

META-ANALYSIS OPEN ACCESS

Tegoprazan as First- and Second-Line Therapy for Eradication of *Helicobacter pylori* Infection: A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: To evaluate the efficacy and safety of tegoprazan (TPZ) compared to conventional proton pump inhibitors (PPIs) for *Helicobacter pylori* eradication as first- and second-line therapies.

Methods: Four databases were searched for randomized controlled trials (RCTs) and retrospective studies comparing TPZ- and PPI-based regimens for *H. pylori* eradication published until October 15, 2024. A random-effects model was used to calculate pooled odds ratio (OR) and 95% confidence interval (CI) based on intention-to-treat and per-protocol analyses. The PROSPERO registration number of the study is CRD42024622705.

Results: Nine studies (three RCTs and six retrospective studies) involving 5228 treatment-naïve patients were included. TPZ was non-inferior to PPIs as a first-line therapy (intention-to-treat: odds ratio [OR] 1.066, 95% confidence interval [CI] 0.929–1.224; per-protocol: OR 1.142, 95% CI: 0.967–1.349). Subgroup analyses showed no significant differences based on study design, therapeutic regimen, or treatment duration. In patients with clarithromycin-resistant strains confirmed by 23S rRNA sequencing, TPZ achieved a higher eradication rate (OR 4.961, 95% CI 1.024–24.030). TPZ was associated with significantly lower odds of abdominal discomfort compared to PPIs (OR 0.490, 95% CI 0.268–0.897). Regarding treatment duration, a 14-day regimen was linked to a lower risk of diarrhea, while a 7-day regimen was associated with a higher risk of abdominal pain. No significant differences were observed in second-line therapeutic outcomes.

Conclusions: TPZ represents a non-inferior alternative to PPIs for *H. pylori* eradication, with potential benefits in clarithromycin-resistant infections and favorable safety profiles. Future studies are warranted to assess higher dosages and address pharmacokinetic limitations.

1 | Introduction

Helicobacter pylori infection remains a significant global health issue [1], particularly due to its association with multiple severe

gastroenteric conditions such as chronic gastritis, peptic ulcers, and gastric cancer [2]. The increasing prevalence of antibiotic-resistant strains, predominantly clarithromycin-resistant *H. pylori*, has compromised the efficacy of conventional proton pump

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inhibitor (PPI)-based triple therapy, which is widely used for *H. pylori* eradication [3]. In East Asia—particularly China, the Republic of Korea, and Japan—where the prevalence of *H. pylori* infection remains high [1], the eradication success rates of certain PPI-based regimens have fallen below 65% [4], raising concerns regarding the critical need for alternative therapeutic regimens that can overcome these challenges.

Potassium-competitive acid blockers (P-CABs) are a novel class of acid-suppressing agents that offer several pharmacological advantages over PPIs. P-CABs, such as vonoprazan (VPZ) and tegoprazan (TPZ), inhibit gastric acid secretion by directly and reversibly blocking the H^+/K^+ -ATPase enzymes, unlike PPIs, which require activation in the acidic environment of parietal cells [5]. P-CABs exhibit a rapid onset of action. Conversely, when comparing VPZ and PPIs to TPZ, it has been found that TPZ is not influenced by cytochrome P450 2C19 (CYP2C19) polymorphism and has a lower potential for drug–drug interactions, particularly with medications metabolized by CYP450 enzymes [6]. TPZ also provides a more sustained acid suppression [7], potentially enhancing the eradication rates of *H. pylori* in infected patients.

Given the urgent need to optimize new treatment strategies in response to rising antibiotic resistance, understanding the role of P-CABs in *H. pylori* eradication is paramount. Although VPZ, which has been approved by the U.S. Food and Drug Administration for *H. pylori* eradication [8], has been extensively studied and shown superior efficacy compared to PPIs, particularly against clarithromycin-resistant strains [9], other P-CABs have not undergone similar levels of investigation. TPZ is a novel P-CAB that was developed and approved in the Republic of Korea for *H. pylori* eradication. The growing number of comparative studies on TPZ-based therapy reflects the increasing clinical interest in TPZ. Initial data suggest that TPZ-based triple therapy may be as effective as PPI-based triple therapy [10]. Recently published meta-analyses have evaluated *H. pylori* eradication and adverse events of TPZ-based therapy compared with PPI-based therapy as first-line treatment [11–13]. However, comprehensive evaluation of TPZ-based regimens as both first- and second-line treatments remains limited, particularly in relation to therapeutic regimen, treatment duration, adherence rate, organ-specific safety outcomes, adverse events based on severity, and effectiveness in patients with clarithromycin-resistant *H. pylori* infection. These domains are critical for fully understanding treatment response and tolerability, and their assessment may clarify the clinical value of TPZ within the broader *H. pylori* eradication strategy.

Therefore, to address this research gap, we conducted this systematic review and meta-analysis aiming to evaluate the efficacy and safety of TPZ-based regimens compared to those of PPI-based regimens as first- and second-line treatments for *H. pylori* eradication, including treatment of patients with confirmed clarithromycin-resistant infections.

2 | Materials and Methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 guidelines [14], and is registered with

PROSPERO (<https://www.crd.york.ac.uk/PROSPERO/>; registration no. CRD42024622705).

2.1 | Search Strategy and Study Selection

We conducted a literature search of PubMed, EMBASE, Web of Science, and Research Information Sharing Service (RISS) databases covering all articles published up to October 15, 2024 to identify eligible studies on P-CABs developed in the Republic of Korea. The RISS database was specifically included to capture studies published exclusively in the Republic of Korea. In addition, gray literature was also searched using bioRxiv, medRxiv, and [ClinicalTrials.gov](https://www.clinicaltrials.gov) databases. Following consensus, three researchers independently screened and selected the pooled studies, resolving any disagreements through discussion. The search strategy used for each database is detailed in Table S1.

2.2 | Inclusion and Exclusion Criteria

To comprehensively include studies on P-CAB developed in the Republic of Korea, no language restriction was applied for study inclusion. Studies that met the following criteria were included: (i) those included treatment-naïve patients positive for *H. pylori* infection; (ii) those compared commercially available P-CABs in the Republic of Korea (i.e., TPZ, fexuprazan, and revaprazan) with a comparable therapeutic regimen of conventional PPIs (e.g., both intervention and comparator arms must include dual, triple or quadruple therapy); (iii) those reported clinical efficacy and safety as the study outcomes; and (iv) randomized clinical trials (RCTs) or retrospective studies with similar baseline characteristics between the intervention and control groups. Literature reviews, editorials, protocols, conference abstracts, case series or case reports, animal studies, meta-analyses, single-arm studies, studies not comparing P-CABs and PPIs, or those including patients who had previously been treated for *H. pylori* infection were excluded from the analysis.

2.3 | Data Collection and Extraction

After reaching a consensus on the extraction criteria, four researchers independently extracted the data from the included studies. The data extracted comprised the first author's name, year of publication, participants' demographics (age and sex), study design, study size and the number of cases, intervention, comparator, dosage of the regimens, and treatment outcomes. The primary outcome was the *H. pylori* eradication rates using first- and second-line therapy, evaluated in both intention-to-treat (ITT) and per-protocol (PP) populations. The secondary outcomes included treatment efficacy in patients with clarithromycin resistance, adherence rates, and adverse events.

When available, adverse events were categorized as mild, moderate, and severe, respectively. The treatment regimens evaluated included the following: (i) triple therapy, including a combination of TPZ or PPI with amoxicillin and clarithromycin; (ii) dual therapy, including TPZ or PPI with amoxicillin; (iii) concomitant therapy, including TPZ or PPI with amoxicillin, clarithromycin, and metronidazole; (iv)

bismuth-containing quadruple therapy, including TPZ or PPI with bismuth or bismuth subcitrate, metronidazole, and tetracycline; and (v) bismuth add-on therapy, including the addition of bismuth to the triple therapeutic regimen. When applicable, the corresponding authors of the original studies were contacted to obtain additional information.

2.4 | Risk-of-Bias Assessment

Two researchers independently assessed the risk of bias using the Risk of Bias (RoB)-2 and the Risk of Bias in Non-randomized Studies—of Interventions (ROBINS-I) V2 tools (<https://www.riskofbias.info/>) for RCTs and retrospective studies, respectively. Any disagreement was resolved through discussion. For RCTs, the quality of studies was categorized as low-risk, high-risk, or some concerns. For retrospective studies, the quality was graded as low, moderate, serious, or critical.

2.5 | Statistical Analysis

All the statistical analyses were conducted using the Comprehensive Meta-Analysis Software (Biostat Inc., Englewood, NJ, USA). Odds ratio (OR) with the corresponding 95% confidence interval (CI) was estimated for *H. pylori* eradication comparing P-CABs and PPIs, based on weighted pooled average effect measures that considered the size and precision of each study. Statistical significance was set at $p < 0.05$. Heterogeneity among studies was evaluated using the I^2 statistics, with $I^2 > 50\%$ indicating substantial heterogeneity, suggesting that real differences existed between study results that were not attributable to chance alone. Random-effects models were employed because of the heterogeneity among the included studies. For efficacy outcomes, subgroup analyses were performed based on study design (RCT or retrospective cohort study), therapeutic regimens (dual, triple, quadruple, concomitant or bismuth add-on therapy), and treatment duration (7, 10, or 14 days). For safety outcomes, results were presented according to treatment duration. Publication bias was assessed using funnel plots for meta-analyses that included more than 10 studies. In addition, sensitivity analysis was performed by sequentially removing one study at a time from the meta-analysis to evaluate the robustness of the overall efficacy findings.

2.6 | Certainty of the Evidence Assessment

The quality of evidence for each meta-analysis was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework. This assessment considered the risk of bias, consistency, directness, precision, and publication bias [15].

3 | Results

3.1 | Study Identification and Selection

Nine studies [16–24] met the eligibility criteria and were included in the analysis. Figure 1 presents the PRISMA flow diagram for study selection. Except for TPZ, no other P-CABs met

the eligibility criteria for our analysis. Details of the excluded articles and reasons for exclusion are provided in Table S2.

3.2 | Characteristics of the Included Studies

Table 1 summarizes the key characteristics of the nine included studies. Three studies were RCTs [16–18], whereas the other six studies were retrospective cohort studies [19–24]. Eight studies were conducted in the Republic of Korea, and one RCT was conducted in China. All studies included treatment-naïve patients, and those conducted in the Republic of Korea specifically involved patients with underlying gastric conditions. One study reported results in Korean language [24]. The regimens and treatment durations varied; five studies treated patients using a triple therapy regimen for 7 or 14 days as the first-line treatment [16, 19, 21, 23, 24], two implemented a 10-day concomitant therapeutic regimen [20, 24], one implemented a 14-day bismuth-containing quadruple regimen [17], one implemented a 14-day dual therapeutic regimen [18], and one implemented a 7-day bismuth-containing add-on regimen as the first-line treatment [22]. In addition, three studies [19, 23, 24] implemented a 14-day bismuth-containing quadruple regimen as a second-line treatment for patients in whom the first-line regimen had failed. One study included multiple comparative regimen groups, but the 7-day TPZ-based triple therapy group lacked a comparative PPI group and therefore was excluded from the analysis [24]. *H. pylori* eradication was assessed using ^{13}C -urea breath test (UBT) in all studies, whereas three studies employed rapid urease test and/or histological evaluation using modified Giemsa staining [19, 20, 23].

3.3 | Risk-of-Bias Assessment

Figure S1 illustrates the risk-of-bias assessment for the RCTs and retrospective cohort studies. Of the three RCTs, one had a low risk of bias, whereas two raised some concerns due to insufficient data on allocation concealment. Two RCTs conducted in the Republic of Korea also received industrial funding. Among the retrospective studies, only one showed a low risk of bias. The other five retrospective studies had bias due to unclear control of confounding variables.

3.4 | Comparative Efficacy Outcomes

3.4.1 | First-Line Eradication Therapy in Treatment-Naïve Patients

When being used as the first-line therapy, TPZ demonstrated comparable *H. pylori* eradication rates to PPI, achieving eradication in 76.51% (1622 of 2120) of the ITT population and in 84.73% (1842 of 2174) of the PP population, when compared to 75.14% (1919 of 2554) of the ITT population and 84.08% (1996 of 2374) of the PP population treated with PPIs, with no significant differences observed between the groups (ITT: OR 1.066, 95% CI 0.929–1.224; PP: OR 1.142, 95% CI 0.967–1.349) (Figure 2A,B). In addition, no differences were observed in the sensitivity analyses (data not shown).

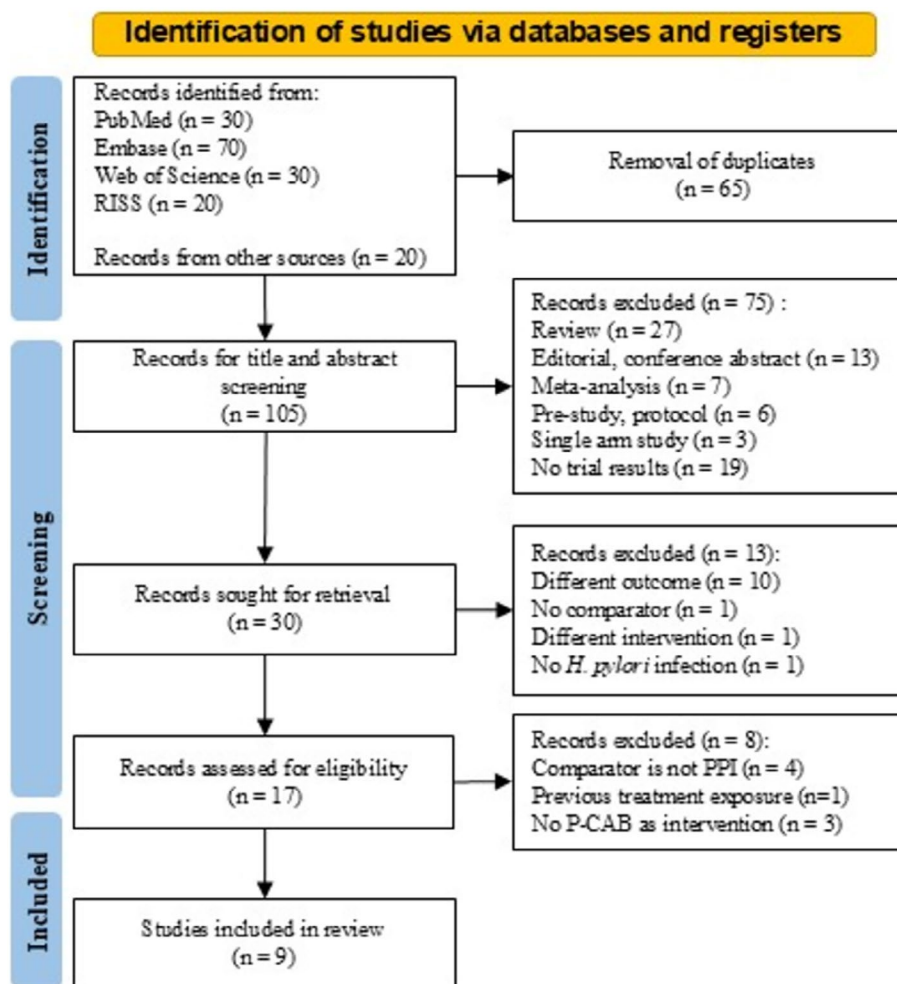


FIGURE 1 | The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart for study inclusion. *H. pylori*, *Helicobacter pylori*; P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor.

Moreover, subgroup analyses based on study type (RCT vs. retrospective cohort study), therapeutic regimen (triple vs. dual vs. concomitant vs. bismuth-containing quadruple vs. bismuth add-on therapy) and treatment duration (7 vs. 10 vs. 14 days) in the ITT or PP population showed no significant difference between TPZ and PPI in the ITT or PP population (Figures 2C,D and 3).

3.4.2 | First-Line Eradication Therapy in Clarithromycin-Resistant Strains

Three studies [16, 22, 24] analyzed *H. pylori* eradication rates in patients with clarithromycin-resistant *H. pylori* infection. Clarithromycin resistance was identified through sequencing analysis (mutation in the 23S ribosomal ribonucleic acid [23S rRNA] region of *H. pylori*) in two studies [22, 24], whereas one study [16] employed a culture method (minimum inhibitory concentration [MIC] > 0.5 µg/mL). TPZ showed superior efficacy compared to PPI in patients with clarithromycin-resistant *H. pylori* infection identified with 23S rRNA gene mutations (OR 4.961, 95% CI 1.024–24.030) (Figure 4).

3.4.3 | Second-Line Eradication Therapy After First-Line Treatment Failure

As a second-line therapy, TPZ achieved *H. pylori* eradication rates of 87.10% (108 of 124) in the ITT population, compared with 84.0% (42 of 50) when using PPI (OR 1.261, 95% CI 0.498–3.193), while TPZ achieved an *H. pylori* eradication rate of 94.70% (125 of 132) in the PP population, compared with 93.26% (83 of 89) with PPI treatment (OR 0.976, 95% CI 0.277–3.445) (Figure S2). These results showed that TPZ and PPI were comparable for *H. pylori* eradication as the second-line therapy.

3.4.4 | Adherence Rates of First- and Second-Line Eradication Therapy

In total, 90.42% (2047 of 2264) and 88.59% (132 of 149) of the patients treated with the TPZ-based regimen as the first- and second-line therapies, respectively, adhered to the regimens when compared with 88.94% (2236 of 2514) and 83.18% (89 of 107) of those treated with the PPI-based regimen. No significant difference was observed in the adherence rates of treatment with either TPZ or PPI (first-line therapy: OR 0.990, 95% CI

TABLE 1 | Characteristics of the nine included studies.

First author (year of publication)	Study type (registration no. for RCT)	Study period	Country	Age, years (mean ± SD)		Sample size, <i>n</i> (male/female)		Dosage of TPZ or PPI	Dosage of antibiotics	Treatment duration	Follow-up (days)	Funding
				TPZ/PPI	TPZ	PPI						
First-line therapy												
Choi (2022) [16]	Phase III, double- blind RCT (NCT03317223)	Oct. 2017 to Jan. 2019	Republic of Korea	54.71 ± 11.24/ 53.19 ± 10.88	175 (85/90)	175 (83/92)	TPZ 50 mg bid.; Lansoprazole 30 mg bid.	A 1000 mg bid.; C 500 mg bid.	7 days	28–56	HK inno.N Corp.	
Kim (2023) [17]	Double- blind RCT (NCT04674774)	Mar. 2020 to Dec. 2021	Republic of Korea	58.0 ± 11.3/57.9 ± 10.0	105 (61/44)	106 (59/47)	TPZ 50 mg bid.; Lansoprazole 30 mg bid.	BS 300 mg qid.; M 500 mg tid.; TC 500 mg qid.	14 days	28	HK inno.N Corp	
Kong (2024) [18]	Open-label RCT (NCT05870683)	May 2023 to Mar. 2024	China	45 (36–54) ^a /42 (33–55) ^a	184 (84/100)	184 (90/94)	TPZ 50 mg bid.; Esomeprazole 20 mg qid.	A 750 mg qid.	14 days	42	Non- industry	
Jung (2023) [19]	Retrospective cohort	Mar. to Jul. 2021	Republic of Korea	56.2 ± 11.4/57.4 ± 11.6	344 (189/155)	333 (181/152)	TPZ 50 mg bid.; Rabeprazole 20 mg bid.	A 1000 mg bid.; C 500 mg bid.	14 days	28	Non- industry	
Jung (2024) [20]	Retrospective cohort	Dec. 2021 to Aug. 2023	Republic of Korea	55.1 ± 11.7/55.7 ± 11.6	620 (291/329)	854 (438/416)	TPZ 50 mg bid; Rabeprazole 20 mg bid.	A 1000 mg bid; C 500 mg BID; M 500 mg bid.	10 days	28	No information	
Kang (2024) [21]	Retrospective cohort	Mar. 2020 to Feb. 2023	Republic of Korea	56 (32–78) ^b /58 (15–89) ^b	64 (42/22)	295 (177/118)	TPZ 50 mg bid.; Lansoprazole 30 mg bid.	A 1000 mg bid.; C 500 mg bid.	14 days	28	None	
Kim (2021) [22]	Retrospective cohort	Jan. to Nov. 2020	Republic of Korea	55.3 ± 11.1/55.7 ± 11.2	193 (91/102)	188 (86/102)	TPZ 50 mg BID; Lansoprazole 30 mg bid.	A 1000 mg bid.; C 500 mg bid.; BS 300 mg bid.	7 days	35	Non- industry	

(Continues)

TABLE 1 | (Continued)

First author (year of publication)	Study type (registration no. for RCT)	Study period	Country	Age, years (mean $\pm$ SD)		Sample size, <i>n</i> (male/female)		Dosage of TPZ or PPI	Dosage of antibiotics	Treatment duration	Follow-up (days)	Funding
				TPZ/PPI		TPZ	PPI					
Park (2023) [23]	Retrospective cohort	Mar. 2021 to Nov. 2022	Republic of Korea	56.0 $\pm$ 11.6/57.1 $\pm$ 10.9		435 (242/193)	419 (210/209)	TPZ 50 mg bid.; Esomeprazole/ sodium bicarbonate 40/800 mg bid.	A 1000 mg bid.; C 500 mg bid.	14 days	28	Non- industry
Song (2024) [24]	Retrospective cohort	Mar. 2021 to Oct. 2022	Republic of Korea	54.9 $\pm$ 11.8/51.8 $\pm$ 10.1		102 (53/49)	38 (17/21)	TPZ 50 mg bid.; Rabeprazole 20 mg bid.	A 1000 mg bid.; C 500 mg bid.	14 days	28	Non- industry
Second-line therapy												
Jung (2023) [19]	Retrospective cohort	Mar. to Jul. 2021	Republic of Korea	54.8 $\pm$ 12.0/56.0 $\pm$ 11.5		220 (107/113)	108 (51/57)	TPZ 50 mg bid.; Rabeprazole 20 mg bid.	A 1000 mg bid.; C 500 mg bid.; M 500 mg bid.	10 days	28	Non- industry
Park (2023) [23]	Retrospective cohort	Mar. 2021 to Nov. 2022	Republic of Korea			83	24	TPZ 50 mg bid.; Rabeprazole 20 mg bid.	B 120 mg qid.; M 500 mg tid.; TC 500 mg qid.	14 days	28	Non- industry
Song (2024) [24]	Retrospective cohort	Mar. 2021 to Oct. 2022	Republic of Korea			25	57	TPZ 50 mg bid.; Rabeprazole 20 mg BID	B 120 mg qid.; M 500 mg tid.; TC 500 mg qid.	14 days	28	Non- industry

Abbreviations: A, amoxicillin; B, bismuth; bid., twice a day; BS, bismuth subcitrate; C, clarithromycin; M, metronidazole; NM, not mentioned; PPI, proton pump inhibitor; qid., four times a day; SD, standard deviation; TC, tetracycline; tid., thrice a day; TPZ, tegoprazan.

^aMedian and interquartile range.

^bMedian and range.

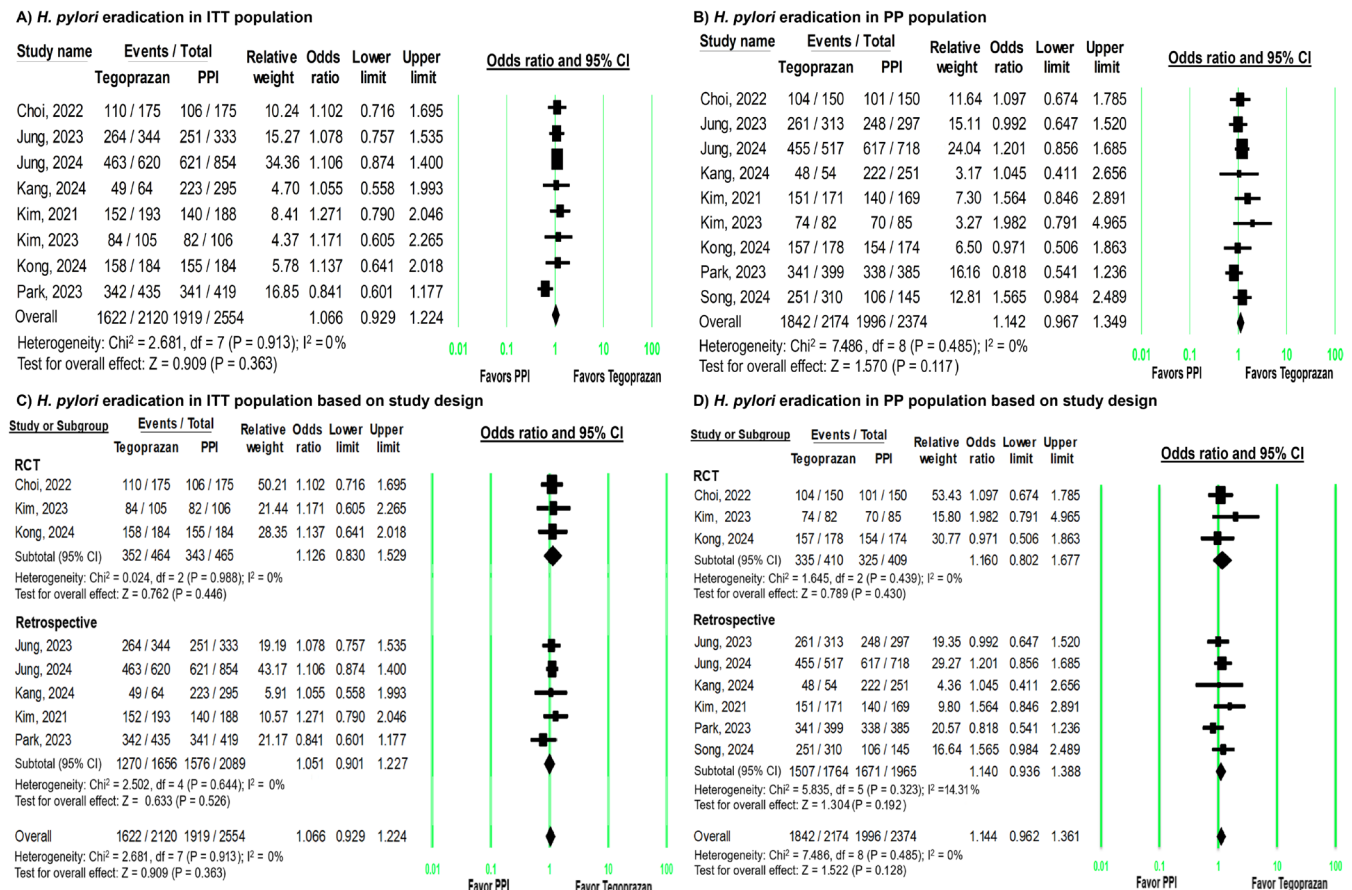


FIGURE 2 | Comparison of tegoprazan and proton pump inhibitor (PPI) as the first-line therapy for *Helicobacter pylori* eradication rates in treatment-naïve patients. Forest plots showing *H. pylori* eradication rates in the (A) intention-to-treat (ITT) and (B) per-protocol (PP) populations, and *H. pylori* eradication rates based on the study design (randomized controlled trial [RCT] vs. retrospective cohort study) in the (C) ITT and (D) PP populations. An odds ratio > 1 indicates that tegoprazan has a higher likelihood of achieving *H. pylori* eradication than PPI-based therapy. CI, confidence interval.

0.814–1.205; second-line therapy: OR 1.642, 95% CI 0.710–3.797) (Figure S3).

3.5 | Comparative Safety Outcomes

3.5.1 | First-Line Eradication Therapy

Patients treated with TPZ and PPI as the first-line regimens had comparable odds of experiencing side effects (OR 0.924, 95% CI 0.759–1.125) (Figure S4). Concerning the severity of adverse events, the 14-day regimen with TPZ was associated with lower odds of experiencing mild adverse events in comparison with the PPI-based regimen (OR 0.660, 95% CI 0.499–0.873) (Figure S5).

Figure 5 summarizes the organ-specific safety events for TPZ and PPI as the first-line therapy for *H. pylori* eradication. Patients treated with TPZ as a first-line therapy had significantly lower overall odds of abdominal discomfort than those treated with PPI (OR 0.490, 95% CI 0.268–0.897) (Figure S6). Conversely, patients on a 7-day TPZ-based regimen had a significantly higher risk of abdominal pain (OR 4.313, 95% CI 1.426–13.051) (Figure S7). However, patients treated with the 14-day TPZ-based regimen experienced significantly fewer

risks of diarrhea than those treated with PPI (OR 0.494, 95% CI 0.350–0.698) (Figure S8). However, no significant differences were observed between TPZ- and PPI-based regimens regarding constipation, dizziness, dysgeusia, general weakness, headache, nausea and/or vomiting, or skin rash, regardless of treatment duration (Figures S9–S15).

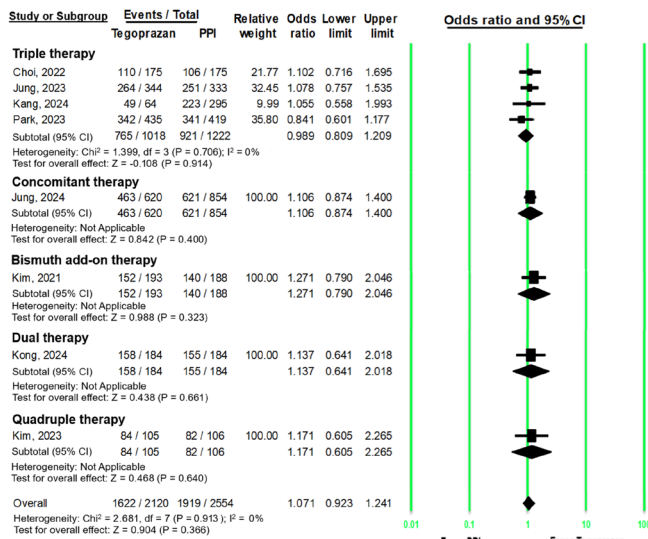
3.5.2 | Second-Line Eradication Therapy

Patients receiving TPZ and PPI for second-line therapy showed comparable odds of experiencing adverse events (Figure S4). Similarly, TPZ and PPI showed comparable organ-specific safety profiles when used as the second-line therapy (Table S3).

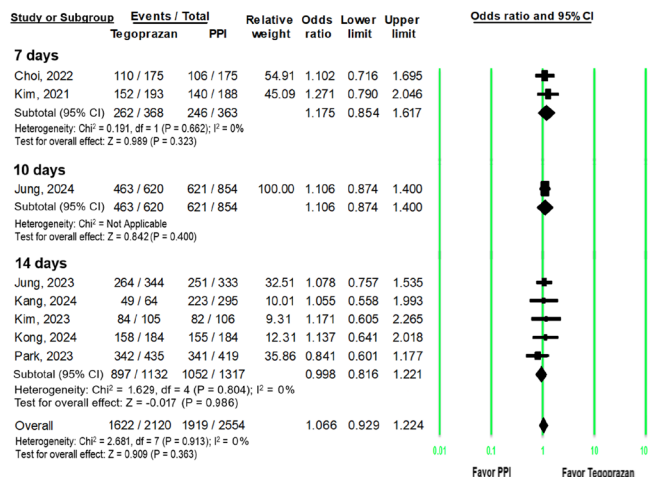
3.6 | Certainty of Evidence Based on GRADE

The GRADE framework rated the certainty of evidence for the efficacy and safety outcomes as very low for both ITT and PPI populations, when comparing TPZ with PPI as first- and second-line therapies. Limitations included small sample sizes, open-label study designs, and reliance on retrospective data in the

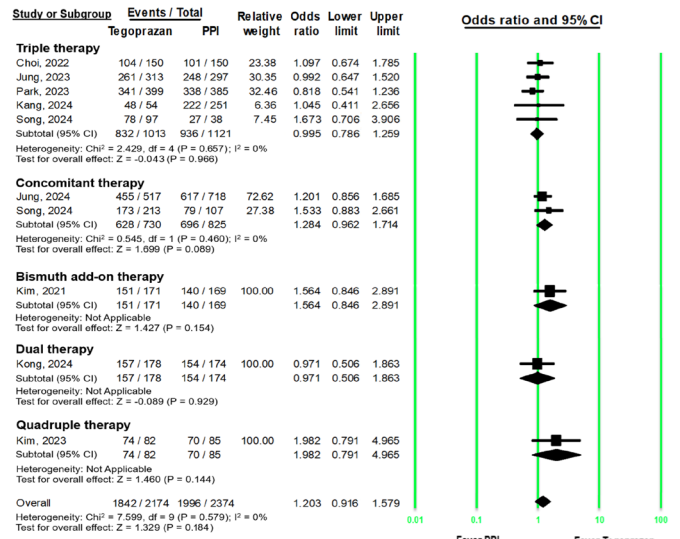
A) *H. pylori* eradication in ITT population based on therapy regimen



C) *H. pylori* eradication in ITT population based on treatment duration



B) *H. pylori* eradication in PP population based on therapy regimen



D) *H. pylori* eradication in PP population based on treatment duration

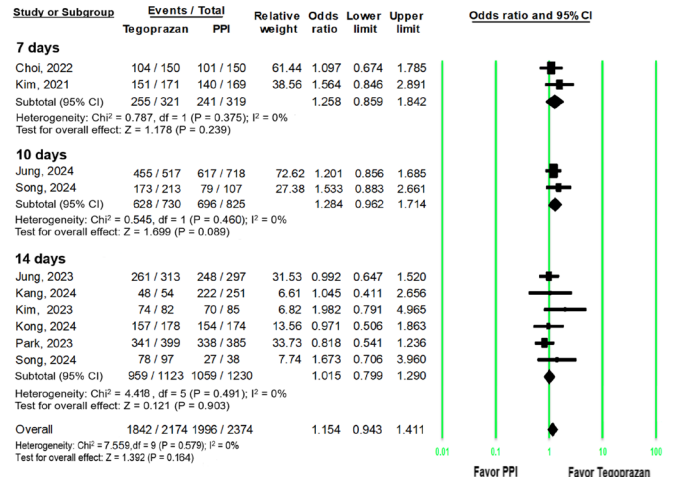


FIGURE 3 | Subgroup analyses of the comparison of tegoprazan and proton pump inhibitor (PPI) as the first-line therapy for *Helicobacter pylori* eradication rate in treatment-naïve patients. Forest plot of subgroup analyses of *H. pylori* eradication rate based on therapeutic regimens (triple vs. dual vs. concomitant vs. bismuth-containing quadruple vs. bismuth add-on therapy) in the (A) intention-to-treat (ITT) and (B) per-protocol (PP) populations, and based on treatment duration (7 vs. 10 vs. 14 days) in the (C) ITT and (D) PP populations. CI, confidence interval.

analysis. Details of the grading evidence for all the efficacy and safety outcomes of the meta-analysis are provided in Table S4.

4 | Discussion

In this study, TPZ- and PPI-based regimens showed comparable *H. pylori* eradication rates as first- and second-line therapies. Most clinical guidelines recommend that therapies for *H. pylori* achieve eradication rates of at least 90% to be considered effective [25]. In the Japanese guidelines updated in 2016, a VPZ-based triple regimen is recommended as the first-line treatment for *H. pylori* eradication [26], as it achieves an eradication rate of at least 80%–85%, meeting the established efficacy threshold [27, 28]. In our study, all TPZ-based regimens were non-inferior to PPI-based regimens, aligning with previous meta-analyses [10, 11, 13, 29]; however, neither regimen achieved eradication rates that met the recommended efficacy thresholds, with the rates being <80% in ITT and <85% in PP

analyses for both groups. In contrast, a recent meta-analysis of RCTs reported superior efficacy of TPZ-based therapy compared to PPI-based therapy [12]. However, the inclusion and pooling of studies with heterogeneous characteristics—such as nonequivalent comparator regimens, participants with prior eradication failures, and the use of full-analysis-set data rather than ITT or PP sets—might have introduced bias into the overall findings. Conducting a sensitivity analysis that excludes the study with the greatest statistical weight could alter the outcome and reveal a less robust effect, highlighting the need for cautious interpretation of these findings.

One possible explanation for these suboptimal results as a first-line treatment may be attributed to the pharmacokinetic and pharmacodynamic properties of TPZ, possibly influenced by the approved dosing levels, which may be insufficient for effective *H. pylori* eradication. Specifically, TPZ has a shorter elimination half-life (3.87–4.57 h) and a lower pKa of 5.1 [30, 31] compared to VPZ, which has a longer half-life (up to 9 h) and a higher pKa of

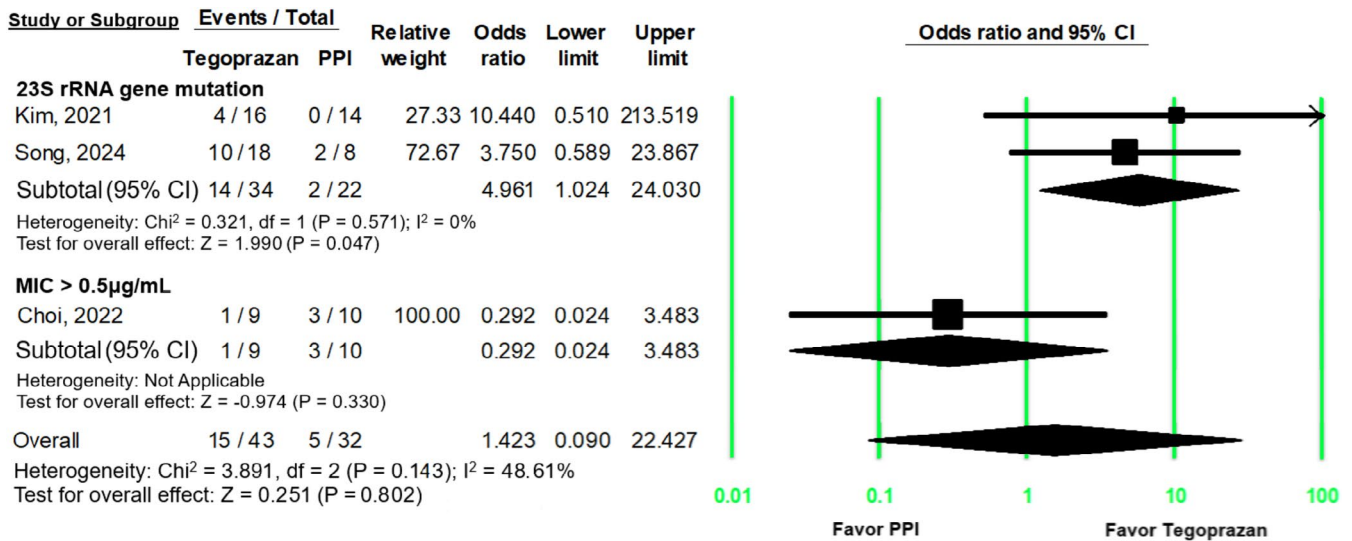


FIGURE 4 | Comparison of tegoprazan and proton pump inhibitor (PPI) as the first-line therapy for *Helicobacter pylori* eradication rate in patients with confirmed clarithromycin-resistant strains. An odds ratio > 1 indicates that tegoprazan had a higher likelihood of achieving *H. pylori* eradication than PPI-based therapy. 23S rRNA, 23S ribosomal ribonucleic acid; CI, confidence interval; MIC, minimum inhibitory concentration.

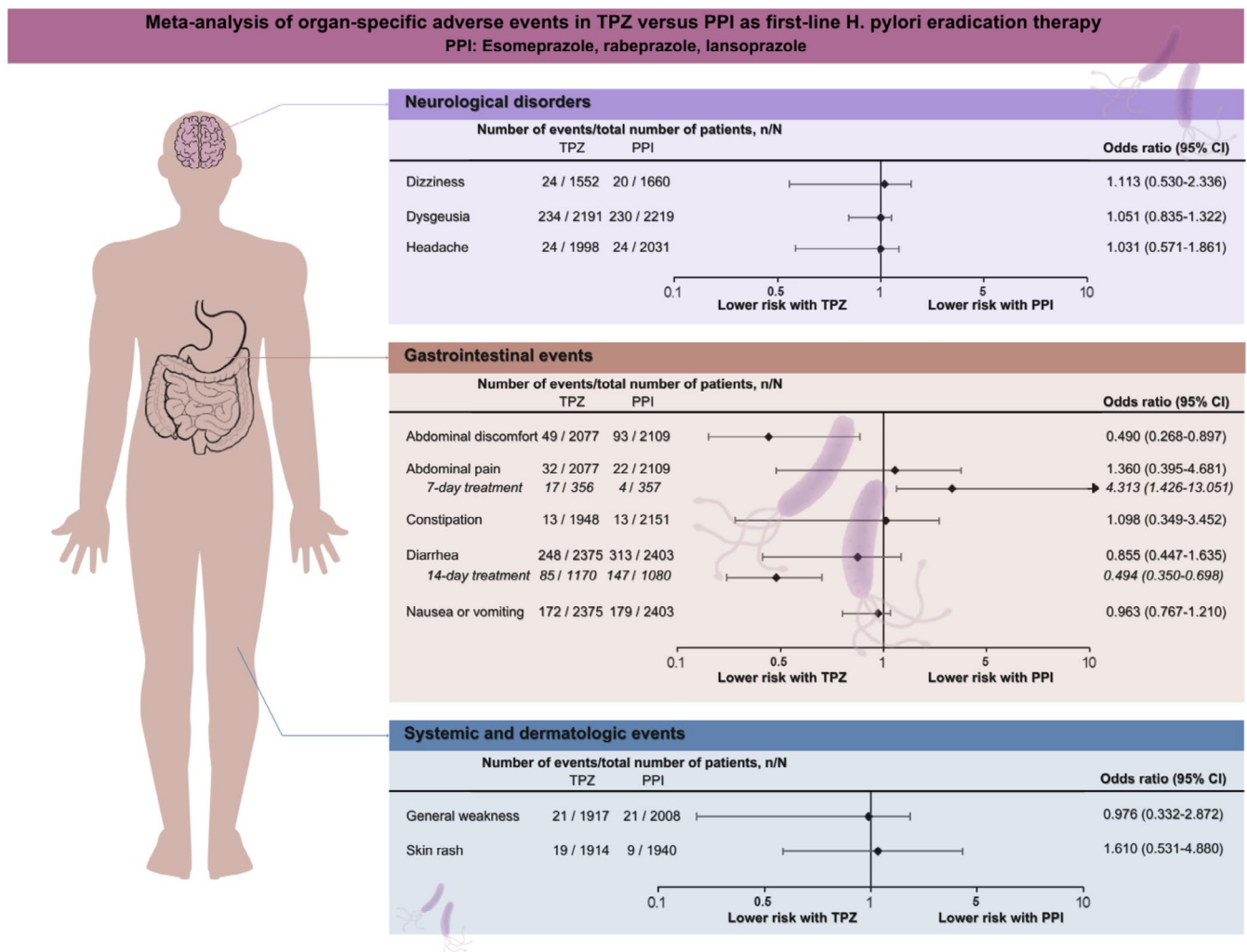


FIGURE 5 | Summary of organ-specific adverse event rates comparing tegoprazan (TPZ) and proton-pump inhibitor (PPI) as the first-line therapy for *Helicobacter pylori* infection. An odds ratio < 1 suggests that tegoprazan was associated with a lower risk of organ-specific adverse events compared to PPI-based therapy. CI, confidence interval.

9.3 [31, 32]. These differences suggest that TPZ may provide less sustained and consistent acid suppression, which is essential for effective *H. pylori* eradication. Achieving a gastric pH of 6.0–8.0 is critical for eradication [33], underscoring the need for more optimized dosing regimens for TPZ.

Although TPZ (50mg) initiates gastric acid suppression faster than VPZ (20mg) or PPI [7], TPZ showed dose-dependent variations in maintaining a pH value > 6.0 [34]. The 50-mg dose quickly achieved a mean pH value of ≥ 4.0 but failed to sustain a pH value of ≥ 6.0 for 12h. In contrast, higher TPZ doses (100 and 200mg) achieved a mean pH value of > 6.0 before meals and maintained a pH value of ≥ 6.0 for an extended period after meal, which may be essential for better eradication outcomes [34]. In addition, for *H. pylori* eradication, PPIs and P-CABs are typically prescribed at doses 4 times higher than those used for non-erosive gastroesophageal reflux disease (NERD), that is, rabeprazole at 40mg for *H. pylori* eradication versus 10mg for NERD, or lansoprazole at 60mg for *H. pylori* eradication versus 15mg for NERD [27, 35]. Similarly, VPZ is administered at 10mg for NERD and at 40mg for *H. pylori* eradication [26, 36]. Conversely, the approved TPZ dosage in the Republic of Korea for *H. pylori* eradication is only twice that used for NERD (100 vs. 50mg daily), potentially limiting its efficacy. These observations highlight the need for further research on high-dose TPZ-based regimens. An exploratory study (NCT05933031) is currently evaluating eradication rates with higher TPZ doses (100mg twice a day) in a 14-day triple-therapy regimen. As more data become available, clinical benefits of TPZ and its potential for achieving superior outcomes in specific patient groups may become clearer.

Our study demonstrated that TPZ-based therapy achieved significantly higher eradication rates than PPI-based therapy in patients with clarithromycin resistance, as identified by sequencing methods targeting 23S rRNA point mutations. A previous meta-analysis on TPZ lacked sufficient power to analyze this subgroup [12]. Our result aligns with previous findings on VPZ-based regimens, which demonstrated improved eradication outcomes in clarithromycin-resistant populations [13, 37]. In clinical practice, conventional culture-based testing for clarithromycin susceptibility and resistance is being replaced by more rapid and cost-effective molecular sequencing methods [38]. Although culture-based testing provides robust resistance data, its application is limited by the slow growth of *H. pylori* and challenging culture conditions, especially in highly prevalent regions. Clarithromycin resistance is driven by multiple mutations [38]; however, the studies in our meta-analysis defined resistance based solely on point mutations at positions A2142G and A2143G [22, 24]. This limited definition reduced the sample size, as it may not have captured the full spectrum of clarithromycin-resistant strains, potentially affecting the observed eradication rates. Expanding future research to include a broader array of resistance mutations and standardized sequencing methods could provide a more comprehensive understanding of the efficacy of TPZ in resistant populations.

Consistent with previous findings [11, 12], our study found no significant difference in the overall incidence of adverse events between TPZ-based and PPI-based therapies. However, TPZ-based therapy was associated with significantly lower odds of abdominal discomfort compared to PPIs (OR 0.490, 95% CI

0.268–0.897), potentially due to their differing effects on gastric motility. PPIs slow gastric emptying [39], whereas TPZ appears to enhance it. Animal studies have suggested that TPZ evokes gastric phase III contractions of the migrating motor complex, a key mechanism that facilitates the movement of non-digestible solids from the stomach to the duodenum during the interdigestive phase [40]. Although human data are limited, enhanced gastric motility may account for the reduced incidence of abdominal discomfort observed with TPZ.

Previous studies have reported that P-CAB-based regimens for 10 or 14 days are associated with a lower risk of adverse events compared to PPI-based regimens [13]. In our study, although the treatment duration did not significantly affect the overall adverse event rates, we observed a downward trend in adverse events with longer TPZ treatment. Specifically, the 14-day TPZ regimen was associated with significantly lower odds of mild adverse events compared to shorter treatment. Meta-analyses have suggested that P-CAB therapies reduce the risk of nausea and/or vomiting and diarrhea without significantly affecting the risk of abdominal pain [13]. One network meta-analysis demonstrated that TPZ-based triple therapy was associated with a higher risk of abdominal pain, while TPZ-based dual therapy had a lower risk of diarrhea, compared to other P-CAB and PPI regimens [29]. Our findings are consistent with this pattern; the 14-day TPZ-based treatment regimen was associated with lower odds of diarrhea, whereas the 7-day TPZ treatment regimen showed higher odds of abdominal pain. This difference may be related to the pharmacological profile of TPZ, which provides rapid and dose-dependent gastric suppression [34, 41]. The 7-day regimen, although potent, may result in insufficient acid suppression or incomplete *H. pylori* eradication [29, 42], causing more intense symptoms like abdominal pain, particularly in patients with existing gastric inflammation or ulcers, as seen in the studies included in our analyses. These findings underscore the need for further research on the mechanisms underlying these effects. Although no significant differences in adherence rates were found in our study across the different treatment regimens, symptoms such as abdominal pain with shorter treatment durations could affect patient tolerance and long-term adherence. Future studies should focus on optimizing TPZ regimens to balance acid suppression, motility effects, and symptom control, thereby ensuring better eradication outcomes and improved patient adherence.

In 2023, the Republic of Korea expanded the national health insurance coverage to include the use of TPZ in combination with antibiotics for *H. pylori* eradication in patients with peptic ulcers [43]. With its comparable efficacy, reduced odds of adverse events, and inclusion in insurance coverage, P-CABs, particularly TPZ-based therapies, are expected to be incorporated into the upcoming Korean guidelines as first-line treatment options for *H. pylori* eradication in patients with gastric conditions.

In the context of second-line therapy, all included studies used bismuth-containing quadruple regimens combining TPZ or PPI with bismuth, metronidazole, and tetracycline. While effective, bismuth-based regimens are often associated with challenges in clinical practice, including regimen complexity, higher rates of adverse events, and poor patient adherence [44]. Although eradication rates between TPZ- and PPI-based regimens were

not significantly different, TPZ-based therapy showed a trend toward slightly higher adherence and adverse event rates (non-significant). Previous studies have similarly reported no significant differences in adverse event profiles between P-CAB-based and PPI-based bismuth-containing quadruple therapies as first-line treatment [13]. These findings highlight that though TPZ may be a viable alternative in second-line therapy, its role must be further clarified through future research with simplified regimens, optimized TPZ dosing strategies, and larger and well-designed trials to fully evaluate its tolerability, patient adherence, and real-world effectiveness.

This study has several limitations that should be acknowledged when interpreting the results. First, the inclusion of retrospective cohort studies due to the scarcity of RCTs fulfilling our inclusion criteria—since the drug was approved only in 2020—might have introduced substantial heterogeneity. As more RCTs become available, future updates to this analysis will be necessary to provide more robust and conclusive evidence. Second, the small sample size in the analysis of *H. pylori* eradication in the clarithromycin-resistant group limited the statistical power and generalizability of our analysis, which is partly due to the non-standardized testing for clarithromycin resistance in different studies. Third, the geographic distribution of the included studies was skewed, with the majority conducted in the Republic of Korea and only one study from China. This regional concentration may restrict the generalizability of our results, as *H. pylori* treatment outcomes can vary across populations due to differences in antibiotic resistance patterns, host genetic factors such as CYP2C19 polymorphisms, and local prescribing practices. Notably, prior meta-analyses have shown no significant difference in eradication efficacy between P-CAB and PPI therapies in Korean populations, whereas improved outcomes with P-CABs were observed in patients from China, Japan, Pakistan, the United States, and Europe [13]. Last but not least, previous meta-analyses have suggested that P-CAB-based dual therapy may achieve higher eradication rates with fewer adverse events than PPI-based regimens [13]. Although several recent RCTs have investigated TPZ-based dual therapy [18, 45, 46], only one was eligible for inclusion in our study. The others compared TPZ-based dual therapy with TPZ- or PPI-based quadruple regimens, rather than with PPI-based dual therapies, and thus did not meet our eligibility criteria. Thus, future direct head-to-head trials or network meta-analyses are needed to fully evaluate the role of TPZ-based dual therapy in *H. pylori* eradication strategies. Nonetheless, this meta-analysis includes a larger number of studies than in previous reviews and provides a more comprehensive evaluation of different TPZ-based therapies as first- and second-line treatment, including a specific analysis of patients with clarithromycin-resistant *H. pylori* infection.

5 | Conclusions

In conclusion, TPZ represents a promising alternative to PPIs for *H. pylori* eradication, demonstrating comparable efficacy as the first- or second-line therapy, with potential benefits in clarithromycin-resistant cases and a favorable safety profile. However, its eradication rates fell slightly below the optimal thresholds, which might be influenced by its pharmacokinetic limitations and current dosing challenges. Notably, PPI-based

regimens in this analysis also struggled to meet the optimal eradication threshold. Future studies should explore higher TPZ dosages and novel dosing strategies to enhance the treatment efficacy of TPZ, particularly in susceptible and resistant populations, and further establish its role in addressing the current challenges in *H. pylori* eradication treatment.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data generated or analyzed during this study are included in this published article and its [Supporting Information](#).

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Summary of risk of bias assessment. (A) Risk-of-bias assessment using the Cochrane Risk of Bias 2 tool for randomized controlled trials (RCTs) in each domain. The risk of bias arising from each item is deemed “low” or “high” or as having “some concerns.” (B) Weighted summary plot of the overall type of bias encountered in the included RCTs. (C) Risk-of-bias assessment using Risk of Bias in Non-randomized Studies—of Interventions (ROBINS-I) V2 tool for retrospective cohort studies in each domain. The risk arising from each item is deemed “low,” “moderate,” “serious,” or “critical.” (D) Weighted summary plot of the overall type of bias encountered in the included retrospective cohort studies. **Figure S2:** *Helicobacter pylori* eradication rate using tegoprazan-based regimen compared with bismuth-containing quadruple therapy as a second-line therapy following first-line treatment failure. Forest plot for the (A) intention-to-treat (ITT) and (B) per-protocol (PP) populations. An odds ratio > 1 indicates that tegoprazan has a higher likelihood of achieving *H. pylori* eradication than proton pump inhibitor (PPI)-based therapy. CI, confidence interval. **Figure S3:** Forest plots on comparison of adherence rate between tegoprazan and proton pump inhibitor (PPI) when used as (A) the first- and (B) second-line therapies based on treatment duration. CI, confidence interval. **Figure S4:** Forest plots on comparison of adverse event rates based on treatment duration between tegoprazan and proton pump inhibitor (PPI) as (A) first- and (B) second-line therapies. CI, confidence interval. **Figure S5:** Comparison of adverse event rates based on severity between tegoprazan- and proton pump inhibitor (PPI)-based regimens. (A) Mild and (B) moderate adverse events based on treatment duration, and (C) severe adverse events. An odds ratio < 1 indicates that tegoprazan is associated with a lower likelihood of adverse events compared to PPI-based therapy. CI, confidence interval. **Figure S6:** Forest plots on comparison of abdominal discomfort between tegoprazan-based and proton pump inhibitor (PPI)-based regimens when used as the first-line therapy according to treatment duration. CI, confidence interval. **Figure S7:** Forest plots on comparison of abdominal pain between tegoprazan-based and proton pump inhibitor (PPI)-based regimens when used as the first-line therapy according to treatment duration. CI, confidence interval. **Figure S8:** Forest plots on comparison of diarrhea between tegoprazan-based and proton pump inhibitor (PPI)-based regimens when used as the first-line therapy according to treatment duration. Notably, one study [22] provided data on loose stools. CI, confidence interval. **Figure S9:** (A) Forest plot of comparison of constipation and (B) statistical analysis between tegoprazan-based and proton pump inhibitor (PPI)-based regimens when used as the first-line therapy based on treatment duration. CI, confidence interval. **Figure S10:** (A) Forest plot of comparison of dizziness and (B) statistical analysis between tegoprazan-based and proton pump inhibitor (PPI)-based

regimens when used as the first-line therapy based on treatment duration. CI, confidence interval. **Figure S11:** (A) Forest plot of comparison of dysgeusia and (B) statistical analysis between tegoprazan-based and proton pump inhibitor (PPI)-based regimens when used as the first-line therapy based on treatment duration. Two studies [17, 22] provided data on bitter taste. CI, confidence interval. **Figure S12:** (A) Forest plot of comparison of general weakness and (B) statistical analysis between tegoprazan-based and proton pump inhibitor (PPI)-based regimens when used as the first-line therapy based on treatment duration. CI, confidence interval. **Figure S13:** (A) Forest plot of comparison of headache and (B) statistical analysis between tegoprazan-based and proton pump inhibitor (PPI)-based regimens when used as the first-line therapy based on treatment duration. CI, confidence interval. **Figure S14:** (A) Forest plot of comparison of nausea and/or vomiting and (B) statistical analysis between tegoprazan-based and proton pump inhibitor (PPI)-based regimens when used as the first-line therapy based on treatment duration. Three studies [16, 17, 24] provided data on nausea only. CI, confidence interval. **Figure S15:** (A) Forest plot of comparison of skin rash and (B) statistical analysis between tegoprazan-based and proton pump inhibitor (PPI)-based regimens when used as the first-line therapy based on treatment duration. CI, confidence interval. **Table S1:** Search strategy. **Table S2:** List of the excluded studies with reasons for their exclusion. **Table S3:** Safety outcomes of tegoprazan (TPZ)- and proton pump inhibitor (PPI)-based regimens when used as second-line therapy [19, 23, 24]. **Table S4:** The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) assessment of efficacy and safety outcomes.