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META-ANALYSIS

Comparative effectiveness of first-line therapies for eradication of antibiotic-resistant *Helicobacter pylori* strains: A network meta-analysis

Shu-Peng Zou, Qian Cheng, Cheng-Yang Feng, Chan Xu, Ming-Hui Sun

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Abstract

BACKGROUND

As a first-line treatment regimen for *Helicobacter pylori* (*H. pylori*) infection, antibiotic therapy is widely used worldwide. However, the question of increasing antibiotic resistance must be considered. Given this issue, we need to find ways to reduce drug resistance. This study examined all currently available first-line regimens and compared them with standard triple treatment through a network meta-analysis of randomized controlled trials (RCTs).

AIM

To compare first-line treatment regimens for eradication of antibiotic-resistant *H. pylori* strains.

METHODS

To compare the effectiveness of the first-line regimens for treating *H. pylori* infection, a Bayesian network meta-analysis was applied to process data extracted from RCTs. The plausible ranking for each regimen was assessed by the surface under the cumulative ranking curve (SUCRA). In addition, we conducted a relevant search by reference citation analysis.

RESULTS

Twenty-five RCTs involving 12029 participants [including 1602 infected with clarithromycin (CAM)-resistant strains and 1716 infected with metronidazole (MNZ)-resistant strains] were included, in which a total of seven regimens were used for *H. pylori* eradication. The results showed that dual therapy containing a high-dose proton pump inhibitor (HDDT) [odds ratio (OR): 4.20, 95% confidence interval (CI): 2.29-8.13] was superior to other therapies for all patients, including those with CAM/MNZ-resistant *H. pylori* infection. In the comparative effectiveness ranking, for CAM-resistant *H. pylori*, HDDT (OR: 96.80, 95%CI: 22.46-

521.9) had the best results, whereas standard triple therapy ranked last (SUCRA: 98.7% *vs* 0.3%). In the subgroup of high cure rates (≥ 90%), HDDT was also generally better than other therapies.

CONCLUSION

For the eradication of CAM- and MNZ-resistant *H. pylori* strains, HDDT exhibited considerable advantages. The studies of CAM-resistant *H. pylori* were based on small samples due to a lack of antibiotic sensitivity tests in many RCTs, but the results showed that all patients, including those with CAM-resistant *H. pylori* infection, had a concordant trend. Overall, HDDT may be a reference for RCTs and other studies of *H. pylori* eradication.

Key Words: *Helicobacter pylori*; Clarithromycin resistance; First-line therapy; Proton pump inhibitors

Core Tip: This is the first study to compare currently available first-line treatment regimens for eradication of antibiotic-resistant *Helicobacter pylori* strains. For clarithromycin-resistant and metronidazole-resistant strains, dual therapy containing a high-dose proton pump inhibitor (HDDT) shows an absolute advantage over other first-line therapies. There was a difference in the effectiveness of HDDT between all patients and patients with clarithromycin-resistant *Helicobacter pylori* infection. In the subgroup of high cure rates (≥ 90%), HDDT was also generally better than other therapies. The use of fewer antibiotics may be better to prevent global antibiotic resistance effectively.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is a severe health problem affecting almost half of the global population; the organism not only causes gastric acid-related diseases but is also closely associated with gastric malignancies[1,2]. In addition, the World Health Organization classified *H. pylori* as a Group 1 carcinogen. For example, in Asia, the percentage of *H. pylori*-infected population varies across countries: 79% in India, 75% in Vietnam, 60% in South Korea, and 58% in China[3]. In 2020, the Taipei Global Consensus highlighted that eradication of *H. pylori* could beat the target of reducing death rates from gastric cancer[4]. It is extremely important to determine the best eradication treatment for *H. pylori* to prevent gastric cancer. However, the eradication rate achieved by the traditional first-line regimen consisting of clarithromycin (CAM), amoxicillin (AMX), and proton pump inhibitors (PPIs) has recently declined due to an increase in CAM-resistant *H. pylori* strains[5]. Univariate and multivariate analyses have identified resistant bacteria, inadequate gastric acid inhibition, and traditional triple therapy as risk factors for eradication failure[6,7]. Additionally, the calculation of total eradication rate considered both antibiotic susceptible and resistant *H. pylori* strains. Depending on drug-resistant bacteria, several treatments have been tried, including sequential therapy, traditional quadruple therapy, combination therapy, and dual therapy containing a high dose PPI (HDDT)[8]. In a meta-analysis performed by Zhu *et al*[9], 15 randomized control trials (RCTs) with 3818 patients were eligible for inclusion. Trial sequential analysis showed reliable evidence that HDDT was equivalent to the recommended regimens, including standard triple therapy, bismuth quadruple therapy (BQT), and non-BQT[9]. Network meta-analysis (NWM) blends direct and indirect evidence in various RCTs and provides a relative and referable result among three or more therapeutic interventions[10]. Although there are recent pairwise meta-analyses including NWM, none have compared the current therapeutic interventions for antibiotic-resistant *H. pylori* strains. The purpose of our current study was to compare the effectiveness of vonoprazan (VPZ)-based and PPI-based first-line treatment regimens using NWM and to rank the treatments. To reach reliable conclusions, we only included RCTs with a minimal risk of bias.

MATERIALS AND METHODS

Search strategy and data sources

The scheme of the study was successfully registered at PROSPERO (registration number: 42022326460). The quality of evidence and data derived from NWM was evaluated using the Grading of Recommendations Assessment, Development and Evaluation and Cochrane Handbook (Version 6.3, 2022).

PubMed, EMBASE, Web of Science, OVID, Cochrane Library (all years up to March 2022), and Cochrane Central Register of Controlled Trials (CENTRAL, all years up to March 2022) were searched using the following keywords: ("vonoprazan", "VPZ", "potassium-competitive acid blocker", "P-CAB", "TAK438", or "TAK-438") OR ("PPI", "proton pump inhibitor", "PPIs") AND ("*Helicobacter pylori*", "*H. pylori*", "HP"). We also manually searched the references of all identified trials, relevant review articles, and conference abstracts about antibiotic-resistant strains. In addition, we conducted a relevant search by reference citation analysis.

Study selection

We formulated the inclusion and exclusion criteria before conducting study searches. Additionally, the latest relevant studies were searched. Appropriate RCTs were included in the NWM according to the following criteria: (1) Adult patients with *Helicobacter pylori* infection; (2) studies reported in English; (3) treatment including VPZ or PPIs; (4) cases stratified by antibiotic susceptibility; (5) *H. pylori* infection before and after treatment confirmed by one or more of the following methodologies: The rapid urease test, culture, the ^{13}C-urea breath test, and the stool *H. pylori* antigen test; (6) RCTs with first-line therapy (except levofloxacin-containing treatments); and (7) human studies[11].

Studies were excluded based on the following criteria: (1) Non-RCTs and observational studies; (2) lack of antibiotic sensitivity testing; and (3) animal studies.

Two investigators (Chan X and Cheng Q) skimmed the literature independently, and standards-compliant studies were extracted and recorded. When a disagreement arose, a consensus was reached by discussion with other investigators.

Data extraction

Two reviewers (Zou S and Feng C) independently used processed data forms to extract the data from the eligible studies. The following information was extracted: First author, study title, year of publication, study design, participants, study period, trial number, treatment period, criteria of eradication, eradication rate (intention-to-treat [ITT]), and other details[11].

Subgroup analysis

In the latest review, Graham *et al* suggested that to be clinically relevant, the primary regimen being tested should achieve a cure rate of ≥ 90% unless it is impossible to achieve with an optimized regimen [12]. To achieve high cure rates, we performed a subgroup analysis of the RCTs in the high cure rate group (≥ 90%).

Statistical analysis

For binary NWM and heterogeneity estimation with Bayesian analysis, we followed the approach described by the Cochrane Handbook and evaluated inconsistencies by node splitting. The NWM accounted for heterogeneity utilizing the random-effects model. The surface under the cumulative ranking curve (SUCRA) metric was used to rank the effectiveness of each treatment and identify the best treatment[10,13]. R (version 4.2.0) and Stata (version 14.0) were used for statistical analyses. All *P* values were two-tailed, and a *P* value < 0.05 represented significant differences for all measurements [10].

RESULTS

Characteristics of studies

A flow diagram of the study selection, including inclusion and exclusion criteria, is shown in Figure 1. As shown in Supplementary Table 1, among 25 studies, 5 RCTs for VPZ and 19 RCTs for PPIs were applied to clarithromycin-susceptible and -resistant *H. pylori* strains[14-38]. Other studies used metronidazole (MNZ) resistance for qualitative examination. A total of 12029 participants (including 1602 participants for CAM resistance) from RCTs were analyzed. The rate of CAM resistance was 13.3% in our network meta-analysis. There were 19 two-arm RCTs and 5 three-arm RCTs, including 12 paired comparisons in total and 9 indirect comparisons in NWM. The characteristics of the above RCTs, such as study ID, type of article, trial number, study design, participants, and treatment duration, are shown in Supplementary Table 1. The seven first-line treatment regimens used were: (1) VPZ dual therapy (Vono-dual therapy at conventional dose); (2) VPZ triple therapy (Vono-triple therapy); (3) sequential therapy (PPI-based therapy); (4) HDDT; (5) PPI-bismuth QT; (6) PPI-nonbismuth QT; and (7) PPI-triple therapy.

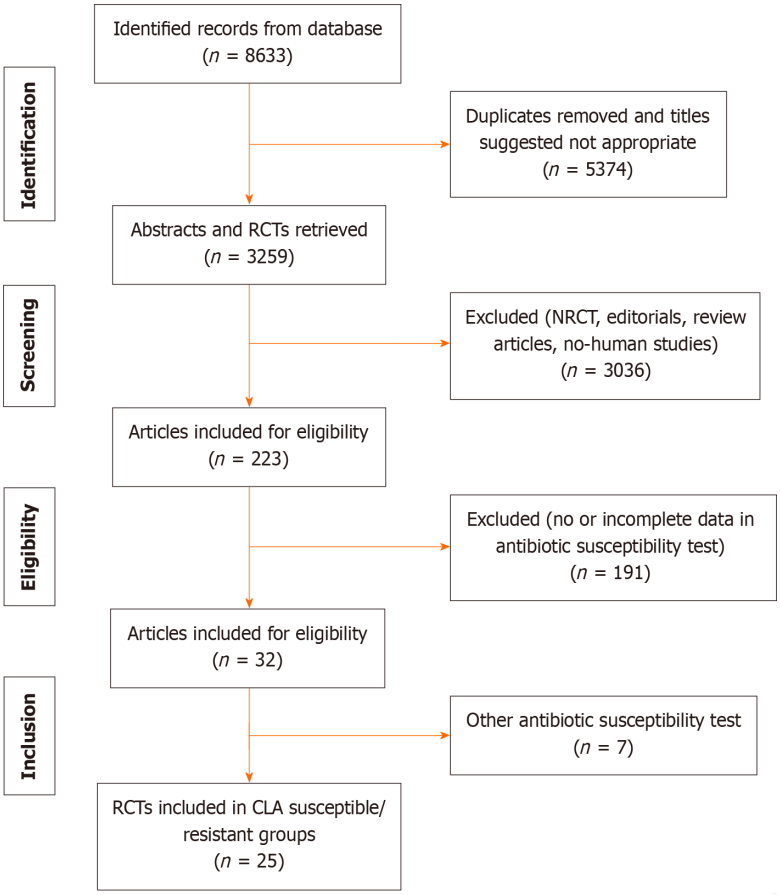

Figure 1 Study selection. Flow diagram of the study, including study screening, inclusion, and exclusion in this systematic review and network meta-analysis. RCTs: Randomized controlled trials; NRCT: Non-randomized controlled trial; CLA: Clarithromycin.

Network map of CAM resistance

The network map of 25 studies from the databases is depicted in Figure 2. The network included direct and indirect comparisons. The inconsistent and consistent model of the network showed no significant difference (P = 0.864, > 0.05). In the map, the node size and edge thickness reflected the number of patients allocated to each regimen. Data were pooled using the random-effects model.

Network meta-analysis of CAM resistance

In our NWM, all therapies for CAM-resistant *H. pylori* were compared with PPI triple therapy. The efficacy of other treatments for all patients and patients with CAM-resistant *H. pylori* infection is depicted in Figure 3A and B. Twenty-five individual direct pair comparisons grouped into 12 pairwise regimens and the heterogeneity of meta-analyses are shown in Supplementary Figure 1. In Figure 3A and B, the comparisons of HDDT *vs* PPI-triple therapy (odds ratio [OR]: 96.80, 95%CI: 22.46-521.9), PPI-BQT *vs* PPI-triple therapy (OR: 34.76, 95%CI: 14.11-98.92), PPI-nonbismuth QT *vs* PPI-triple therapy (OR: 9.73, 95%CI: 4.01-29.94), Vono-dual therapy *vs* PPI-triple therapy (OR: 6.97, 95%CI: 1.90-27.6), Vono-triple therapy *vs* PPI-triple therapy (OR: 3.89, 95%CI: 1.47-9.69), and sequential therapy *vs* PPI-triple therapy (OR: 2.60, 95%CI: 1.26-5.89) all yielded significant results for CAM-resistant *H. pylori* and were consistent with the results on all patients. In Figure 4, the network forest plot of the league matrix illustrates all 21 pair network comparisons of regimens included in the RCTs. Furthermore, the comparisons of Vono-dual therapy *vs* sequential therapy (OR: 2.69, 95%CI: 0.56-12.4), HDDT *vs* PPI-nonbismuth QT (OR: 10.0, 95%CI: 1.74-53.7), and PPI-bismuth QT *vs* PPI-nonbismuth QT (OR: 3.56, 95%CI: 1.08-10.08) yielded significant results. In Supplementary Figure 3, the node-splitting analysis was non-significant for all results (P > 0.05), meaning that indirect comparisons of our NWM were consistent with direct comparisons. On the other hand, the loop-specific heterogeneity showed that each loop of NWM was congruent, as shown in Supplementary Figures 4 and 5.

For CAM-resistant *H. pylori*, we found apparent differences compared with all patients in Figure 4A and B: PPI-nonbismuth QT *vs* PPI-bismuth QT (OR: 0.29, 95%CI: 0.12-0.73), HDDT therapy *vs* Vono-triple therapy (OR: 16.16, 95%CI: 4.10-63.69), PPI-bismuth QT *vs* Vono-triple therapy (OR: 5.7, 95%CI: 2.06-15.80), and PPI-nonbismuth QT *vs* sequential therapy (OR: 2.78, 95%CI: 1.18-6.54).

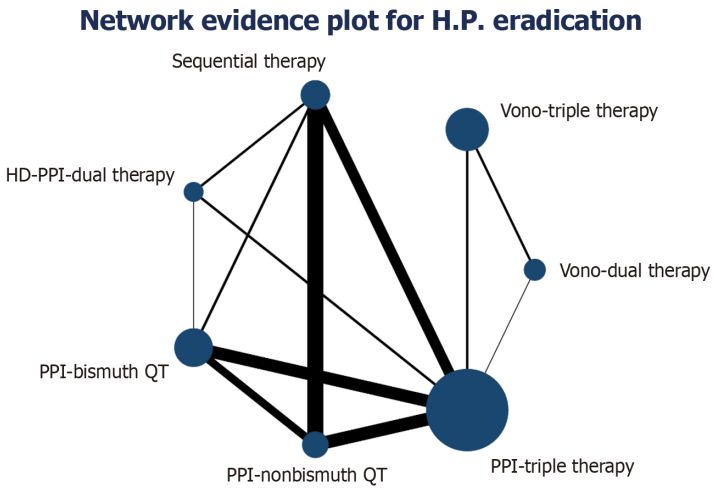

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Figure 2 Network map for clarithromycin resistance. The node size is positively associated with the number of patients in each regimen, and the precision is proportional to the edge thickness, namely, the standard errors of each direct comparison. Vono: Vonoprazan; PPI: Proton pump inhibitor; HD: High-dose; QT: Quadruple therapy.

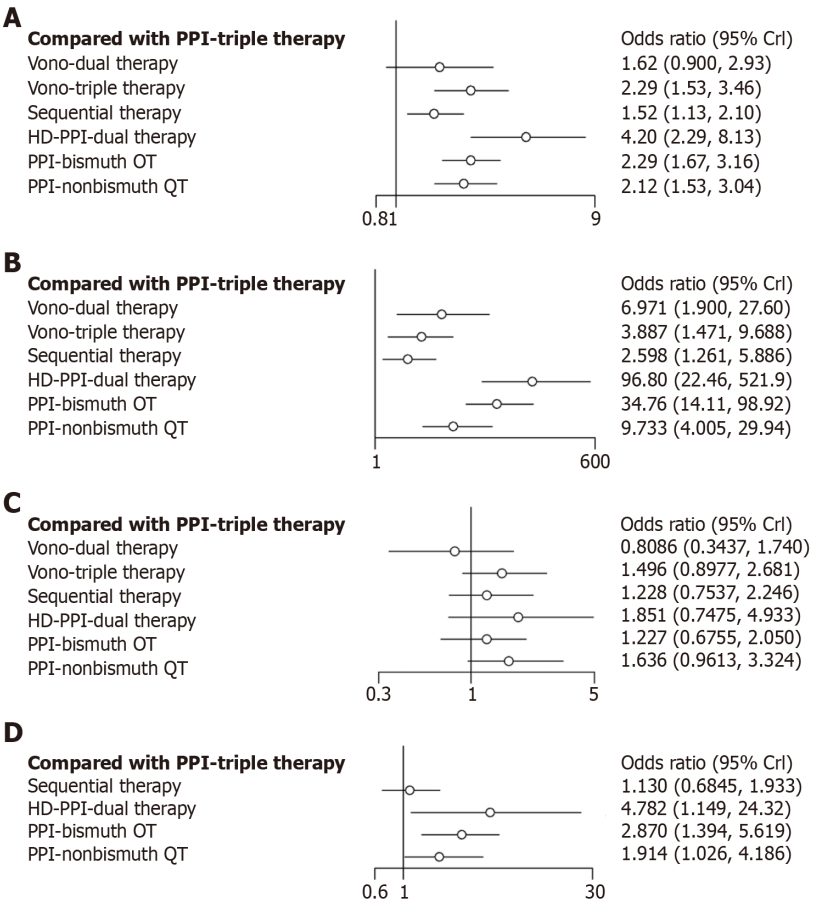

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Figure 3 Network forest plots. A: Network forest plot [odds ratio (OR); 95% credible interval [CrI]) of all patients (intention-to-treat) showing the regimens compared directly with the proton pump inhibitor-triple therapy regimen as the reference; B: Network forest plot (OR; 95% CrI) of clarithromycin-resistant strains showing that the efficacy of the regimens compared with PPI-triple therapy was consistent with that in network forest plot A; C: Network forest plot of clarithromycin-susceptible strains describing the efficacy of the regimens compared directly with the PPI-triple therapy regimen as the reference; D: Network forest plot of metronidazole-resistant strains showing the efficacy of the regimens compared directly with the PPI-triple therapy reference regimen. CrI: Credible interval; ITT: Intention-to-treat; Vono: Vonoprazan; PPI: Proton pump inhibitor; HD: High-dose; QT: Quadruple therapy.

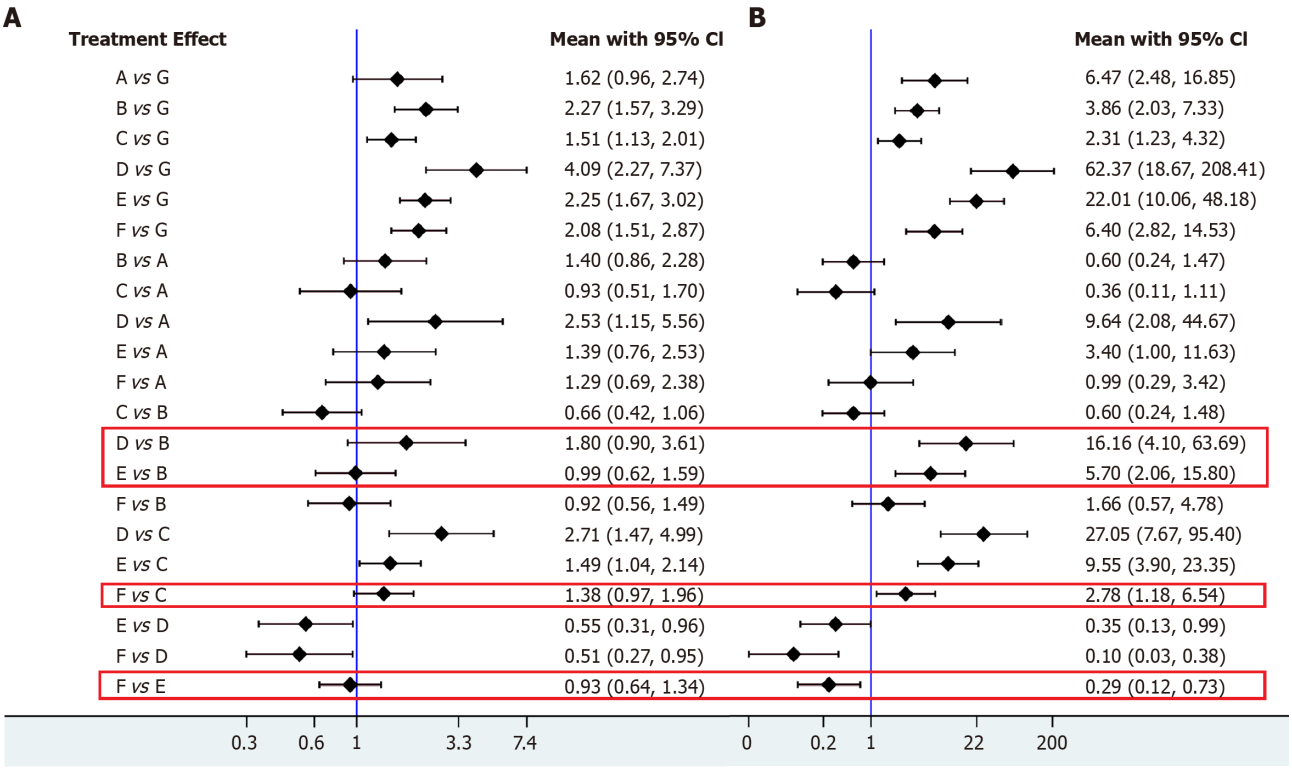

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Figure 4 Forest plots of the league matrix in randomized controlled trials among all patients (A) and those infected with clarithromycin-resistant strains (B). A: Vonoprazan-dual therapy; B: Vonoprazan-triple therapy; C: Sequential therapy; D: Dual therapy containing a high-dose proton pump inhibitor; E: Proton pump inhibitor bismuth quadruple therapy; F: Proton pump inhibitor nonbismuth quadruple therapy; G: Proton- pump inhibitor triple therapy. RCTs: Randomized controlled trials; CrI: Credible interval.

According to the league matrix and the SUCRA in NWM, the comparative efficacies of the seven regimens are shown in Figure 5. The results might be unexpected; nevertheless, they were reliable. The SUCRA value of HDDT as the best treatment was 98.7% and that of PPI-triple therapy as the worst treatment was 0.3%. Remarkably, the number of VPZ-related studies was not so considerable.

Risk of bias analysis and funnel plot of CAM sensitivity

In the quality evaluation of the included RCTs, the risk of bias is shown in Supplementary Figure 6 and Figure 6A. According to the risk of bias tool (Cochrane Handbook, 2.0), blinding of participants and personnel was the main source of potential bias[2]. This was the result of fifteen studies using an open-label design, whereas seven studies were double-blinded and three studies were indeterminate. In Figure 6B, the relevant funnel plot showed perfect symmetry, and there was no evidence of publication bias.

For CAM-susceptible strains, the network forest plot is displayed in Figure 3C. The results showed that the seven different regimens were almost coincident in confidence intervals. Overall, the comparisons of HDDT *vs* PPI-triple therapy (OR: 1.85, 95%CI: 0.75-4.93) and PPI-nonbismuth QT *vs* PPI-triple therapy (OR: 1.64, 95%CI: 0.96-3.32) yielded significant results.

Network forest plot of MNZ resistance

Figure 3D shows the eradication of MNZ-resistant strains. Twenty-two included studies only contained PPI-based researches. Therefore, there were only efficacy comparisons between C, D, E, F, and G. Compared with PPI-triple therapy, HDDT (OR: 4.78, 95%CI: 1.15-24.32) and PPI-bismuth QT (OR: 2.87, 95%CI: 1.39-5.62) showed obvious curative effects. Other antibiotic-resistant strains, including levofloxacin and amoxicillin, were not analyzed in our study because few RCTs completed antibiotic sensitivity tests.

Subgroup of high cure rates (≥ 90%)

As shown in Figure 6C, the network forest plot shows that HDDT (OR: 5.04, 95%CI: 1.92-15.15) and Vono-based therapy (OR: 4.00, 95%CI: 1.74-9.42) had substantial advantages over PPI-triple therapy (≥ 85%) in all patients (Figure 6C). In Figure 6D, the network forest plot shows that HDDT was slightly superior to PPI-triple therapy (≥ 85%) in CAM-susceptible *H. pylori* strains.

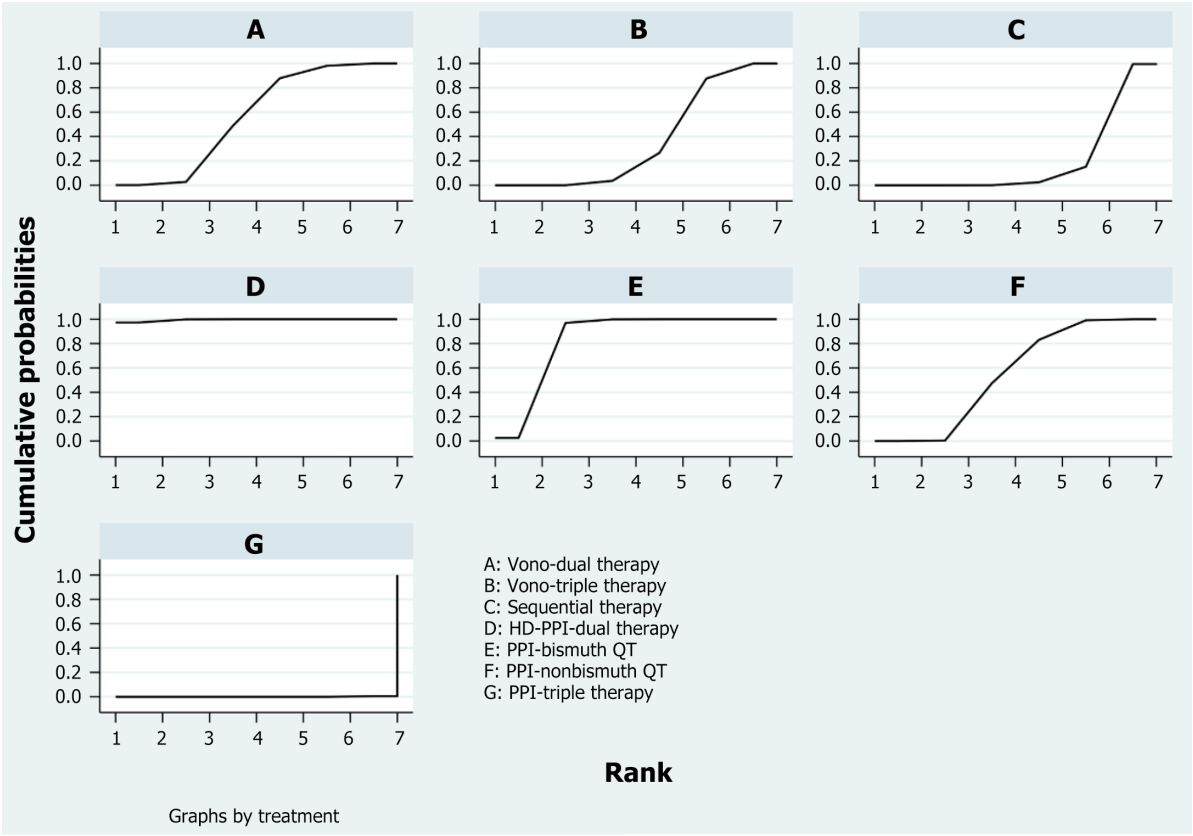

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Figure 5 Cumulative probability of rank in this network meta-analysis. Vono: Vonoprazan; PPI: Proton pump inhibitor; HD: High-dose; QT: Quadruple therapy.

DISCUSSION

In the present network study, the random model that we used showed great convergence diagnostics, as shown in Supplementary Figure 5. Some differences between CAM-resistant and other *H. pylori* strains were found (Figure 4). Compared with PPI-triple therapy, HDDT showed tremendous advantages. PPI-bismuth QT (OR: 2.29, 95%CI: 1.67-3.16) and PPI-nonbismuth QT (OR: 2.12, 95%CI: 1.53-3.04) also yielded significant results in all patients. Compared to PPI-triple therapy in patients infected with CAM-resistant *H. pylori* strains, Vono-based therapy was unlikely to be better than other PPI-based therapies. However, the number of Vono-based RCTs was much less than that of PPI-based RCTs in our study. Similarly, sequential therapy also failed to achieve the desired result, because it included different antibiotics and methods. In CAM-susceptible strains, the curative effects of other treatments might be similar to those of PPI-triple therapy. The results also showed that HDDT probably had the best effect. *H. pylori* can cause peptic ulcers and finally result in stomach cancer in certain conditions[39]. According to relevant recommendations for the diagnosis from the European and American College of Gastroenterology, people with *H. pylori* infection are suggested to receive eradication therapy[40]. Because antibiotic resistance is increasing worldwide, we need to find ways to reduce drug resistance. The standard triple therapy for *H. pylori* eradication, including PPI, AMX, and CAM, has been used as the first-line therapy[41]. As both primary and secondary resistance to amoxicillin remain rare in most countries, HDDT may be an accessible and reasonable option for eradicating *H. pylori*. Moreover, HDDT, which uses fewer antibiotics than other eradication regimens, restrains the development of resistance[42]. Furthermore, the dose frequency is essential for efficacy of PPI-amoxicillin dual therapy [43]. In a subgroup analysis of HDDT, a more significant effect was observed in trials dosing four times daily in comparison with trials dosing three times daily[9].

The primary problem of *H. pylori* eradication is the increasing antimicrobial-resistant strains[44]. Unregulated use of antibiotics will only result in serious drug-resistant consequences[42]. Therefore, intelligent use of antibiotics may be one of the best and most effective ways to solve the problem[44]. HDDT adopts a high dose of PPI and AMX and does not include more antibiotics. In 2015, a multicenter randomized controlled trial by Yang *et al* reported the use of dual therapy with rabeprazole (20 mg, qid) and AMX (750 mg, qid) for *H. pylori* eradication in Taiwan[22]. Their results showed an evident advantage (95.3% in ITT and 96.6% in per-protocol [PP] analyses), even in CAM-resistant strains (95.7% in PP analyses). HDDT would be superior to standard first-line therapy and can be used as a rescue

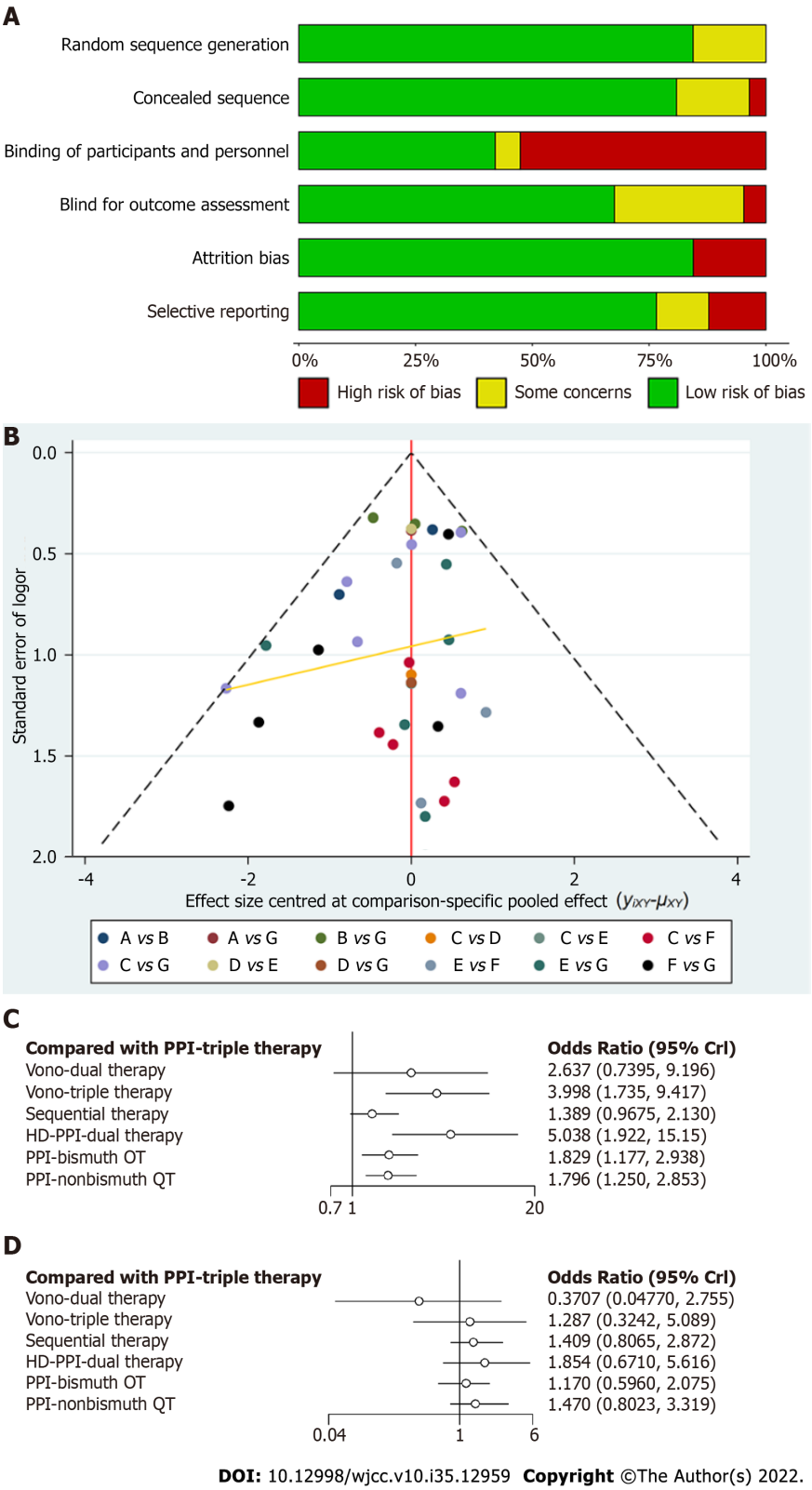

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Figure 6 Risk of bias graph and the funnel plot. A: Risk of bias graph displaying each item as the percentage in all studies; B: Funnel plot. The symmetrical appearance indicates the absence of publication bias or small study effects in the network; C: Network forest plot of all patients (intention-to-treat) in the subgroup with high cure rates (≥ 90%) showing that dual therapy containing a high-dose proton pump inhibitor (HD-PPI) and Vono-based therapy have advantages over PPI-triple therapy; D: Network forest plot of clarithromycin-susceptible *H. pylori* in the subgroup with high cure rates (≥ 90%) showing that HD-PPI-dual therapy was slightly superior to PPI-triple therapy. CrI: Credible interval; ITT: Intention to treat; Vono: Vonoprazan; PPI: Proton pump inhibitor; HD: High dose; QT: Quadruple therapy.

therapy for *H. pylori* infection[42]. However, Hu *et al*[45] showed no satisfactory *H. pylori* eradication rates (81.6% in ITT and 83.5% in PP analyses) achieved by HDDT in China. In 2019, Yang *et al*[46] in a single-center randomized controlled study, compared 14 d dual therapy with bismuth-containing

quadruple therapy for *H. pylori* eradication and found an advantage of 14 d achieved by dual therapy. In addition, VPZ-based therapy is superior to conventional PPI-based therapy in many studies[39,47,48].

Our findings have the following limitations: (1) VPZ-based therapy and HDDT was used in only two RCTs, respectively, and the results might be underrated or overrated because of the lack of antibiotic sensitivity tests in many studies; (2) VPZ was only recommended as a first-line regimen in Japan, and there were few reported applications of VPZ-based therapy for *H. pylori* eradication in other countries; (3) in our network study, we did not consider the therapy duration of *H. pylori* eradication; (4) to ensure the consistency of first-line treatments, we excluded levofloxacin-based therapy and other line regimens; and (5) little data was obtained in children, which limited the generalizability of our findings.

CONCLUSION

In conclusion, this is the first study to compare first-line treatments for eradication of antibiotic-resistant *H. pylori* strains. The therapeutic effect of VPZ-based therapy for eradicating CAM-susceptible *H. pylori* strains is nearly the same as that of PPI-based therapy. However, for CAM-resistant and MNZ-resistant strains, HDDT shows absolute advantages over PPI-triple therapy. According to included RCTs, HDDT is superior to major PPI- and VPZ-based therapies for eradication of CAM-resistant *H. pylori* strains. In our study, we can observe the immense potential of HDDT, which perhaps solves the problem of antibiotic resistance in *H. pylori* eradication. On the other hand, we found that many RCTs were excluded because of the lack of antibiotic sensitivity tests. Therefore, our study provides physicians and researchers with more options. In fact, *H. pylori* therapy should be based on its absolute cure rates and local conditions. However, additional multicenter studies are required to confirm this assumption and the conclusion.

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We thank all the technicians at the Department of Pharmacy, Tongji Hospital for their technical support.

ARTICLE HIGHLIGHTS

Research background

Helicobacter pylori (*H. pylori*) bacteria can cause peptic ulcers and finally result in stomach cancer in certain conditions. Meanwhile, the question of increasing antibiotic resistance must be considered. Given this issue, we need to find ways to reduce drug resistance. This study examined all first-line regimens and compared them with standard triple treatment through a network meta-analysis of randomized controlled trials (RCTs).

Research motivation

To the best of our knowledge, there are no relevant network meta-analyses comparing first-line treatment regimens for eradication of antibiotic-resistant *H. pylori* strains.

Research objectives

To compare first-line treatment regimens for eradication of antibiotic-resistant *H. pylori* strains.

Research methods

A comprehensive search was performed in databases such as PubMed, EMBASE, Web of Science, OVID, Cochrane Library (all years up to March 2022), and Cochrane Central Register of Controlled Trials (all years up to March 2022).

Research results

Twenty-five RCTs consisting of 12029 participants [including 1602 infected with clarithromycin (CAM)-resistant strains and 1716 infected with metronidazole (MNZ)-resistant strains] were included, in which seven regimens were used for *H. pylori* eradication. The results showed that dual therapy containing a high-dose proton pump inhibitor (HDDT) [odds ratio (OR): 4.20, 95% confidence interval (CI): 2.29-8.13] was superior to other therapies for all patients, including those infected with CAM/MNZ-resistant *H. pylori* strains. In the comparative effectiveness ranking, for CAM-resistant *H. pylori* strains, HDDT (OR: 96.80, 95%CI: 22.46-521.9) had the best results, whereas standard triple therapy ranked last (SUCRA: 98.7% *vs* 0.3%). In the subgroup of high cure rates (≥ 90%), HDDT was also generally better than other therapies.

Research conclusions

For eradication of CAM- and MNZ-resistant *H. pylori* strains, HDDT have a considerable advantage. Overall, HDDT may be a reference for RCTs and other studies of *H. pylori* eradication.

Research perspectives

Additional multicenter studies are required to confirm the conclusion of this study.

FOOTNOTES

Author contributions: Zou SP and Cheng Q performed the research as well as screening, inclusion, and exclusion of randomized controlled trials, and wrote the paper; Sun MH designed the study; Feng CY and Xu C reviewed the data extracted from the study.

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