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Comparative efficacy, safety and compliance with dual, triple and quadruple therapy as the first-line treatment regimens for *Helicobacter pylori* eradication: a systematic review and network meta-analysis

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ABSTRACT

Objective To assess the efficacy, safety and compliance with dual, triple and quadruple therapy first-line regimens for *Helicobacter pylori* eradication.

Design A systematic review and network meta-analysis (NMA) reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses NMA guidance.

Data sources PubMed, Cochrane Library, ProQuest and Scopus were searched until 12 October 2025.

Eligibility criteria Randomised controlled trials (RCTs) published in English that measured the eradication rate, adverse events and compliance rates of dual therapy compared with triple or quadruple therapy for *H. pylori* first-line treatment.

Data extraction and synthesis Data extraction and risk-of-bias assessment were performed by two independent reviewers. The data were analysed and represented as pooled ORs. Heterogeneity was assessed using meta-regression and trim-and-fill analyses.

Results Pairwise meta-analysis of 56 RCTs showed that dual therapy had no different eradication rates than triple therapy (intention-to-treat (ITT): OR 0.88, 95% CI 0.60 to 1.29; per-protocol (PP): OR 0.76, 95% CI 0.46 to 1.25). Dual therapy outperformed quadruple therapy (OR 1.20, 95% CI 1.04 to 1.39) with fewer adverse events (OR 0.32, 95% CI 0.28 to 0.38) and higher compliance rates (OR: 1.49, 95% CI 1.26 to 1.76). Based on the NMA, RAC-7 has the highest probability of effective treatment for both ITT (P-score=0.9436) and PP (P-score=0.9545).

Conclusion Dual therapy represents a promising first-line option, demonstrating comparable efficacy and adverse event rates with higher compliance, although triple therapy showed the highest probability of being the most effective first-line regimen in the NMA, followed by quadruple therapy. Further studies in non-Asian populations, along with resistance-guided treatment approaches, are needed to refine global eradication strategies.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The promising results for dual therapy in prior studies were still lacking detailed comparisons among specific regimens, duration of the treatment and the compliance rate of each regimen.

WHAT THIS STUDY ADDS

⇒ This study showed that Potassium-Competitive Acid Blocker (P-CAB)-based dual therapy, particularly 7-day or 10-day vonoprazan with amoxicillin regimens, has comparable efficacy with superior safety and higher compliance compared with other dual therapy and quadruple therapy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ P-CAB-based dual therapy, particularly vonoprazan with amoxicillin, was seen to be a safe and effective regimen with a high compliance rate as the *H. pylori* first-line treatment, particularly in Asian regions.

⇒ However, to establish the generalisability, future studies involving non-Asian populations are warranted to extend the applicability of the study.

INTRODUCTION

Helicobacter pylori is a bacterium that causes chronic gastritis, peptic ulcer disease, gastric cancer and gastric mucosa-associated lymphoid tissue lymphoma.[1–3] The burden of gastric cancer was estimated to cause 800 000 deaths in 2020,[4] particularly in Asian countries.[5 6] Eradication lowers gastric cancer incidence.[7] However, it is still challenging to decide the optimal eradication regimen[8] because of antibiotic resistance. A recent meta-analysis reported the high burden of *H. pylori* resistance to metronidazole (35.3%),

clarithromycin (32.6%), tetracycline (2.1%), levofloxacin (13.2%) and amoxicillin (4.8%).[9]

This was aggravated by the inconsistency of antibiotic sensitivity test recommendations among several guidelines, which are recommended by ACG Clinical Guidelines, Maastricht VI/Florence Consensus and the revised Japan guidelines in 2016,[10–12] but are not yet recommended by other guidelines.[13–15]

Adequate compliance is associated with higher efficacy of *H. pylori* eradication. Several factors (adverse events, history of eradication failure, long duration of treatment, high pill burden, drug availability, low education level and patients with non-investigated dyspepsia) are associated with non-compliance to therapy.[16 17] Several meta-analyses showed similar compliance, high eradication rates and lower adverse events from dual therapy compared with other first-line treatments.[13 18–20] Rokkas *et al* showed that vonoprazan triple therapy had the highest efficacy among 68 randomised controlled trials (RCTs) and concluded that it was the most effective first-line regimen.[21] Four years later, with fewer included studies (n=25), they reported that a Potassium-Competitive Acid Blocker (P-CAB)-based dual therapy was preferable with acceptable eradication rates and a higher safety profile.[22] However, a lack of understanding of the comparison of specific regimens, duration of treatment and compliance rate needed to be elaborated. Therefore, this network meta-analysis (NMA) aimed to evaluate the efficacy, safety and compliance of specific regimens of dual, triple and quadruple therapies (bismuth quadruple therapy (BQT) and concomitant therapy) using robust data from RCTs.

METHODS

Study design

This systematic review and meta-analyses are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for NMA reporting guidelines (online supplemental material).[23] This study employed a pairwise meta-analysis followed by NMA to compare direct and indirect evidence derived from the included RCTs. The study protocol was not prospectively registered.

Search strategy

A systematic search until 12 October 2025 was conducted across four electronic databases (PubMed, The Cochrane Library, ProQuest and Scopus).[24] The search strategy (online supplemental table S1) was developed to obtain RCTs and meta-analyses that evaluate the efficacy, safety and compliance of dual therapy compared with triple and quadruple therapy as *H. pylori* first-line treatment. The inclusion of previous meta-analyses was intended to capture additional studies that may not have been identified through the predefined search strategy.

Eligibility criteria

The inclusion criteria for this review were as follows: (1) RCTs (published in English) conducted on adult patients (>18 years old) with confirmed *H. pylori* infection and treatment-naïve patients; (2) Intervention groups receiving dual therapy and comparator groups receiving triple or quadruple therapy; and (3) Outcomes reported as eradication rates (intention-to-treat (ITT) and per-protocol set (PP)), adverse events and compliance.

Study selection

The study selection process was independently conducted by two reviewers who screened the titles and abstracts for relevance. Full-text reviews were performed on potentially eligible studies, and disagreements were resolved through consensus. Data (study author and year, country, treatment regimens, duration, eradication rates (ITT and PP), adverse events and compliance rates) were systematically extracted.

Data extraction and synthesis

The primary outcome was eradication rate, which was measured as the OR with 95% CIs. Publication bias was assessed using funnel plots and the Egger regression test. If a small study effect was observed, a trim-and-fill analysis was conducted to adjust for potential publication bias. Heterogeneity among studies was evaluated using I^2 statistics and Cochran's Q test. Meta-regression with several covariates (region, antiacid type, antibiotic dose and duration of each protocol) was performed for analysis with high heterogeneity (I^2>70%) to evaluate the covariates associated with the variance of the pooled effect size. The results were visualised as a regression table and coefficient plot. Subgroup analyses were performed based on the treatment combinations.

To enhance the robustness of the comparisons beyond conventional pairwise meta-analysis, a frequentist method for NMA was performed.[25] A random-effects model was applied and surface under the cumulative ranking (Surface Under the Cumulative Ranking Curve (SUCRA) probabilities were computed to rank treatments. The analysis was visualised using network plots, forest plots, league table and table of SUCRA probabilities.[25] The statistical analyses were conducted using R Studio (Posit Software, PBC) using metafor and netmeta packages.[25 26]

Risk-of-bias assessment

The risk of bias in the included studies was assessed using the revised Cochrane Risk of Bias Tool for Randomised Trials (RoB 2) that evaluates five key domains.[27]

RESULTS

Study selection

We identified 994 records screened for eligibility and excluded 926 articles to get 68 articles for review; 45 were excluded due to different study arms (n=4), duplication (n=39) and unavailability of full-text articles (n=2). The 23 newly identified studies met the inclusion criteria and were added to 33 studies included in prior meta-analyses by Zhang *et al* (n=10),[18] Zhou *et al* (n=12),[28] Huang

et al (n=3),[20] Liu *et al* (n=4),[19] Rokkas *et al* (a)[21] (n=2) and Rokkas *et al* (b)[22] (n=2). All included studies were published in English (online supplemental table S1 and online supplemental figure S1).

Risk of bias

The risk-of-bias assessment using RoB 2 indicated that most studies had a low risk of bias. Notably, six studies (Sapmaz *et al*, Horii *et al*, Yun *et al*, Niu *et al*, Cheung KS *et al* and Liu Z *et al*) were assessed as having a high risk of bias. Despite these limitations, the overall methodological quality of the included studies is robust (online supplemental figure S2).

Study characteristics

The study characteristics are listed in online supplemental table S2.[29–79]

Dual therapy versus triple therapy

The results of the pairwise meta-analysis are presented in table 1. The ITT analysis showed that dual therapy was not significantly different from triple therapy, with a pooled OR of 0.88 (95% CI 0.60 to 1.29; I^2=73.50%). This finding was also shown in subgroup analyses that revealed no significant differences in eradication rates between P-CAB-based dual therapy and Proton Pump Inhibitor

Table 1 Summary of pooled ORs from pairwise meta-analyses—overall and subgroup analysis

Pairwise meta-analysis variable	k	Weight (%)	OR	95% CI	I^2
Outcome 1: Efficacy					
Efficacy: Dual therapy versus triple therapy—intention to treat					
Subgroup 1: PPI-based dual therapy versus PPI-based triple therapy	3	22.00	1.71	0.56 to 5.17	79.30
Subgroup 2: P-CAB-based dual therapy versus PPI-based triple therapy	3	20.40	0.39	0.07 to 1.49	87.80
Subgroup 3: P-CAB-based dual therapy versus P-CAB-based triple therapy	8	57.60	0.83	0.52 to 1.33	67.10
Pooled analysis (n=3468)	14	100.00	0.88	0.60 to 1.29	73.50
Efficacy: Dual therapy versus triple therapy—per protocol					
Subgroup 1: PPI-based dual therapy versus PPI-based triple therapy	3	22.20	1.44	0.25 to 8.43	89.40
Subgroup 2: P-CAB-based dual therapy versus PPI-based triple therapy	3	21.20	0.36	0.05 to 2.83	90.70
Subgroup 3: P-CAB-based dual therapy versus P-CAB-based triple therapy	8	56.60	0.75	0.47 to 1.22	54.60
Pooled analysis (n=3199)	14	100.00	0.76	0.46 to 1.25	78.40
Efficacy: Dual therapy versus quadruple therapy—intention to treat					
Subgroup 1: PPI-based dual therapy versus PPI-based bismuth quadruple therapy	23	57.60	1.12	0.93 to 1.35	51.70
Subgroup 2: P-CAB-based dual therapy versus PPI-based bismuth quadruple therapy	15	31.30	1.39	1.07 to 1.82	48.70
Subgroup 3: P-CAB-based dual therapy versus P-CAB-based bismuth quadruple therapy	4	6.90	1.10	0.71 to 1.71	4.30
Subgroup 4: PPI-based dual therapy versus PPI-based concomitant therapy	2	4.20	1.15	0.68 to 1.95	0.00
Pooled analysis (n=13 904)	46	100.00	1.20	1.04 to 1.39	47.90
Efficacy: Dual therapy versus quadruple therapy—per protocol set					
Subgroup 1: PPI-based dual therapy versus PPI-based bismuth quadruple therapy	23	81.00	1.08	0.87 to 1.34	44.80
Subgroup 2: P-CAB-based dual therapy versus PPI-based bismuth quadruple therapy	4	6.70	0.98	0.53 to 1.80	0.00
Subgroup 3: P-CAB-based dual therapy versus P-CAB-based bismuth quadruple therapy	4	6.70	0.98	0.53 to 1.80	0.00
Subgroup 4: PPI-based dual therapy versus PPI-based concomitant therapy	2	5.60	0.98	0.32 to 3.02	63.10
Pooled analysis (n=9556)	32	100.00	1.05	0.88 to 1.26	31.30
Outcome 2: Compliance					
Compliance of dual therapy versus triple therapy	6	100.00	0.79	0.46 to 1.35	16.00
Compliance of dual therapy versus quadruple therapy	40	100.00	1.49	1.26 to 1.76	0.00
Outcome 3: Safety					
Adverse events comparison of dual therapy versus triple therapy	11	100.00	0.97	0.54 to 1.76	91.40
Adverse events comparison of dual therapy versus quadruple therapy	42	100.00	0.32	0.28 to 0.38	63.50

(PPI)-based triple therapy (OR: 0.39; 95% CI 0.07 to 1.49; I^2=87.80%), PPI-based dual therapy and PPI-based triple therapy (OR: 1.71; 95% CI 0.56 to 5.17; I^2=79.30%) and P-CAB-based dual therapy and P-CAB-based triple therapy (OR: 0.83; 95% CI 0.52 to 1.33; I^2=67.10%) (online supplemental figure S3). The PP set analysis similarly showed no significant difference in eradication rates (OR: 0.76; 95% CI 0.46 to 1.25; I^2=78.40%). All subgroup analyses revealed no significant differences in eradication rates between P-CAB-based dual therapy and PPI-based triple therapy (OR 0.36; 95% CI 0.05 to 2.83; I^2=90.70%), P-CAB-based dual therapy and P-CAB-based triple therapy (OR 0.75; 95% CI 0.47 to 1.22, I^2=54.60%) or PPI-based dual therapy and PPI-based triple therapy (OR 1.44; 95% CI 0.25 to 8.43, I^2=89.40%) (online supplemental figure S4). Treatment compliance and adverse events did not differ significantly (OR: 0.79; 95% CI 0.46 to 1.35; I^2=16.00%) (online supplemental figure S5) and (OR: 0.32; 95% CI 0.54 to 1.76; I^2=91.40%) (online supplemental figure S6).

Dual therapy versus quadruple therapy

In online supplemental figure S7, the ITT analysis demonstrated that dual therapy achieved a higher eradication rate (pooled OR: 1.20; 95% CI 1.04 to 1.39; I^2=47.90%). In the subgroup analysis, PPI-based dual therapy (OR: 1.08; 95% CI 0.87 to 1.34; I^2=51.70%) showed no significantly higher eradication rates than PPI-based BQT, in contrast to P-CAB-based dual therapy (OR: 1.39; 95% CI 1.07 to 1.82; I^2=48.70%), which showed higher eradication. However, neither P-CAB-based dual therapy regimen outperformed P-CAB-based BQT (OR: 1.10; 95% CI 0.71 to 1.71; I^2=4.30%) or concomitant therapy (OR: 1.15; 95% CI 0.68 to 1.95; I^2=0.00%).

As illustrated in online supplemental figure S8, the PP meta-analysis confirmed the non-inferiority of dual therapy compared with quadruple therapy overall (pooled OR: 1.05; 95% CI 0.88 to 1.26; I^2=31.30%). Moreover, patients in the dual therapy group exhibited higher treatment compliance (OR: 1.49; 95% CI 1.26 to 1.76; I^2=0.00%) (online supplemental figure S9) and a lower incidence of adverse events (OR: 0.32; 95% CI 0.28 to 0.38; I^2=63.50%) (online supplemental figure S10).

NMA results

Online supplemental figure S11 illustrates the network of comparisons among various *H. pylori* eradication regimens based on (a) ITT and (b) PP analyses. In contrast, online supplemental figure S12 presents network plots for (a) Treatment compliance and (b) The occurrence of adverse events across the regimens.

Figure 1 presents forest plots from the NMA, which was conducted using random-effects models to compare all treatment regimens with vonoprazan plus high-dose amoxicillin dual therapy for 14 days (VHA-14). The superiority of the 'other' to 'reference' was represented as log(OR) of >0, and its inferiority was represented as log(OR) or Treatment Effect (TE)<0. In the ITT-based NMA (figure 1a), RAC-7 showed lower eradication rates based on ITT analysis than VHA-14 (log(OR) =−1.89 (95% CI −3.48 to −0.30)). A similar pattern was observed in the PP-based NMA (figure 1b), where RAC-7 (TE=−1.89; 95% CI −3.48 to −0.30) showed lower treatment effects, followed by RBTC-14 (log(OR) =−1.09; 95% CI−1.93 to −0.25), than VHA-14. The complete league tables were visualised in the NMA for further comparison of each regimen (online supplemental tables S3 and S4). In contrast, the SUCRA ranking probabilities that evaluated overall performance (table 2) showed that RAC-7 had the highest probability of being the most effective treatment (P-score=94.36%), followed by RBTC-14 (P-score=83.81%) and vonoprazan amoxicillin (VA)-7 (P-score=78.85%). RAC-7 remained as the probable most effective treatment (P-score=95.45%) in PP analysis (table 3), followed by PPI-based BQT and VA-10, included in the top five of highest probability (P-score=76.45%) (online supplemental tables S5 and S6). Overall, while RAC-7 demonstrated the highest effectiveness based on NMA, dual therapy regimens (VA-7 and VA-10) continued to show clinically adequate potential in NMA and did not demonstrate inferiority in pairwise meta-analysis.

Figure 2 shows forest plots from the NMA of compliance rates and adverse events. In terms of compliance rate (figure 2a), no treatment showed a significantly higher compliance rate than VA-14. Similarly, in the analysis of adverse events (figure 2b), none of the treatments demonstrated significantly fewer adverse events than VA-14 did; however, the BQT (EBTeM-14, Esomeprazole, Bismuth, Amoxicillin and Metronidazole for 14 days (EBAM-14), Rabeprazole, Bismuth, Amoxicillin and Clarithromycin for 14 days (RBAC-14), Rabeprazole, Bismuth, Amoxicillin and Furazolidone for 14 days (RBAF-14), RBTeM-10) showed higher frequency of adverse events compared with VA-14.

Publication bias

In the ITT analysis comparing dual versus triple therapy, Egger's test showed significant evidence of small study effects (p=0.02). In contrast, PP analysis showed no significant funnel plot asymmetry despite the high heterogeneity among the studies (p=0.148). Similarly, Egger's regression test for ITT analysis of dual versus quadruple therapy showed no significant small-study effects, with moderate between-study variability (p=0.491). PP analysis for dual versus quadruple therapy also did not indicate significant asymmetry, with moderate heterogeneity among the studies (p=0.163) (online supplemental figure S13). To address the small-study effects with high between-study variability in the ITT and PP analyses of dual versus triple therapy, a trim-and-fill analysis was performed. After adjustment, the overall effect size of ITT was 1.40 (95% CI 0.93 to 2.10; I^2=80.2%) and PP was 1.16 (95% CI 0.68 to 1.97; I^2=81.8%), which means that

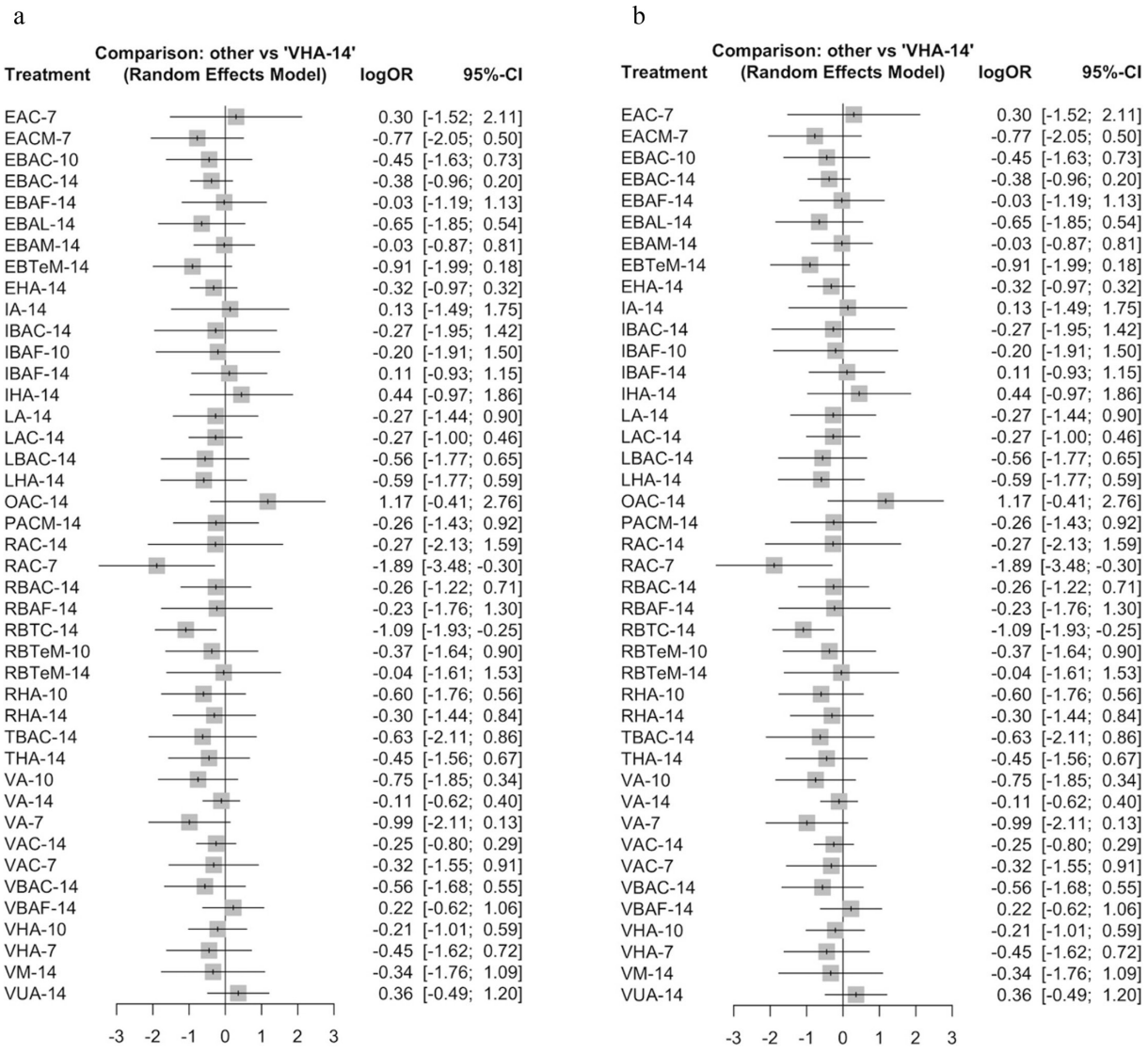


Figure 1 Forest plot network meta-analysis of efficacy: (a) Intention-to-treat (ITT) network meta-analysis and (b) Per-protocol (PP) network meta-analysis.

the overall result size was not affected by publication bias (online supplemental figure S16).

Egger's regression test was performed for adverse events and compliance; however, compliance with dual versus triple therapy was not performed because the number of included studies was insufficient (k=6). The test for adverse events (online supplemental figure S14) revealed significant small-study effects with high between-study variability in dual therapy versus quadruple therapy (p=0.04). However, a symmetrical distribution was found between dual therapy and triple therapy (p=0.77). In contrast, compliance between dual and quadruple therapies (online supplemental figure S15) showed no significant small-study effects, with moderate between-study variability (p=0.418). To address the observed small study effects in the analysis of adverse events of dual versus triple and quadruple therapies, trim-and-fill analyses (online supplemental figure S17) were conducted to adjust for potential publication bias. After adjustment, the overall effect size of dual therapy versus triple therapy still showed no difference in safety (OR=0.97; 95% CI 0.53 to 1.75; I^2=91.2%). In addition, the trim-and-fill analysis of dual therapy versus quadruple therapy remained statistically significant (OR=0.41; 95% CI 0.34 to 0.49, I^2=75.5%), although the magnitude of the pooled effect was attenuated compared with the original estimate.

Meta-regression

To address the covariates associated with high heterogeneity in the results of the pairwise meta-analysis in the ITT and PP analyses of dual therapy versus triple therapy and adverse events in all studies, meta-regression was performed. Meta-regression of ITT analysis (online supplemental figure S18a) of dual versus triple therapy showed that the model had a substantial proportion of heterogeneity (R^2=38.94%), with variation in the anti-acid regimen in dual therapy as the main contributor to the observed heterogeneity (online supplemental table S7). In line with the meta-regression in the ITT analysis

Table 2 SUCRA rankings of ITT network meta-analysis

Treatment	P-score (common)	P-score (random)
RAC-7	0.9656	0.9436
RBTC-14	0.8948	0.8381
VA-7	0.8287	0.7885
EBTeM-14	0.8252	0.7542
VA-10	0.7442	0.7027
EACM-7	0.7338	0.6928
EBAL-14	0.686	0.6499
RHA-10	0.6461	0.6318
LHA-14	0.7092	0.6263
TBAC-14	0.6618	0.6252
VBAC-14	0.6596	0.6126
LBAC-14	0.6627	0.6098
THA-14	0.5765	0.5629
VHA-7	0.6188	0.5612
EBAC-10	0.5522	0.5589
EBAC-14	0.5854	0.5445
RBTeM-10	0.3646	0.5297
VM-14	0.4474	0.5105
EHA-14	0.4927	0.5056
VAC-7	0.5783	0.5012
RHA-14	0.4267	0.4958
IBAC-14	0.5067	0.4926
RAC-14	0.4303	0.4846
LA-14	0.5171	0.4814
LAC-14	0.5219	0.4796
PACM-14	0.4566	0.4742
VAC-14	0.5426	0.4729
RBAC-14	0.3864	0.4715
IBAF-10	0.4748	0.4681
RBAF-14	0.395	0.4661
VHA-10	0.3876	0.4414
VA-14	0.3942	0.3921
RBTeM-14	0.3051	0.3903
EBAF-14	0.372	0.3785
EBAM-14	0.3514	0.3576
IA-14	0.3228	0.3394
VHA-14	0.2974	0.3188
IBAF-14	0.2937	0.3128
EAC-7	0.2725	0.239
VBAF-14	0.2211	0.251
IHA-14	0.1681	0.2106
VUA-14	0.1678	0.2007
OAC-14	0.0546	0.0773

Continued

Table 2 Continued

Treatment	P-score (common)	P-score (random)

EBAC-10, Esomeprazole, Bismuth, Amoxicillin, and Clarithromycin for 10 days ; EBAC-14, Esomeprazole, Bismuth, Amoxicillin, and Clarithromycin for 14 days ; EBAF-14, Esomeprazole, Bismuth, Amoxicillin, and Furazolidone for 14 days ; EBAL-14, Esomeprazole, Bismuth, Amoxicillin, and Levofloxacin for 14 days ; EBAM-14, Esomeprazole, Bismuth, Amoxicillin, and Metronidazole for 14 days; EHA-14, Esomeprazole High-dose Amoxicillin for 14 days ; IBAC-14, Ilaprazole, Bismuth, Amoxicillin, and Clarithromycin for 14 days ; ITT, intention-to-treat; LHA-14, Lansoprazole High-dose Amoxicillin for 14 days ; RBAC-14, Rabeprazole, Bismuth, Amoxicillin, and Clarithromycin for 14 days; RBAF-14, Rabeprazole, Bismuth, Amoxicillin, and Furazolidone for 14 days ; RBTeM-10, Rabeprazole, Bismuth, Tetracycline, and Metronidazole for 10 days ; RHA-14, Rabeprazole High-dose Amoxicillin for 14 days ; SUCRA, surface under the cumulative ranking; VAC-7, Vonoprazan, Amoxicillin, and Clarithromycin for 7 days; VBAF-14, Vonoprazan, Bismuth, Amoxicillin, and Furazolidone for 14 days ; VHA-7, vonoprazan plus high-dose amoxicillin dual therapy for 7 days; VHA-10, vonoprazan plus high-dose amoxicillin dual therapy for 10 days; VHA-14, vonoprazan plus high-dose amoxicillin dual therapy for 14 days.

(online supplemental figure S16b), the variation in the antiacid regimen in dual therapy showed a significant association with high heterogeneity; however, the multivariate model failed to explain the variability across studies (online supplemental table S8). In the multivariate meta-regression of adverse events (online supplemental figure S19a) between dual and triple therapies, the variation in anti-acid regimens in dual therapy was a significant contributor to between-study heterogeneity, with an R^2 value of 100% (online supplemental table S9). In contrast, no covariate in the dual versus quadruple comparison showed a significant association with heterogeneity (online supplemental figure S19b), with the overall R^2 of the model being 0% (online supplemental table S10).

DISCUSSION

This comprehensive meta-analysis included 56 studies, encompassing 19 598, mostly originated in Asian countries. Variations in acid-suppressing agents (P-CAB versus PPI) and treatment duration (7–14 days) were found. In comparison to East Asian studies, we found four studies conducted in other regions that only used a 14-day protocol. Leow *et al's* study was conducted in the southeast Asian region (Malaysia) that used RHA or RAC.[35] Similar to that study, Sapmaz *et al* in the Middle East region (Iran) also used RHA; however, they compared it to RBTeM.[32] In comparison, Zuberi *et al* in South Asia (Pakistan) conducted a Randomised Controlled Trial (RCT) using VHA compared with OAC.[52] Chey *et al* in the USA used VHA compared with VAC.[41]

The latest ACG guidelines recommend optimised BQT as the preferred first-line treatment. In contrast, P-CAB dual therapy, specifically vonoprazan combined with amoxicillin, is positioned as a third-line option among first-line treatment choices.[11] In contrast, the revised Japanese guidelines (2019) and the Indonesian

Table 3 SUCRA rankings of PP network meta-analysis

Treatment	P-score (common)	P-score (random)
RAC-7	0.9803	0.9545
EBAL-14	0.867	0.8445
RBTC-14	0.8585	0.7912
RBTM-10	0.8056	0.7671
VA-10	0.8244	0.7645
EACM-7	0.7472	0.7406
VM-14	0.7517	0.7322
LA-14	0.7234	0.6836
IBAC-14	0.7482	0.6821
RHA-10	0.7138	0.6663
IBAF-10	0.718	0.6582
TBAC-14	0.6528	0.6549
RHA-14	0.6096	0.6025
EBAC-10	0.6305	0.5993
VA-7	0.6098	0.5945
EBAC-14	0.5898	0.5807
RAC-14	0.5738	0.5742
EHA-14	0.5218	0.5731
THA-14	0.5338	0.5717
RBAC-14	0.5452	0.5679
LBAC-14	0.5641	0.5525
LHA-14	0.5394	0.5408
RBAF-14	0.5192	0.5297
RBTeM-10	0.4527	0.5205
VHA-10	0.4953	0.4947
RBTeM-14	0.4618	0.4846
IHA-14	0.5052	0.4795
VHA-7	0.5172	0.4773
LAC-14	0.4082	0.4412
EBAM-14	0.3982	0.4264
PACM-14	0.3099	0.3912
IBAF-14	0.3858	0.3774
VAC-7	0.4182	0.3695
VHA-14	0.3752	0.364
IA-14	0.3337	0.3362
EBTeM-14	0.272	0.2948
VA-14	0.2526	0.2908
EBTM-14	0.2326	0.2846
VAC-14	0.2069	0.2841
VBAC-14	0.2594	0.2623
VBAF-14	0.2013	0.2165
EBAF-14	0.1365	0.1655
EAC-7	0.1217	0.1461
OAC-14	0.06	0.085
VUA-14	0.0678	0.0812

Continued

Table 3 Continued

Treatment	P-score (common)	P-score (random)

EBAC-10, Esomeprazole, Bismuth, Amoxicillin, and Clarithromycin for 10 days ; EBAC-14, Esomeprazole, Bismuth, Amoxicillin, and Clarithromycin for 14 days ; EBAF-14, Esomeprazole, Bismuth, Amoxicillin, and Furazolidone for 14 days ; EBAL-14, Esomeprazole, Bismuth, Amoxicillin, and Levofloxacin for 14 days; EBAM-14, Esomeprazole, Bismuth, Amoxicillin, and Metronidazole for 14 days; EHA-14, Esomeprazole High-dose Amoxicillin for 14 days ; IBAC-14, Ilaprazole, Bismuth, Amoxicillin, and Clarithromycin for 14 days ; LHA-14, Lansoprazole High-dose Amoxicillin for 14 days ; PP, per-protocol; RBAC-14, Rabeprazole, Bismuth, Amoxicillin, and Clarithromycin for 14 days; RBAF-14, Rabeprazole, Bismuth, Amoxicillin, and Furazolidone for 14 days ; RHA-14, Rabeprazole High-dose Amoxicillin for 14 days ; SUCRA, surface under the cumulative ranking; vac-7, Vonoprazan, Amoxicillin, and Clarithromycin for 7 days; VBAF-14, Vonoprazan, Bismuth, Amoxicillin, and Furazolidone for 14 days ; VHA-10, vonoprazan plus high-dose amoxicillin dual therapy for 10 days; VHA-14, vonoprazan plus high-dose amoxicillin dual therapy for 14 days.

consensus statement (2022) continue to recommend triple therapy as the first-line treatment.[12 15] The latest Taipei global consensus II (2025) stated BQT as the first-line eradication regimen for the empirical option in high clarithromycin resistance, after their previous consensus recommended antibiotic sensitivity test-guided treatment.[80 81] These variations were also reflected in the differing efficacy of various regimens reported in another NMAs by Rokkas *et al*, which showed that levofloxacin-based triple therapy had the highest eradication rate (>90%), followed by rabeprazole-based hybrid therapy in Western countries.[21]

To address the variety of options and evaluate the efficacy of different first-line *H. pylori* eradication regimens, we conducted both pairwise and network meta-analyses based on the ITT and PP data sets. Subgroup analyses were performed according to the type of acid-suppressive agent used, followed by specific regimen comparisons. The pooled results indicated the non-inferiority of dual therapy over triple therapy in the overall and subgroup analyses. Compliance rates and adverse events did not significantly differ between dual and triple therapies. In addition, dual therapy offers comparable compliance and safety profiles. When comparing dual therapy with quadruple therapy, ITT analysis demonstrated the superiority of dual therapy over quadruple therapy, except when comparing P-CAB-based dual therapy with P-CAB-based BQT, where no significant difference was observed. Initially, this superiority was attributed to the higher compliance rate in the dual therapy group. The efficacy and high compliance observed in the dual therapy group were further supported by the significantly lower adverse event rate than that of quadruple therapy.

To evaluate the efficacy of specific regimens, an NMA was performed using VHA-14 as the baseline comparator. Pooled pairwise meta-analysis and NMA showed the non-inferiority of dual therapy to triple or quadruple therapy. However, based on the SUCRA probabilities for the ITT analysis, the RAC-7 regimen ranked highest in the ITT, followed by RBTC-14, VA-7, EBTeM-14 and VA-10. In the

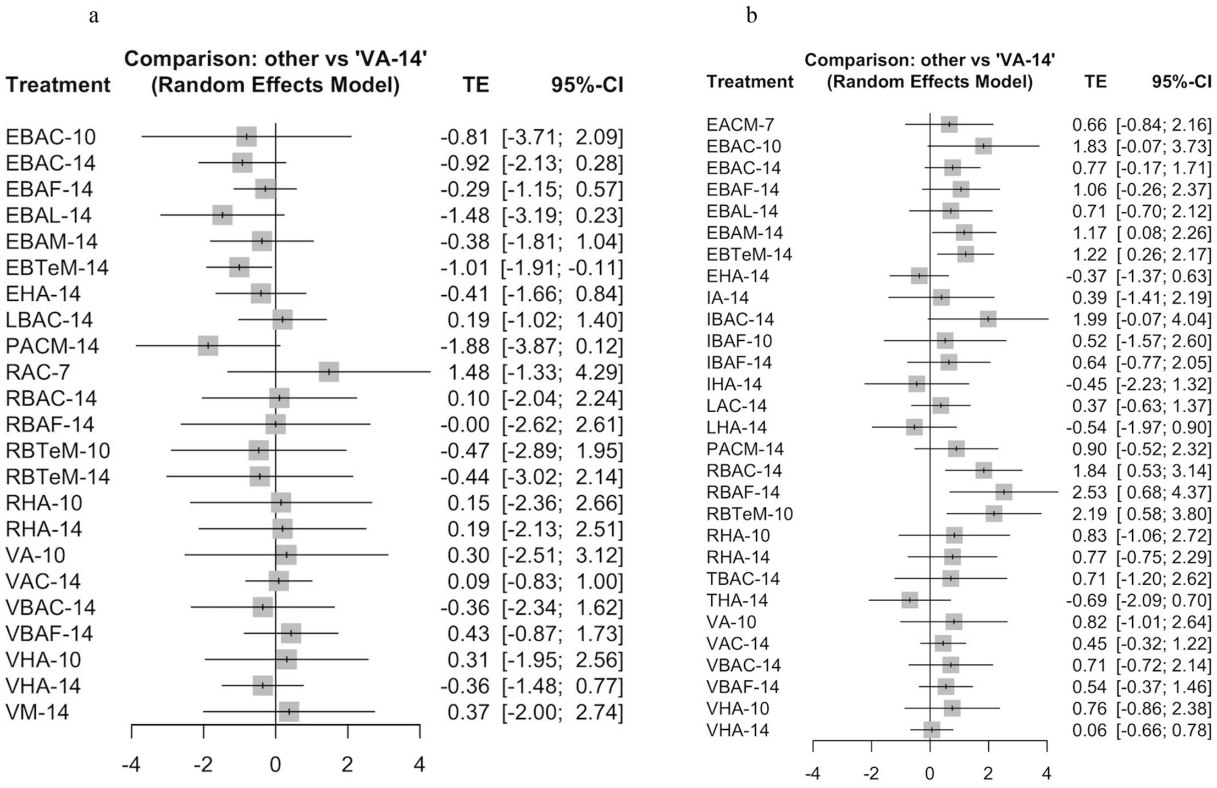


Figure 2 Forest plot network meta-analysis of efficacy: (a) Compliance and (b) Any adverse effect.

PP analysis, RAC-7 remained the most effective treatment with the highest probability, followed by Esomeprazole, Bismuth, Amoxicillin and Levofloxacin for 14 days (EBAL-14), RBTC-14, RBTM-10 and VA-10.

These findings demonstrate the resilience of PPI-based triple therapy, particularly rabeprazole, for *H. pylori* eradication treatment. In addition, VA-7 and VA-10 are potential first-line regimens for *H. pylori* eradication, with non-inferior efficacy to triple therapy, high probability in SUCRA ranking, high compliance rate and fewer adverse events. In line with this result, Rokkas *et al* showed that dual therapy may be effective for specific populations, such as East Asians, as their findings demonstrated comparable eradication rates between vonoprazan-based dual therapy and triple therapy in regions with high clarithromycin resistance, including Japan.[80] This finding may be associated with the capacity of these two antiacid regimens to achieve pH 4 holding time ratios as high as 88.2% (vonoprazan) and 73.5% (rabeprazole).[82–84] In addition, the higher compliance and fewer adverse events in the dual therapy and triple therapy groups compared with the quadruple therapy group play a key role in this finding. A report by Huguet *et al* showed that the subjects who had longer duration of regimens (10–14 days) reported adverse events.[16] However, the use of BQT should not be minimised because the NMA showed that RBTC-14, EBAL-14 and RBTM-10 still had high probability of high eradication, but their risk of adverse events and low compliance rate should be the most challenging to implement these regimens. Even after the reduced duration of BQT, Yang *et al* showed that EBTeM-10 has comparable efficacy to EBTeM-14, but it is not significantly decreasing adverse events nor increasing the compliance rate.[3]

Several considerations should be taken into account while choosing the appropriate regimens in addition to the statistical results; these are the long-term effects of antiacid therapy, antibiotic resistance or sensitivity patterns in each region, and the availability and cost of the regimens. First, whereas P-CAB-based dual therapy showed comparable efficacy with higher short-term safety and higher compliance rate, the long-term effect of P-CAB should be considered. Studies that elaborate *H. pylori* recurrence, reinfection rates or the impact of eradication on gastric cancer risk of P-CAB-based eradication treatments are limited. Okamoto *et al* reported hypomagnesaemia in a 66-year-old man who had long-term P-CAB use.[85] A recent report from an RCT of vonoprazan versus lansoprazole in erosive oesophagitis for 260 weeks (5 years) showed that the vonoprazan group had higher parietal cell hyperplasia (97.1% versus 86.5%) and foveolar hyperplasia (14.7% versus 1.9%) compared with the lansoprazole group.[86] This finding may be associated with the increase of lipopolysaccharide biosynthesis after an increase of intraluminal pH after the long-term use of P-CAB.[87 88] The shifting of small-intestine microbiota was also reported in a mice study, with reduced microbial diversity. In the same report, gastric emptying was significantly decreased in mice treated with PPI or P-CAB.[89]

Second, antibiotic resistance patterns remain a key factor in determining the most appropriate first-line regimen for *H. pylori* eradication. Unfortunately, this

report lacks an evaluation of the antibiotic sensitivity patterns. Schulz *et al* reported that resistance to clarithromycin was highest in the Asia-Pacific region (7.7–92.1%), followed by Africa (13.6–66.7%) and South America (13.5–29.0%). The resistance to amoxicillin was dominated by Africa (97.1%), followed by Asia-Pacific (0.0–50.0%) and South America (2.7%).[90] This means that our findings may not be generalised to the African and South American regions that had high clarithromycin resistance and moderate-to-high amoxicillin resistance. Compliance is a critical factor that contributes to the efficacy of *H. pylori* eradication treatment. In a multicentre RCT by Liou *et al*, poor compliance was identified as a major predictor of treatment failure. Among 5454 subjects, those with good compliance had significantly higher eradication rates (85%–94%) compared with those with poor compliance (39%–53%).[91] Poor compliance also contributes to increased antibiotic resistance.[92]

Thus, the use of an AST (Antibiotic Sensitivity Test)-guided eradication therapy may also be beneficial in the regions with high resistance. A prior single-arm meta-analysis by Lin *et al* showed a high eradication rate of 7-day AST-guided tailored therapy (93.0%).[93] A recent multicentre RCT by Amiot *et al* showed the non-inferiority of 14-day tailored PCR-guided triple therapy to 14-day concomitant therapy.[94]

However, in a paradoxical manner to the antibiotic resistance pattern, RAC-7, VA-10 and VA-7 still showed tolerable efficacy in our analysis dominated by data from East Asia, which is considered as the region with high levels of resistance to clarithromycin and amoxicillin. This finding may be caused by higher compliance to regimens that prevent treatment failure and antibiotic resistance. Therefore, even the risk of long-term effect of antiacid therapy is still lacking understanding (particularly P-CAB) and high antibiotic resistance pattern in Asia, but as long as the use of antiacid is within a manageable timeframe (7–10 days) with its promise to increase the compliance of dual therapy or triple therapy, it can still be effective for eradicating *H. pylori*.[95]

The third consideration is the availability and cost of the regimen. Based on a report by Schulz *et al*, PPI is available and reimbursed by government health insurance in almost all continents. However, for P-CAB, the availability and reimbursement are not equally distributed, particularly in Africa, South-East Asia and Europe.[90] The studies that analyse the cost-effectiveness of *H. pylori* eradication regimens are limited. In a report by Miwa *et al* from a patient with GERD, the cost analysis showed that the healthcare cost was higher in patients who had PPI than P-CAB.[96] Yokoya *et al* also reported that a cost-utility analysis in a patient with GERD showed the expected cost over 5 years for vonoprazan ($240), esomeprazole ($507) and rabeprazole ($272), but with higher quality-adjusted life years in the vonoprazan group.[95] For the *H. pylori* regimen, a study based on a Japanese health insurance claims database showed that the total costs were only slightly lower in a P-CAB-based triple therapy ($86) than in a PPI-based triple therapy ($87).[97] The use of P-CAB may be limited to the regions with its availability and reimbursement. However, even with the comparable cost between PPI-based triple therapy and P-CAB-based triple therapy, the cost for PPI also varied. Our study showed that an effective PPI-based triple therapy was RAC-7, which consists of rabeprazole ($0.74/unit) and esomeprazole ($0.72/unit) that are included in expensive PPIs.[98]

This study had several limitations. First, variations in treatment duration and dosage across studies may have influenced the outcomes. For instance, the different PPI or P-CAB used, dose of antibiotics and duration of treatment could affect eradication rates. Nevertheless, our NMA attempted to address this by comparing the efficacy of specific regimens, despite the potential lack of direct head-to-head trials. Second, the study did not account for individual antibiotic resistance profiles, which are critical for successful *H. pylori* eradication. Given the increasing global resistance to clarithromycin, metronidazole and levofloxacin, regional differences in resistance rates may significantly impact treatment efficacy. Future studies incorporating resistance-adjusted analyses may yield clinically relevant insights. Third, most of the included studies originated from East Asian countries, which may limit the generalisability of the findings to other populations. Regional variations in antibiotic use, healthcare practices and treatment accessibility could influence eradication outcomes. Fourth, this study did not evaluate long-term outcomes, such as *H. pylori* recurrence, reinfection rates or the impact of eradication on gastric cancer risk.

CONCLUSIONS

In this NMA, triple therapy (RAC-7) showed the highest probability as the most effective treatment. However, dual therapy demonstrated comparable efficacy, compliance and a more favourable safety profile in pairwise meta-analyses. The SUCRA rankings further underscore dual therapy (VA-7 and VA-10) as a competitive alternative to rabeprazole-based triple therapy and quadruple therapy. Given its simplified administration and lower incidence of adverse events, dual therapy has emerged as a promising first-line option. However, further RCTs across diverse populations are required to validate these findings.

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