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SYSTEMATIC REVIEW OPEN ACCESS

Safety of Potassium-Competitive Acid Blockers Compared With Proton Pump Inhibitors in Patients With Gastroesophageal Reflux Disease and Peptic Ulcer Disease: A Systematic Review and Meta-Analysis

Yewon Jang[1] | Jongho Park[2] | Dahee Kang[1] | Jae Hyun Kim[3] | Hyuk Soon Choi[4] | Ha-Lim Jeon[3] | Hankil Lee[5]

[1]College of Pharmacy, Ajou University, Suwon, Republic of Korea | [2]Department of BioHealth Regulatory Science, Graduate School of Ajou University, Suwon, Republic of Korea | [3]School of Pharmacy and Institute of new Drug Development, Jeonbuk National University, Jeonju, Republic of Korea | [4]Department of Internal Medicine, Korea University College of Medicine, Seoul, South Korea | [5]College of Pharmacy, Ewha Womans University, Seoul, Republic of Korea

Correspondence: Ha-Lim Jeon (hrjeon@jbnu.ac.kr) | Hankil Lee (hankil@ewha.ac.kr)

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ABSTRACT

Background and Aim: Potassium-competitive acid blockers (P-CABs) are a novel class of acid suppressants developed to overcome the limitations of proton pump inhibitors (PPIs), providing rapid and sustained acid suppression. While PPI-related adverse events (AEs) are well-documented, safety data on P-CABs remain limited. This study systematically reviewed AEs of P-CABs compared with PPIs, with a meta-analysis focusing on hypergastrinemia.

Methods: Following a preregistered PROSPERO protocol (CRD42024565011), we searched for randomized controlled trials (RCTs) and observational studies comparing P-CABs and PPIs in patients with gastroesophageal reflux disease or peptic ulcer disease. Frequently reported AEs and serious AEs (SAEs) were qualitatively synthesized; hypergastrinemia was quantitatively analyzed using a random-effects model.

Results: Ten RCTs and one observational study were included. Nine studies reported specific AEs, with diarrhea reported in seven studies and constipation, nasopharyngitis, and liver-related events, each reported in three. Most AEs had reporting rates below 5%, except diarrhea, nasopharyngitis, and upper respiratory tract inflammation, which exceeded 5% in both groups. Fracture demonstrated the largest relative difference between the groups, with a threefold higher rate in the P-CAB group. SAEs were observed in fewer than 10% of patients in both groups in most studies. A meta-analysis of six studies showed greater serum gastrin elevation in the P-CAB group compared with the PPI group (mean difference: 130.92 pg/mL, 95% confidence intervals: 36.37–225.47).

Conclusions: P-CABs demonstrate a comparable AE risk to PPIs but monitoring for hypergastrinemia and hepatic dysfunction is essential. Further research is required to support safer clinical use.

1 | Introduction

Gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD) are among the most common gastrointestinal (GI) disorders worldwide, affecting millions of people and driving a significant increase in the use of acid-suppressant drugs [1, 2]. Acid suppressants, particularly proton pump inhibitors (PPIs), have been widely used for the treatment of these acid-related GI

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conditions [3, 4]. Since their approval by the FDA in 1989, PPIs have been considered the standard therapy, effectively inhibiting gastric acid secretion by irreversibly binding to the H^+/K^+-ATPase in gastric parietal cells [5].

However, despite their widespread use and effectiveness, PPIs have several limitations, including a slow onset of action, the need for acid activation, and interindividual variability in response [6]. Moreover, growing evidence has suggested that long-term PPI use is associated with a range of adverse events (AEs) including abdominal pain, diarrhea, and headache, as well as potential associations with more severe conditions such as fracture risk, pneumonia, infections, anemia, kidney disease, hypomagnesemia, vitamin B12 deficiency, and dementia [7, 8].

These limitations have prompted the development of potassium-competitive acid blockers (P-CABs), a novel class of acid suppressants. P-CABs, unlike PPIs, do not require acid activation and reversibly bind to the H^+-K^+-ATPase. This results in rapid absorption and accumulation in gastric wall cells, thereby allowing P-CABs to achieve superior acid suppression compared to PPIs [9, 10]. Since their first introduction in 2015, prescriptions for P-CABs have notably increased, particularly in Asian countries, including South Korea and Japan [11, 12]. With vonoprazan receiving FDA approval in 2022, clinical interest in P-CABs is rapidly expanding. Nevertheless, evidence regarding their safety profile remains limited, especially in comparison to PPIs.

Previous systematic reviews and meta-analyses comparing the safety profiles of P-CABs and PPIs have evaluated AEs across various indications, including *Helicobacter pylori* (*H.pylori*) infection [13, 14]. In contrast, this study deliberately excluded the indication of *H.pylori* infection, as its standard treatment includes antibiotics, to isolate the potential AEs associated with P-CABs and PPIs in patients with GERD or PUD.

Given the increasing global use of P-CABs and the lack of comparative safety data, this study aims to systematically review and meta-analyze available evidence from randomized controlled trials (RCTs) and observational studies to assess the safety of P-CABs in comparison to PPIs, with a focus on reported AEs.

2 | Methods

The systematic review and meta-analysis were conducted according to a pre-established protocol developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15]. This protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; Registration No. CRD42024565011).

2.1 | Search Strategy

A comprehensive literature search was conducted across three major databases: MEDLINE, Embase, and the Cochrane Library. To enhance the sensitivity of the search strategy, we applied the PICO (Patients, Intervention, Comparison, Outcomes) framework, combining P (GERD, PUD), I (P-CAB), and C (PPI) using the Boolean operator "AND", while excluding the outcomes element to avoid narrowing the scope. The literature search was performed on June 3, 2024, by two independent reviewers, with no restrictions on publication year or language.

2.2 | Selection Criteria

All studies that included randomized clinical trials (RCTs) and observational studies and met the following criteria were included:

1. Studies that included patients with GERD or PUD. GERD included erosive esophagitis (EE) and non-erosive reflux disease (NERD), whereas PUD included duodenal ulcer (DU) and gastric ulcer (GU).
2. Studies in which P-CABs were used as the intervention, including vonoprazan, tegoprazan, revaprazan, fexuprazan, zastaprazan, soraprazan, linaprazan, and keverprazan.
3. Studies that used PPIs as the comparator, including omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, rabeprazole, ilaprazole, tenatoprazole, and s-pantoprazole.
4. Studies that reported any safety-related outcomes.

Additionally, case reports, systematic reviews, cost-utility studies, gray literature, and pilot studies were excluded.

All literature retrieved from the key databases was initially imported in EndNote20 and subsequently exported to Covidence, where duplicates were removed. Two researchers independently screened the studies in two consecutive stages based on pre-established inclusion and exclusion criteria. In the first stage, titles and abstracts were reviewed to select relevant studies. In the second stage, the full texts of these selected articles were examined to exclude studies that did not meet the inclusion criteria. Disagreement between the two researchers was resolved by a third researcher.

2.3 | Data Extraction and Quality Assessment

Data extraction was performed using Microsoft Excel. Following the initial extraction of data from the selected studies by a single researcher, a second researcher independently reviewed the extracted data. Disagreements between the two researchers were resolved by a third researcher. The extracted data included the name of the first author, year of publication, study design, country where the study was conducted, observation period, patient indications, number of patients in the intervention and control groups, active ingredient and dosage of intervention and control drugs, and safety outcomes (specific AE names, frequency, and measurement methods). All specific AE names were standardized to the Preferred Terms (PT) level using the Medical Dictionary for Regulatory Activities (MedDRA) [16].

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The risk of bias for RCTs included in this study was evaluated using the Revised Cochrane Risk-of-Bias Tool for Randomized Trials (RoB2) [17]. The RoB2 tool assesses bias across five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Each domain was rated as having a high, low, or unclear risk of bias.

For observational studies, the risk of bias was assessed using the Risk of Bias in Non-randomized Studies—of Interventions (ROBINS-I) tool [18]. This tool evaluates bias across seven domains: bias due to confounding, bias in selection of participants, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported result. Each domain was rated as having a critical, serious, moderate, or low risk of bias.

2.4 | Qualitative and Quantitative Analysis

For the qualitative analysis, safety outcomes reported as specific AEs were reviewed, with frequently reported AEs (defined as those mentioned in at least three studies) summarized. To minimize potential bias from study-specific findings, specific AEs reported in at least two studies were identified, and the average reporting rates for each AE were calculated. These events were then grouped into broader AE categories. Serious AEs (SAEs) were analyzed separately, and the number and proportion of affected patients were summarized. Additionally, the incidence rates and types of drug-related SAEs, SAEs defined as those likely associated with the study drug, were reported for both the P-CAB and PPI groups.

For the quantitative analysis, hypergastrinemia was evaluated. We focused on this specific AE, as both PPIs and P-CABs are known to elevate serum gastrin levels as a compensatory response to gastric acid suppression [19, 20]. Data on serum gastrin levels were extracted from studies that reported either baseline or end-of-treatment (EoT) values. The increase in serum gastrin levels was calculated as the difference between EoT and baseline values, and the mean difference in these increases between the P-CAB and PPI groups was analyzed. Only studies that reported serum gastrin levels before and after treatment were included in the primary analysis. Subgroup analyses were conducted for individual P-CAB agents to account for potential variations between compounds within the P-CAB class. A random-effects model was employed to account for the heterogeneity across studies, and results were presented visually using a forest plot.

3 | Results

3.1 | Study Selection

A total of 395 studies were identified and imported into Covidence for screening. After removing 22 duplicates, 373 studies were screened by title and abstract, excluding 236 studies that did not meet the inclusion criteria. Subsequently, 137 full-text articles were assessed for eligibility, of which 126 were excluded, resulting in 11 studies included for data extraction and six studies included in the quantitative synthesis (Figure 1).

3.2 | Study Characteristics

The 11 included studies were published between 2017 and 2024 and conducted in four countries: South Korea, the United States, Japan, and China. These studies involved 5896 patients, with 3483 in the P-CAB groups and 2413 in the PPI groups. The observation period ranged from 6 to 24 weeks.

Of the 11 studies, 10 were RCTs, and one was a self-controlled observational study. Nine studies reported specific AEs, while 10 provided data on the overall frequency of AEs. The P-CAB treatments included vonoprazan, fexuprazan, tegoprazan, and keverprazan, while the PPI treatments included lansoprazole, esomeprazole, rabeprazole, and omeprazole. Vonoprazan was the most frequently studied P-CAB (six studies), followed by tegoprazan (two studies), keverprazan (two studies) and fexuprazan (one study). Lansoprazole was the most commonly studied PPI, included in nine studies.

Indications for treatment included erosive esophagitis (five studies), nonerosive reflux disease (one study), duodenal ulcer (three studies), gastric ulcer (two studies), and peptic ulcer (one study) (Table 1).

3.3 | Risk of Bias Assessment

The risk of bias in RCTs was evaluated using the RoB2 tool, and all 10 studies were found to have a low risk of bias across the five assessment domains (Figure S1). For the single observational study, the risk of bias was assessed using the RoBINS-I tool, revealing a moderate overall risk of bias due to identified risks in domains such as confounding, intervention classification, and outcome measurement. These risks were attributed to the open-label design and small sample size, which limited the statistical power to control for time-dependent confounding variables. Low risk was observed in the domains of participant selection, deviations from intended interventions, missing outcome data, and selective reporting (Figure S2).

3.4 | Analysis of Safety Outcomes

3.4.1 | Specific AEs

Among the 11 included studies, nine reported 55 specific AEs, with 22 events included in at least two studies. Frequently reported AEs, defined as those reported in at least three studies, included diarrhea, constipation, upper respiratory tract inflammation (URI), nasopharyngitis, nausea, alanine aminotransferase (ALT) elevation and abnormal liver function tests (LFTs).

Diarrhea was the most frequently reported AE, assessed in seven of the nine studies. Constipation and URI were reported in

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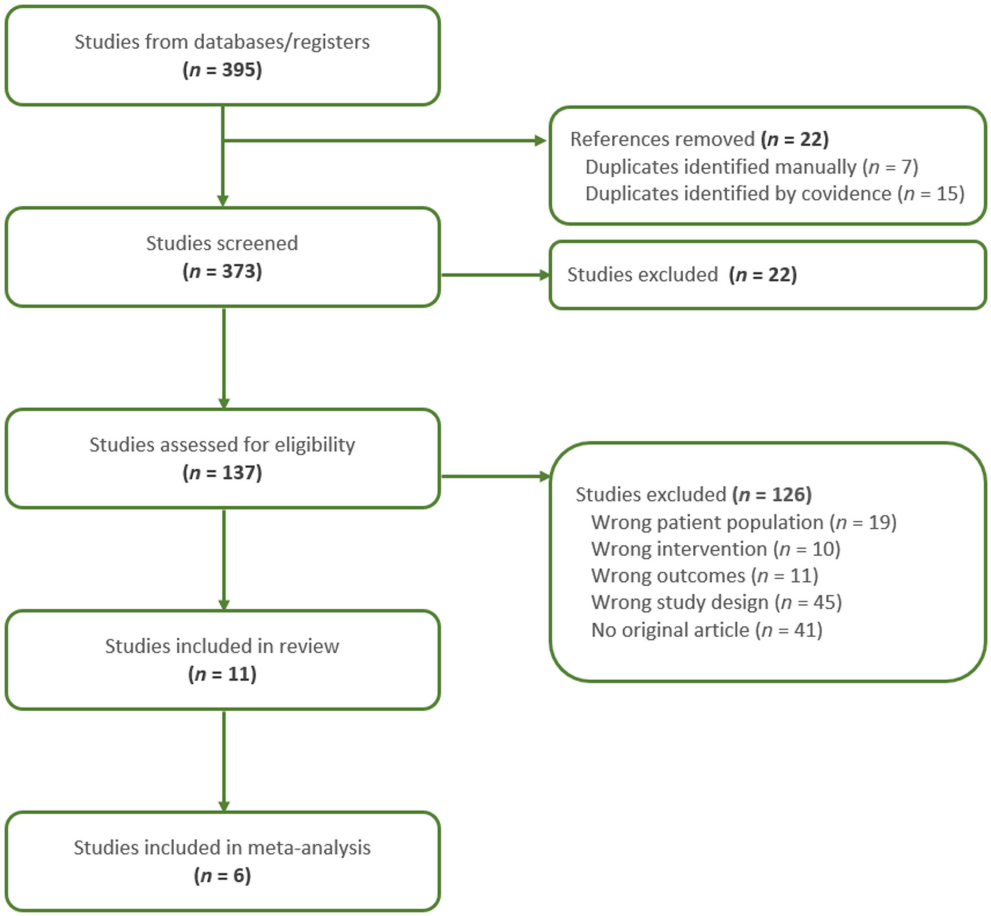


FIGURE 1 | Study selection flow chart.

four studies, while nasopharyngitis, nausea, and liver function-related AEs, such as ALT elevation and abnormal LFT, were each reported in three studies (Table 2).

Among the nine studies that reported specific AEs, all studies reported GI disorders and more than half of the studies reported abnormal liver function. The average reporting rate was below 5% across most AE categories in both groups. In the P-CAB group, nasopharyngitis (16.4%), URI (7.4%), and diarrhea (5.2%) showed the highest reporting rates, with similar patterns observed in the PPI groups. These AEs had reporting rates exceeding 5% in both groups. Fracture demonstrated the largest relative difference between the two groups, with the P-CAB group (1.3%) exhibiting a threefold higher rate compared to the PPI group (0.4%). All liver-related AEs were less frequently reported in the P-CAB group compared to the PPI group; however, the difference was minimal. Notably, liver-related AEs were reported even in studies that excluded patients with pre-existing liver conditions. (Table 3).

3.4.2 | SAEs

Nine studies reported on the frequency of SAEs. Among these, seven studies (78%) reported that SAEs occurred in less than 10% of patients in either group. The reporting rates of SAEs in the P-CAB group ranged from 0% to16.3% and in the PPI group from 0% to 14.7%. Four studies reported drug-related SAEs, with a total of 11 cases out of 3435 (0.3%) in the P-CAB group and 5 cases out of 2363 (0.2%) in the PPI group.

In the P-CAB group, the following drug-related SAEs were reported: atrial fibrillation, abnormal liver function, acute pancreatitis, colon polyps, cholelithiasis, thrombotic cerebral infarction, diabetic neuropathy, enteritis, oral tumor, gastric cancer, and gastric polyp. In the PPI group, the reported drug-related SAEs included acute pancreatitis, cervical adenocarcinoma, acute kidney injury, interstitial lung disease, and pulmonary hypertension (Table 4).

3.4.3 | Meta-Analysis of Hypergastrinemia

Out of the 11 selected studies, nine studies (81.8%) reported changes in serum gastrin levels, with seven studies providing specific values. In the P-CAB groups, baseline serum gastrin levels ranged from 23.63 to 160 pg/mL, while EoT levels varied between 54.37 and 672 pg/mL. In the PPI groups, baseline levels ranged from 27.89 to 147.2 pg/mL, with EoT levels ranging from 16.46 to 289.3 pg/mL.

With the exception of one study, all others reported increases in serum gastrin levels, with larger increases observed in the P-CAB groups. Notably, these studies demonstrated that higher P-CAB doses were associated with greater increases in serum gastrin levels (Table 5).

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TABLE 1 | Characteristics of selected studies.

First author (published year)	Study design	Country	Observation period (weeks)	Indications	P-CAB group		PPI group	
					Treatment (dose)	No. of patients	Treatment (dose)	No. of patients
Ashida (2018) [21]	RCT	Japan	24	Erosive esophagitis	VPZ (10 mg,20 mg)	406	LPZ (15 mg)	201
Cho (2020) [22]	RCT	South Korea	8	Gastric ulcer	TPZ (50 mg,100 mg)	204	LPZ (30 mg)	100
Kawai (2018) [23]	RCT	Japan	24	Peptic ulcer	VPZ (10 mg, 20 mg)	404	LPZ (15 mg)	217
Kim (2023) [24]	RCT	South Korea	2	Erosive esophagitis	TPZ (50 mg)	22	EPZ (40 mg)	24
Laine (2023) [25]	RCT	United States	8	Erosive esophagitis	VPZ (20 mg)	514	LPZ (30 mg)	510
			24		VPZ (20 mg, 10 mg)	592	LPZ (15 mg)	297
Lee (2022) [26]	RCT	South Korea	8	Erosive esophagitis	FPZ (40 mg)	131	EPZ (40 mg)	131
Miwa (2017) [27]	RCT	Japan	8	Erosive esophagitis	VPZ (20 mg)	244	LPZ (30 mg)	238
			6		VPZ (20 mg)	183	LPZ (30 mg)	185
Niikura (2018) [28]	Observational Study	Japan	12	Non-erosive reflux disease	VPZ (10 mg, 20 mg)	26	RPZ (10 mg, 20 mg) LPZ (15 mg, 30 mg) OPZ (10 mg, 20 mg) EPZ (10 mg, 20 mg)	26
Tan (2022) [29]	RCT	China	6–10	Duodenal ulcer	KPZ (20 mg, 30 mg)	116	LPZ (30 mg)	64
Tan (2023) [30]	RCT	China	6–10	Duodenal ulcer	KPZ (20 mg)	180	LPZ (30 mg)	178
Xiao (2024) [31]	RCT	China	24	Erosive esophagitis	VPZ (10 mg, 20 mg)	461	LPZ (15 mg)	242

Abbreviations: EPZ, esomeprazole; FPZ, fexuprazan; KPZ, keverprazan; LPZ, lansoprazole; OPZ, omeprazole; RCT, randomized controlled trials; RPZ, rabeprazole; TPZ, tegoprazan; VPZ, vonoprazan.

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TABLE 2 | Frequently reported specific adverse events (AEs) reported in P-CAB and PPI groups.

First author (published year)	Indications	P-CAB group	PPI group	AE (PT)
Ashida (2018)	Erosive esophagitis	VPZ	LPZ	Diarrhea
				Constipation
				Upper respiratory tract inflammation
				Nasopharyngitis
				Alanine aminotransferase increased
				Liver function test abnormal
Cho (2020)	Gastric ulcer	TPZ	LPZ	Diarrhea
				Constipation
				Alanine aminotransferase increased
Kawai (2018)	Peptic ulcer	VPZ	LPZ	Diarrhea
				Constipation
				Upper respiratory tract inflammation
				Nasopharyngitis
Laine (2023)	Erosive esophagitis	VPZ	LPZ	Liver function test abnormal
Lee (2022)	Erosive esophagitis	FPZ	EPZ	Diarrhea
Niikura (2018)	Nonerosive reflux disease	VPZ	EPZ, LPZ, OPZ, RPZ	Diarrhea
				Constipation
				Upper respiratory tract inflammation
				Nausea
Tan (2022)	Duodenal ulcer	KPZ	LPZ	Nausea
				Liver function test abnormal
Tan (2023)	Duodenal ulcer	KPZ	LPZ	Diarrhea
				Nausea
				Liver function test abnormal
Xiao (2024)	Erosive esophagitis	VPZ	LPZ	Diarrhea
				Upper respiratory tract inflammation
				Nasopharyngitis
				Alanine aminotransferase increased

Abbreviations: EPZ, esomeprazole; FPZ, fexuprazan; KPZ, keverprazan; LPZ, lansoprazole; OPZ, omeprazole; PT, preferred terms; RPZ, rabeprazole; TPZ, tegoprazan; VPZ, vonoprazan.

A meta-analysis of six studies revealed that the pooled mean difference in serum gastrin level between the P-CAB and PPI groups was 130.92 pg/mL (95% CI: 36.37–225.47), with significant heterogeneity ($I^2 = 98\%$) (Figure 2A). With the exception of one study, all other studies consistently indicated that P-CABs resulted in greater increases in serum gastrin levels compared to PPIs, with statistically significant differences ($p < 0.01$).

Furthermore, a subgroup analysis of three studies comparing vonoprazan and lansoprazole demonstrated that the pooled mean difference in serum gastrin increases was 174.03 pg/

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TABLE 3 | Adverse events (AE) categories and average reporting rates of AEs in P-CAB and PPI groups.

AE category (no. of reported studies in total)	AE (PT)	No. of reported studies	P-CAB group			PPI group		
			No. of patients reporting AE	No. of total patients in reporting studies	Average reported (%)	No. of patients reporting AE	No. of total patients in reporting studies	Average reported (%)
GI disorders ($n=9$)	Abdominal pain upper	2	16	665	2.41	12	342	3.51
	Constipation	4	36	1040	3.46	21	544	3.86
	Diarrhea	7	94	1812	5.19	57	1095	5.21
	Dyspepsia	2	30	665	4.51	12	342	3.51
	Gastric polyps	2	24	641	3.74	8	420	1.90
	Nausea	3	3	322	0.93	1	268	0.37
	Clostridium difficile infection	2	0	1510	0.00	0	1024	0.00
	Pancreatitis acute	2	2	382	0.52	1	395	0.25
	Gastroenteritis	2	28	810	3.46	7	418	1.67
Abnormal liver function ($n=5$)	Alanine aminotransferase increased	3	31	1071	2.89	17	543	3.13
	Liver function test abnormal	3	17	1808	0.94	13	1250	1.04
Respiratory tract infection ($n=4$)	Nasopharyngitis	3	208	1271	16.37	107	660	16.21
	Upper respiratory tract inflammation	4	96	1297	7.40	35	686	5.10
Skeletal muscle disorder ($n=3$)	Back pain	2	32	810	3.95	6	418	1.44
	Fracture	2	19	1510	1.26	4	1024	0.39

Abbreviations: GI, gastrointestinal; PT, preferred terms.

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TABLE 4 | Reporting rates of serious adverse events (SAEs) and drug-related SAEs in P-CAB and PPI groups.

	P-CAB group					PPI group				
First author (published year)	**Treatment**	**No. of reported patients**	**No. of total patients**	**Reported (%)**	**Drug-related SAE**	**Treatment**	**No. of reported patients**	**No. of total patients**	**Reported (%)**	**Drug-related SAE**
Ashida (2018)	VPZ (10 mg)	5	203	2.5	—	LPZ (15 mg)	4	201	2.0	—
	VPZ (20 mg)	4	203	2.0	Atrial fibrillation, Abnormal liver function					
Cho (2020)	TPZ (50 mg)	3	102	3.0	—	LPZ (30 mg)	1	100	1.0	—
	TPZ (100 mg)	2	102	2.0	—					
Kawai (2018)	VPZ (10 mg)	33	202	16.3	Acute pancreatitis, Colon polyps, Cholelithiasis, Thrombotic cerebral infarction, Diabetic neuropathy,	LPZ (15 mg)	32	217	14.7	Acute pancreatitis, Cervical adenocarcinoma, Acute kidney injury
	VPZ (20 mg)	32	202	15.8	Enteritis, Oral tumor, Gastric cancer					
Laine (2023)	VPZ (20 mg)	5	514	1.0	—	LPZ (30 mg)	7	510	1.4	—
	VPZ (20 mg)	31	296	10.4	—	LPZ (15 mg)	15	297	5.1	—
	VPZ (10 mg)	18	296	6.1	—					
Lee (2022)	FPZ (40 mg)	0	131	0	—	ESP (40 mg)	0	131	0	—
Miwa (2017)	VPZ (20 mg)[a]	6	244	2.5	—	LPZ (30 mg)	4	238	1.7	
	VPZ (20 mg)[b]	6	183	3.3	—	LPZ (30 mg)	4	185	2.2	
Tan (2022)	KPZ (20 mg)	0	55	0.0	—	LPZ (30 mg)	2	64	3.1	—
	KPZ (30 mg)	1	61	1.6	—					

(Continues)

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TABLE 4 | (Continued)

First author (published year)	P-CAB group					PPI group				
	Treatment	No. of reported patients	No. of total patients	Reported (%)	Drug-related SAE	Treatment	No. of reported patients	No. of total patients	Reported (%)	Drug-related SAE
Tan (2023)	KPZ (20 mg)	3	180	1.7	Gastric polyp	LPZ (30 mg)	1	178	0.6	Interstitial lung disease, Pulmonary hypertension
Xiao (2024)	VPZ (10 mg)	10	235	4.3	—	LPZ (15 mg)	12	242	5.0	—
	VPZ (20 mg)	8	226	3.5	—					

[a]Gastric ulcer.
[b]Duodenal ulcer.
Abbreviations: EPZ, esomeprazole; FPZ, fexuprazan; KPZ, keverprazan; LPZ, lansoprazole; TPZ, tegoprazan; VPZ, vonoprazan.

mL (95% CI: 78.43–269.52), indicating a greater increase with vonoprazan ($I^2 = 98\%$) (Figure 2B). All studies consistently reported greater increases in serum gastrin levels in the vonoprazan group, with statistically significant differences ($p < 0.01$).

4 | Discussion

As the use of P-CABs continues to expand globally, this study was conducted to identify notable differences between the two drug classes and comprehensively evaluate the safety profiles of P-CABs compared with PPIs [11, 12]. While comparing the safety profiles of P-CABs to those of PPIs—whose long-term AEs are relatively frequently studied, the primary focus of this study was to detect specific AEs specifically associated with P-CABs. In this systematic review, we found that the overall patterns of P-CABs were comparable to those of PPIs, suggesting a similar safety profile. However, serum gastrin levels were significantly elevated in patients receiving P-CABs compared to those receiving PPIs, highlighting a distinct difference between the two drug classes. This study offers deeper insights into the safety of P-CABs and PPIs by comparing not only the incidence rates but also the types, categories, and severity of reported AEs between the two drug classes.

The findings of this study are consistent with previous systematic reviews and meta-analyses that compared the safety of P-CABs and PPIs. Simadibrata (2022) evaluated 15 studies analyzing the prevalence of treatment-emergent adverse events (TEAE) in patients receiving PPI or P-CAB treatment using a random-effects model. Most studies focused on vonoprazan and reported no significant differences in the risk of TEAEs between vonoprazan and PPIs across various indications. The relative risk (RR) of TEAEs with vonoprazan compared with PPIs was 1.05 (95% CI 0.90–1.22) for erosive esophagitis, 0.20 (95% CI 0.01–4.15) for GERD, 0.84 (95% CI 0.69–1.02) for *H. pylori* eradication therapy, 1.47 (95% CI 0.43–5.05) for GU, and 1.37 (95% CI 1.19–1.59) for DU. These findings suggest no significant differences in TEAE risks between the two drug classes for most indications, with the exception of duodenal ulcer.

Additionally, a meta-analysis conducted by Xu (2023) on vonoprazan reported statistically similar major AE rates between patients treated with vonoprazan and PPIs, further supporting their comparable safety profiles. However, vonoprazan use was associated with increased serum gastrin levels (OR = 6.25, 95% CI 4.08–9.59, $p < 0.01$) and elevated pepsinogen I levels (OR = 3.49, 95% CI 2.40–5.10, $p < 0.01$). The results of this study align with existing literature, reinforcing that while P-CABs and PPIs share similar safety profiles, the stronger acid suppression effect of P-CABs may lead to higher serum gastrin levels in P-CAB users.

Mild GI-related AEs were the most consistently reported across studies, with a total of nine studies documenting such events, followed by abnormal liver function. Given that both P-CABs and PPIs undergo hepatic metabolism, the potential for hepatotoxicity is a known risk associated with both drug classes [32, 33]. Among the 11 included studies, five reported elevations in liver enzyme

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TABLE 5 | Mean values and changes in serum gastrin levels in P-CAB and PPI groups.

First author (published year)	Observation period (Weeks)	Indications	P-CAB group					PPI group				
			Treatment	No. of patients	Mean serum gastrin level (SD)			Treatment	No. of patients	Mean serum gastrin level (SD)		
					Baseline[a]	EoT[a]	Difference[b]			Baseline[a]	EoT[a]	Difference[b]
Cho (2020)	8	GU	TPZ 50 mg	102	54.84 (59.26)	85.52 (77.97)	30.68▲	LPZ 30 mg	100	70.92 (107.08)	121.75 (114.84)	50.83▲
			TPZ 100 mg	102	55.63 (46.4)	119.54 (94.05)	63.91▲					
Kawai (2018)	24	PU	VPZ 10 mg	202	159.5 (81, 370)[c]	529.5 (302, 727)[c]	370▲	LPZ 15 mg	217	134 (79, 291)[c]	249 (129, 454)[c]	115▲
			VPZ 20 mg	202	160 (93, 335)[c]	672 (415, 858)[c]	512▲					
Laine (2023)	8	EE	VPZ 20 mg	514	—	158.3 (143.6)	—	LPZ 30 mg	510	—	64.1 (68.6)	—
	24	EE	VPZ 20 mg	296	—	223.0 (216.6)	—	LPZ 15 mg	297	—	74.1 (96.1)	—
			VPZ 10 mg	296	—	166.0 (189.8)	—					
Miwa (2017)	8	GU	VPZ 20 mg	244	156.3 (181.6)	394.1 (307.3)	237.80▲	LSP 30 mg	238	147.2 (124.9)	289.3 (250.3)	142.10▲
	6	DU	VPZ 20 mg	183	117.1 (103.3)	514.3 (255.9)	397.20▲	LSP 30 mg	185	118.2 (84.2)	245.8 (177.5)	127.60▲
Tan (2022)	6–10	DU	KPZ 20 mg	55	58.467 (17.603)	92.913 (42.655)	34.45▲	LPZ 30 mg	64	58.222 (17.649)	66.718 (24.119)	8.80▲
			KPZ 30 mg	61	56.811 (12.054)	96.282 (49.982)	39.47▲					
Tan (2023)	6–10	DU	KPZ 20 mg	180	42.4 (32.6)	237.6 (187.7)	195.20▲	LPZ 30 mg	178	41.6 (29.7)	105.1 (67)	63.50▲

(Continues)

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TABLE 5 | (Continued)

First author (published year)	Observation period (Weeks)	Indications	P-CAB group					PPI group				
			Treatment	No. of patients	Mean serum gastrin level (SD)			Treatment	No. of patients	Mean serum gastrin level (SD)		
					Baseline[a]	EoT[a]	Difference[b]			Baseline[a]	EoT[a]	Difference[b]
Xiao (2024)	24	EE	VPZ 10 mg	235	23.63 (10.6, 55.6)[c]	54.37 (27.9, 105.7)[c]	30.74▲	LPZ 15 mg	242	27.89 (11.6, 64.3)[c]	16.46 (7.6, 39.4)[c]	−11.43▽
			VPZ 20 mg	226	25.36 (9.3, 47.7)[c]	82.19 (36.8, 177.3)[c]	56.83▲					

Abbreviations: DU, duodenal ulcer; EE, erosive esophagitis; EoT, end of treatment; GU, gastric ulcer; PU, peptic ulcer.

[a]pg/mL.

[b](EoT) − (baseline).

[c]Median (Q1, Q3).

levels. Notably, four of these five studies excluded patients with pre-existing liver dysfunction; however, liver-related AEs were still observed. This finding emphasizes the importance of monitoring for hepatotoxicity, as liver-related AEs can develop in patients without prior liver conditions. Furthermore, although the P-CAB group showed lower reporting rates than the PPI group, no substantial differences in hepatic AEs were observed between the two drug classes—a finding supported by a previous study comparing the risk of hepatotoxicity between tegoprazan and six classes of PPIs [34]. These results suggest that hepatic function should be monitored in all patients receiving either P-CABs or PPIs.

The types and reporting rates of AEs in the P-CAB group were comparable to those observed in the PPI group. The ranking of frequently reported AEs in the P-CAB group closely aligned with that of the PPI group, suggesting that the overall AE profile of P-CABs does not significantly differ from that of PPIs. Notably, the largest difference was observed in the category of skeletal muscle disorders, which were reported two to three times more frequently in the P-CAB group. Although current literature does not directly address the risk of fractures associated with P-CABs, previous studies have identified hypergastrinemia as a significant contributor to fracture risk in long-term PPI users [35]. Given that P-CABs also induce increases in serum gastrin levels, it is plausible that they may carry similar risks. Therefore, further investigation is warranted, particularly in patients at risk for osteoporosis, to evaluate the long-term safety of P-CABs.

The proportion of patients experiencing SAEs was below 10% in both groups, with minimal differences in SAE rates attributable to either drug. The lowest SAE reporting rate was 0% in both the P-CAB and PPI groups, as observed in one study. Similarly, the highest SAE reporting rate for both groups originated from the same study, suggesting that variations in SAE reporting rates may be due to differences in how each study defined SAEs. However, given that most studies reported SAEs below 10%, and the differences in SAE rates between the P-CAB and PPI groups were minimal, it can be inferred that there is no significant difference in SAEs between the two drug classes.

The risk of hypergastrinemia is well-established for both P-CABs and PPIs, as it results from the compensatory mechanism of gastrin secretion triggered by the suppression of gastric acid secretion. Given that P-CABs exert a more potent and sustained acid-suppressive effect compared to PPIs, a greater elevation in serum gastrin levels is expected with their use. Hypergastrinemia was reported in 81.8% (9 out of 11) of the included studies, highlighting it as a frequently monitored AE. Moreover, aligning with the expectation that P-CABs would induce a greater elevation in serum gastrin levels, the meta-analysis results revealed that P-CABs increased serum gastrin levels by an average of 130.92 pg/mL more than PPIs. This finding not only indicates a higher risk of hypergastrinemia with P-CABs but also supports their stronger acid suppression effect compared to PPIs.

4.1 | Limitations

Some limitations warrant consideration when understanding these findings. One limitation is associated with the most frequently reported AE, GI disorders. Given that the study population in all

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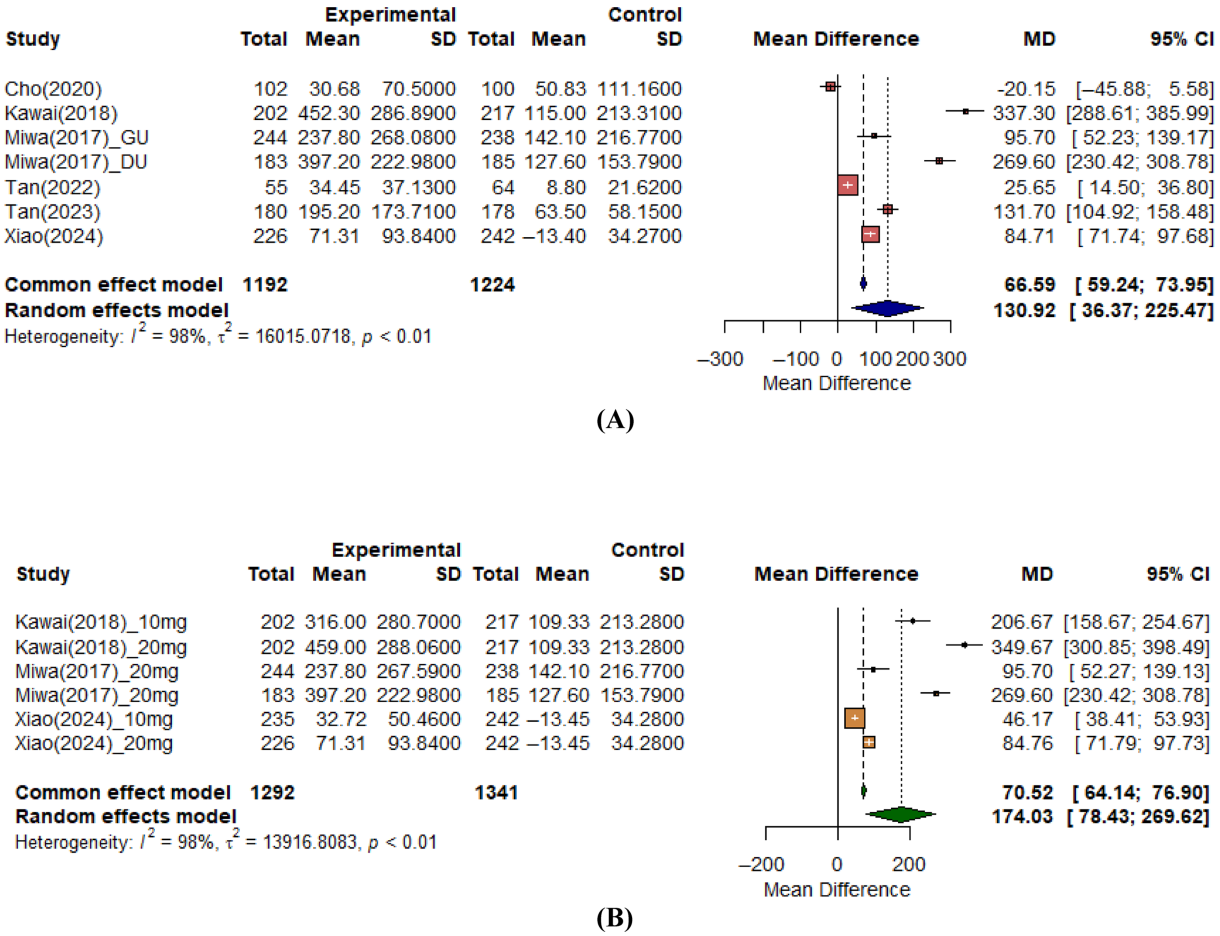


FIGURE 2 | Forest plots of mean differences in serum gastrin level increase. (A) Between P-CAB and PPI group. (B) Between vonoprazan and lansoprazole group.

the included studies comprised individuals with GERD or PUD, it is challenging to definitively attribute these AEs to the treatment itself. Additionally, the incidence rates of AEs were not reported separately within each individual study; instead, the total number of AE reports from all included studies was aggregated and divided by the total number of patients across those studies. This approach may have underestimated the true incidence of AEs, necessitating a cautious interpretation of direct numerical comparisons between the two groups. Furthermore, significant heterogeneity ($I^2 = 98\%$) was observed in the meta-analysis of serum gastrin level differences, likely due to substantial differences in baseline serum gastrin levels and disease stages across the study populations. Despite this variability, the differences in serum gastrin levels between the two groups were minimal within individual studies, supporting the reliability of the data.

While acknowledging these limitations, this study still provides meaningful insights into the safety profiles of P-CABs and PPIs by specifically focusing on AEs related to these drug classes and including P-CABs other than vonoprazan, thereby offering valuable guidance for clinical practice.

5 | Conclusion

In conclusion, P-CABs do not appear to pose a significantly elevated risk of SAEs compared to PPIs. However, vigilant monitoring for potential excessive increases in serum gastrin levels is essential in patients receiving P-CAB therapy. Moreover, both P-CAB and PPI users require awareness regarding the potential hepatic dysfunction, even in the absence of pre-existing liver conditions. Further studies are needed to better understand these safety considerations and to guide clinical decision-making in the use of these acid-suppressive therapies.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Risk of bias assessment of RCTs using RoB2 tool. **Figure S2:** Risk of bias assessment of observational study using RoBINS-I tool.

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