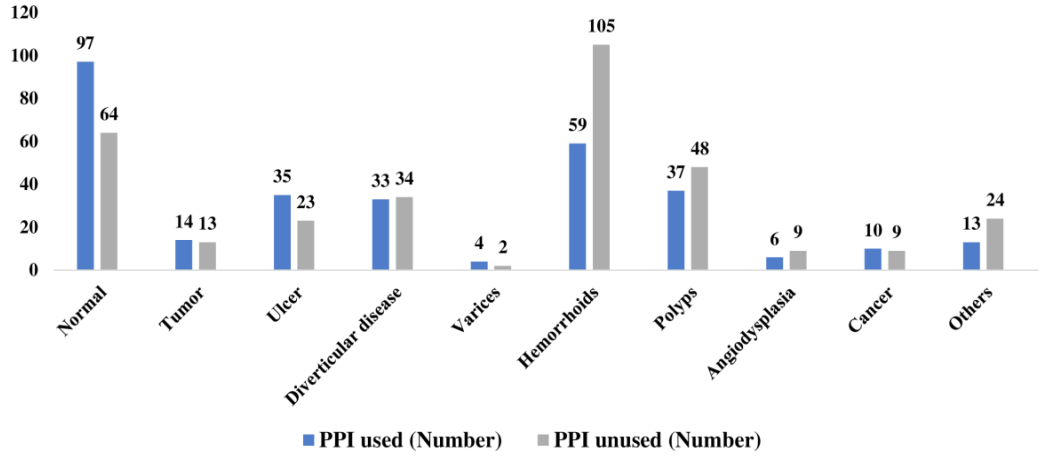
Table II. The relation between PPI and anticoagulant use and GI bleeding.

Number of anti-coagulant drugs	PPI				P-value
	Used		Unused		
	Count	Percentage %	Count	Percentage %	
None	222	74.00%	78	26.00%	0.19
Used 1	107	48.90%	112	51.10%	0.07
Used 2	42	28.00%	108	72.00%	<.001*
Used 3	14	20.30%	55	79.70%	0.02*
Used 4	1	6.30%	15	93.80%	0.0001*
Used 5	1	33.30%	2	66.70%	0.12
Used 6	1	33.30%	2	66.70%	0.44



PPI: Proton pump inhibitors

Figure 1. Endoscopic findings for upper GI bleeding in relation to PPI use.



PPI: Proton pump inhibitors

Figure 2. Endoscopic findings for lower GI bleeding in relation to PPI use.

Table III. The relation between PPI-induced GI bleeding and age.

Age	Proton Pump Inhibitors (PPI)				P-value
	Used		Unused		
	Count	Percentage %	Count	Percentage %	
< 30	28	51.90%	26	48.10%	1.18
31 - 40	37	69.80%	16	30.20%	<0.05*
41 - 50	41	59.40%	28	40.60%	0.048*
51 -60	67	50.76%	65	49.24%	0.08
61 - 70	79	51.60%	74	48.40%	0.12
>70	136	45.50%	163	54.50%	1.07

PPI: Proton Pump Inhibitors

The relationship between PPI use and GIB also showed age-related differences. In the age group 31-40 years, PPI users experienced significantly higher rates of GIB (69.8%) compared to non-users (30.2%), with a statistically significant difference ($P < 0.05$). Similarly, a significant increase in GIB cases was noted in the age group 41-50 years among PPI users (59.4%) compared to non-users (40.6%) ($P = 0.048$). These findings suggest that younger patients on PPIs may have different risk profiles or underlying conditions predisposing them to GIB, warranting further investigation into age-specific management strategies (Table III).

The comparison of hospitalization incidence, GIB, and mortality between patients using anticoagulants with and without PPI co-treatment is presented in Table IV. The use of Rivaroxaban combined with PPIs was associated with a reduced risk of GI bleeding (Adjusted Hazard Ratio [AHR]: 0.81; 95% Confidence Interval [CI]: 0.67-0.89) compared to Rivaroxaban alone. Similarly, combining PPIs with Dabigatran or Apixaban resulted in lower AHRs for GI bleeding and mortality, suggesting a beneficial effect of PPI co-therapy. These findings emphasize the clinical importance of adjusting anticoagulant treatment regimens to include PPI therapy in order to minimize adverse outcomes, particularly in patients with a high risk of GI bleeding.

The adjusted hazard ratios reported in table IV indicate that patients on anticoagulants with PPI co-treatment had a lower relative risk of hospitalization and mortality compared to those not receiving PPIs. For example, the AHR for hospitalization was 1.02 (95% CI: 0.92-1.57) for Rivaroxaban with PPI use versus 1.15 (95% CI: 0.98-2.35) without. These data highlight the potential of PPIs to offer additional protection beyond their acid-suppressing effects, particularly in complex cases involving multiple anticoagulant therapies.

Table IV. Comparison of hospitalization incidence, gastrointestinal bleeding, and mortality in patients with anti-coagulants and co-treatment with proton pump inhibitors.

With concomitant proton pump inhibitors (PPI)										
Anti-coagulant drugs	Hospitalization				GI Bleeding			Mortality		
	N	Events	Adjusted Hazard Ratio	(95% Confidence Interval)	Events	Adjusted Hazard Ratio	(95% Confidence Interval)	Events	Adjusted Hazard Ratio	(95% Confidence Interval)
Rivaroxaban	760	189	1.02	(0.92-1.57)	264	0.81	(0.67-0.89)	403	1.00	(0.84-1.11)
Dabigatran		349	0.81	(0.69-1.03)	97	0.68	(0.59-0.81)	189	0.77	(0.64-0.94)
Apixaban		238	0.78	(0.61-0.93)	116	0.75	(0.68-0.84)	337	0.90	(0.76-1.03)
Non-Vitamin K antagonist		219	0.91	(0.82-1.15)	252	0.68	(0.55-0.83)	311	0.79	(0.62-0.90)
Without concomitant proton pump inhibitors (PPI)										
Anti-coagulant drugs	Hospitalization				GI Bleeding			Mortality		
	N	Events	Adjusted Hazard Ratio	(95% Confidence Interval)	Events	Adjusted Hazard Ratio	(95% Confidence Interval)	Events	Adjusted Hazard Ratio	(95% Confidence Interval)
Rivaroxaban	760	304	1.15	(0.98-2.35)	486	0.97	(0.82-1.04)	447	1.12	(0.90-1.37)
Dabigatran		493	0.89	(0.70-0.98)	258	0.84	(0.76-0.98)	326	0.93	(0.81-0.99)
Apixaban		418	1.03	(0.95-1.29)	502	0.97	(0.91-1.30)	491	1.01	(0.85-114)
Non-Vitamin K antagonist		395	0.99	(0.85-1.05)	322	0.76	(0.61-0.85)	472	0.95	(0.89-1.07)

Discussion

Our study demonstrated the improved safety of PPIs as co-treatment with anticoagulants, resulting in a reduced risk of gastrointestinal bleeding. Our results also supported the statistically significant increase of GIB cases among PPI users in certain age groups compared to non-PPI users, one possible explanation could be the presence of underlying comorbidities and the complexity of medication regimens in older populations, which may predispose them to increased bleeding events, thus warranting further investigation into these factors.

Additionally, we examined the risk of hospitalization, GIB, and mortality in patients using different anti-coagulants with or without PPIs. The results indicated a reduction in the risk of GIB, hospitalization, and mortality with the addition of PPIs to anti-coagulant medicines. Different studies reported a reduced risk of GIB among high-risk patients with the incorporation of PPIs in the treatment regimen of oral anticoagulants [14,15]. A meta-analysis comparing randomized controlled trials (RCTs) of intravenous PPI treatment with an 80-milligram dose as a bolus and then continuous infusion of 8 mg per hour, compared to placebo for a total of seventy-two hours post endoscopy, reported a significant decline in mortality (relative risk: 0.41; 95% CI: 0.20–0.84), and reduced GIB (relative risk: 0.40; 95% CI: 0.28–0.59) among high-risk patients [16,17].

In our study, the risk of GIB was reported as high in PPI users, which aligns with some other studies that have found similar occurrences of GI bleeding. However, our findings differ in the type of bleeding expected. For instance, a study involving 1008 subjects with GIB, all of whom were taking antiplatelet agents, aspirin, anticoagulants, or NSAIDs in conjunction with PPIs, reported a reduced likelihood of upper GIB but not lower GIB [18]. Conversely, studies have reported an increased frequency of lower GIB in patients on platelet agglutination inhibitors with concomitant PPI treatment [19]. Furthermore, our study identified age as a significant factor, with increased GI bleeding cases in older PPI users. This was supported by research indicating the highest protective effect of PPIs among high-risk geriatric patients with a HAS-BLED score greater than three with the use of non-vitamin K anti-coagulant [20]. A multicenter cross-sectional study assessed the effect of aspirin among patients over three months using endoscopic capsule evaluation, reporting mucosal lesions in 57.6% of patients at a minimum of one site. The study analyzed the parallel use of PPI as a self-regulating hazard to mucosal injury [21]. Another RCT divided fifty-seven patients into two groups, one receiving NSAIDs (celecoxib) and the other PPIs for 2 weeks. Capsule endoscopy performed at the start and end of the trial revealed an increased rate of small bowel injury in the PPI group [22].

Literature also reports an increase in PPI-associated injuries such as small bowel wounds from aspirin and NSAIDs, likely due to changes in intestinal microbiota [23-25]. In an animal model, concurrent treatment with PPIs and NSAIDs increased the rate of small bowel ulceration and bleeding. This study observed that PPI treatment was associated with changes in small bowel microbiota,

including a reduction in jejunal actinobacterial and Bifidobacteria species. Probiotic treatment helped restore physiological microbiota and prevented intestinal mucosal injury [26].

Another RCT compared PPI (Omeprazole) combined with aspirin and a probiotic (Lactobacillus casei) versus placebo over ninety days. Endoscopy showed that adding probiotics strengthened the GI mucosal protective layer when combined with NSAID and PPI treatment [27].

Some studies have proposed explanations for the association between the use of PPI and acute LGIB: (1) lack of the PPIs' protective effect in the lower gastrointestinal tract; (2) increased negative influence of aspirin and NSAIDs when used with PPIs; (3) PPIs may enhance pre-existing abrasions; and (4) direct effects of drugs used with PPIs [28-31]. All this evidence suggests that PPIs do not only fail to protect the lower gastrointestinal tract from ulceration but may also increase the risk of LGIB.

In our study, we found that about 48.9% had used PPIs for at least one month before the occurrence of GI bleeding. Although most of the cases experienced acute upper GI bleeding, the source of the bleeding was not always related to the acidic disturbances that PPIs were intended to treat. For instance, in patients treated with PPI for peptic ulcer disease, bleeding might originate from another source unrelated to the initial ulcer. This factor may mask the true incidence of lower GIB, making it appear more common when these other sources are excluded.

Limitations, strengths, and future recommendations

Despite the informative findings in our study regarding the safety and effectiveness of PPIs co-administered with anticoagulant drugs for GIB, it is important to recognize certain study limitations that could influence result interpretation. Firstly, the retrospective study that primarily relies on medical records may not include all relevant variables. This could impact the comprehensiveness of the analysis, as some important factors, such as patient compliance with medication, lifestyle factors (like smoking and diet), or other undocumented treatments, may not have been consistently recorded. Additionally, the retrospective nature limits our ability to control for timing differences in the administration of medications or interventions, which could potentially affect outcomes. For instance, patients may have received PPIs at different stages of their condition, influencing the risk of GIB recurrence or hospitalization.

Using a convenience sampling technique may introduce the risk of selection bias, potentially limiting the generalizability of our conclusions. Patients included in the sample may differ from the broader population, particularly those treated at smaller hospitals or who did not present with severe symptoms. As a result, the findings may not fully represent all patient demographics or healthcare settings, especially in contexts where resources and treatment protocols vary. Moreover, despite thorough statistical analyses, the possible influence of unmeasured confounding factors on the outcomes cannot be entirely ruled out. While we adjusted for several key variables, including age and comorbidities, other confounders, such as differences in clinical practice patterns or physician decision-making processes, might have impacted the results.

An additional limitation is the reliance on medical records, which might be incomplete or inconsistent, potentially leading to information bias. Some patients' records might not fully capture all the medications they were taking or the severity of their condition, which could skew the data analysis. Furthermore, the retrospective nature of the study means that we could not account for all potential biases, such as "immortal time bias", where patients might have been incorrectly classified during periods when they were not truly at risk of the outcome being measured.

Our study's strength lies in its meticulous data collection, involving a broad range of patient demographics, medical history, and medication profiles. Including two tertiary care hospitals in our multicenter approach improves the sample's diversity and representativeness, ensuring a wide range of cases from different backgrounds and health statuses. The substantial cohort size supports the statistical power of our analyses, facilitating strong assessments of the relationships between PPI use, anticoagulant co-treatment, and various clinical outcomes.

We recommend future research to consider prospective designs and controlled interventions to establish causal relationships and exclude potential biases. For instance, randomized controlled trials (RCTs) could offer a more robust understanding of how PPIs interact with anticoagulant therapy in preventing GIB. Prospective studies could also control for the timing and dosing of PPIs more effectively, helping to clarify their protective effect across different stages of treatment.

Additionally, collecting more granular data on patient lifestyle factors, adherence to prescribed therapies, and over-the-counter drug use would provide a more comprehensive picture of the variables that influence GIB outcomes. This should provide a more rigorous framework for evaluating the causal impact of PPIs when administered concurrently with anticoagulant therapy and help address gaps in the current literature.

Conclusions

In conclusion, our study demonstrated that the concomitant use of proton pump inhibitors (PPIs) with anticoagulant therapy significantly reduces the risk of gastrointestinal bleeding, hospitalization, and mortality, particularly in the geriatric population. These findings underscore the importance of integrating PPIs into clinical practice to enhance patient safety and outcomes

when prescribing anticoagulants. Furthermore, this study highlights the need for refined clinical guidelines that consider the risk-benefit profile of PPI use in various patient populations. Future research should focus on elucidating the mechanisms underlying the protective effects of PPIs and evaluating their role in different treatment regimens, thereby providing a robust framework for optimizing anticoagulant therapy while minimizing adverse gastrointestinal events.

Ethical approval

This study was approved by the institutional review boards of the included hospitals (King Abdullah International Medical Research Centre, Riyadh, No. IRBC/0507/21, dated 23 February 2021, and King Fahad Medical City, Riyadh, No. 22-022, dated 26 July 2022. The need for consent was waived because of the retrospective nature of this study. The study was conducted in accordance with the 2010 updated Declarations of Helsinki.

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