High-dose dual therapy *versus* bismuth-containing quadruple therapy for *Helicobacter pylori* eradication: a systematic review and meta-analysis with trial sequential analysis

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Abstract

Background and objective: Recently, a large number of trials on proton pump inhibitor-amoxicillin-containing high-dose dual therapy (HDDT) *versus* bismuth-containing quadruple therapy (BQT) for *Helicobacter pylori* (*H. pylori*) eradication have been published with controversial and inconsistent conclusions. The aim of this meta-analysis was to determine the effects of HDDT for *H. pylori* eradication compared to BQT.

Design: A systematic review and meta-analysis was conducted.

Methods: PubMed, Embase, and the Cochrane library database were searched to collect all randomized controlled trials (RCTs) assessing the effects of HDDT *versus* BQT to *H. pylori* eradication from inception to September 2022. Meta-analysis was conducted to estimate the pooled relative risk (RR) with 95% confidence intervals (CIs) using a random-effects model. Quality of evidence was appraised using Grading of Recommendations, Assessment, Development and Evaluation system. Trial sequential analysis (TSA) was performed to determine the reliability and conclusiveness.

Results: A total of 14 RCTs with 5121 patients were included. The results of meta-analysis showed that there was no statistical significance in the eradication rate between HDDT and BQT (intention-to-treat analysis: 86.7% *versus* 85.1%, RR = 1.01, 95% CI: 0.98–1.04; per-protocol analysis: 89.9% *versus* 89.4%, RR = 1.01, 95% CI: 0.98–1.03; moderate-quality evidence). The incidence of total adverse effects in HDDT group was significantly lower than in BQT group (5.9% *versus* 34.1%, RR = 0.42, 95% CI: 0.34–0.50; low-quality evidence). No statistical significance was observed in compliance between HDDT and BQT (RR = 1.01, 95% CI, 1.00–1.03, *p* = 0.07; low-quality evidence). The TSA result for *H. pylori* eradication rate indicated that the effect was conclusive.

Conclusions: Evidence from our updated meta-analysis suggests that HDDT is as effective as BQT in eradicating *H. pylori*, with fewer adverse effects and similar compliance.

Registration: Open Science Framework registries (No: osf.io/th4vd)

Keywords: amoxicillin, bismuth-containing quadruple therapy, *Helicobacter pylori*, high-dose dual therapy, meta-analysis

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Introduction

Helicobacter pylori (*H. pylori*) has become a common global public health problem with reported prevalence rates of 50.8% in developing countries

and 34.7% in developed countries.[1] There were approximately 4.4 billion individuals with *H. pylori* infection worldwide.[2] *H. pylori* is not only the main cause of upper gastrointestinal

diseases, including chronic gastritis, peptic ulcer, and gastric cancer, but also may be associated with many extra-gastrointestinal diseases.[3,4] Eradicating *H. pylori* can prevent these diseases and hinder their progress.

With the continuous increase in antibiotic resistance, the eradication rate of standard triple therapy has been far below 80%.[5] Currently, bismuth-containing quadruple therapy (BQT), consisting of proton-pump inhibitor (PPI), bismuth, and two antibiotics (amoxicillin, clarithromycin, tetracycline, or metronidazole), which has been highly recommended as first-line therapy for *H. pylori* eradication according to the latest Maastricht VI/Florence consensus report,[3] the Fifth Chinese National Consensus Report,[4] the Toronto Consensus,[6] and ACG clinical guideline.[7] Although the eradication rate has improved, BQT still has some limitations: not available in some regions, complicated dosing regimen, more adverse events, poor drug compliance, and high cost.[8,9] Therefore, it is urgent to discover and identify novel regimens with high efficacy, less use of antibiotics, and fewer adverse events to eradicate *H. pylori*.

Recently, high-dose dual therapy (HDDT), which gives amoxicillin and PPI more than two times daily, has become one of the most discussed hot topics in the field of *H. pylori* eradication. Of late, Yin *et al.*[9] conducted a meta-analysis and demonstrated that HDDT is equally effective with BQT in eradicating *H. pylori*, with fewer side effects and better compliance. However, the search time was from inception to March 2021, and their meta-analysis missed some multicenter trials. Furthermore, the previous study did not provide detailed subgroup analyses and comprehensive sensitivity analyses due to the small number of studies included. In addition, numerous new high-quality randomized controlled trials (RCTs) have been published with controversial and inconsistent conclusions in the latest 2 years. These newly published trials have prompted our interest in updating current evidence. Based on the above considerations, we conducted an updated meta-analysis to assess the efficacy, adverse events, and patient compliance of HDDT compared with BQT for *H. pylori* eradication.

Methods

Registration of review protocol and implementing guidance
The protocol for this study was registered in advance with Open Science Framework registries (No: osf.io/th4vd). This systematic review was conducted in accordance with the latest Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[10]

Data sources and literature search strategy
We conducted electronic searches in PubMed, Embase, and the Cochrane library database using pre-established search terms from inception to September 2022. The search terms were as follows: 'helicobacter pylori', 'campylobacter pylori', '*H. pylori*', 'Hp', amoxicillin, amoxycillin, dual therapy, high-dose dual therapy, high dose dual therapy, bismuth. We used MeSH headings and text word terms searching, without language restriction. The detail of search strategy for each database is shown in Supplemental Table S1. Additional potential eligible studies were manually searched through the reference lists of relevant systematic reviews and included studies.

Study selection
Two reviewers (ZBG and MYZ) independently screened the studies by reading titles and abstracts, and obtained full texts of potentially relevant studies using the following selection criteria. Any disagreement was resolved by consensus. If any overlapping studies were identified, only the study with the most comprehensive data was included. For relevant studies with multiple arms, the data were combined to create a new study group and a new control group according to the following inclusion criteria. Inclusion criteria were as follows: (a) participants: *H. pylori*-infected patients; (b) intervention: HDDT group: PPI plus amoxicillin, PPI and amoxicillin were both administered 3 or 4 times a day and amoxicillin >2.0 g/day; (c) comparator: BQT group: PPI, bismuth, and two antibiotics; (d) outcomes: (i) primary outcome: *H. pylori* eradication rate; (ii) secondary outcomes: adverse effects and compliance; (e) study design: RCTs. Exclusion criteria were set as below: (a) non-RCTs, animal studies, comments, editorials, letters, reviews, and meta-analyses; (b) amoxicillin

was not administered at a dosage >2.0 g/day and either PPI or amoxicillin was given no more than twice daily; (c) regimens contained probiotics or herbs; (d) duplicate publications; and (e) studies without sufficient data.

Data extraction

Two reviewers (ZBG and MYZ) independently extracted the data from eligible studies using pre-designed data extraction form. The following information was extracted from each eligible study: surname of the first author, year of publication, country of study, study design, participant characteristics, number of participants, specific details of eradication regimens (dose, frequencies, and duration), diagnostic tests to confirm *H. pylori* infection before and after eradication, confirmed testing time after eradication, *H. pylori* susceptibility to antibiotics, relevant data of the eradication rate, adverse effects, and compliance. Any discrepancies were resolved by a third author (ZM).

Risk of bias and grading the strength of evidence

The risk of bias was independently appraised using the Cochrane Collaboration's tool for RCTs.[11] We developed summary of findings tables with the use of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) profiler sofware (GradePro Version 3.6.1). The quality of evidence was categorized into four levels (i.e. very low, low, moderate, and high) in the GRADE system.[12] Two reviewers (ZBG and MYZ) independently appraised the risk of bias of each study and quality of evidence. Consensus between two reviewers was used to resolve any disagreement.

Statistical analysis

We used the Review Manager software (Version 5.3, The Cochrane Collaboration, Nordic Cochrane Centre, Copenhagen, Denmark) to calculate pooled relative risk (RR) with 95% confidence intervals (CIs) for each study.

The data were analyzed with intention-to-treat (ITT) analysis and per-protocol (PP) analysis for *H. pylori* eradication rate. Data were pooled using the random-effects model to give a more conservative estimate.[13] The standard chi-square and I^2 statistic were used to evaluate the statistic heterogeneity among studies. $p < 0.10$ for the Q test was considered statistically significant. I^2 values of 0–25%, 26–50%, 51–75%, and more than 75% indicated insignificant, low, moderate, and high heterogeneity, respectively.[14] Subgroup analyses based on ITT analysis were further utilized to explore potential sources of heterogeneity and possible factors affecting the overall results. Sensitivity analyses were conducted for *H. pylori* eradication rate (ITT data) as follows: (a) using fixed-effect model; (b) excluding conference abstracts; (c) excluding studies published in non-English; and (d) omitting one study at a time. Publication bias was assessed by Begg's test and Egger regression asymmetry test using STATA/SE 12.0 (STATA Corporation, Texas, USA).

Meta-analyses may result in type I and type II errors due to the increased risk of random error when analyzing sparse data and due to repeated significance testing when a cumulative meta-analysis is updated with new trials.[15,16] To assess the risk of type I and type II errors, a trial sequential analysis (TSA) was performed for the primary outcome of *H. pylori* eradication rate. This analysis was conducted using TSA software (version 0.9.5.10, Copenhagen Trial Unit, Copenhagen, Denmark).

Results

Literature search results and study selection process

The literature search identified 360 potentially relevant records. Among these records, 137 duplicate records were excluded, 181 records were further excluded by reading titles or abstracts, leaving 42 potential eligible articles. Of these articles, 28 articles were further excluded based on the selection criteria (characteristics of the excluded studies are shown in Supplemental Table S2). Finally, 14 RCTs[17–30] were included in the meta-analysis. The article selection process is presented in the PRISMA flowchart in Figure 1.

Study characteristics of included studies

A total of 14 studies[17–30] involving 5121 patients were eligible for our meta-analysis. All included studies were published between 2003 and 2022, of which six were multicenter RCTs[17,18,22,25,26,29] and eight were single-center RCTs.[19–21,23,24,27,28,30] Among these included studies, 11 studies were
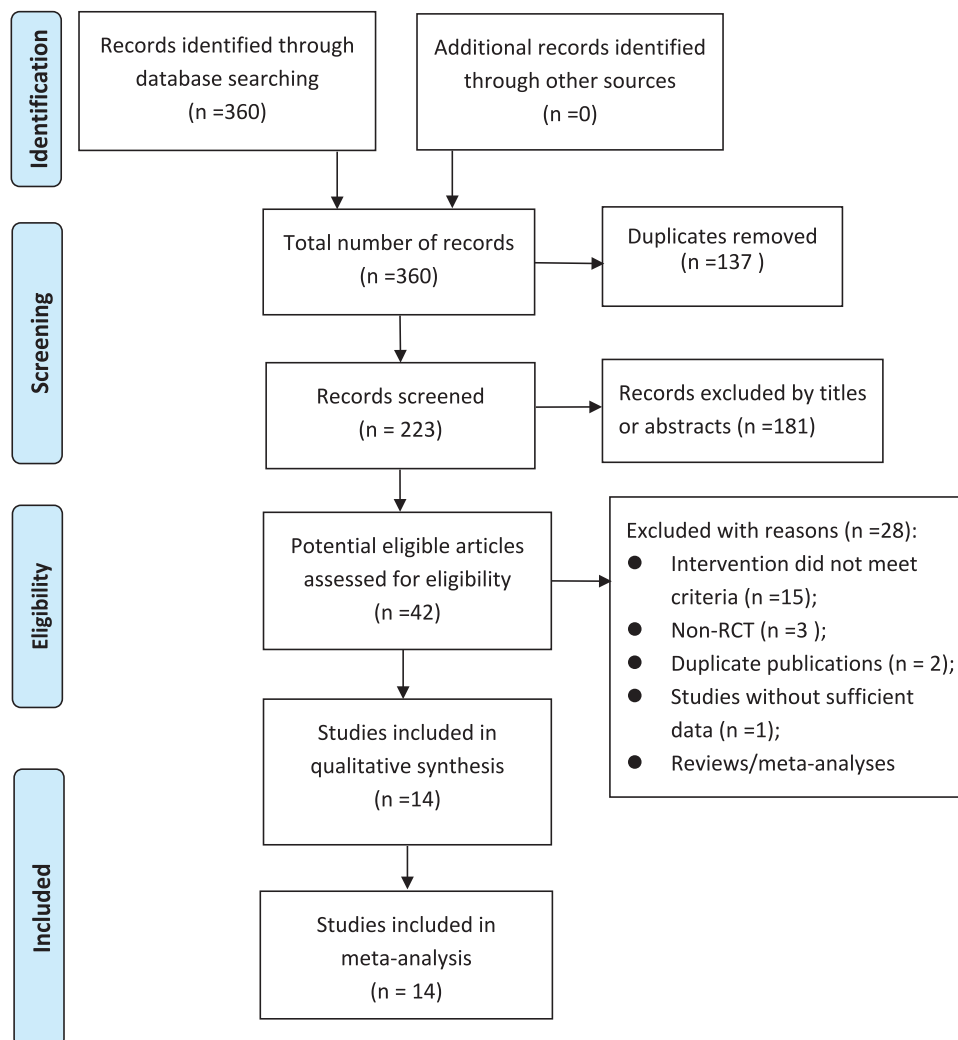
Figure 1 flowchart boxes:

Identification

Records identified through database searching (n =360)

Additional records identified through other sources (n =0)

Screening

Total number of records (n =360)

Duplicates removed (n =137)

Records screened (n = 223)

Records excluded by titles or abstracts (n =181)

Eligibility

Potential eligible articles assessed for eligibility (n =42)

Excluded with reasons (n =28):
- Intervention did not meet criteria (n =15);
- Non-RCT (n =3);
- Duplicate publications (n = 2);
- Studies without sufficient data (n =1);
- Reviews/meta-analyses

Included

Studies included in qualitative synthesis (n =14)

Studies included in meta-analysis (n = 14)

Figure 1. PRISMA flowchart of study selection process.
PRISMA, preferred reporting items for systematic reviews and meta-analysis.

performed in China,[18,19,21–26,28–30] one in Germany and Austria,[17] one in Turkey,[20] and one in Colombia.[27] Concerning publication language, 12 studies were published in English,[17–20, 22–26, 28–30] one in Chinese,[21] and one in Spanish.[27] Among these studies, three of which were published as conference abstracts.[18,22,25] The sample size of included studies ranged from 84 to 971 patients. As to *H. pylori* eradication treatment experience, two studies were rescue therapy[17,22] and these remaining studies were initial therapy. Two studies[17,30] performed antibiotic susceptibility tests, two studies[23,24] conducted antibiotic susceptibility tests and CYP2C19 gene polymorphism analysis simultaneously. With regard to HDDT regimen, the types of PPI are mainly esomeprazole or rabeprazole, and only one early study[17] used omeprazole to eradicate *H. pylori*; the total dose of amoxicillin was 3000 mg, administered three or four times daily. The duration of HDDT regimen for all included studies were 14 days. Regarding the duration of BQT regimen, three studies were 10 days,[18,22,25] and the remaining studies were 14 days. The main characteristics of included studies are summarized in Table 1.

Risk of bias
Supplemental Figures S1 and S2 show the details of risk of bias assessment. Among these 14 studies, nine studies[17,19,20,23,24,26,27,29,30] reported sufficient random sequence generation methods (computer-generated randomization and randomized digital table) and were judged as low risk,

Table 1. Characteristics of included studies in the meta-analysis.

First author and year	Country, language	Publication	Study design	Patients	No. of patients (Exp/Con)	HDDT	BQT	Diagnostic methods of *H. pylori* (initial/rechecking)	Outcomes
Miehlke, 2003	Germany and Austria, English	Full text	RCT, multicenter	Rescue therapy	84 (41/43)	Omeprazole 40 mg qid, amoxicillin 750 mg qid, 14 days	Omeprazole 20 mg bid, bismuthcitrate 107 mg qid, metronidazole 0.5 g qid, tetracycline 0.5 g qid, 14 days	H, C/H, C, RUT, UBT	①③
Hu CT, 2017	China (Taiwan), English	Abstract	RCT, multicenter	Initial therapy	340 (170/170)	Rabeprazole 20 mg qid, amoxicillin 750 mg qid, 14 days	Rabeprazole 20 mg bid, tripotassium dicitrate bismuthate 300 mg qid, metronidazole 250 mg qid, tetracycline 500 mg qid, 10 days	H, C/UBT	①②③
Hu JL, 2017	China, English	Full text	RCT, single center	Initial therapy	263 (174/89)	Rabeprazole 10 or 20 mg qid, amoxicillin 750 mg qid, 14 days	Rabeprazole 20 mg bid, bismuth potassium citrate 220 mg bid, amoxicillin 1000 mg bid, clarithromycin 500 mg qid, 14 days	C, RUT, UBT/C, RUT, UBT	①②③
Sapmaz, 2017	Turkey, English	Full text	RCT, single center	Initial therapy	196 (98/98)	Rabeprazole 20 mg tid, amoxicillin 750 mg tid, 14 days	Rabeprazole 20 mg bid, bismuth subcitrate 120 mg qid, tetracycline 500 mg qid, metronidazole 500 mg tid, 14 days	H/H	①③
Gao, 2018	China, Chinese	Full text	RCT, single center	Initial therapy	142 (70/72)	Esomeprazole 20 mg qid, amoxicillin 750 mg qid, 14 days	Esomeprazole 20 mg bid bismuth potassium citrate 220 mg bid, amoxicillin 1000 mg qid, clarithromycin 500 mg qid, 14 days	UBT, H/UBT, H	①②③
Hu, 2018	China (Taiwan), English	Abstract	Multicenter	Rescue therapy	311 (156/155)	Rabeprazole 20 mg qid, amoxicillin 750 mg qid, 14 days	Rabeprazole 20 mg bid, tripotassium dicitrate bismuthate 300 mg qid, metronidazole 250 mg qid, tetracycline 500 mg qid, 10 days	H, C/UBT	①②③
Yang, 2019	China, English	Full text	RCT, single center	Initial therapy	232 (116/116)	Esomeprazole 20 mg qid, amoxicillin 750 mg qid, 14 days	Esomeprazole 20 mg bid, bismuth potassium citrate 220 mg bid, amoxicillin 1000 mg bid, clarithromycin 500 mg qid, 14 days	RUT, UBT/RUT, UBT	①②③
Song, 2020	China, English	Full text	RCT, single center	Initial therapy	760 (380/380)	Esomeprazole 20 mg qid, amoxicillin 750 mg qid, 14 days	Esomeprazole 20 mg bid, bismuth potassium citrate 220 mg bid, amoxicillin 1000 mg bid, clarithromycin 500 mg qid, 14 days	RUT, C/RUT, C	①②③
Hsu, 2021	China (Taiwan), English	Abstract	RCT, multicenter	Initial therapy	400 (200/200)	Rabeprazole 20 mg qid, amoxicillin 750 mg qid, 14 days	Rabeprazole 20 mg bid, tripotassium dicitrato bismuthate 300 mg qid, tetracycline 500 mg qid, metronidazole 250 mg qid, 10 days	NR	①②③

(Continued)

Table 1. (Continued)

First author and year	Country, language	Publication	Study design	Patients	No. of patients (Exp/Con)	HDDT	BQT	Diagnostic methods of *H. pylori* (initial/rechecking)	Outcomes
Guan, 2022	China, English	Full text	RCT, multicenter	Initial therapy	700 (350/350)	Esomeprazole 20 mg qid, amoxicillin 1000 mg tid, 14 days	Esomeprazole 20 mg bid, bismuth potassium citrate 220 mg bid, amoxicillin 1000 mg bid, clarithromycin 500 mg bid, 14 days	UBT, H/UBT, H	①②③
Llano, 2022	Colombia, Spanish	Full text	RCT, single center	Initial therapy	266 (133/133)	Esomeprazole 40 mg tid, amoxicillin 1000 mg tid, 14 days	Esomeprazole 40 mg bid, Bismuth subsalicylate 262 mg bid, amoxicillin 1000 mg bid, levofloxacin 500 mg bid, 14 days	H/UBT	
Shao, 2022	China, English	Full text	RCT, single center	Initial therapy	240 (120/120)	Rabeprazole 20 mg tid, amoxicillin 1000 mg tid, 14 days	Rabeprazole 20 mg bid, bismuth potassium citrate 220 mg bid, amoxicillin 1000 mg bid, Furazolidone 100 mg bid, 14 days	UBT, H/UBT, H	①②③
Shen, 2022	China, English	Full text	RCT, multicenter	Initial therapy	971 (496/475)	Esomeprazole 20 mg qid, amoxicillin 750 mg qid, 14 days	Esomeprazole 20 mg bid, bismuth potassium citrate 220 mg bid, amoxicillin 1000 mg bid, clarithromycin 250 mg bid, 14 days	UBT, RUT, H/UBT, RUT, H	①②③
Yun, 2022	China, English	Full text	RCT, single center	Initial therapy	216 (108/108)	Esomeprazole 40 mg tid, amoxicillin 750 mg qid, 14 days	Esomeprazole 20 mg, bid, bismuth potassium citrate 220 mg bid, amoxicillin 1000 mg bid, clarithromycin 500 mg bid, 14 days	UBT, RUT, C/UBT, RUT, C	①②③

bid, twice daily; BQT, bismuth-containing quadruple therapy group; C, culture; Con, control group (BQT); Exp, experimental group (HDDT); H, histology; HDDT, high-dose dual therapy group; NR, not reported; qid, four times daily; RCT, randomized controlled trials; RUT, rapid urease test; SAT, stool antigen test; tid, three times daily; UBT, urea breath test; ①Eradication rate; ②Total side effects; ③Compliance.

Table 2. Results of subgroup analyses for *H. pylori* eradication rate.

Subgroups	No. of studies	Sample size	RR (95% CI)	P_{effect}	I^2 (%)	$P_{heterogeneity}$
Study design						
Multicenter RCTs	6[17,18,22,25,26,29]	2806	1.02 (0.97–1.07)	0.42	62	0.02
Single-center RCTs	8[19–21,23,24,27,28,30]	2315	1.01 (0.97–1.05)	0.61	13	0.33
Study location						
Asia	12[18–26,28–30]	4771	1.01 (0.98–1.05)	0.45	47	0.04
Non-Asia	2[17,27]	350	1.03 (0.94–1.12)	0.56	0	0.34
Treatment experience						
Initial therapy	12[18–21,23–30]	4726	1.01 (0.98–1.04)	0.52	45	0.05
Rescue therapy	2[17,22]	395	1.03 (0.93–1.15)	0.54	22	0.26
Frequency of HDDT administration						
PPI and amoxicillin, qid	10[17–19,21–25,29–30]	3719	1.01 (0.97–1.05)	0.71	51	0.03
PPI and amoxicillin, tid	3[20,27,28]	702	1.00 (0.95–1.06)	0.89	0	0.54
PPI qid, amoxicillin tid	1[26]	700	1.06 (1.00–1.12)	0.06	–	–
BQT duration						
10 days	3[18,22,25]	1051	1.01 (0.92–1.10)	0.90	81	0.006
14 days	11[17,19–21,23,24,26–30]	4070	1.03 (1.00–1.04)	0.06	4	0.40
Overall results	14[17–30]	5121	1.01 (0.98–1.04)	0.36	40	0.06

BQT, bismuth-containing quadruple therapy; CI, confidence interval; *H. pylori*, *Helicobacter pylori*; HDDT, high-dose dual therapy; PPI, proton-pump inhibitor; RCTs, randomized controlled trials; RR, relative risk.

while the other five studies were judged as unclear risk of randomization. Only two studies[24,26] provided sufficient data for allocation concealment and were judged as low risk. With regard to blinding participants and personnel, seven studies were open trial,[19,23,24,26,28–30] and the remaining seven studies[17,18,20–22,25,27] were judged as unclear risk due to insufficient information. All these studies showed low risk in blinding of outcome assessment, incomplete outcome data, and other bias. As to selective reporting (reporting bias), two studies[17,20] were judged as high risk due to the absence of total side effects, all the remaining studies were judged as low risk of bias.

Primary outcome: H. pylori *eradication rate*
Overall eradication rates. A total of 14 studies[17–30] (involving 5121 patients) reported data on

H. pylori eradication rate. Based on the data analyzed by ITT analysis, the eradication rate in the HDDT group was higher than BQT group (86.7% *versus* 85.1%), but there was no statistical significance between them (RR = 1.01, 95% CI: 0.98–1.04, *p* = 0.36) with low significant heterogeneity (I^2 = 40%, *p* = 0.06) (Figure 2). For the PP analysis, similar result was also observed (89.9% *versus* 89.4%; RR = 1.01, 95% CI: 0.98–1.03, *p* = 0.62) with low significant heterogeneity (I^2 = 41%, *p* = 0.05) (Figure 3).

Trial sequential analysis. Based on ITT data, we conducted a TSA to examine the reliability and conclusiveness. We estimated the required information size (RIS) and adjusted significance thresholds based on the following assumptions: a two-sided adjusted random effects model with 5% risk of type I error, 20% risk of the
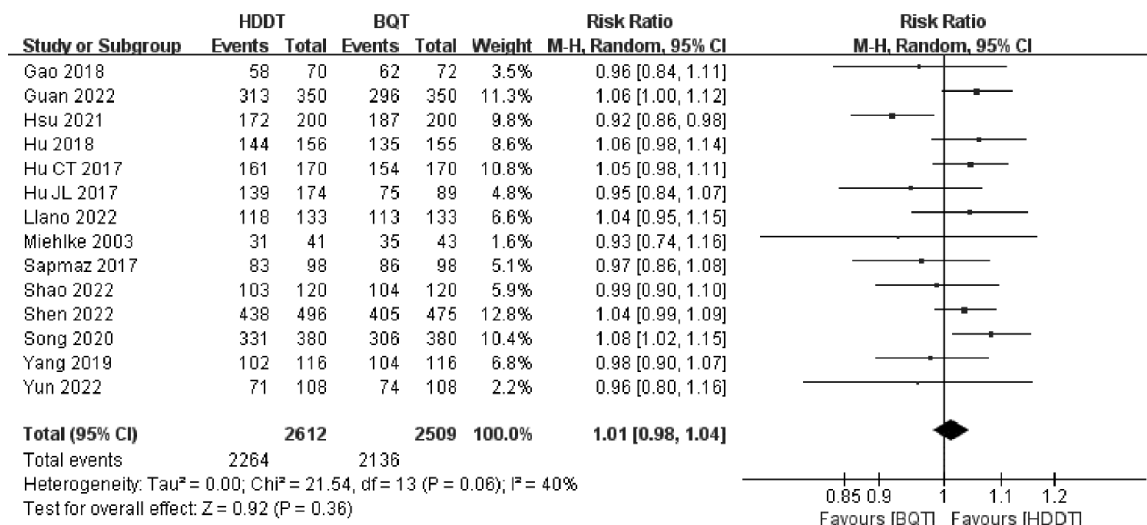
Figure 2. Forest plot of the effect of HDDT *versus* BQT on *H. pylori* eradication rate according to ITT analysis.
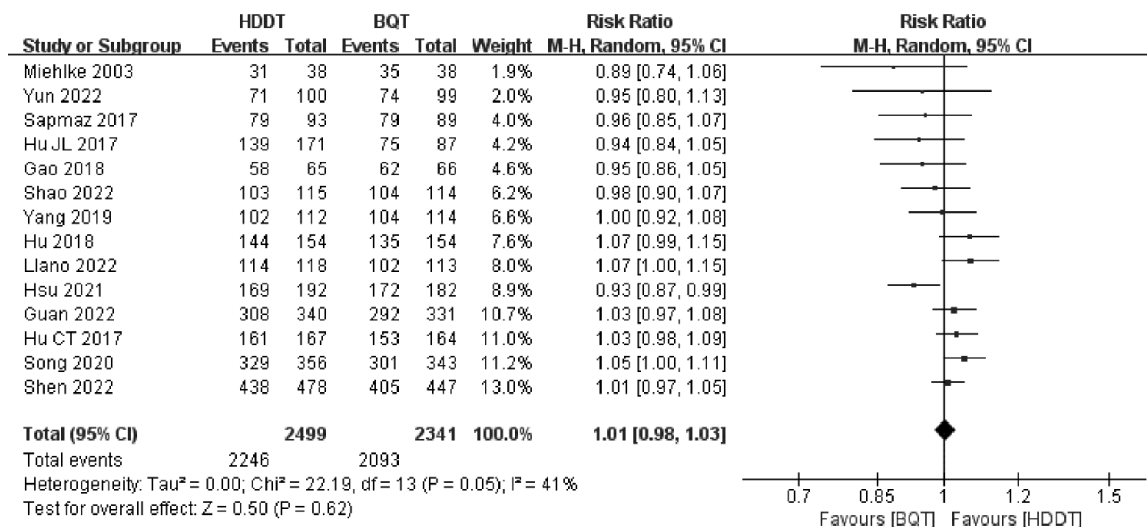BQT, bismuth-containing quadruple therapy; ITT, intention to treat; HDDT, high-dose dual therapy.

Figure 3. Forest plot of the effect of HDDT *versus* BQT on *H. pylori* eradication rate according to PP analysis.
BQT, bismuth-containing quadruple therapy; HDDT, high-dose dual therapy; PP, per-protocol.

type II error (power of 80%), an anticipated RR reduction of −5%, and the pooled control group eradication rates of 85.1%. As shown in Supplemental Figure S3, the cumulative z curve did not cross the TSA boundary and the traditional significance boundary, but crossed the futility boundary and RIS line, supporting the findings of the conventional meta-analysis, and also confirming that true negative. The RIS was 3681 patients. The TSA adjusted CI was 0.98–1.05.

Subgroup analyses. We performed subgroup analyses based on study design, study location, treatment experience, frequency of HDDT administration, and BQT duration. The details of the results of subgroup analyses are presented in Table 2. In subgroup analysis based on study design, the eradication rate had no significant difference between multicenter RCTs subgroup (RR = 1.02, 95% CI: 0.97–1.07, *p* = 0.42) and single-center RCTs subgroup (RR = 1.01, 95%
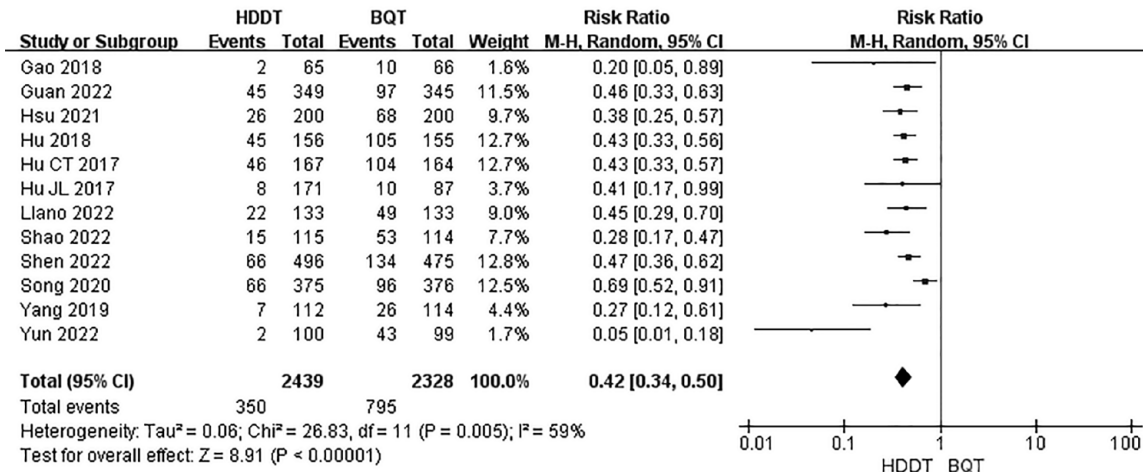
Figure 4. Forest plot of the effect of HDDT *versus* BQT on total adverse effects.
BQT, bismuth-containing quadruple therapy; HDDT, high-dose dual therapy.

CI: 0.97–1.05, $p = 0.61$). Similar results were observed when the subgroup analyses were stratified by study location, treatment experience, frequency of HDDT administration, and BQT duration (Supplemental Figures S4–S8).

Sensitivity analyses. Sensitivity analyses were conducted to confirm the robustness of overall results and explore potential sources of heterogeneity. Similar results were observed for *H. pylori* eradication when using fixed-effect model, excluding conference abstracts, and excluding studies published in non-English. When omitting one study at a time and combining the remaining studies for sensitivity analyses, except for the study conducted by Hsu *et al.*,[25] exclusion of any other study did not significantly alter the overall results. Notably, when excluding conference abstracts and the study conducted by Hsu *et al.*[25] (published also as conference abstract), these I^2 were dramatically reduced to 4%, 0%, respectively, indicating that the study may be a source of statistical heterogeneity. These results of sensitivity analyses are presented in Supplemental Table S3.

Secondary outcomes
Total adverse effects. In all, 12 studies[18,19,21–30] including 4767 patients reported the incidence of total adverse effects. The incidence of total adverse effects in HDDT group was significantly lower than in BQT group (5.9% *versus* 34.1%, RR = 0.42, 95% CI: 0.34–0.50, $p < 0.00001$).

There was moderate statistical heterogeneity between studies ($I^2 = 59\%$, $p = 0.005$) (Figure 4).

Compliance. In all, 14 studies[17–30] involving 5121 patients reported data on patient compliance. The compliance in HDDT group was statistically higher than that of the BQT group (96.7% *versus* 94.7%), but there was no significant difference (RR = 1.01, 95% CI, 1.00–1.03, $p = 0.07$) with low statistical heterogeneity ($I^2 = 45\%$, $p = 0.04$) (Figure 5).

Quality of evidence
We assessed the quality of evidence using the GRADE approach. For *H. pylori* eradication rate based on ITT data, the GRADE assessment of the quality of the evidence was judged as moderate quality, mainly because of risk of bias in study design (unclear random sequence generation and allocation concealment, unclear or no blinding, and selective reporting). For the incidence of total adverse effects and compliance, the quality of the evidence was rated as low quality, which were mainly due to risk of bias in study design, statistical heterogeneity, or reporting bias. The details of GRADE evidence profiles for all these outcomes are presented in Supplemental Table S4.

Publication bias
For *H. pylori* eradication rate based on ITT analysis data, the funnel plot was asymmetrical distribution by visual inspection (Supplemental Figure S9). However, the results of Begg's test
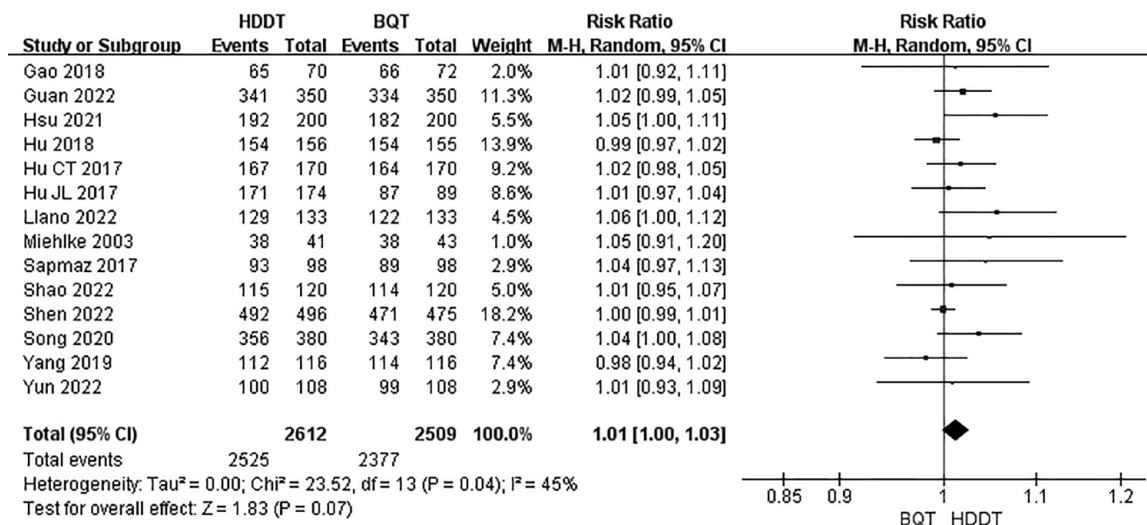
Figure 5. Forest plot of the effect of HDDT *versus* BQT on compliance.
BQT, bismuth-containing quadruple therapy; HDDT, high-dose dual therapy.

and Egger's test indicated no evidence of substantial publication bias ($P_{begg} = 0.08$, $P_{egger} = 0.07$, respectively). For the incidence of total adverse effects and compliance, the funnel plots were both asymmetrically distributed (Supplemental Figures S10 and S11). The results of Begg's test and Egger's test for the incidence of total adverse effects indicate that there may be publication bias ($P_{begg} = 0.047$, $P_{egger} = 0.013$, respectively). For compliance, the result of Begg's test did not confirm the presence of publication bias ($P_{begg} = 0.189$), but the result of Egger's test showed that there may be publication bias ($P_{egger} = 0.025$).

Discussion

Summary of main findings
To the best of our knowledge, this study provides the most comprehensive, systematic, up to date evidence on the effects of HDDT compared with BQT for *H. pylori* eradication. Our updated meta-analysis demonstrated that, compared with BQT, HDDT has similar efficacy and compliance, with fewer adverse effects in eradicating *H. pylori*.

For *H. pylori* eradication rate, similar results were observed in all conducted subgroup analyses and most of sensitivity analyses. The GRADE quality of the evidence was appraised as moderate quality. The result of the TSA was conclusive. For adverse effects and compliance, the GRADE

quality of the evidence was appraised as low quality.

Potential explanations and implications
In 1989, Unge *et al.*[31] initially reported that the dual therapy consisting of amoxicillin (750 mg bid) and omeprazole (40 mg qid) was used to eradicate *H. pylori*, with low eradication rate of only 62%. Subsequently, a multicenter study conducted by Bayerdörffer *et al.*[32] in Germany showed that the *H. pylori* eradication rate was 91% in the omeprazole (40 mg tid) plus amoxicillin (750 mg tid) group. At that time, however, this regimen may not be adopted by physician because of the high dose and frequency of drugs. Thereafter, investigators have further conducted a series of clinical trials on standard dose of dual therapy for *H. pylori* eradication, but the eradication rate is significantly lower than triple therapy and quadruple therapy.[33,34] Therefore, routine dual therapy has not become the standard treatment for *H. pylori* eradication. In recent years, with the in-depth research on the pharmacokinetics and pharmacodynamics of amoxicillin and PPI, the mechanism of the dual therapy has been gradually clarified, and the HDDT has attracted clinicians' attention again. The mechanism of the effectiveness of HDDT in eradicating *H. pylori* was summarized as follows: (i) antibiotic resistance remains the most important challenge to successful *H. pylori* eradication; however, the

resistance rate of *H. pylori* strain to amoxicillin is very low (<5%).[4,35,36] (ii) amoxicillin is a time-dependent antibiotic, and its bactericidal effect depends on the time when the plasma concentration is higher than the minimum inhibitory concentration.[37] After taking amoxicillin for 6–8 h, its concentration decreased significantly, and the effective plasma concentration of amoxicillin could be maintained by increasing the frequency of administration. To increase and maintain blood concentration, amoxicillin should be administered 3–4 times a day to achieve a good eradication effect. (iii) Amoxicillin has been shown to be pH dependent, when the intragastric pH is 6 or greater, *H. pylori* is in proliferation state and becomes highly susceptible to amoxicillin. Therefore, it is necessary to use high-dose PPI to fully inhibit gastric acid secretion while using amoxicillin.[37–39] (iv) The effect of PPI on inhibiting gastric acid secretion is affected by CYP2C19 gene polymorphism. Nevertheless, some studies have shown that when PPI is given at high dose and multiple frequencies, the effect of CYP2C19 gene polymorphism could be basically ignored.[40,41] Thus, high-dose and high-frequency administration of HDDT are expected to improve its effectiveness for *H. pylori* eradication.

In our meta-analysis of 14 RCTs, HDDT achieved similar eradication rate compared to the BQT recommended by current mainstream guidelines. Considering that racial differences may affect the eradication effect of HDDT,[42] we conducted the subgroup analysis based on study location, the result showed that HDDT and BQT have similar eradication rates in both Asia subgroup and non-Asia subgroup. However, in the non-Asia subgroup, there were only two studies[17,27] from Europe and Oceania. Thus, the effect still needs to be verified by further large sample RCTs in non-Asian population.

Of the 14 studies included, PPI and amoxicillin were administered at different frequencies in HDDT, four times daily in 10 studies[17–19,21–25,29–30] and three times daily in three studies,[20,27,28] whereas PPI was administered four times daily and amoxicillin three times daily in one study.[26] We further conducted subgroup analysis based on frequency of HDDT administration, similar eradication rates were observed in these subgroups. Although it is convenient for HDDT to be administered three times a day, which can increase patient compliance and obtain similar

eradication rate compared to BQT, the number of clinical trials is small and the sample size is limited, so we cannot draw a definite conclusion. In the future, further clinical trials are needed to verify the efficacy of HDDT administered three times a day compared with BQT in the eradication of *H. pylori*.

For eradication rate, we further conducted sensitivity analyses to confirm the robustness of overall results. When omitting one study conducted by Hsu *et al.*[25] and combining the remaining studies for sensitivity analysis, the eradication rate in the HDDT group was higher than BQT group (RR = 1.03, 95% CI: 1.01–1.06). Notably, with the exception of the study conducted by Hsu *et al.*[25], I^2 were dramatically reduced to 0%, which may be attributed to the study was published as conference abstract, indicating that publication type may be a source of low statistical heterogeneity.

Compliance is an important factor affecting the *H. pylori* eradication rate, adverse effects are the crucial factors that affect patient compliance.[43] Adverse effects and patient compliance were also analyzed in our study. In our meta-analysis, HDDT has a lower incidence of total adverse effects compared to BQT (5.9% *versus* 34.1%), which may be related to fewer kinds of medications used in the regimen. Nevertheless, no significant difference was observed in the compliance between HDDT and BQT. Although HDDT increased the number of daily doses and frequency of administration, which may decrease patient compliance, HDDT has fewer adverse effects and fewer kinds of medications, so compliance does not decrease compared to BQT.[37,42]

In view of increasing antibiotic resistance and high incidence of adverse effects of BQT, the results of our meta-analysis have important clinical implications. For one thing, HDDT may be a good alternative treatment for those who cannot obtain bismuth or tolerate the adverse effects of BQT. For the other thing, HDDT is also applicable to patients of rescue treatment, especially when drug susceptibility test cannot be conducted. In addition, vonoprazan, a novel potassium-competitive acid blocker, has been recently attracted considerable attention. A meta-analysis by Lyu *et al.*[44] showed that vonoprazan-based triple therapy is superior to that of PPI-based triple therapy for first-line *H. pylori* eradication.

Compared to PPI, vonoprazan provides a stronger and longer-lasting effect on gastric acid suppression, and is not affected by diet and CYP2C19 polymorphism.[9] In the future, RCTs on vonoprazan–amoxicillin dual therapy *versus* BQT for *H. pylori* eradication should be further conducted.

Comparison with previous studies

In 2019, a smaller meta-analysis conducted by Yang *et al.*,[45] including four RCTs with 829 patients, showed that both HDDT and BQT achieved similar efficacy of eradication rate and compliance, but side effects were more likely in BQT. Recently, Yin *et al.*,[9] who included six RCTs with 1677 patients, demonstrated that HDDT achieved similar eradication rate compared with BQT. However, HDDT showed fewer side effects and better compliance compared to BQT. In these two published meta-analyses, our meta-analysis covers all of their included studies. Compared to previous studies,[9,45] our updated meta-analysis further validates these above conclusions and advances the findings of this past work. Our meta-analysis covers the most comprehensive studies ($n=14$ RCTs) and greatly increases the total sample size ($n=5121$ patients), especially by including the most updated large sample and multicenter studies published between 2021 and 2022, providing the latest, most timely and more sufficient evidence on the topic.

Strengths and limitations

Our study has several strengths. First, our study is the most current and largest meta-analysis to date on the effects of HDDT compared with BQT for *H. pylori* eradication. The large number of sample size provided high statistical power. Second, we used rigorous and transparent methodology according to the Cochrane Handbook and the PRISMA statement, conducted a limited number of subgroup analyses and comprehensive sensitivity analyses, and assessed the quality of evidence with GRADE approach, which made our results more convincing and reliable. Third, we applied TSA to increase the reliability of the meta-analysis and estimate the RIS, which further draws firm evidence.

Despite these strengths, several limitations should not be neglected. First, many of included studies in our meta-analysis did exist risk of bias, such as unclear randomization, allocation concealment, and no blinding, which might affected the reliability of our results. Further large, well-designed RCTs are needed to validate our findings. Second, there are few trials (only two trials [17,22]) regarding HDDT *versus* BQT for *H. pylori* rescue therapy. More large sample multicenter trials are needed in the future to verify the effect of HDDT *versus* BQT as a rescue therapy for *H. pylori*. Third, for secondary outcomes (total adverse effects and compliance), there may be publication bias, which may have a certain impact on the results. Fourth, this regimen may not be applicable to patients who are allergic to amoxicillin. Finally, study patients in our meta-analysis were mainly from Asia (mostly from China), a paucity of evidence from other regions. Therefore, the evidence of this review is mainly applicable to Asian populations (especially China), whether the evidence are suitable for other populations should be confirmed by conducting further studies. In spite of the limitations aforementioned, we are reasonably confident in our results and provide valuable updated evidence for *H. pylori* eradication in clinical practice.

Conclusion

In conclusion, evidence from our updated meta-analysis demonstrate that HDDT is as effective as BQT in eradicating *H. pylori*, with fewer adverse effects and similar compliance. Increasing the total dose and administration frequency of PPI and amoxicillin is more conducive to maintaining a stable blood concentration of PPI, and forming a stable high pH environment in the stomach, which helps *H. pylori* enter the proliferation state and increase its sensitivity to amoxicillin. In addition, high dose and multiple frequencies of PPI also helps to overcome the impact of CYP2C19 gene polymorphism. The scientific evidence supports that HDDT can be used as an alternative regimen to BQT regimen for *H. pylori* infection eradication in clinical practice.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Availability of data and materials
All data generated or analyzed during this study are included in this published article and its supplementary information files.

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Supplemental material
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