Systematic Review/Meta-Analysis

Vonoprazan-amoxicillin dual therapy for *Helicobacter pylori* eradication: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Vonoprazan-amoxicillin (VA) dual therapy has recently been proposed to eradicate *Helicobacter pylori* (*H. pylori*) with controversial results. We, therefore, conducted a meta-analysis to assess the effect of this therapy for *H. pylori* eradication.

Methods: We searched PubMed, Embase, Cochrane Library, and Web of Science database from inception until November 2022, collecting randomized controlled trials (RCTs) comparing VA dual therapy with other regimens for *H. pylori* eradication. Pooled relative risks (RRs) were calculated using random effects model.

Results: Five RCTs were ultimately included. Compared with the vonoprazan-amoxicillin-clarithromycin (VAC) triple therapy, the eradication rate of VA dual therapy was lower in intention-to-treat (ITT) analysis (n = 3 RCTs, RR = 0.94, 95% CI: 0.88–0.99, $P = 0.03$), but there was no significant difference between them in the per-protocol (PP) analysis (RR = 0.96, 95% CI: 0.91–1.01, $P = 0.11$). For clarithromycin-resistant *H. pylori* strains, the eradication rate of VA dual therapy was significantly higher than that of the VAC triple therapy (n = 2 RCTs, RR = 1.20, 95% CI: 1.03–1.39, $P = 0.02$). Compared with the PPI-based triple therapy (PAC), VA dual therapy had a superior eradication rate (n = 2 RCTs, ITT analysis: RR = 1.13, 95% CI: 1.04–1.23, $P = 0.003$; PP analysis: pooled RR = 1.14, 95% CI: 1.06–1.22, $P = 0.0004$). Compared with VAC or PAC triple therapy, VA dual therapy has a similar incidence of total adverse events and compliance.

Conclusions: VA dual therapy had a similar effect compared to VAC triple therapy and was superior to PAC triple therapy. Future RCTs are needed to ascertain the optimal dosage and duration of vonoprazan and amoxicillin, and the effect of VA dual therapy compared with the mainstream regimens recommended by current guidelines.

Keywords: Amoxicillin, Dual therapy, *Helicobacter pylori*, Meta-analysis, Vonoprazan

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INTRODUCTION

Helicobacter pylori (*H. pylori*) has become a worldwide bacterial infection, with an infection rate exceeding 50 percent of the world's population.[1] It is widely accepted that *H. pylori* infection is associated with several conditions, such as non-ulcer dyspepsia, gastritis, peptic ulcer disease, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma.[2,3] Eradication of the *H. pylori* can effectively control their progress and reduce the risk of the above related diseases.

For a long time, the standard triple therapy, which consists of a proton-pump inhibitor (PPI) and two antibiotics (amoxicillin and clarithromycin/metronidazole), has been recommended as the first-line treatment for *H. pylori* eradication.[4] Unfortunately, the eradication rate of the standard triple therapy has been unsatisfactory due to the increasing resistance to antibiotics, especially clarithromycin and metronidazole.[5,6] To improve the eradication rate, recent guidelines[3,7-9] recommend several therapies, including bismuth-containing quadruple therapy (BQT), concomitant therapy (CT), sequential therapy (ST), or hybrid therapy. Nevertheless, these therapies contain two–three kinds of antibiotics for 10–14 days, which has several disadvantages: more adverse events, high cost, and poor compliance. Hence, it is necessary to develop new regimens and strategies that allow for minimal antibiotic usage and a shortened treatment period while still achieving satisfactory eradication rates.

Recently, dual therapy composed of a PPI and amoxicillin has attracted increasing attention. However, the efficacy of this therapy was not satisfactory in many studies, which may be partly attributed to inadequate inhibition of gastric acid, leading to the inability to obtain a high pH state (pH >6) in the stomach, thus making *H. pylori* insensitive to amoxicillin.[10,11] Vonoprazan, a new potassium-competitive acid blocker (P-CAB), has been widely used to cure acid-related disorders and *H. pylori* eradication in Japan. In comparison with PPI, vonoprazan has been demonstrated to be more effective in terms of gastric acid suppression, as it is faster and stronger and provides a longer-lasting effect.[12,13] Thus, it is anticipated that vonoprazan will exhibit greater efficacy compared to PPI in conjunction with amoxicillin for the treatment of *H.pylori* eradication. In Japan, the most frequently administered treatment for anti-*H. pylori* is the vonoprazan-amoxicillin-clarithromycin (VAC) triple therapy, which garners over one million prescriptions annually.[14] However, the prevalence of clarithromycin resistance in *H. pylori* is significantly high.[5] The utilization of VA dual therapy in the eradication of *H. pylori* is expected to yield satisfactory results and presents the benefit of reducing the amount of antibiotics required.[14,15]

To date, two previous meta-analyses[15,16] have suggested that VA dual therapy and VAC triple therapy have similar effects. However, these previous two meta-analyses incorporated data from non-randomized controlled trials (NRCTs) with low levels of evidence, which weakened the accuracy and reliability of the findings. In addition, these meta-analyses did not compare the effects of VA dual therapy and PPI-based triple therapy (PAC). Therefore, we conducted a meta-analysis that included only randomized controlled trials (RCTs) to assess the efficacy and safety of VA dual therapy versus other therapies for *H. pylori* eradication.

MATERIALS AND METHODS

The protocol of this review was registered in advance on PROSPERO platform (registration number: CRD42022374802). This systematic review and meta-analysis were conducted according to the latest Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[17]

Data sources and literature search

The literature search was conducted in PubMed, Embase, the Cochrane library, and Web of Science database using pre-established search terms, from inception to November 10, 2022, without language restrictions. The search terms were as follow: "helicobacter pylori," "campylobacter pylori," "*H.pylori*," "Hp," amoxicillin, amoxycillin, vonoprazan, vonaprazan, "TAK-438," "TAK438," "TAK 438," takecab, "potassium-competitive," and "potassium competitive." We used MeSH headings and text word terms searching. The reference lists of relevant systematic reviews and included studies were also hand-searched for additional relevant studies. The details of search strategies for all databases are presented in the online Supplementary Table S1.

Study selection

Two reviewers independently evaluated studies by examining titles and abstracts and identified full texts of relevant studies that fulfilled the established criteria for inclusion and exclusion. In the event of any overlapping studies, only the study with the most comprehensive data was considered for inclusion. Discrepancies were addressed through discussion. Data from studies with multiple arms were combined to form a new study group and a new control group that met the inclusion criteria.

The criteria for inclusion were as follows: (a) participants: *H.pylori*-infected adult patients, without a history of *H. pylori* eradication, *H. pylori* infection was confirmed by one or more of the following tests: urea breath test (UBT), rapid urease test (RUT), *H. pylori* stool antigen, culture, or histology; (b) intervention: VA dual therapy, without restriction on the dose and duration; (c) comparator: including vonoprazan-based triple therapy (VAC): vonoprazan + amoxicillin + clarithromycin, PPI-based triple therapy (PAC): PPI + amoxicillin + clarithromycin, VA dual therapy with different doses and durations; (d) outcomes: (i) primary outcome: *H.pylori* eradication rate, confirmation of *H. pylori* eradication was done by above generally accepted methods at least four weeks after completion of treatment; (ii) secondary outcomes: adverse events and compliance; (e) study design: RCTs. The criteria for exclusion were the following: (a) non-RCTs, conference abstracts, comments, editorials, letters, trial protocol, animal studies, guidelines, reviews, and meta-analyses; (b) studies without full-text or sufficient data; (c) duplicate publications; and (d) ongoing trials.

Data extraction

Two reviewers independently extracted the data from eligible studies using a predesigned data extraction form, and resolved any discrepancies through discussion. The extracted information was as follows: the first author, publication year, publication journal, study country, study design (multicenter or single-center RCT), participant characteristics, total sample size, specific details of eradication regimens (dosage, frequencies, and duration), diagnostic tests to ascertain *H.pylori* infection before and after eradication, time after eradication for confirming the test results, data relating to the eradication rate, adverse events, and compliance.

Risk of bias and evidence appraisal

Two reviewers independently appraised the risk of bias of each study and quality of evidence, with any disagreements resolved through discussion. The risk of bias of eligible studies was appraised using the Cochrane risk of bias tool.[18] The quality of evidence was appraised using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system with the use of the Profiler software (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, which considers risk of bias, imprecision, inconsistency, indirectness, and publication bias of the included studies.[19]

Statistical analysis

The Review Manager software (Version 5.3, The Cochrane Collaboration, Copenhagen, Denmark) was used to calculate summary relative risk (RR) with 95% confidence intervals (CI) for each study. To be more conservative in our estimate, we utilized the random effects model to pool the data.[20] The data were evaluated using both intention-to-treat (ITT) and per-protocol (PP) analysis to determine the *H.pylori* eradication rate. The statistical heterogeneity was evaluated using Q tests and I^2 statistic. $P<0.10$ was determined to be statistically significant for the Q test. Heterogeneity can be categorized as insignificant, low, moderate, and high based on I^2 values from 0 to 25%, 26 to 50%, 51 to 75%, and more than 75%, respectively.[21] For *H. pylori* eradication rate, if there was heterogeneity, subgroup analyses based on ITT data were further utilized to explore potential sources of heterogeneity and possible factors affecting the overall results. To confirm the robustness of the results, sensitivity analyses were conducted by using the fixed-effects model and omitting one study at a time. If sufficient primary studies were included ($n \geq 10$),[22] the possibility of publication bias was assessed by visual funnel plots and Egger's test[23] using STATA/SE 12.0 (STATA Corporation, Texas, USA). The results were considered statistically significant with two-sided P values <0.05.

RESULTS

Literature search results and study selection process

A total number of 785 records were identified through a systematic search of four electronic databases. After removing 325 duplicates, 460 records were further screened by titles and abstracts, 38 articles of which were selected for consideration by full-text evaluation. Finally, five RCTs[24-28] were included based on inclusion and exclusion criteria. The PRISMA flowchart depicting the selection process of studies is displayed in Figure 1. The details of the excluded studies are shown in the online Supplementary Table S2.

Study characteristics of included studies

As given in Table 1, five studies were conducted between 2020 and 2022. Among these studies, two studies[26,27] were conducted in China, one in Japan,[24] one in the United States and Europe,[24] and one in Pakistan.[28] Of the five studies, three were multicenter RCTs,[24,25,27] two of which[24,25] were published in GUT and Gastroenterology, the top journals for digestive diseases. The sample sizes ranged from 119 to 1046. Three studies[25-27] included multiple trial arms. Regarding interventions administered, three studies[24,25,27] compared VA dual therapy to VAC triple therapy, two studies[25,28] compared VA dual therapy to PAC triple therapy, one study[26] evaluated the efficacy of VA dual therapy with two different amoxicillin doses (low

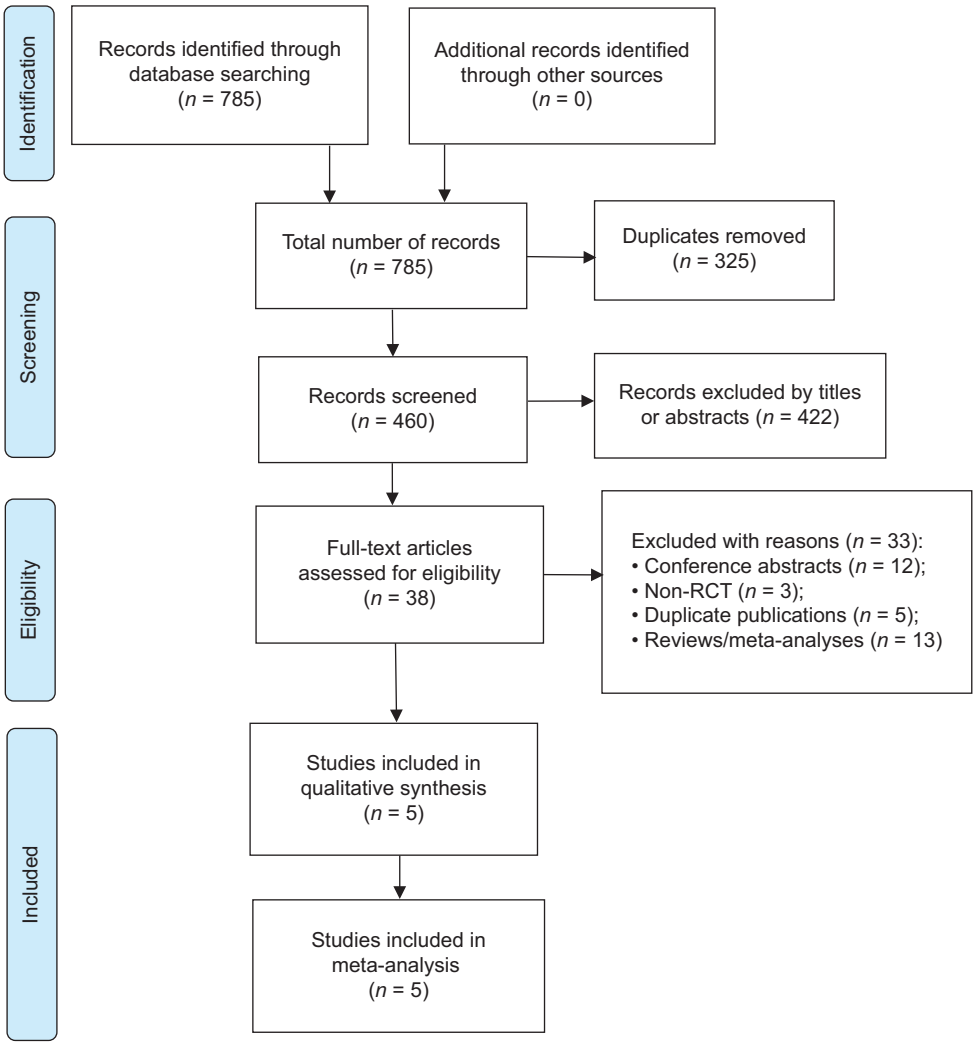

Figure 1: PRISMA flowchart of the study selection process

dose: 1 g bid. vs. high dose: 1 g tid) and two different durations (7 days vs. 10 days). The durations of VA dual regimen were 7–14 days.

Risk of bias

All studies reported random sequence generation methods (computer-generated randomization and random number table). One study[25] reported the method of allocation concealment (centralized distribution). Three studies[24,25,27] were open-label trials. One study[25] was funded by Phathom Pharmaceuticals. The details of the risk of bias assessment were presented in online Supplementary Figures S1 and S2.

VA dual therapy versus VAC triple therapy

Primary Outcome: H. pylori eradication rate

Three multicenter RCTs[24,25,27] with 1263 patients (686 in the VA dual therapy group and 577 in the VAC triple therapy group) reported data on *H. pylori* eradication rate. In the ITT analysis, the eradication rate of the VA dual therapy group was significantly lower than that of the VAC triple therapy group (72.2% vs. 79.5%, pooled RR = 0.94, 95% CI: 0.88-0.99, $P = 0.03$) with no significant heterogeneity ($I^2 = 0\%$, $P = 0.71$) [Figure 2]. However, in the PP analysis, there was no significant difference in eradication rate between the VA dual therapy group and VAC triple therapy group (78.6% vs. 84.8%, pooled RR = 0.96, 95% CI: 0.91–1.01, $P = 0.11$) with no significant heterogeneity ($I^2 = 0\%$, $P = 0.83$) [Figure 3].

Two RCTs[24,25] provided data on clarithromycin-resistant strains. The clarithromycin resistance rates of VA dual and VA triple therapy were 20.8% and 24.2%, respectively. Among individuals with clarithromycin-resistant strains, the eradication rate of the VA dual therapy group was significantly higher than that of the VAC triple therapy group (85.5% vs. 71.0%, pooled RR = 1.20, 95% CI: 1.03–1.39, $P = 0.02$) with no significant heterogeneity ($I^2 = 0\%$, $P = 0.87$) [Figure 4].

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

Study	Country	Publication Journal	Study design	No. of patients (Exp/Con)	VA group	Control group	*H. pylori* detection methods (Initial/Rechecking)
Suzuki (2020) [24]	Japan	Gut	Multicenter RCT	335 (168/167)	Vonoprazan 20 mg bid, amoxicillin 750 mg bid, 7 days	VAC group: vonoprazan 20 mg bid, amoxicillin 750 mg bid, clarithromycin 200 mg bid, 7 days	Culture/UBT
Chey (2022) [25]	United States and Europe	Gastroenterology	Multicenter RCT	1046 (349/349/348)	Vonoprazan 20 mg bid, amoxicillin 1 g tid, 14 days	VAC group: vonoprazan 20 mg bid, amoxicillin 1 g bid, clarithromycin 500 mg bid, 14 days; PAC group: lansoprazole 30 mg bid, amoxicillin 1 g bid, clarithromycin 500 mg bid, 14 days	UBT + histology, culture/UBT
Hu (2022) [26]	China	Helicobacter	Single-center RCT	119 (21/24/37/37)	H-VA-7: vonoprazan 20 mg bid, amoxicillin 1 g tid, 7 days; L-VA-7: vonoprazan 20 mg bid, amoxicillin 1 g bid, 7 days	H-VA-10: vonoprazan 20 mg bid, amoxicillin 1000 mg tid, 10 days; L-VA-10: vonoprazan 20 mg bid, amoxicillin 1000 mg bid, 10 days	UBT, histology/UBT
Lin (2022) [27]	China	Annals of Translational Medicine	Multicenter RCT	230 (85/84/61)	H-VA-7: Vonoprazan 20 mg bid, amoxicillin 750 mg qid, 7 days; L-VA-7: vonoprazan 20 mg bid, amoxicillin 500 mg qid, 7 days	VAC group: vonoprazan 20 mg bid, amoxicillin 750 mg bid, clarithromycin 500 mg bid, 7 days	UBT/UBT
Zuberi (2022) [28]	Pakistan	Pakistan Journal of Medical Sciences	Single-center RCT	192 (96/96)	Vonoprazan 20 mg bid, amoxicillin 1 g bid, 14 days	PAC group: omeprazole 20 mg bid, amoxicillin 1 g bid, clarithromycin 500 mg bid, 14 days	SAT, histology/SAT

Notes: Exp, VA (vonoprazan-amoxicillin) group; Con, control group; RCT, randomized controlled trials; bid, twice daily; tid, three times daily; qid, four times daily; H-VA; high-dose amoxicillin (3000 mg/day) combined with vonoprazan; L-VA; low-dose amoxicillin (2000 mg/day) combined with vonoprazan; VAC, vonoprazan + amoxicillin + clarithromycin; PAC, proton-pump inhibitor (PPI) + amoxicillin + clarithromycin; UBT, urea breath test; SAT, stool antigen test

Based on data from ITT analysis, we conducted subgroup analyses to explore the impact of antibiotic doses and durations of treatment of VA dual therapy on the results. In subgroup analysis based on different doses of amoxicillin of VA dual therapy [Figures S3], there was no significant difference in eradication rate between VA dual therapy and VAC triple therapy in high-dose amoxicillin subgroup (n = 2 RCTs, pooled RR = 0.93, 95% CI: 0.86–1.01, $P = 0.07$) and low-dose amoxicillin subgroup (n = 2 RCTs, pooled RR = 0.95, 95% CI: 0.88–1.03, $P = 0.19$). In subgroup analysis based on duration of VA dual therapy [Figures S4], the eradication rate of VA dual therapy was significantly lower than that of the VAC triple therapy in 14-day subgroup (n = 1 RCT, pooled RR = 0.92, 95% CI: 0.84–1.00, $P = 0.05$), while there was no significant difference between them in 7-day subgroup (n = 2 RCTs, pooled RR = 0.95, 95% CI: 0.88-1.03, $P = 0.24$). The results of subgroup analyses are presented in Table 2.

We further performed sensitivity analyses based on ITT analysis data. As shown in the online Supplementary Table S3, when using fixed-effect model, the result was consistent with that of the random effect model. When conducting sensitivity analyses by omitting one study at a time and combining the remaining studies, the results showed that when Suzuki *et al.*[24] and Chey *et al.*[25] are omitted, respectively, there is no statistical difference in eradication rate between VA dual therapy and VAC triple therapy, which indicates that the results of sensitivity analyses are relatively unstable.

Secondary outcomes: total adverse events and compliance

Three RCTs[24,25,27] provided data on the incidence of total adverse events and compliance. The incidence of total adverse events of the VA dual therapy group was lower than that of the VAC triple therapy group (25.8% vs. 32.0%), but no significant difference was observed (pooled RR = 0.86,

Table 2: Results of subgroup analyses of eradication rates of VA dual versus VAC triple therapy

Subgroups	No. of studies	Sample size	RR (95%CI)	P_{effect}	I^2 (%)	$P_{heterogeneity}$
Different doses of amoxicillin of VA dual therapy						
High-dose amoxicillin (3000 mg/day)	2	844	0.93 (0.86–1.01)	0.07	0	0.33
Low-dose amoxicillin (≤2000 mg/day)	2	480	0.95 (0.88–1.03)	0.19	0	0.91
Duration of VA dual therapy						
7 days (Asia)	2	565	0.95 (0.88–1.03)	0.24	0	0.60
14 days (Europe and USA)	1	698	0.92 (0.84–1.00)	0.05	-	-

RR, relative risk; CI, confidence interval; VA, VAC, vonoprazan + amoxicillin; VAC, vonoprazan + amoxicillin + clarithromycin

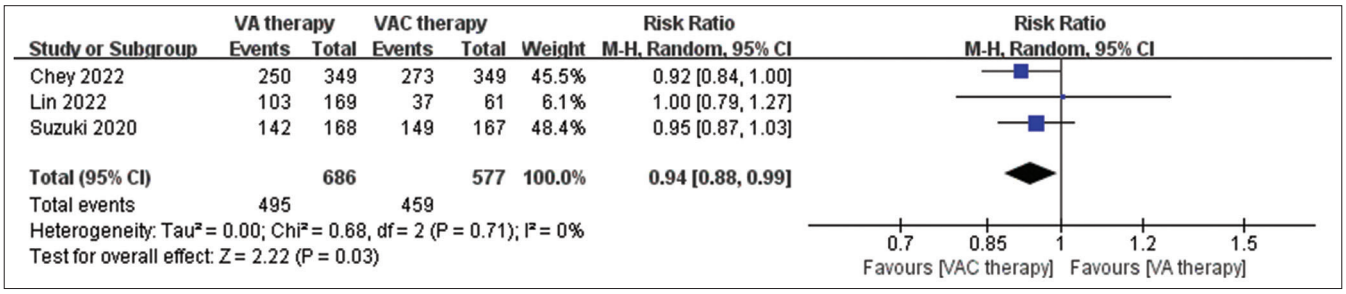

Figure 2: Forest plot of *H. pylori* eradication rate of VA dual therapy versus VAC triple therapy in ITT analysis. VA, vonoprazan + amoxicillin; VAC, vonoprazan + amoxicillin + clarithromycin; ITT, intention-to-treat

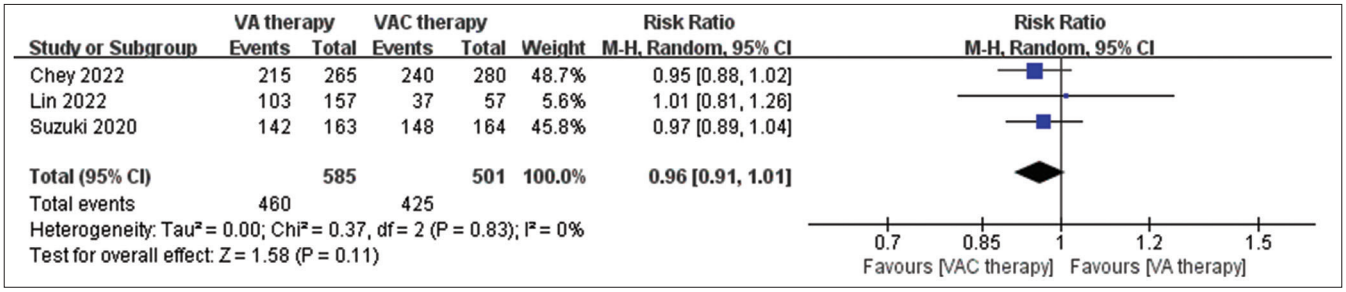

Figure 3: Forest plot of *H. pylori* eradication rate of VA dual therapy versus VAC triple therapy in PP analysis. VA, vonoprazan + amoxicillin; VAC, vonoprazan + amoxicillin + clarithromycin; PP, per-protocol

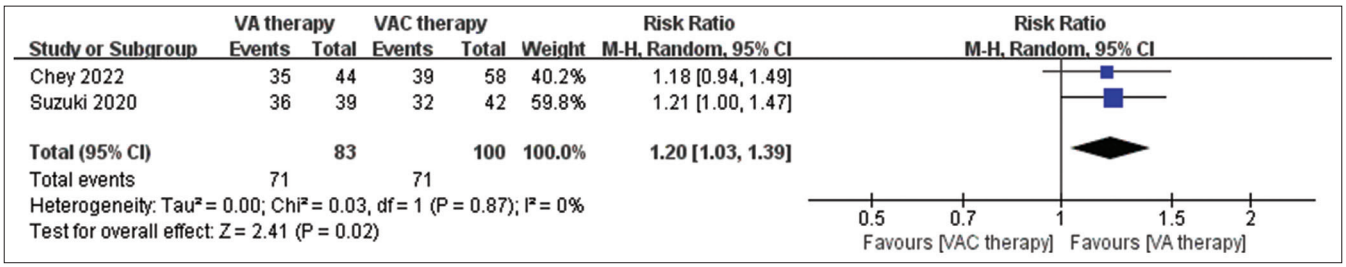

Figure 4: Forest plot of *H. pylori* eradication rate of VA dual therapy versus VAC triple therapy in clarithromycin-resistant strains. VA, vonoprazan + amoxicillin; VAC, vonoprazan + amoxicillin + clarithromycin

95% CI: 0.72–1.02, $P = 0.08$). No significant statistical heterogeneity was observed ($I^2 = 0\%$, $P = 0.54$) [Figure S5]. Similar result was observed in compliance (85.6% vs. 86.8%, pooled RR = 0.98, 95% CI: 0.95–1.02, $P = 0.39$) with low statistical heterogeneity ($I^2 = 23\%$, $P = 0.27$) [Figure S6].

VA dual therapy versus PAC triple therapy

Primary Outcome: H. pylori eradication rate

Two RCTs[25,28] with 889 patients (445 in the VA dual therapy group and 444 in the PAC triple therapy group) reported data on *H. pylori* eradication rate. In the ITT analysis, the eradication rate of VA dual therapy group was significantly higher than that of the PAC triple therapy group (75.5% vs. 67.3%, pooled RR = 1.13, 95% CI: 1.04–1.23, $P = 0.003$) with no significant heterogeneity ($I^2 = 0\%$, $P = 0.42$) [Figure 5]. A similar result was observed in PP analysis (84.3% vs. 73.4%, pooled RR = 1.14, 95% CI: 1.06–1.22, $P = 0.0004$) with no significant heterogeneity ($I^2 = 0\%$, $P = 0.57$) [Figure 6].

Secondary outcomes: total adverse events and compliance

Two RCTs[25,28] provided data on the incidence of total adverse events and compliance. The incidence of total adverse events of the VA dual therapy group was lower than that of the PAC triple therapy group (26.1% vs. 34.5%), but no significant difference was observed (pooled RR = 0.59, 95% CI: 0.25–1.38, $P = 0.22$). High statistical heterogeneity was observed ($I^2 = 86\%$, $P = 0.007$) [Figure S7]. A similar result was observed in compliance (80.2% vs. 82.0%, pooled RR = 1.00, 95% CI: 0.90–1.13, $P = 0.93$) with high statistical heterogeneity ($I^2 = 77\%$, $P = 0.04$) [Figure S8].

Comparison of different doses of amoxicillin and duration of VA dual therapy

To optimize VA dual therapy, two RCTs[26,27] compared the effects of 7-day high-dose amoxicillin (3000 mg/day,

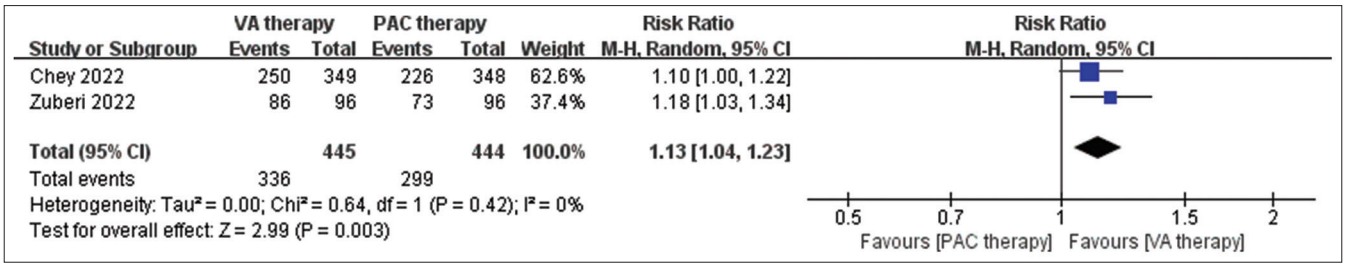

Figure 5: Forest plot of *H. pylori* eradication rate of VA dual therapy versus PAC triple therapy in ITT analysis.VA, vonoprazan + amoxicillin; PAC, PPI + amoxicillin + clarithromycin, ITT, intention-to-treat

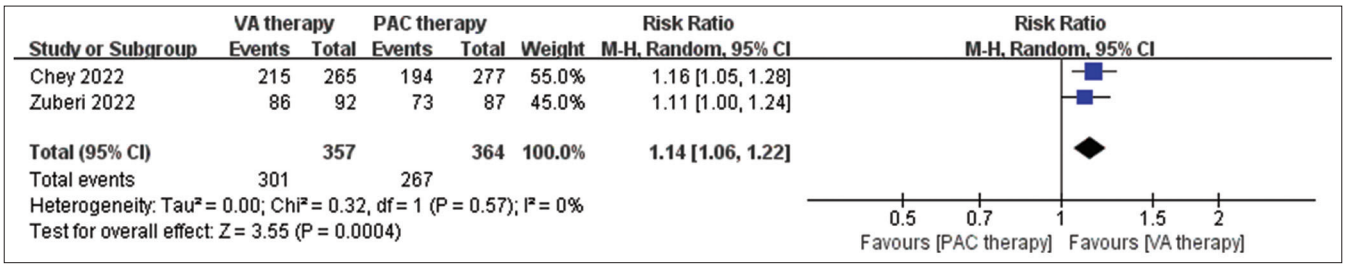

Figure 6: Forest plot of *H. pylori* eradication rate of VA dual therapy versus PAC triple therapy in PP analysis.VA, vonoprazan + amoxicillin; PAC, PPI + amoxicillin + clarithromycin, PP, per-protocol

H-VA-7) group and 7-day low-dose amoxicillin (2000 mg/day, L-VA-7) group. In the ITT analysis, there was no significant statistical difference in eradication rate between the H-VA-7 group and L-VA-7 group (67.0% vs. 60.2%, pooled RR = 1.13, 95% CI: 0.92–1.38, $P = 0.24$) with no significant heterogeneity ($I^2 = 0\%$, $P = 0.61$) [Figure S9]. Similar result was observed in PP analysis (68.3% vs. 67.7%, pooled RR = 1.02, 95% CI: 0.85–1.23, $P = 0.81$) with no significant heterogeneity ($I^2 = 0\%$, $P = 0.54$) [Figure S10]. Regarding the incidence of total adverse events, there was also no significant statistical difference between H-VA-7 group and L-VA-7 group (18.3% vs. 14.0%, pooled RR = 1.32, 95% CI: 0.70–2.49, $P = 0.39$) with no significant heterogeneity ($I^2 = 0\%$, $P = 0.88$) [Figure S11]. One small sample study[26] was conducted to explore the effect of the combination of vonoprazan (20 mg bid) with two different doses of amoxicillin (1 g bid vs. 1 g tid) and different durations of treatment (7 days vs. 10 days). This single-center RCT from China included 119 individuals divided into four groups:(1) H-VA-10: high-dose amoxicillin (1000 mg tid) and vonoprazan for 10 days; (2) L-VA-10: low-dose amoxicillin (1000 mg bid) and vonoprazan for 10 days; (3) H-VA-7: high-dose amoxicillin (1000 mg tid) and vonoprazan for 7 days; (4) L-VA-7: low-dose amoxicillin (1000 mg bid) and vonoprazan for 7 days. In the ITT analysis, the eradication rate was 81.1% (30/37) for H-VA-10, 89.2% (33/37) for L-VA-10, 81.0% (17/21) for H-VA-7, and 66.7% (16/24) for L-VA-7. There were no significant differences of the eradication rate among the four groups. Similar results were observed in the PP analysis. The incidence of total adverse events was 24.3% for H-VA-10, 29.7% for L-VA-10, 23.8% for H-VA-7, and 16.7% for L-VA-7. No significant differences of total adverse events were observed among the four groups.

Quality of evidence

We applied the GRADE approach to assess the quality of evidence. For primary outcome (*H. pylori* eradication rate), the quality of evidence was appraised as moderate quality because of the risk of bias in the study design in all these comparisons. For secondary outcomes, the quality of the evidence was varied, ranging from very low to moderate, mainly caused by the risk of bias in study design, inconsistency, or imprecision. The online Supplementary Table S4 presents the details of the GRADE evidence summary for these outcomes.

DISCUSSION

In 2015, vonoprazan was approved for the purpose of eradicating *H. pylori* in Japan.[29] As mentioned previously, vonoprazan is a new P-CAB that suppresses H+/K+ ATPases in a rapid, strong, or stable manner, which produce a stronger and longer-lasting effect on gastric acid inhibition than PPIs.[12,13] Furthermore, the pharmacokinetic characteristics of this drug are not impacted by dietary habits or CYP2C19 polymorphism.[12,30] The strong acid inhibition effect of vonoprazan contributes to maintain a near-neutral pH in the stomach, thus making *H. pylori* sensitive to amoxicillin, which would contribute to the successful eradication of *H. pylori*.

In this study, we found that compared with VAC triple therapy, VA dual therapy had a lower eradication rate in ITT analysis (72.2% vs. 79.5%, RR = 0.94, 95% CI: 0.88–0.99). However, it is worth noting that the upper limit of the 95% CI is closely approaching the threshold of invalidity, suggesting that the difference in eradication rates between the two therapies may be negligible. Similarly, there is no significant difference in the eradication rate between them in PP analysis. Based on data from ITT analysis, we further analyzed the impact of amoxicillin doses and durations of treatment of VA dual therapy on the results. The results showed that VA dual and VAC triple therapies have similar eradication rates regardless of amoxicillin doses and durations of VA dual therapy. However, the pooled eradication rate of VA dual therapy was an unacceptable grade (＜80%) according to Graham's grading report card on *H. pylori* eradication.[31] Among three multicenter RCTs,[24,25,27] VA dual therapy had an acceptable eradication rate in ITT analysis (85%) and PP analysis (87%) in Japan; conversely, in the United States, Europe, and China, the eradication rate was unsatisfactory, particularly in China, where it was only 61% in ITT analysis. The unsatisfactory eradication rate could be attributable to different populations, doses, and durations of VA dual therapy. Hence, future research should focus on optimizing VA dual therapy for different populations.

Increasing antibiotic resistance brings great challenges to *H. pylori* eradication, and clarithromycin resistance is very common.[5,32] We therefore further analyzed the data on clarithromycin-resistant strains. The meta-analysis of two RCTs showed that VA dual therapy had a superior eradication rate compared to VAC triple therapy in clarithromycin-resistant strains (85.5% vs. 71.0%). The clarithromycin-resistant eradication difference could be attributed to the pharmacokinetic interaction of vonoprazan and clarithromycin. When vonoprazan is taken with clarithromycin, the maximum plasma concentration will increase, and the maximum pH level may rise or the duration of this effect may be extended. However, *H. pylori* grows in a restricted external pH range between 6 and 7 and is susceptible to growth-dependent amoxicillin. The interaction of vonoprazan-clarithromycin may lead to suboptimal gastric acid pH levels (i.e., higher than 7), thus reducing the *H. pylori* sensitivity to amoxicillin in the VAC triple therapy.[24]

In regions of low clarithromycin resistance, PAC triple therapy was recommended as the first-line empirical treatment.[3] Recently, Sun *et al.*[33] conducted a meta-analysis of six RCTs and showed that VAC triple therapy had superior eradication efficacy to PAC triple therapy. Our study found that compared with 14-day PAC triple therapy, VA dual therapy had a superior eradication rate based on both ITT and PP analysis. VA dual therapy has less antibiotic usage compared to PAC triple therapy.

In our meta-analysis, the incidence of adverse events and compliance of VA dual therapy were also assessed. Compared with VAC or PAC triple therapy, the incidence of adverse events and compliance of VA dual therapy were lower, but there were no significant differences between them. In view of the small number of included studies, more large sample studies are needed to explore safety and compliance in the future.

Previously, Ouyang *et al.*[15] performed a smaller meta-analysis that included one RCT[24] and two NRCTs[34,35] and demonstrated that there was no significant difference in eradication rate between the VA dual and VAC triple therapy. A similar result was observed in the incidence of adverse events between them. Subsequently, Wang *et al.*[16] conducted a meta-analysis which included 1490 patients from seven studies, and the results also indicated that there was no significant difference in the eradication rate between VA dual and VAC triple therapy (ITT analysis: 82.8% vs. 84.6%; PP analysis: 84.8% vs. 87.0%). However, the incidence of adverse events of the VA dual therapy was lower than that of the VAC triple therapy. In addition, their study also showed that the eradication rate of clarithromycin-resistant strains in the VA dual therapy was higher than that in the VAC triple therapy. This latter meta-analysis contained all the studies included in the former meta-analysis. Notably, this latter meta-analysis included three small sample size conference abstracts[36-38] from the same first author, who subsequently published a slightly larger retrospective study in 2020.[34] We think that the meta-analysis may include duplicate articles, which could affect the reliability of the results.

Compared with two previous meta-analyses, our meta-analysis did not include NRCTs and these possibly published repeated conference abstracts;[36-38] instead, it encompassed three additional newly published RCTs[26-28] in 2022. Our meta-analysis only included data from RCTs, providing more high-quality evidence on the topic. In addition, our study also provides several findings that have been not reported in previous studies. For one thing, our study found that VA dual therapy was superior to PAC triple therapy. However, the number of studies conducted is limited, thus further research is necessary to confirm its efficacy in regions with low clarithromycin resistance. Secondly, our study compared the efficacy of different doses of amoxicillin and the duration of VA dual therapy,

where two Chinese studies[26,27] with small sample sizes revealed that there was no significant difference between the 7-day high-dose and low-dose group, and its eradication rate was unsatisfactory. This implied that 7-day VA dual therapy may not be suitable for China. Consequently, future research should focus on optimizing VA dual therapy.

To our knowledge, this is the first systematic review and meta-analysis to only include RCTs investigating the effect of VA dual therapy for *H. pylori* eradication. Our study was conducted with several strengths, such as registering on PROSPERO, employing a systematic search strategy, setting out clear selection criteria, assessing study quality rigorously, strictly adhering to the latest PRISMA statement for reporting, and utilizing the random effects model to merge data, thus making our findings more transparent and reliable.

Nonetheless, there are several limitations that should be taken into account in our meta-analysis. Firstly, many of the studies included had the risk of bias, including open-label trials (no blinding) and unclear allocation concealment, which may have a minimal effect on *H. pylori* eradication rate (as it is measured objectively), yet still have an influence on the secondary outcomes such as adverse events and compliance. Thus, well-designed RCTs are needed. Secondly, our meta-analysis included a limited number of RCTs in each analysis, lacking evidence of comparison of different doses of amoxicillin and different durations of VA dual therapy. Furthermore, there is no relevant clinical trial regarding VA dual therapy versus other regimens recommended by the guidelines, such as BQT, CT, and ST. Further large-sample, high-quality RCTs should be conducted focusing on these circumstances to assess the eradication effect of VA dual therapy on *H. pylori*. Thirdly, a few studies did not provide information on antibiotic resistance, which may have a certain impact on the overall results. Fourthly, our study focuses on VA dual therapy as the first-line treatment for *H. pylori* infection, and no clinical trial was conducted to evaluate the effectiveness of VA dual therapy as a rescue treatment for *H. pylori*. Therefore, future studies should explore the effect of VA dual therapy in treating this condition. Fifthly, since this regimen contains amoxicillin, it is not appropriate for those with an allergy to penicillin. Sixthly, the frequency of administration (bid, tid, qid) and doses of amoxicillin are different in the studies included. In view of the limited number of studies, we are unable to evaluate their impact on the eradication rate. A large number of clinical trials are currently underway on the optimization of VA dual regimens. We look forward to timely updating our evidence after more relevant studies are published in the near future. Finally, due to the limited number of studies included, we did not conduct the publication bias test, thus the possibility of publication bias cannot be completely ruled out. Despite the aforementioned limitations, we are confident in our findings and provide the most recent, high-quality evidence on the effect of VA dual therapy in *H. pylori* eradication in clinical practice.

As discussed previously, antibiotic resistance is still the most significant obstacle to successful *H. pylori* eradication.[5,32,39] Two recent studies[39,40] have demonstrated that the rate of resistance to clarithromycin, metronidazole, and levofloxacin surpasses 30% in both the United States and China. However, there has been a decrease in the development of new antibiotic drugs in the past few years.[41] Hence, the findings of our meta-analysis have important implications for clinical practice. Compared with VAC or PAC triple therapy, VA dual therapy, which contains only one antibiotic, is simpler and uses fewer drugs. More importantly, this therapy can avoid unnecessary usage of clarithromycin and prevent widespread antibiotic resistance.

In view of the limitation of the quantity and quality of studies included, and with the current eradication rate of VA dual therapy which still varies among studies, our study also provides some insights for future research in this area. Future research is required to address the following questions. First and foremost, future trials should further optimize the dose and duration of VA dual therapy in different regions, particularly in China, since the *H. pylori* eradication rate of the previous two small sample-size studies on VA dual therapy in China was not acceptable. Second, future trials should evaluate the effect of VA dual therapy compared with the mainstream regimens recommended by the current guidelines. Third, future trials should explore the effect of VA dual therapy as the second or third-line treatment for *H. pylori* infection.

In conclusion, VA dual therapy had a similar eradication effect compared to VAC triple therapy and was superior to PAC triple therapy. It has a similar incidence of adverse events and compliance compared to the VAC and PAC triple therapies. Owing to its simplicity and fewer antibiotic usage, VA dual therapy is an extremely promising therapeutic strategy for first-line *H. pylori* eradication. Nevertheless, the evidence is still limited. In the future, larger, more high-quality, multicenter RCTs are needed to ascertain the optimal dosage and duration of vonoprazan and amoxicillin and the efficacy and safety of VA dual therapy compared with the mainstream regimens recommended by the current guidelines.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary online materials

Table S1 Search strings and results (from inception to November 10, 2022)

Databases	Search strings	Results
PubMed	("helicobacter"[MeSH Terms] OR helicobacter[tiab] OR "helicobacter pylori"[MeSH Terms] OR "helicobacter pylori"[tiab] OR "H.pylori"[tiab] OR "Hp"[tiab] OR "campylobacter pylori"[tiab]) AND (Vonoprazan[tiab] OR Vonaprazan[tiab] OR TAK-438[tiab] OR TAK438[tiab] OR TAK 438 [tiab] OR Takecab[tiab] OR "potassium-competitive"[tiab] OR (potassium AND competitive)[tiab]) AND ("amoxicillin"[MeSH Terms] OR amoxicillin[tiab] OR amoxycillin[tiab])	**112**
EMBASE	#1 'helicobacter'/exp OR helicobacter:ab,ti	77372
	#2 'helicobacter pylori'/exp OR 'helicobacter pylori':ab,ti	73230
	#3 'H.pylori':ab,ti OR 'Hp':ab,ti	79751
	#4 'campylobacter pylori':ab,ti	1180
	#5 #1 OR #2 OR #3 OR #4	11321
	#6 'Vonoprazan'/exp OR Vonoprazan:ab,ti	909
	#7 Vonaprazan:ab,ti	2
	#8 'tak-438':ab,ti OR 'tak 438':ab,ti OR 'tak438':ab,ti	38
	#9 Takecab:ab,ti	6
	#10 'potassium-competitive':ab,ti	555
	#11 #6 OR #7 OR #8 OR #9 OR #10	1103
	#12 'amoxicillin'/exp OR amoxicillin:ab,ti	79823
	#13 'amoxycillin'/exp OR amoxycillin:ab,ti	73037
	#14 #12 OR #13	80555
	#15 #5 AND #11 AND #14	**309**
Cochrane library	#1 MeSH descriptor: [Helicobacter] explode all trees	2078
	#2 (helicobacter):ti,ab,kw	5726
	#3 MeSH descriptor: [Helicobacter pylori] explode all trees	2074
	#4 (Helicobacter pylori):ti,ab,kw	5627
	#5 (H.pylori OR Hp):ti,ab,kw	6832
	#6 (campylobacter pylori):ti,ab,kw	95
	#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6	8612

	#8 (Vonoprazan):ti,ab,kw	296
	#9 (Vonaprazan):ti,ab,kw	3
	#10 (tak-438 OR tak 438 OR tak438):ti,ab,kw	49
	#11 (Takecab):ti,ab,kw	9
	#12 (potassium-competitive):ti,ab,kw	150
	#13 #8 OR #9 OR #10 OR #11 OR #12	383
	#14 MeSH descriptor: [amoxicillin] explode all trees	3021
	#15 (amoxicillin):ti,ab,kw	6242
	#16 (amoxycillin):ti,ab,kw	873
	#17 #14 OR #15 OR #16	6547
	#18 #7 AND #13 AND #17	**119**
Web of science	TS=(helicobacter OR "helicobacter pylori" OR "H.pylori" OR "Hp" OR "campylobacter pylori") AND TS=(Vonoprazan OR Vonaprazan OR TAK-438 OR TAK438 OR TAK 438 OR Takecab OR "potassium-competitive") AND TS=(amoxicillin OR amoxycillin)	**206**

Table S2. Description of excluded studies at the stage of eligibility according to the PRISMA flow chart.			
No.	**First author**	**Publication year**	**Reason for exclusion**
1.	Furuta	2016	Conference abstract
2.	Furuta	2016	Conference abstract
3.	Furuta	2017	Conference abstract
4.	Furuta	2017	Conference abstract
5.	Furuta	2018	Conference abstract
6.	Li	2018	Systematic review and meta-analysis
7.	Furuta	2019	Conference abstract
8.	Lyu	2019	Meta-analysis
9.	Putra	2019	Meta-analysis
10.	Sugimoto	2019	Review
11.	Suzuki	2019	conference abstract
12.	Azlina	2020	Systematic review and meta-analysis
13.	Furuta	2020	Non-RCT (observational study)
14.	Gatta	2020	Meta-analysis (Conference abstract)
15.	Gatta	2020	Meta-analysis (Conference abstract)
16.	Gotoda	2020	Non-RCT (observational study)
17.	Kasai	2020	Conference abstract
18.	Lee	2020	Meta-analysis (Conference abstract)
19.	Sanglutong	2020	Conference abstract
20.	Chey	2021	Conference abstract
21.	Eto	2021	Duplicate publication
22.	Gatta	2021	Meta-analysis (Conference abstract)
23.	Horii	2021	Duplicate publication
24.	Huang	2021	Meta-analysis
25.	Khoo	2021	Conference abstract
26.	Suzuki	2021	Duplicate publication
27.	Gao	2022	Non-RCT (observational study)
28.	Hu	2022	Duplicate publication
29.	Hu	2022	Duplicate publication
30.	Ouyang	2022	Systematic review and meta-analysis

31.	Ratana-Amornpin	2022	Conference abstract
32.	Wang	2022	Systematic review and meta-analysis
33.	Yin	2022	Systematic review and meta-analysis

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Table S3 Results of sensitivity analyses of eradication rates of VA dual versus VAC triple therapy (ITT data)

Sensitivity analyses	RR (95% CI)	P_{effect}	Heterogeneity
Using fixed-effect model	0.94(0.88-1.00)	0.04	I^2 = 0%, P = 0.71
Studies omitted			
Suzuki (2020)	0.93 (0.85-1.00)	0.06	I^2 = 0%, P =0.46
Chey (2022)	0.95 (0.88-1.03)	0.24	I^2 = 0%, P =0.60
Lin (2022)	0.93 (0.88-0.99)	0.02	I^2 = 0%, P =0.56

Table S4 GRADE evidence profile

VA dual therapy versus VAC triple therapy												
Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**VA**	**VAC**	**Relative (95% CI)**	**Absolute**		
***H. pylori* eradication rate-ITT analysis**												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	495/686 (72.2%)	459/577 (79.5%)	RR 0.94 (0.88 to 0.99)	48 fewer per 1000 (from 8 fewer to 95 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								78.2%		47 fewer per 1000 (from 8 fewer to 94 fewer)		
***H. pylori* eradication rate-PP analysis**												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	460/585 (78.6%)	425/501 (84.8%)	RR 0.96 (0.91 to 1.01)	34 fewer per 1000 (from 76 fewer to 8 more)	⊕⊕⊕O MODERATE	CRITICAL
								85.7%		34 fewer per 1000 (from 77		

										fewer to 9 more)		
***H. pylori* eradication rate-Clarithromycin-resistant strains**												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	71/83 (85.5%)	71/100 (71%)	RR 1.2 (1.03 to 1.39)	142 more per 1000 (from 21 more to 277 more)	⊕⊕⊕O MODERATE	CRITICAL
								71.7%		143 more per 1000 (from 22 more to 280 more)		
Total adverse events												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	174/675 (25.8%)	183/571 (32%)	RR 0.86 (0.72 to 1.02)	45 fewer per 1000 (from 90 fewer to 6 more)	⊕⊕OO LOW	IMPORTANT
								30.5%		43 fewer per 1000 (from 85 fewer to 6 more)		
Compliance												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	587/686 (85.6%)	501/577 (86.8%)	RR 0.98 (0.95 to 1.02)	17 fewer per 1000 (from 43 fewer to 17 more)	⊕⊕⊕O MODERATE	IMPORTANT

								93.4%		19 fewer per 1000 (from 47 fewer to 19 more)		
VA dual therapy versus PAC triple therapy												
Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**VA**	**PAC**	**Relative (95% CI)**	**Absolute**		
***H. pylori* eradication rate-ITT analysis**												
2	randomised trials	Serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	336/445 (75.5%)	299/444 (67.3%)	RR 1.13 (1.04 to 1.23)	88 more per 1000 (from 27 more to 155 more)	⊕⊕⊕O MODERATE	CRITICAL
								70.5%		92 more per 1000 (from 28 more to 162 more)		
***H. pylori* eradication rate-PP analysis**												
2	randomised trials	Serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	301/357 (84.3%)	267/364 (73.4%)	RR 1.14 (1.06 to	103 more per 1000 (from 44 more to 161	⊕⊕⊕O MODERATE	CRITICAL

									1.22)	more)		
								77%		108 more per 1000 (from 46 more to 169 more)		
Total adverse events												
2	randomised trials	Serious[4]	Serious[5]	no serious indirectness	serious[3]	none	116/444 (26.1%)	152/441 (34.5%)	RR 0.59 (0.25 to 1.38)	141 fewer per 1000 (from 259 fewer to 131 more)	⊕OOO VERY LOW	IMPORTANT
								34.4%		141 fewer per 1000 (from 258 fewer to 131 more)		
Compliance												
2	randomised trials	Serious[4]	Serious[6]	no serious indirectness	no serious imprecision	none	357/445 (80.2%)	364/444 (82%)	RR 1 (0.9 to 1.13)	0 fewer per 1000 (from 82 fewer to 107 more)	⊕⊕OO LOW	IMPORTANT
								85.1%		0 fewer per 1000 (from 85 fewer to 111 more)		
Different doses of amoxicillin and duration of VA dual therapy												

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**7-day high-dose group**	**7-day low-dose group**	**Relative (95% CI)**	**Absolute**		
***H. pylori* eradication rate-ITT analysis**												
2	randomised trials	Serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	71/106 (67%)	65/108 (60.2%)	RR 1.13 (0.92 to 1.38)	78 more per 1000 (from 48 fewer to 229 more)	⊕⊕⊕O MODERATE	CRITICAL
								62.5%		81 more per 1000 (from 50 fewer to 237 more)		
***H. pylori* eradication rate-PP analysis**												
2	randomised trials	Serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	71/104 (68.3%)	65/96 (67.7%)	RR 1.02 (0.85 to 1.23)	14 more per 1000 (from 102 fewer to 156 more)	⊕⊕⊕O MODERATE	CRITICAL
								69.5%		14 more per 1000 (from 104 fewer to 160		

										more)		
Total adverse events												
2	randomised trials	Serious[7]	no serious inconsistency	no serious indirectness	Serious[3]	none	19/104 (18.3%)	14/100 (14%)	RR 1.32 (0.7 to 2.49)	45 more per 1000 (from 42 fewer to 209 more)	⊕⊕OO LOW	
								14.9%		48 more per 1000 (from 45 fewer to 222 more)		

[1] Unclear allocation concealment (2 trials), no blinding (3 trials), other bias (1 trial).

[2] Unclear allocation concealment (1 trial), no blinding (2 trials), other bias (1 trial).

[3] Confidence interval (CI) is relatively wide,without excluding appreciable benefit or harm.

[4] Unclear allocation concealment (1 trial), no or unclear blinding (2 trials), other bias (1 trial).

[5] $I^2 = 86\%$.

[6] $I^2 = 77\%$.

[7]Unclear allocation concealment (2 trials), no or unclear blinding (2 trials).

Figure S1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

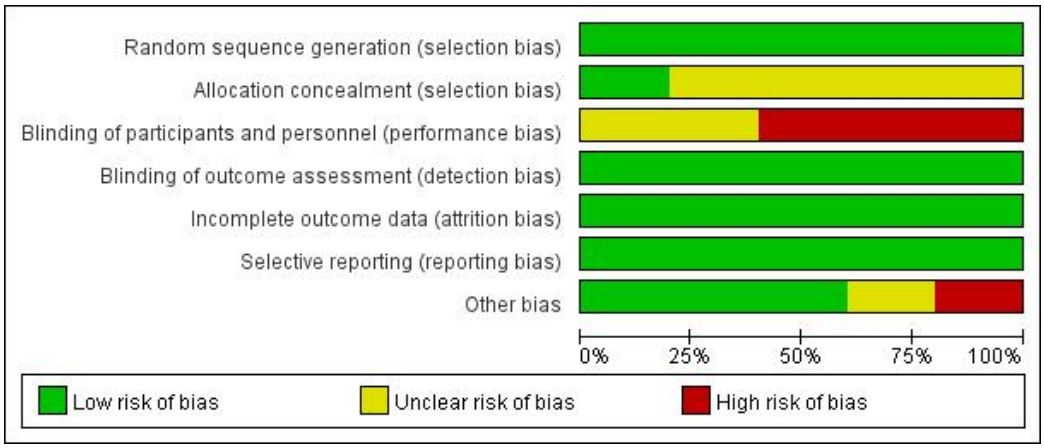

Figure S2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

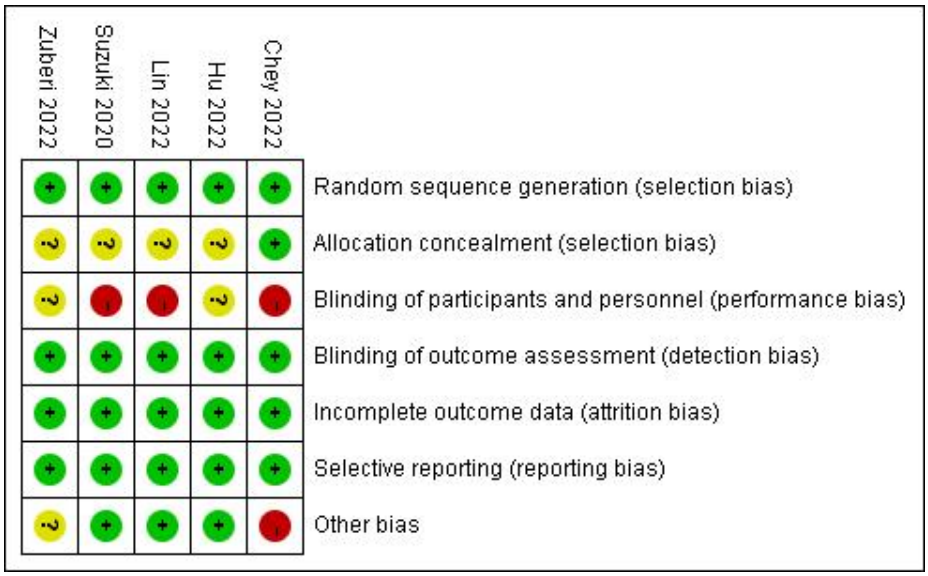

Figure S3. Forest plot of subgroup analysis based on different doses of amoxicillin of VA dual therapy in *H. pylori* eradication rate. VA, vonoprazan+amoxicillin.

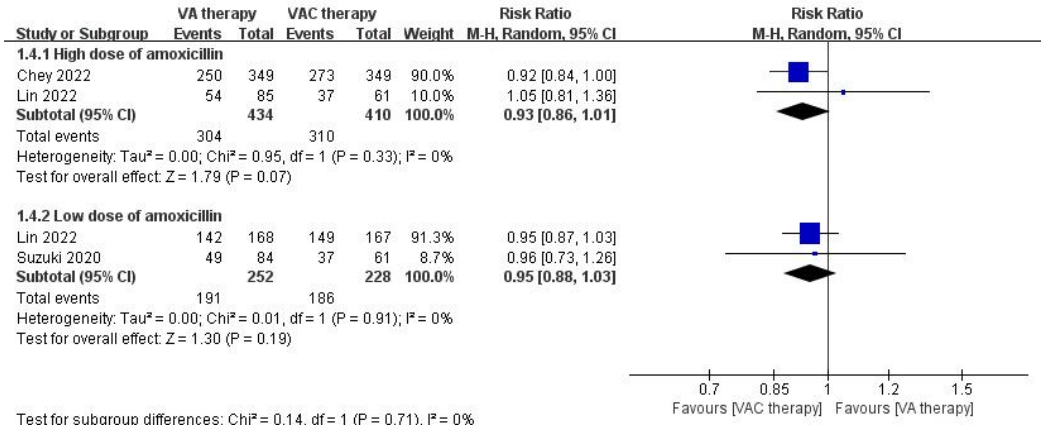

Figure S4. Forest plot of subgroup analysis based on duration of VA dual therapy in *H.pylori* eradication rate. VA, vonoprazan+amoxicillin.

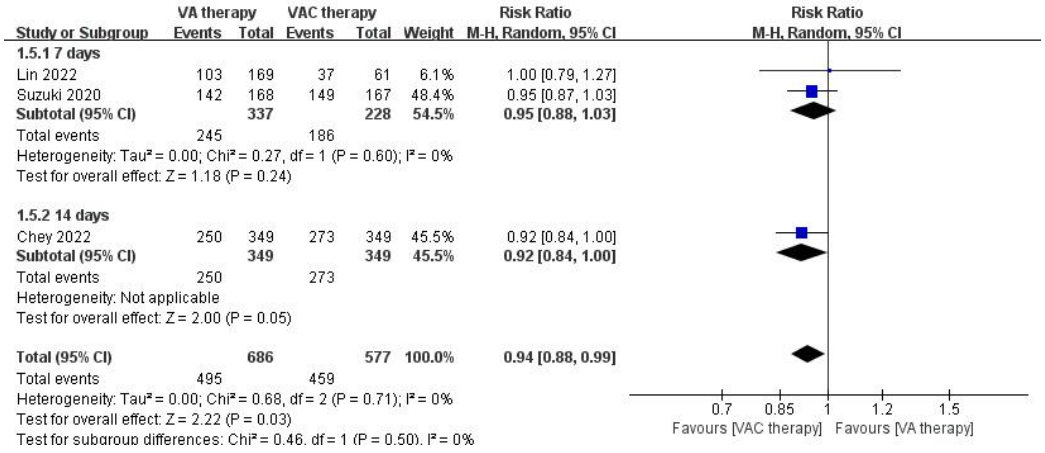

Figure S5. Forest plot of total adverse events of VA dual therapy versus VAC triple therapy.

VA, vonoprazan+amoxicillin; VAC, vonoprazan+amoxicillin+clarithromycin.

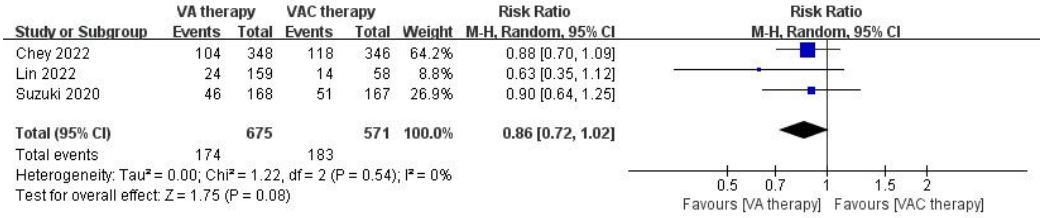

Figure S6. Forest plot of compliance of VA dual therapy versus VAC triple therapy.

VA, vonoprazan+amoxicillin; VAC, vonoprazan+amoxicillin+clarithromycin.

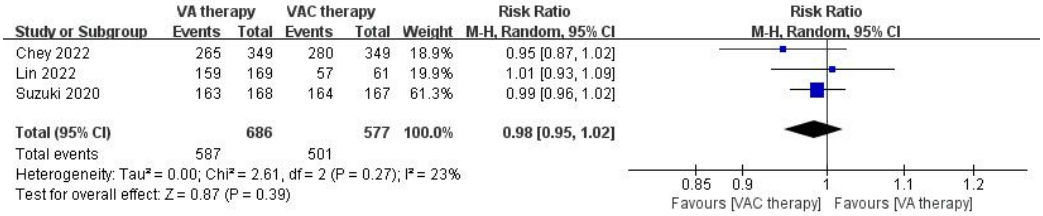

Figure S7. Forest plot of total adverse events of VA dual therapy versus PAC triple therapy.

VA, vonoprazan+amoxicillin; PAC, PPI+amoxicillin+clarithromycin.

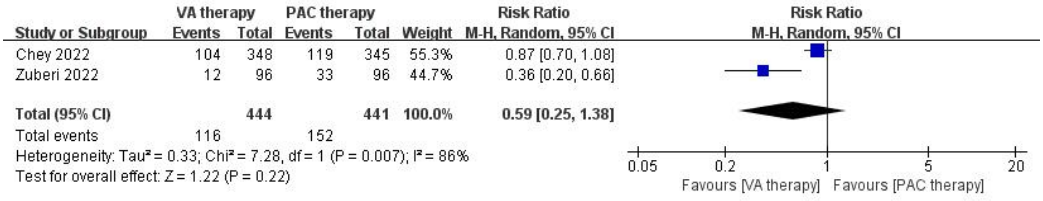

Figure S8. Forest plot of compliance of VA dual therapy versus PAC triple therapy.

VA, vonoprazan+amoxicillin; PAC, PPI+amoxicillin+clarithromycin.

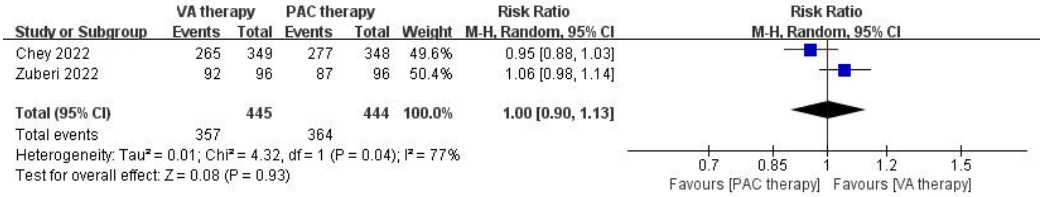

Figure S9. Forest plot of *H.pylori* eradication rate of 7-day high-dose amoxicillin group versus 7-day low-dose amoxicillin group in VA dual therapy (ITT analysis). VA, vonoprazan+amoxicillin; ITT, intention to treat.

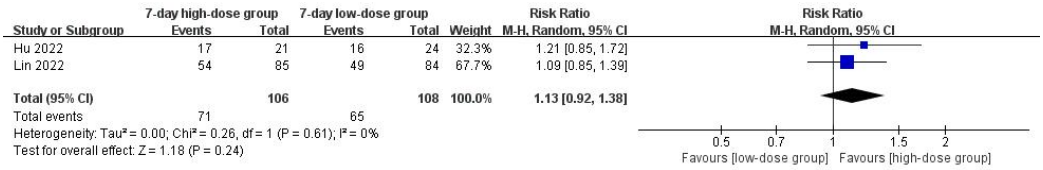

Figure S10. Forest plot of *H.pylori* eradication rate of 7-day high-dose amoxicillin group versus 7-day low-dose amoxicillin group in VA dual therapy (PP analysis). VA, vonoprazan+amoxicillin; PP, per-protocol.

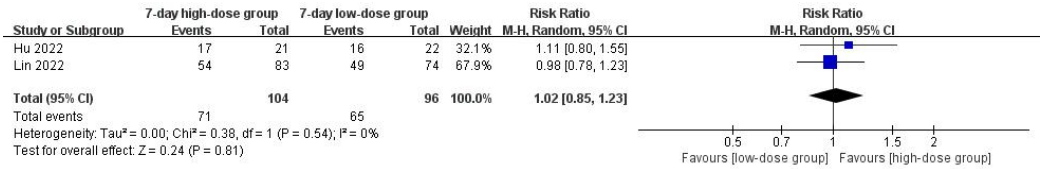

Figure S11. Forest plot of total adverse events of 7-day high-dose amoxicillin group versus 7-day low-dose amoxicillin group in VA dual therapy. VA, vonoprazan+amoxicillin.