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The Efficacy and Safety of Bismuth-Based Quadruple Therapy for *Helicobacter Pylori* Infection: A Meta-Analysis

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Abstract

Objective: To assess the safety and efficacy of bismuth-based quadruple therapy for *Helicobacter pylori* (*H. pylori*) infection.

Methods: We searched the PubMed, Cochrane and EMBASE databases updated to January 2015 for randomized controlled trials (RCTs) comparing bismuth-based quadruple therapy (Bismuth quadruple therapy) with non-bismuth standard triple therapy (standard therapy) for *H. pylori* infection. Literature qualities were assessed using Cochrane assessment system. Meta-analysis was carried out with Stata 11.0 and Review Manager 5.3. Risk ratio (RR) and their 95% confidence interval (95% CI) were computed. Subgroup analysis and sensitivity analysis were performed. Egger's test was performed to evaluate publication bias among studies.

Results: Ten RCTs were eligible and enrolled. In the overall analysis, bismuth quadruple therapy achieved comparable intention-to-treat cure rates (RR = 0.90, 95% CI: 0.62~1.30, *P* = 0.57), per-protocol cure rates (RR = 1.29, 95% CI: 0.54~3.09, *P* = 0.57), and recrudescence rates (RR = 0.98, 95% CI: 0.49~1.98, *P* = 0.96) to the standard triple therapy. Side-effects were also similar between those two therapies (RR = 0.91, 95% CI: 0.73~1.13, *P* = 0.40). Moreover, subgroup analysis indicated bismuth quadruple therapy had significantly higher intention-to-treat cure rates (RR = 0.72, 95% CI: 0.55~0.93, *P* = 0.01), but comparable per-protocol cure rates (RR = 0.71, 95% CI: 0.49~1.04, P = 0.08) and side-effects (RR = 0.97, 95% CI: 0.76~1.23, *P* = 0.79) to the standard triple therapy.

Conclusions: Bismuth quadruple therapy had similar safety to the standard triple therapy, whereas it was more effective than standard triple therapy in the treatment of *H. pylori* infection.

Keywords: *Helicobacter pylori*; Bismuth; Quadruple therapy; Standard triple therapy; Meta-analysis; Sub-group analysis

Introduction

Helicobacter pylori (*H. pylori*) has been firstly identified in 1983 from patients with active chronic gastritis [1]. Since then, *H. pylori* infection has been thought intensely related to peptic ulcer disease [2], with incidences range from 0.03% to 0.19% every year [3]. Once *H. pylori* infect the stomach, they can persistently exist for decades in the acidic gastric environment, where they disrupt gastric mucosa, alter the patterns of hormone secretion, and ultimately lead to chronic gastritis and peptic ulcer disease [4]. More dangerously, chronic infection of *H. pylori* may result in the development of malignancies of stomach via complex interactions [5], the elimination of infected *H. pylori* can inversely exert a preventative effect on gastric carcinogenesis [6]. Thus, there is an urgent need to effectively eradicate the infected *H. pylori* in patients with gastrointestinal diseases.

Multiple combination therapies to treat *H. pylori* infection are available clinically. Previously, the standard triple therapy consisting of a proton pump inhibitor (PPI), clarithromycin (C) and amoxicillin (A) is usually used as the first-line regimen for peptic ulcer with H. Pylori infection [7]. However, a recent study reveals that the resistance of *H. pylori* to C has exceeded 80% [8]. Due to the widespread occurrences of antibiotic resistance, the overall eradication rates of infected *H. pylori* by employing the standard therapy has dropped to an unacceptable level at 66.6% [9]. Thereafter, a bismuth quadruple therapy emerges as an alternative therapy to the widely used standard triple therapy with the advantages of cost-effectiveness [10,11].

A few studies have been performed to evaluate the efficacy and safety of bismuth quadruple therapy for *H. pylori* infection. However, the results from those studies were inconsistent Two studies showed that the bismuth quadruple therapy has higher eradication rates than the standard triple therapy [11,12], other studies demonstrated that the bismuth quadruple therapy has lower eradication rates of *H. pylori* than the standard triple therapy [13-15]. Moreover, a few meta-analyses also had inconsistent conclusions. Two of the meta-analysis studies revealed that bismuth quadruple therapy is less tolerated and less efficient than levofloxacin or moxifloxacin-based triple therapy [16,17], one meta-analysis indicates that the bismuth quadruple therapy is more effective than the standard triple therapy [18].

Thus, we conducted an updated meta-analysis, with more outcome measurements, and stricter inclusion/exclusion criteria, in order to get a more comprehensive view of efficacy and safety of the bismuth quadruple therapy.

Methods

Literature search

Literatures were identified by searching the electronic databases

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PubMed, EMBASE (Excerpt Medica Database), and Cochrane library from their establishment to January 2015. Also, literatures were traced back to obtain the related randomized controlled trials (RCTs). The key search terms were "*Helicobacter Pylori*" or "*H. pylori*" or "*HP*" And "peptic ulcer" or "PU" And "quadruple" And "bismuth" And "random".

Inclusion and exclusion criteria

The inclusion criteria in the meta-analysis were: (1) studies were RCTs; (2) participants in the study were patients with *H. pylori* infection; (3) studies involved the comparison of bismuth quadruple therapy (study group) and the standard triple therapy (control group); (4) studies presented the outcomes such as eradication rates of *H. pylori* infection or side effects of the therapy; (5) studies with more comprehensive data and higher quality were selected when it has multiple publication versions; (6) Studies were published in English. On the contrary, the exclusion criteria were: (1) publications were non-original studies, such as reviews, conference abstracts and letters; (2) studies compared the efficacy and side effects of bismuth quadruple therapy with different intervention duration; (3) studies compared between bismuth quadruple therapy with dual therapy, bismuth-containing triple therapy, sequential therapy or other bismuth-based quadruple therapy.

Data extraction and quality assessment

On the basis of the pre-defined protocol, data were extracted independently by two researchers. Disagreement were resolved by discussion with a third investigator. For every enrolled study, the information listed below was abstracted: research type, research time, the state, the first author name, the year of publication, follow-up time, the population, the number of patients distributed in two groups, the average age, the treatment duration and the outcomes including side-effects and eradication rates of *H. pylori*. The quality of the eligible studies was evaluated based on Cochrane assessment system containing 7 evaluation parameters [19].

Statistical analysis

Statistical analysis was conducted by Stata 11.0 (Stata Corp, http://www.stata.com/) and Review Manager 5.3 software (http://tech.cochrane.org/revman). For each eligible study, the risk ratio (RR) and corresponding 95% confidence interval (95% CI) were calculated to assess efficacy and side effects of the two kinds of therapies. Statistical heterogeneities among studies were estimated on the basis of Cochrane based Q statistical analysis, and the $P<0.05$ and I^2 >50% represented statistically significant heterogeneity [20]. The summary RRs were calculated by random effects model if there was significant heterogeneity among studies [21] and otherwise, the fixed effect model was employed [22]. Subgroup analysis was performed stratified by the types of triple therapy, in which we only studied the outcomes with the standard triple therapy as the control group. The fixed effects model was chosen for intention-to-treat cure rates, per-protocol cure rates as well as side effects analysis ($P > 0.05$, $I^2 < 50\%$). The fixed effects model was chosen for intention-to-treat cure rates, per-protocol cure rates as well as side effects analysis (P>0.05, I2<50%). To identify the source of heterogeneity, meta-regression analysis was performed based on various therapy durations of bismuth quadruple therapy (<7, 7, 10 and 14 days) and the standard triple therapy (7, 10 and 14 days) [23]. Egger's test was employed to evaluate publication biases and $P<0.1$ was selected as the criterion for potential bias [24]. In addition, sensitivity analysis was performed to evaluate the stability of the pooled results by comparing the pooled RR under random effect model and fixed effect model for each outcome.

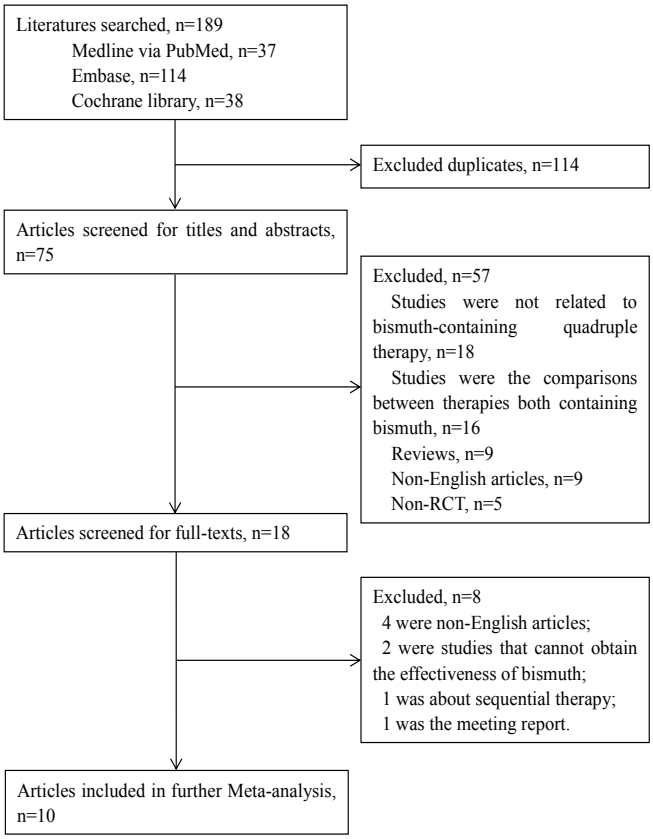


Figure 1: Flow diagram of the procedures of selecting studies for the meta-analysis.

Results

Eligible studies

In total, 75 potentially relevant studies published in English were identified after removing the duplicated publications from the 189 studies from the preliminary screening, whereas only 10 RCTs [13-15,25-31] met with the inclusion criteria. The detailed selection process is shown in Figure 1 and the characteristics of the selected study were presented in Table 1. There were 1722 *H. pylori*-infected patients consisting of 837 treated with bismuth quadruple therapy and 885 treated by the standard triple therapy. The studies were performed in various countries including Spain, Korea, USA, China, Iran and India. In most of the enrolled studies, patients in the study group were treated with the Bismuth quadruple therapy consisting of 2PPI, A and bismuth [13-15,25-28] and in five of the enrolled studies [13, 25,28-30], patients in control group were treated with the combined regimen of PAC, the standard triple therapy.

Quality assessment

Base on the Cochrane assessment system, the results of quality assessment were shown in Figure 2. As most of the enrolled studies did not describe the detailed explanation on how to generate random variables and whether double-blind analysis was performed, the selection bias and performance bias of the studies were considered as unknown risks. Besides, due to the lack of enough information, the reporting bias was also defined as unknown risks. Additionally, among all the enrolled studies, only one study [14] was identified with huge

Author, year	Study type	Study period	Follow-up	Country	Population	Bismuth-containing quadruple therapy				Control			
						n (M/F)	Age	Drug	Therapy time	n (M/F)	Age	Drug	Therapy time
Calvet 1998	RCT	1994.07-1996.02	12 months	Spain	Patients with PU and *H. pylori* positive	42 (35/7)	51.9±15.5[1]	O 40 mg b.i.d.; A 2500mg once daily; M 500 mg t.i.d.; B 360 mg t.i.d.	2 days	39 (27/12)	52.5±13.9	O 20 mg b.i.d.; A 1000 mg t.i.d.; M 500 mg t.i.d.	14 days
Calvet 2002	RCT	1999.04-2001.01	6 months	Spain	Patients diagnosed of PU and *H. pylori*	168 (120/48)	52.6±17.4	O 20 mg b.i.d.; T 500 mg t.i.d.; M 500 mg t.i.d.; B: 120 mg t.i.d.	7 days	171 (117/54)	51.5±15.9	O 20 mg b.i.d.; A 1000 mg t.i.d.; C 500 mg t.i.d.	7 days
Kim 2013	RCT	2003-2010	12 months	Korea	Patients with persistent *H. pylori* infection	59 (35/24)	56.1±9.3	E 20 mg b.i.d.; M 500 mg t.i.d.; T 500 mg q.i.d.; B 300 mg q.i.d.;	14 days	116 (69/47)	56.8±9.5	M 400 mg q.i.d.; E 20 mg b.i.d.; A 1000 mg b.i.d.	14 days
Lara 2003	RCT	1998.08-2000.12	NR	USA	Patients with dyspepsia and *H. pylori* infection	80 (36/44)	46±12	M 500 mg q.i.d.; A 2000 mg q.i.d.; Lan 30*2mg once; B 262*2 mg q.i.d.	7 day	80 (33/47)	53±16	C 500 mg b.i.d.; A 500*2 mg b.i.d.; Lan 30 mg b.i.d.	7 days
Liao 2013	RCT	2012	NR	China	Patients diagnosed of *H. pylori* positive	80 (43/37)	46.7 (23-78)[2]	Lan 30 mg b.i.d.; A 1000 mg b.i.d.; Lev 500 mg once; B 220 mg b.i.d.	14 days	81 (46/35)	48.9 (23-75)	Lan 30 mg b.i.d.; A 1000 mg b.i.d.; Lev 500 mg once	14 days
Momeni 2014	Double-blind RCT	NR	NR	Iran	Patients diagnosed of PU and *H. pylori* positive	30 (13/17)	40.8±15.5	O 20 mg b.i.d.; A 1000 mg b.i.d.; M 500 mg b.i.d.; B 262*2 mg b.i.d.	NR	30 (14/16)	42.2 ± 15.8	M 500 mg b.i.d.; A 1000 mg b.i.d.; O 20 mg b.i.d.; licorice 380 mg b.i.d.	NR
Pai 2003	RCT	NR	NR	India	Patients with *H. pylori* infection	33 (32/1)	37.5 (18-64)	Lan 30 mg b.i.d.; M 400 mg t.i.d.; T 500 mg q.i.d.; B 120 mg q.i.d.	10 days	35 (32/3)	41.5 (19-69)	Lan 30 mg b.i.d.; A 500 mg q.i.d.; C 500 mg b.i.d.	10 days
Raoufi 2014	RCT	2012.07-2012.12	6 months	Iran	Patient with persistent dispepsia	55	NR	F 100 mg q.i.d.; T 250 mg q.i.d.; O 20 mg b.i.d.; B 120 mg q.i.d.	14 days	55	NR	O 20 mg b.i.d.; A 1000 mg b.i.d.; C 500 mg b.i.d.	14 days
Seyedmajidi 2013	Double-blind RCT	2007.03-2011.09	NR	Iran	Patients diagnosed of *H. pylori* positive	110 (40/60)	44.0±3.2	O 20 mg b.i.d.; A 1000 mg b.i.d.; M 500 mg b.i.d.; B 240 mg b.i.d.	14 days	98 (55/43)	43.3±3.3	O 20 mg b.i.d.; A 1000 mg b.i.d.; C 500 mg b.i.d.	14 days
Xie 2014	Multi-center RCT	2010.01-2011.06	NR	China	Patients with *H. pylori* infection	180 (118/62)	39.6±13.6	R 10 mg b.i.d.; A 1000 mg b.i.d.; F 100 mg b.i.d.; B 220 mg b.i,d,	7 days	180 (105/75)	41.4±12.6	R 10 mg b.i.d.; A 1000 mg b.i.d.; F 100 mg b.i.d.	7 days

Abbreviations: RCT: randomized controlled trial; M/F: male/female; PU: peptic ulcer; b.i.d.: bis in die (=twice a day); t.i.d.: ter in die (=three times a day); q.i.d.: quater in diē (=four times a day); B: bismuth; O: omeprazole; A: amoxicillin; M: metronidazole; T: tetracycline; C: clarithromycin; E: esomeprazole; Lan: lansoprazole; Lev: levofloxacin; F: furazolidone; R: rabeprazole; NR: not reported.
1 Data were given as mean±SD; 2 Data were given as mean (range).

Table 1: Characteristics of the selected studies.

bias risk and low quality for the lack of intention-to-treat analysis and lack of comprehensive description. In summary, the qualities of the enrolled studies were average.

Overall analysis

In overall analysis, a total of 4 outcomes were compared between the study group and the control group, including per-protocol cure rates, intention-to-treat cure rates, recrudescence rates and side-effects. Random effects model was selected for per-protocol cure rates and intention-to-treat cure rates analysis ($P<0.05$, $I^2>50\%$). On the other hand, fixed effects model was chosen for recrudescence rates and side effects analysis ($P > 0.05$, $I^2<50\%$). For intention to treat cure rates and per-protocol cure rates analysis, 8 studies and 6 studies were employed respectively. Accordingly, the meta-analysis revealed there were comparable intention to treat cure rates (RR = 0.90, 95% CI: 0.62~1.30, $P = 0.57$) (Figure 3A) and per-protocol cure rates (RR = 1.29, 95% CI: 0.54~3.09, $P = 0.57$) (Figure 3B) between the two groups. Besides, 3 studies reported that the recrudescence rates was also similar between the two groups (RR = 0.98, 95% CI: 0.49~1.98, $P = 0.96$) (Figure 3C). Additionally, by analyzing 8 relative studies, the two therapies showed similar side effects (RR = 0.91, 95% CI: 0.73~1.13, $P = 0.40$) (Figure 3D). Based on the Egger's studies, there was no obvious publication bias between studies ($P > 0.1$).

Subgroup analysis

In total, 5 studies compared intention-to-treat cure rates and showed the rate was significantly higher in the bismuth quadruple therapy than the standard triple therapy (RR = 0.72, 95% CI: 0.55~0.93, $P = 0.01$) (Figure 4A). Besides, 3 studies reported that bismuth quadruple therapy achieved a comparable per-protocol cure rates to the standard triple therapy (RR = 0.71, 95% CI: 0.49~1.04, P = 0.08) (Figure 4B). In addition, 5 studies compared the side effects and demonstrated no significant difference in side effects between the two therapies (RR = 0.97, 95% CI: 0.76~1.23, $P = 0.79$) (Figure 4C).

Meta-regression analysis

For intention-to-treat cure rates, one of the main outcomes in this study, there was significant heterogeneity between studies in overall analysis; therefore meta-regression analysis was performed to investigate the sources of heterogeneity. However, the therapy duration did not induce significant heterogeneity ($P > 0.05$) (Table 2).

Sensitivity analysis

Based on the sensitivity analysis, the pooled RR of the intention-to-treat cure rates, per-protocol cure rates, recrudescence rates and side effect using random effects model and fixed effects model were

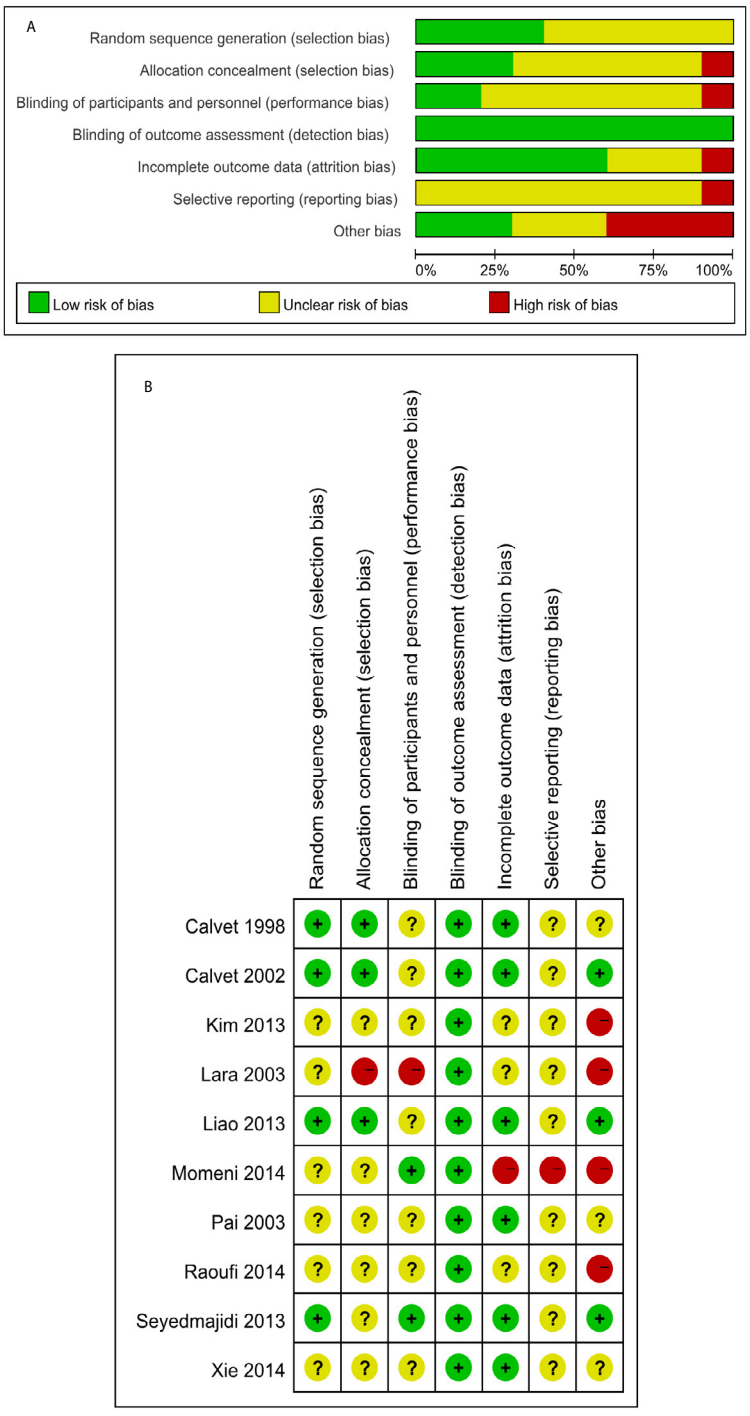


Figure 2: Assessment of bias risk. A, Methodological quality graph: researchers' judgment about each quality item listed as percentages among all included studies; B, Summary of methodological quality of the included studies: researchers' judgment for every quality item for each included study. "+" represents low risk of bias; "?" represents unclear risk of bias; "-" represents high risk of bias.

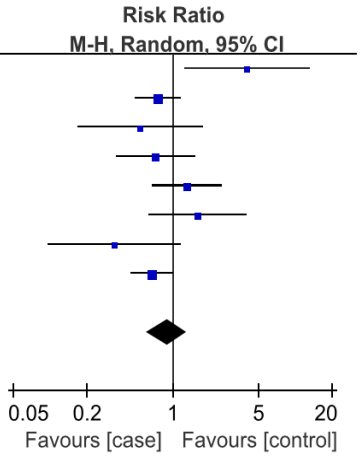
Log RR	Coef.	Std. Err.	t	P>|t|	[95% Conf. Interval]
Therapy time_ case	-0.51	0.27	-1.89	0.118	(-1.19, 0.18)
Therapy time_ control	0.40	0.29	1.51	0.193	(-0.29, 1.09)
_cons	-0.11	0.29	-0.39	0.715	(-0.87, 0.64)

Table 2: Meta regression.

A

Study or Subgroup	case Events	case Total	control Events	control Total	Weight	Risk Ratio M-H, Random, 95% CI
Calvet 1998	13	42	3	39	7.3%	4.02 [1.24, 13.06]
Calvet 2002	29	168	39	171	20.0%	0.76 [0.49, 1.16]
Lara 2003	4	77	7	73	7.3%	0.54 [0.17, 1.77]
Liao 2013	10	80	14	81	13.0%	0.72 [0.34, 1.53]
Momeni 2014	13	30	10	30	14.9%	1.30 [0.68, 2.49]
Pai 2003	9	33	6	35	10.3%	1.59 [0.64, 3.98]
Raoufi 2014	3	55	9	55	6.7%	0.33 [0.10, 1.17]
Xie 2014	31	180	46	180	20.6%	0.67 [0.45, 1.01]
Total (95% CI)		**665**		**664**	**100.0%**	**0.90 [0.62, 1.30]**
Total events	112		134			

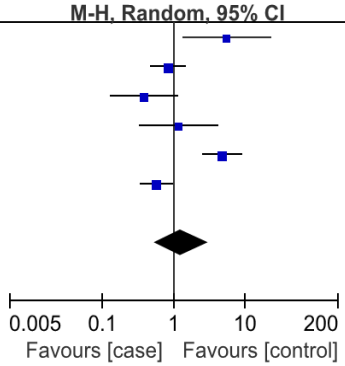
Heterogeneity: Tau² = 0.13; Chi² = 14.52, df = 7 (P = 0.04); I² = 52%
Test for overall effect: Z = 0.57 (P = 0.57)



B

Study or Subgroup	case Events	case Total	control Events	control Total	Weight	Risk Ratio M-H, Random, 95% CI
Calvet 1998	12	41	2	38	13.3%	5.56 [1.33, 23.25]
Calvet 2002	18	157	21	153	19.0%	0.84 [0.46, 1.51]
Liao 2013	4	74	11	78	15.6%	0.38 [0.13, 1.15]
Pai 2003	4	28	4	33	14.3%	1.18 [0.32, 4.29]
Seyedmajidi 2013	44	100	9	98	18.6%	4.79 [2.47, 9.28]
Xie 2014	18	167	31	165	19.2%	0.57 [0.33, 0.98]
Total (95% CI)		**567**		**565**	**100.0%**	**1.29 [0.54, 3.09]**
Total events	100		78			

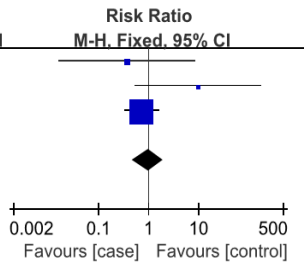
Heterogeneity: Tau² = 0.96; Chi² = 34.47, df = 5 (P < 0.00001); I² = 85%
Test for overall effect: Z = 0.57 (P = 0.57)



C

Study or Subgroup	case Events	case Total	control Events	control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Calvet 1998	0	26	1	29	9.7%	0.37 [0.02, 8.71]
Calvet 2002	4	84	0	91	3.3%	9.74 [0.53, 178.25]
Kim 2013	7	59	19	116	87.1%	0.72 [0.32, 1.62]
Total (95% CI)		**169**		**236**	**100.0%**	**0.98 [0.49, 1.98]**
Total events	11		20			

Heterogeneity: Chi² = 3.31, df = 2 (P = 0.19); I² = 40%
Test for overall effect: Z = 0.04 (P = 0.96)



D

Study or Subgroup	case Events	case Total	control Events	control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Calvet 1998	11	42	16	39	13.5%	0.64 [0.34, 1.20]
Calvet 2002	50	168	54	171	43.5%	0.94 [0.68, 1.30]
Lara 2003	23	77	27	73	22.5%	0.81 [0.51, 1.27]
Liao 2013	4	80	6	81	4.8%	0.68 [0.20, 2.30]
Momeni 2014	0	30	0	30		Not estimable
Pai 2003	5	33	4	35	3.2%	1.33 [0.39, 4.52]
Raoufi 2014	3	55	0	55	0.4%	7.00 [0.37, 132.40]
Xie 2014	16	180	15	180	12.2%	1.07 [0.54, 2.09]
Total (95% CI)		**665**		**664**	**100.0%**	**0.91 [0.73, 1.13]**
Total events	112		122			

Heterogeneity: Chi² = 4.17, df = 6 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.84 (P = 0.40)

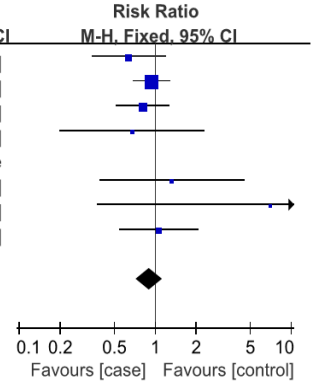


Figure 3: Forest plots of bismuth-based quadruple therapy and non- bismuth-containing triple therapy in the overall analysis. (A) Forest plot for intention-to-treat cure rates based on random effects model; (B) Forest plot for per-protocol cure rates based on random effects model; (C) Forest plot for recrudescence rates based on fixed effects model; (D) Forest plot for side effect based on fixed effects model.

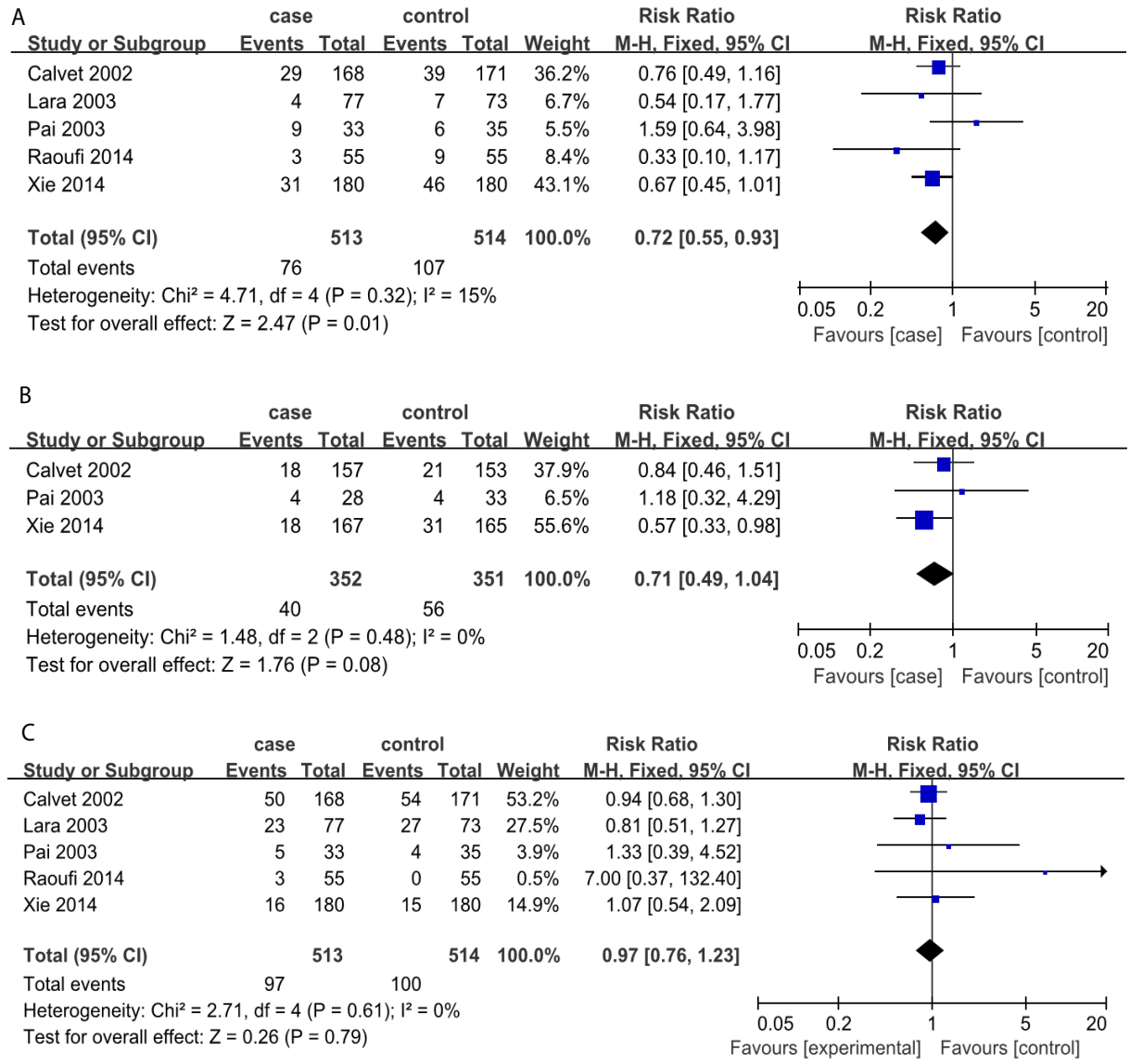


Figure 4: Forest plots of bismuth-based quadruple therapy and standard triple therapy in the subgroup analysis. (A) Forest plot for intention-to-treat cure rates based on fixed effects model; (B) Forest plot for per-protocol cure rates based on fixed effects model; (C) Forest plot for side effect based on fixed effects model.

Outcomes	Random effect model		Fixed effect model	
	RR (95% CI)	P	RR (95% CI)	P
Intention to treat cure rates	0.90 (0.62, 1.30)	0.57	0.84 (0.67, 1.05)	0.12
Per-protocol cure rates	1.29 (0.54, 3.09)	0.57	1.27 (0.96, 1.68)	0.09
Recrudescence rate	1.09 (0.23, 5.19)	0.91	0.98 (0.49, 1.98)	0.96
Side effect	0.89 (0.71, 1.11)	0.29	0.91 (0.73, 1.13)	0.40

Abbreviations: RR: risk ratio; CI: confidence interval.

Table 3: Sensitivity analysis (random effect model *vs.* fixed effect model).

respectively consistent and free of obvious fluctuation, indicating reliable and stable results of this meta-analysis (Table 3).

Discussion

Recently, the standard triple therapy (non-bismuth-containing triple therapy), commonly used as the first-line therapy, has dropped its therapeutic efficacy in eradicating the infected *H. pylori* due to a poor patient compliance and bacterial resistance [32]. And bismuth quadruple therapy has been suggested recently as a first-line therapy for *H. pylori* infection [2,33]. Besides, it could also be used as a second-line remedy method after failure of the standard triple therapy [34]. Additional bismuth supplement can effectively reduce bacterial amount and overcome the *H. pylori* resistance to antibacterial agents [35,36]. The bismuth quadruple therapy shows higher *H. pylori* eradication rates

and cost-effectiveness in comparison with non-bismuth-containing triple therapy [11]. And a recent research reports that four bismuth-based quadruple therapies all achieve greater than 90% eradication rates of *H. pylori* infection [37]. Besides, bismuth-based quadruple therapy remains highly effective even if reducing the treatment duration from 14 days to 10 days or decreasing the frequencies used in per day [38,39]. As compared with the commonly used triple therapy without bismuth, the bismuth-based quadruple therapy is reported to achieve comparable eradication rates [40,41]. Notably, by extracting non-bismuth-containing triple therapy as control groups in our meta-analysis, the subgroup analysis results revealed that the bismuth quadruple therapy had a higher intention-to-treat cure rates than the control groups (RR = 0.72, 95% CI: 0.55-0.93, $P = 0.01$).

Bismuth compounds were concerns about toxicity in some countries, especially as a result of their potential neurological sequelae. Common adverse events include: abdominal pain, dark stools, diarrhoea, dizziness, headache, metallic taste, and so on. Although side effects occurred in 33.6% of subjects with bismuth-containing quadruple therapies, the research report also said that it was mainly caused by antibiotics, especially metronidazole [42]. And the results of the previous meta-analysis revealed that bismuth-based quadruple therapy was as safe as non-bismuth-containing therapy for *H. pylori* infection. Additionally, it also indicated that the combined regimen of bismuth compounds and antibiotics was well-tolerated in treatment of *H. pylori* infection [43]. Lee SK pointed out that the repeated bismuth quadruple therapy was also safe after failure of first quadruple therapy [44]. Similar in our meta-analysis, bismuth quadruple therapy had the same safety as non-bismuth-containing triple therapy. Thus, the bismuth quadruple therapy might be used as an alternative therapy for *H. pylori* infection.

The results of our meta-analysis provided more reliable evidence for the assessment of the superiority of bismuth quadruple therapy than non-bismuth-containing triple therapy for the following reasons. Firstly, the enrolled studies were all RCTs from 1998 to 2014, which were representative of the safety and efficacy of the therapies. Secondly, we conducted subgroup analysis and the heterogeneity was not significant. Thirdly, no significant publication bias existed, suggesting a reliable and stable outcome. Nevertheless, there were some limitations in our meta-analysis. Firstly, for the *H. pylori* infection recurrence analysis, only a few studies involved in this index, which may reduce the power of our analysis and thus more attention should be paid for this aspect. Secondly, the general quality of the enrolled study established a barrier to determine the level of risk bias. Finally, we were unable to gather the data that were unpublished, which make it difficult to determine the results tendency.

In conclusion, this systematic and meta-analysis provided strong evidence that the bismuth quadruple therapy had similar safety with non-bismuth-containing triple therapy. Otherwise, bismuth-based quadruple therapy was superior over the non-bismuth-containing triple therapy for its higher eradication rates of *H. pylori* infection.

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