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Systematic Review and Meta-Analysis: Bismuth Enhances the Efficacy for Eradication of *Helicobacter pylori*

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ABSTRACT

Background: In the eradication of *Helicobacter pylori*, the efficacy of bismuth remains inconclusive. We aimed to compare the efficacy of bismuth on various *H. pylori* eradication regimens.

Methods: Randomized controlled trials were collected to compare the efficacy of bismuth to nonbismuth regimens in *H. pylori* eradication. We pooled information to study eradication, adverse events, and drug compliance. In addition, subgroup analyses for eradication efficacy were performed according to high or low clarithromycin-resistance area, bismuth drug form, and amount of bismuth element.

Results: Records for a total of 2506 patients in 15 trials from 13 randomized controlled studies were included. The eradication of *H. pylori* was superior when bismuth compared to nonbismuth regimen (odds ratio [OR] = 1.63, 95% confidence interval [CI], 1.33–2.00 in intention-to-treat [ITT]; OR = 2.05, 95% CI, 1.58–2.68 in per-protocol [PP] analyses), without significant difference in drug compliance or adverse events. Bismuth regimens in the high clarithromycin resistance area tend to enhance the eradication rate (OR = 1.66, 95% CI, 1.34–2.05 in ITT; OR = 2.22, 95% CI, 1.67–2.95 in PP analyses). Bismuth potassium citrate and bismuth subcitrate were more effective drug forms in regard to eradication rate. Bismuth at a dosage of < 500 mg/day was significantly higher for the eradication rate.

Conclusions: Bismuth to the *H. pylori* eradication regimens achieve a higher eradication rate, especially in the high clarithromycin resistance area. It could be an eradication option achieving sufficient resistance rates without increasing antibiotic resistance, side effects, or poor compliance.

1 | Introduction

The global resistance of *Helicobacter pylori* to antibiotics has reached concerning levels, as it leads to obstacles in treatment effectiveness. The success rate of *H. pylori* eradication treatment has seen a drastic decline. A recent meta-analysis revealed that the prevalence of primary clarithromycin resistance exceeds 15% in various regions [1]. Notably, the South-East Asian Region

experienced a significant increase in clarithromycin resistance from 13% (95% confidence interval (CI), 4%–22%) during 2006–2008 to 21% (95% CI, 1%–42%) during 2012–2016 [2, 3]. Consequently, the clarithromycin-containing regimens are no longer considered suitable for empirical use due to their inadequate ability to eliminate the bacteria. Therefore, new eradication regimens are being explored to overcome the high rates of antibiotic resistance.

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The alarming global levels of *H. pylori* resistance in treatment-naïve patients are correlated with the increasing and uncontrolled application of antibiotics commonly used in *H. pylori* empirical therapy. A recent study demonstrated that the regions with the highest macrolide prescription rates experienced the most significant failures in eradication rates [4]. The current concern needs to be addressed regarding nonantibiotic alternative regimens that can improve the eradication rate of clarithromycin-containing regimens. The Maastricht IV/Florence consensus report recommended bismuth-containing quadruple therapy, which consists of proton pump inhibitor (PPI), bismuth, tetracycline, and metronidazole as an alternative first-line therapeutic option in areas with a high prevalence of clarithromycin resistance [5]. Bismuth-containing quadruple therapy could achieve a satisfactory eradication success rate of more than 80%. However, if bismuth-containing quadruple therapy as the first-line treatment fails to eradicate *H. pylori*, it would be difficult to identify an adequate second-line regimen.

The role of bismuth as a component of quadruple therapy composed of bismuth, PPI, tetracycline, and metronidazole of *H. pylori* is already established. However, this approach is usually recommended as secondary therapy. To date, no concrete role of bismuth as a component of primary therapy for *H. pylori* infection has been established. Several studies have reported higher success rates in eradicating *H. pylori* when bismuth is added to clarithromycin-containing regimens, even though a regimen of clarithromycin only is inadequate for *H. pylori* eradication. A prospective study conducted in Korea included 104 patients who completed clarithromycin-containing regimens with the addition of bismuth. The study demonstrated an eradication rate of 90.4% per protocol (PP) and 87.9% by intention-to-treat (ITT) analysis [6]. In China, the expected cure rates for *H. pylori* strains resistant to clarithromycin without the addition of bismuth range from 35% to 40%. The cure rate has increased by an additional 30% to 40% with the addition of bismuth [7]. Conversely, a few studies have reported that bismuth to clarithromycin-containing regimens do not improve the eradication of *H. pylori* [8]. A recent study in Taiwan showed slightly higher but still unsatisfactory eradication results when bismuth was added to a 7-day clarithromycin-containing regimen [9]. Additionally, a randomized controlled trial conducted in Southeast Asia found that bismuth to a 7-day clarithromycin-containing regimen did not result in an increase in the eradication rate [8].

Therefore, in the eradication of *H. pylori*, the efficacy of bismuth remains inconclusive. We conducted a meta-analysis for randomized controlled trials (RCTs) to compare the efficacy of bismuth to various *H. pylori* eradication regimens in first-line treatment.

2 | Methods

2.1 | Search Strategy and Study Selection

A systematic literature search was performed up to March 2024, using PubMed, EMBASE, CINAHL, and the Cochrane Library database for potentially eligible studies from January 1990 to

March 2024 by a methodology expert (M Choi). The search was conducted using the following keywords: (“*Helicobacter pylori* infection,” “*Helicobacter pylori* eradication,” “*H. pylori* infection,” “*H. pylori* eradication”) and (“bismuth,” “amoxicillin,” “clarithromycin,” “metronidazole,” “proton-pump inhibitor,” “PPI,” and “omeprazole, pantoprazole, lansoprazole, esomeprazole, rabeprazole”). Included were all of the studies conducted with medications that had bismuth: bismuth subnitrate, bismuth subcitrate, tripotassium dicitrate bismuthate and bismuth potassium citrate. To search for additional studies, similar or related articles were screened. The inclusion criteria were as follows: (a) RCTs, (b) identification of *H. pylori* infection as confirmed by one or more of the following diagnostic modalities: rapid urea test, histology, culture, and urea breath test, (c) bismuth as eradication therapy, (d) comparing the efficacy of bismuth therapy with nonbismuth therapy for *H. pylori* eradication in treatment-naïve patients, (e) studies of human subjects, (f) publications in English, (g) literature published after 1990. The exclusion criteria were as follows: (a) varied treatment durations for bismuth therapy and nonbismuth therapy, (b) bismuth therapy including Pylera (Allegran, Dublin, Ireland), (c) studies published in languages other than English, (d) incomplete articles, (e) animal studies. The reporting of the current study follows the PRISMA guidelines (Table S1).

2.2 | Data Extraction

The following data were extracted from each source by two investigators (AR Choe and CH Tae): name of the first author, year of publication, country where the study was conducted, eradication regimens (dose of bismuth element, PPI, antibiotics), treatment duration, number of subjects who were successfully treated in each regimen, adverse events, and drug compliance.

2.3 | Definition

The Maastricht VI/Florence consensus report recommends that clarithromycin-based first-line antibiotics should only be used empirically if the prevalence of resistance is <15%. According to the prevalence of clarithromycin-resistance proportion up to and including 2022, countries with a clarithromycin-resistant rate of more than 15%, including Italy (40.4%), China (34.1%), Spain (27.4%), Taiwan (17.0%), Turkey (25.8%), and Brazil (15.3%), were categorized as “high clarithromycin-resistant area.” Meanwhile, the Netherlands (9.2%) was categorized as a “low clarithromycin-resistant area” [10–12].

2.4 | Calculation for Amount of Bismuth Element

The chemical formula of bismuth potassium citrate is $C_6H_5BiKO_7^+$. The atomic weight of bismuth is approximately 208.98 g/mol. It is necessary to calculate the molecular weight of bismuth potassium citrate, which is the sum of the atomic weights of bismuth, potassium, and citrate ions. The total molecular weight of bismuth potassium citrate is 437.18 g/mol. In 600 mg of bismuth potassium citrate, the amount of bismuth is 285.50 mg. Bismuth subcitrate contains approximately

58% bismuth element; thus, the amount of bismuth element in 360mg of bismuth subcitrate would be approximately 208.80mg. The chemical formula of bismuth subnitrate is $\text{Bi}(\text{NO}_3)_3$, and the atomic weight of nitrate ion (NO_3^-) is approximately 62.00g/mol. Therefore, the total molecular weight of bismuth subnitrate is 395.98g/mol. In 300mg of bismuth subnitrate, the amount of bismuth element is 158.27mg. The chemical formula of bismuth subsalicylate is $\text{Bi}(\text{C}_7\text{H}_5\text{O}_3)_3$, and the atomic weight of bismuth is approximately 208.98g/mol. The atomic weight of the salicylate ion ($\text{C}_7\text{H}_5\text{O}_3^-$) is approximately 138.12g/mol. The total molecular weight of bismuth subsalicylate is 623.30 mg; in 562 mg of bismuth subsalicylate, the amount of bismuth is 188.4 mg.

2.5 | Quality Assessment and Risk of Bias

Two independent reviewers assessed the potential bias of enrolled studies using the Cochrane risk-of-bias tool for RCTs (RoB 2) (Figure S1) [13]. It was categorized as randomization, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome data. We resolved disagreements between investigators by discussion. To assess the presence of publication bias, we drew a funnel plot which demonstrated no prominent asymmetric distributions of the studies ($p=0.096$; Figure S2).

2.6 | Data Synthesis and Statistical Analysis

We pooled data using a random effects model to give a more conservative estimate of the effect of *H. pylori* eradication therapy on the addition of bismuth therapy as compared to nonbismuth therapy, allowing for any heterogeneity between studies [14]. All statistical analyses were performed with Review Manager Version 5.4 software (Revman; The Cochrane Collaboration Oxford, UK). The pooled data analyses with 95% CI in bismuth therapy and nonbismuth therapy were calculated. We investigated heterogeneity between studies by using I^2 statistics. I^2 was calculated as $I^2 (\%) = 100 \times (Q - \text{df}) / Q$. We considered I^2 values of 25%, 50%, and 75% to be low, moderate, and high degrees of heterogeneity, respectively [15].

3 | Results

3.1 | Study Selection and Characteristics of Studies

The process of selecting studies included in the meta-analysis is shown in Figure 1. All enrolled studies were limited to randomized control trials and a total of 2972 studies with a comparison of bismuth and nonbismuth regimens in *H. pylori* eradication were included. Ultimately, 15 trials from 13 RCTs with bismuth (1254 patients) and nonbismuth (1252 patients) regimens were included. Table 1 presents the main characteristics of the studies [9, 16–26].

All studies used one among dual, triple, quadruple, and segmental therapies as a first-line regimen for *H. pylori* eradication. Participants were randomized into the bismuth and non-bismuth groups. In terms of bismuth drug form, various drugs such as colloidal bismuth pectin, bismuth potassium citrate, bismuth subcitrate, bismuth nitrate, and bismuth subsalicylate were used.

3.2 | Eradication Efficacy

The pooled eradication rates of nonbismuth regimens were 77.3% in ITT and 82.8% in PP analyses. Meanwhile, the pooled eradication rates of bismuth regimens were 84.6% in ITT and 90.1% in PP analyses, which achieved an eradication rate above the accepted threshold of 80%. In meta-analyses, bismuth regimens compared to nonbismuth regimens had higher efficacy of *H. pylori* eradication rate (OR = 1.63, 95% CI, 1.33–2.00, $p < 0.00001$, $I^2 = 0\%$ in ITT; OR = 2.05, 95% CI, 1.58–2.68, $p < 0.00001$, $I^2 = 0\%$ in PP analyses; Figure 2).

In subgroup analyses according to the *H. pylori* eradication regimens, bismuth in standard triple therapy provided superior eradication rates of 85.2% and 92.1% in ITT and PP analyses compared with nonbismuth therapy (OR = 1.63, 95% CI, 1.29–2.07, $p < 0.0001$, $I^2 = 0\%$ in ITT; OR = 2.18, 95% CI, 1.58–2.99, $p < 0.00001$, $I^2 = 0\%$ in PP analyses; Figure 3). However, bismuth in dual and sequential therapies did not yield superior eradication rates compared with nonbismuth therapy.

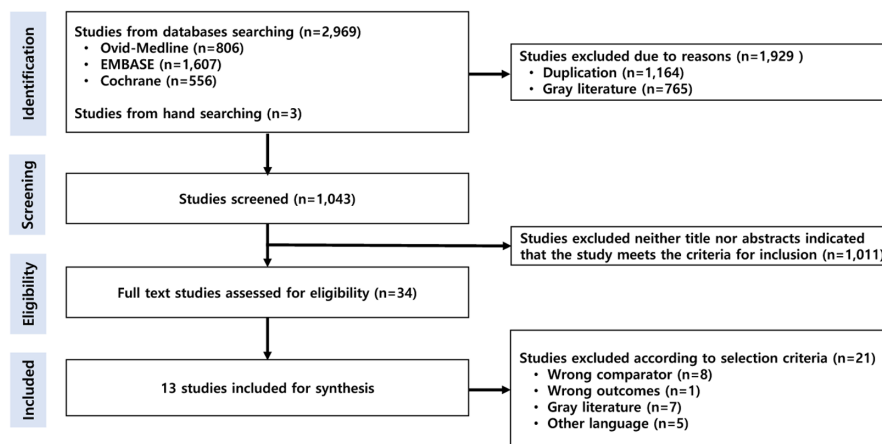


FIGURE 1 | Flow chart diagram demonstrating study selection for meta-analyses.

TABLE 1 | Characteristics of studies included in the meta-analysis.

Author (year)	Nation	Classification	Nonbismuth	Bismuth	Duration (days)	Eradication, ITT (n)				Eradication, PP (n)			
						Bismuth		Nonbismuth		Bismuth		Nonbismuth	
						Eradicated number	Total number	Eradicated number	Total number	Eradicated number	Total number	Eradicated number	Total number
Aksoy (2017) [19]	Turkey	Triple	R 20mg bid A 1g bid Lf 500mg qd	Bismuth subsalicylate 562mg bid	14	93	111	80	107	93	102	80	101
Cavalho (1998) [17]	Brazil	Dual	O 20mg bid A 500mg qd	Bismuth subnitrate 300mg qid	14	18	25	13	25	18	22	13	21
Ciccaglione (2012) [16]	Italy	Triple	P 20mg bid A 1g bid M ₂ 400mg bid	Bismuth subcitrate 240mg bid	10	46	50	44	57	46	49	44	56
Forne (1995) [21]	Spain	Dual	O 20mg bid C 500mg bid	Colloidal bismuth subnitrate 120mg qid	7	25	31	15	30	25	31	15	30
Liao (2013) [23]	China	Triple	L 30mg bid Lf 500mg qd A 1g bid	Bismuth potassium citrate 220mg bid	14	70	80	67	81	70	74	67	78
Long (2018) [14]	China	Triple	E 20mg bid C 500mg bid M ₁ 400mg qid	Bismuth potassium citrate 600mg bid	14	28	33	21	33	24	25	21	30
Luo (2020) [20]	China	Triple	E 20mg bid A 1g tid M 400mg tid	Bismuth potassium citrate 600mg bid	14	98	108	96	108	94	96	90	95
Ozturk (2017) [38]	Turkey	Triple	O 20mg bid C 500mg bid A 1g bid	Bismuth subcitrate 600mg bid	10	39	51	30	49	39	49	30	40
Su (2017) [22]	China	Sequential	O 20mg bid A 1g bid	Bismuth subcitrate 600mg bid	10	43	52	34	47	43	48	34	46
			O 20mg bid C 500mg bid										
			M ^a 500mg tid										
Su (2017) [22]	China	Triple	E 20mg bid Lf 500mg qd A 1g bid	Colloidal bismuth pectin 200mg bid	7	78	90	68	90	78	87	68	83
Tan (1997) [18]	Netherlands	Dual	O 40mg bid A 500mg qid	Bismuth subcitrate 120mg qid	14	68	85	65	87	68	84	65	83
Wu (2017) [9]	Taiwan	Triple	R 20mg bid A 1g bid Lf 500mg qd	Bismuth subcitrate 120mg qid	7	63	81	59	81	63	77	59	79

(Continues)

TABLE 1 | (Continued)

Author (year)	Nation	Classification	Nonbismuth	Bismuth	Duration (days)	Eradication, ITT (n)				Eradication, PP (n)			
						Bismuth		Nonbismuth		Bismuth		Nonbismuth	
						Eradicated number	Total number	Eradicated number	Total number	Eradicated number	Total number	Eradicated number	Total number
Xie (2018) [15]	China	Triple	E 20mg bid F 100mg bid A 1g bid	Bismuth 220mg	10	161	186	154	187	161	170	154	170
			E 20mg bid F 100mg bid A 1g bid	Bismuth 220mg	7	158	189	149	192	158	174	149	175
Yu (2019) [13]	China	Dual	E 40mg bid A 1g tid	Bismuth potassium citrate 600mg bid	14	71	80	74	80	70	75	73	76

Abbreviations: A, amoxicillin; B, bismuth; C, clarithromycin; E, esomeprazole; F, furazolidone; ITT, intention-to-treat; L, lansoprazole; M₁, metronidazole; M₂, moxifloxacin; O, omeprazole; P, pantoprazole; PP, per protocol; R, rabeprazole.

^aIn this sequential therapy, bismuth with triple therapy was given in only the remaining 5 days after dual therapy for the first 5 days.

In addition, the efficacy of bismuth regimens was maintained in a high clarithromycin-resistance area (OR=1.66, 95% CI, 1.34–2.05, $p < 0.0001$, $I^2 = 0\%$ in ITT; OR=2.22, 95% CI, 1.67–2.95, $p < 0.0001$, $I^2 = 0\%$ in PP analyses), but the efficacy of bismuth was not remarkable in low clarithromycin-resistance area (OR=1.35, 95% CI, 0.66–2.78 in ITT; OR=1.18, 95% CI, 0.55–2.50 in PP analyses) (Figure S3). Out of a total of 15 trials, information regarding antimicrobial resistance was provided in four trials. We have added the table on antimicrobial resistance in the included trials to Table S2.

In order to identify a suitable bismuth drug form that increases the *H. pylori* eradication rate, a subgroup analysis was performed. Both bismuth potassium citrate and bismuth nitrate significantly increased the *H. pylori* eradication rate (OR=1.48, 95% CI, 1.13–1.94, $p = 0.005$, $I^2 = 0\%$, in bismuth potassium citrate; OR=1.90, 95% CI, 1.10–3.30, $p = 0.02$, $I^2 = 0\%$, in bismuth subcitrate; Figure S4). Other types of bismuth formulation did not indicate a significant difference between bismuth and non-bismuth regimens.

Regarding daily bismuth dosage, regimens of <500 mg of bismuth formula per day showed an effective eradication (OR=3.40, 95% CI, 1.03–11.22, $p = 0.04$ in 246 mg of bismuth; OR=1.55, 95% CI, 1.24–1.95, $p = 0.0001$, $I^2 = 0\%$, in 440–490 mg of bismuth). However, the *H. pylori* eradication rate was not significantly increased at dosages above 500 mg (Figure S5).

3.3 | Adverse Events and Drug Compliance

The pooled adverse event rate of bismuth regimens was 22.3% and nonbismuth regimens were 19.1% without significant differences in adverse event rate between the two groups (OR=1.21, 95% CI, 0.88–1.65, $p = 0.24$, $I^2 = 38\%$, Figure S6). Poor drug compliance rates between bismuth (4.2%) and nonbismuth regimens (3.5%) were comparable (OR=1.16 95% CI, 0.68–1.99, $p = 0.58$, $I^2 = 0\%$; Figure S7).

4 | Discussion

Our results confirmed that bismuth could result in a superior eradication rate above the accepted threshold of 80% when compared to non-bismuth regimens, as bismuth increased the eradication rate by approximately 7% in both ITT and PP analyses. According to the Maastricht V/Florence Consensus report, PPI-clarithromycin containing triple therapy should be abandoned because of <80% eradication rates in areas with high clarithromycin resistance rates over 15% [5]. However, we demonstrated that the eradication rates of bismuth to the triple therapy were acceptable at 85.1% and 92.1% by ITT (OR=1.64, 95% CI, 1.30–2.07) and PP (OR=2.18, 95% CI, 1.58–2.99) analyses, despite in high clarithromycin resistance area. Additionally, regimens bismuth demonstrate similar adverse events and satisfactory compliance when compared with nonbismuth regimens.

Since bismuth in patients with gastric ulcers was introduced in 1785, it has been used for the treatment of diarrhea, peptic

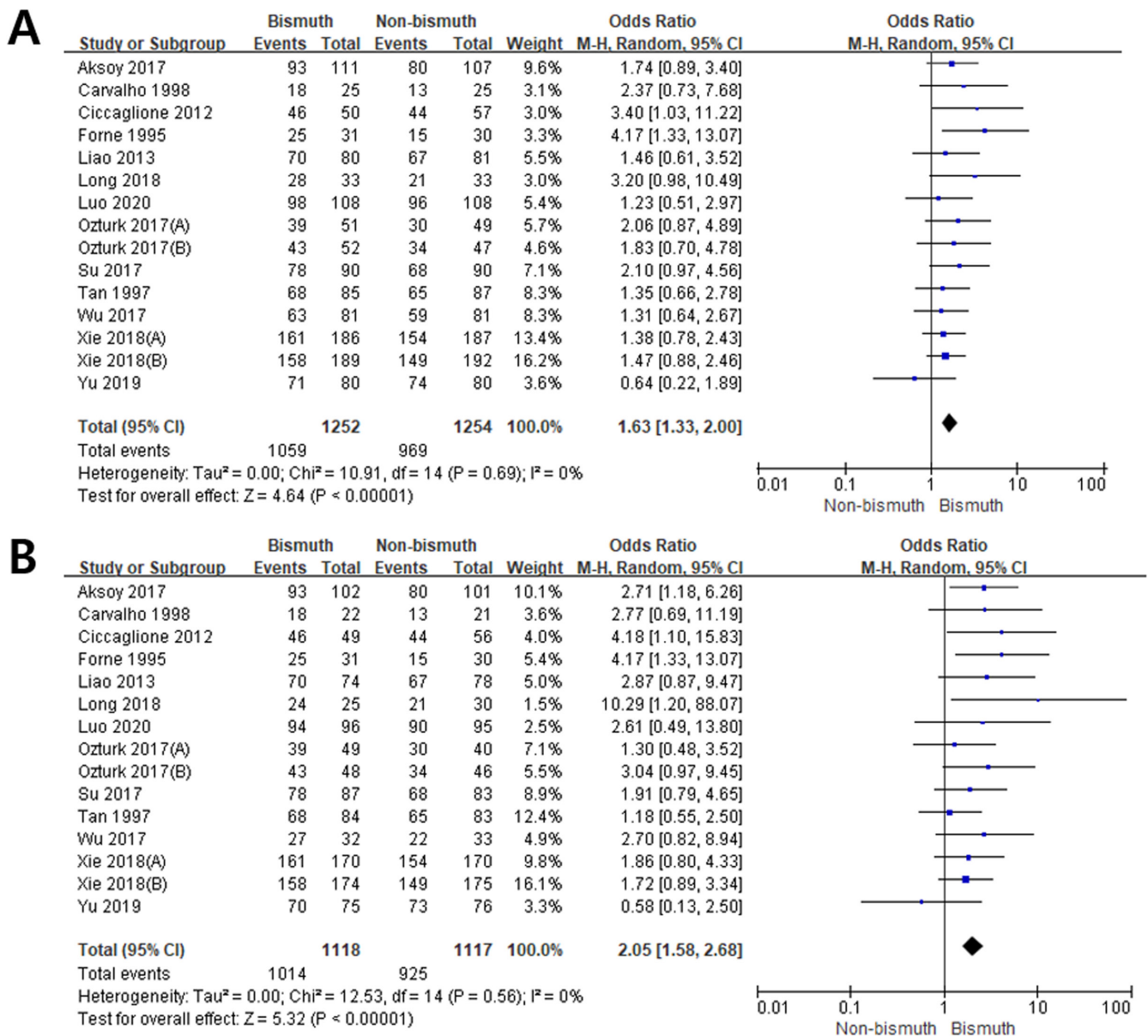


FIGURE 2 | Forest plots on effect of bismuth vs. nonbismuth regimens on *Helicobacter pylori* eradication in ITT (A) and PP (B) analyses for a total of 15 trials.

ulcer, and eye infection. There are various proven roles of bismuth efficacy even though its mechanism is still not well documented. Bismuth prevents the adhesion of *H. pylori* on surface gastric epithelial cells by forming non-soluble polymers in the *H. pylori* wall and periplasmic space [27, 28]. It possesses antimicrobial activity by inhibiting various enzymes produced by *H. pylori* such as urease, catalase, fumarase, alcohol dehydrogenase, and lipid/phospholipase [29, 30]. In addition, it inhibits the ATP synthesis of *H. pylori*, activity of F1-F0 ATPase, TCA cycle following oxidative stress, and suppresses energy production of *H. pylori* in local effect [31, 32]. These characteristics provide evidence for including bismuth in *H. pylori* eradication treatment.

In addition, we demonstrated that adverse effects were comparable between bismuth and nonbismuth regimens. Given both bismuth's antibacterial action by direct interaction with *H. pylori* and its very low body absorption rate of <1%, it could be

determined that a low dose of bismuth may be sufficient for the eradication of *H. pylori* with minimal adverse events. Similarly, it was demonstrated that a low daily dose of <500 mg was effective for *H. pylori* eradication when compared to a higher dose. At the time of this writing, the ideal drug form, dosage, dosing interval, and relation to food intake for the administration of bismuth remain unclear. Some studies reported that administration twice daily, 5–8 bismuth subsalicylate tablets, and low-dose bismuth citrate (108 mg) at four to five times daily have all demonstrated efficacy when administered as part of a multidrug therapy [33, 34].

The differences in chemical composition, solubility, and bio-availability of the bismuth compounds can influence their antibacterial activity and effectiveness in eradicating *H. pylori* [35]. Bismuth subcitrate is known for its ability to form a protective barrier over ulcers, thereby aiding in the healing process and preventing *H. pylori* from adhering to the gastric mucosa.

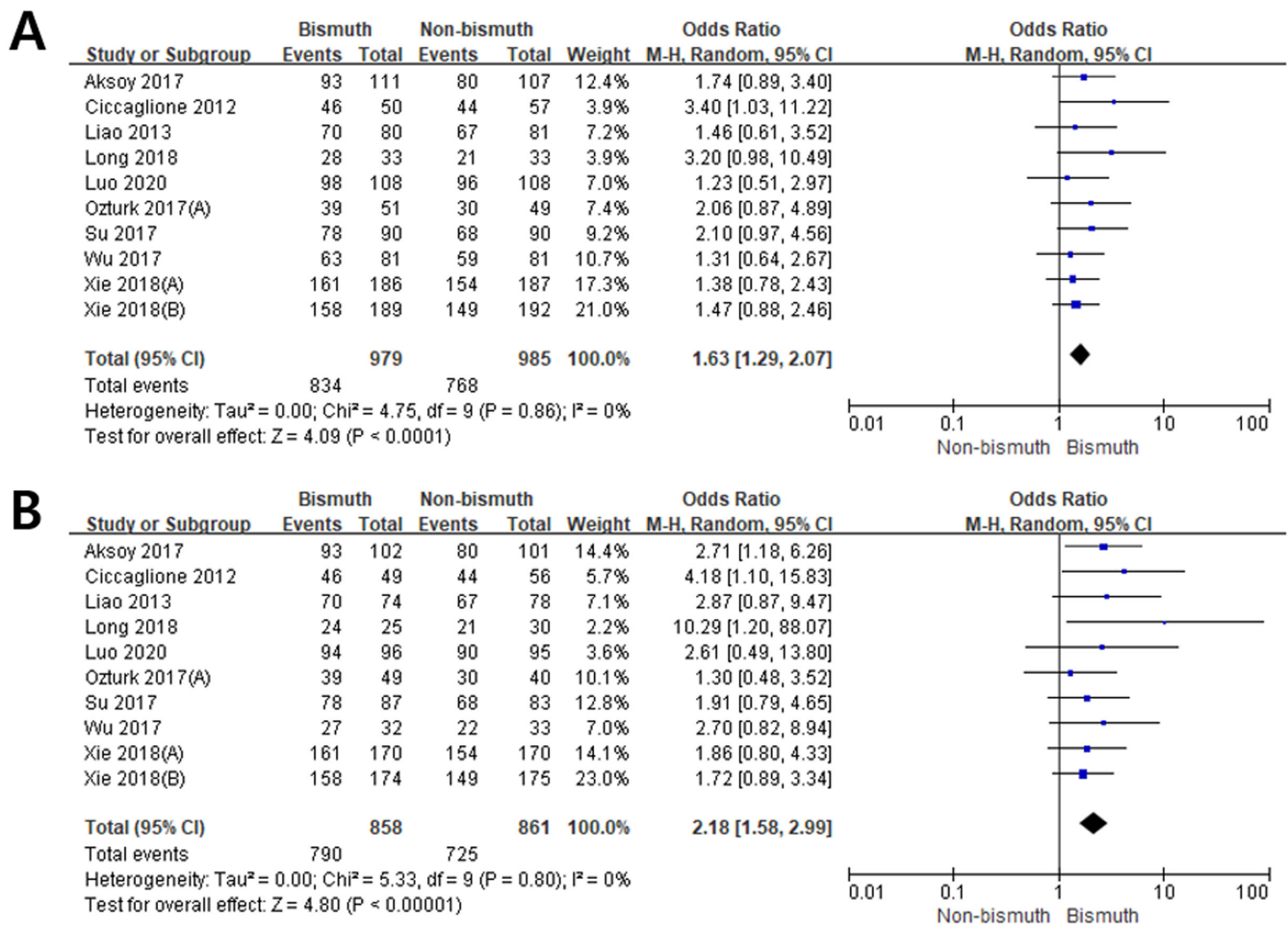


FIGURE 3 | Forest plots on effect of bismuth vs. nonbismuth regimens on *Helicobacter pylori* eradication in ITT (A) and PP (B) analyses of 10 standard triple studies.

Particularly, bismuth subcitrate has a direct antibacterial effect on *H. pylori* [36]. This effect is due to the disruption of the bacterial cell wall and inhibition of bacterial enzymes. Different bismuth salts may vary in their ability to disrupt bacterial cell walls and inhibit bacterial growth. Therefore, different forms in the chemical compositions of bismuth could have an impact on the results of *H. pylori* eradication treatments.

In our analysis, bismuth potassium citrate and bismuth subcitrate at <490mg/day were the most effective drug forms and dosage. In a total of 13 pooled studies, 6 of the studies were conducted in China. Standard recommendations in the Fifth Chinese National Consensus report on the management of *H. pylori* infection are bismuth potassium citrate at a dosage of 220mg twice daily before meals [37]. Korean guidelines for the treatment of *H. pylori* infection recommend 120mg of element bismuth 4 times a day [1].

Our analysis had some limitations. First, all studies comparing the efficacy of bismuth had varying treatment durations of 7–14 days; however, we did not consider this in our analysis. Second, the real-world availability of bismuth drug forms varies among countries despite demonstrated efficacy of drug form and dose per day in the reviewed studies. Thus, it is a limitation for adaptation of these results.

Previous reports have highlighted the potential efficacy of bismuth as a first-line regimen for clarithromycin-resistant strains. However, there has been a lack of comprehensive meta-analyses comparing the effectiveness of different bismuth compounds and their appropriate dosages. This meta-analysis provides a unique contribution by addressing the specific forms and optimal dosages of bismuth that are most effective. By systematically evaluating these variables, this study offers novel insights and guidance for clinical practice that were not previously available in the existing literature.

In summary, bismuth to the *H. pylori* eradication regimens could achieve up to 90% eradication rate. The addition of bismuth could provide an eradication option of sufficient efficacy without increasing antibiotic resistance, side effects, or poor compliance, even in high clarithromycin resistance areas.

Author Contributions

A Reum Choe: data curation, writing – original draft. **Chung Hyun Tae:** conceptualization, investigation, data curation, formal analysis, writing – review and editing. **Miyoung Choi:** methodology, formal analysis, supervision. **Ki-Nam Shim:** writing – review and editing, supervision. **Hye-Kyung Jung:** writing – review and editing, supervision.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.