Annals of Gastroenterology (2026) **39,** 1-9

Vonoprazan–amoxicillin dual therapy improves 14-day eradication and reduces adverse events in patients with *Helicobacter pylori* infection: an updated landmark systematic review and meta-analysis of 11 randomized trials with subgroup analysis

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Abstract

Background Vonoprazan, a potassium-competitive acid blocker (P-CAB), may enhance *Helicobacter pylori* (*H. pylori*) eradication in combination with amoxicillin. With increasing drug resistance, dual therapy is a potential alternative to standard triple and quadruple regimens. This systematic review and meta-analysis evaluated the efficacy and safety of vonoprazan dual therapy (VDT) as first-line treatment for *H. pylori* infection.

Methods A comprehensive systematic search on PubMed, Embase, Scopus and Cochrane Library identified 11 randomized controlled trials (RCTs) involving 2877 patients (1439 VDT; 1438 control), comparing VDT with standard triple therapy, quadruple therapy or individualized treatment regimens for *H. pylori* eradication, up to March 2025. Pooled risk ratios (RRs) with 95% confidence intervals (CIs) were calculated using the Mantel-Haenszel method for dichotomous outcomes. Random or fixed-effects models were applied based on heterogeneity, assessed using the Higgins I^2 statistic. A P-value <0.05 was considered statistically significant.

Results VDT significantly improved eradication rates compared to standard therapy (RR 1.06, 95%CI 1.00-1.12; P<0.0001), driven primarily by 14-day regimens (RR 1.08, 95%CI 1.01-1.15; P=0.0001); no benefit was seen for 7-day regimens (RR 0.97, 95%CI 0.91-1.04; P=0.30), with low heterogeneity (8.6%). There was no significant difference in drug compliance (RR 1.02, 95%CI 0.99-1.05; P=0.03), with moderate heterogeneity (50.3%). VDT demonstrated significantly fewer adverse events (RR 0.66, 95%CI 0.52-0.84; P<0.001).

Conclusions VDT is as effective as standard therapies overall, but shows clear superiority in 14-day regimens, with no advantage in 7-day durations. The observed heterogeneity was probably due to differences in treatment duration and regional variability in resistance.

Keywords *Helicobacter pylori*, vonoprazan, dual therapy, triple therapy, amoxicillin

Ann Gastroenterol 2026; 39 (2): 1-9

Received 4 July 2025; accepted 26 November 2025; published online 26 January 2026

DOI: https://doi.org/10.20524/aog.2026.1033

Introduction

Helicobacter pylori (*H. pylori*) is a gram-negative, microaerophilic bacterium that infects the epithelial lining of the small intestine. Affecting about half of the world's population, it is one of the most widespread infections globally [1]. This bacterial infection causes gastric problems, including gastritis and gastroduodenal ulcers, sometimes resulting in gastric

malignancies with high morbidity and mortality if treatment is delayed. Several extra-gastric complications have been associated with *H. pylori* infection: iron-deficiency anemia, immune thrombocytopenic purpura, vitamin B12 deficiency, diabetes mellitus, cardiovascular diseases, and certain neurological disorders [2]. Eradication is necessary to avoid recurrence or complication [3].

The triple therapy proton pump inhibitor (PPI) plus clarithromycin, and amoxicillin b.i.d. for 10-14 days is the most common first-line treatment for eradicating *H. pylori* [4]. However, evidence suggests that the efficacy of this regimen has decreased globally [5]. Quadruple therapy—PPI b.i.d., bismuth, metronidazole and a tetracycline q.d.s. for 10-14 days—is an effective alternative regimen, especially in regions of clarithromycin (>15%) and metronidazole resistance [4,6]. However, disadvantages of these regimes, such as poor patient compliance, rapid metabolism of PPI and cost of drugs, have challenged researchers to formulate alternative regimens with fewer drugs to improve compliance [7,8].

Because of increasing microbial resistance to therapy, eradication rates have sharply declined over the past decade [9]. Eradication rates also have a negative relationship with rates of *H. pylori* prevalence—with some areas, like China, reporting a high rate of 83.4% [10,11], prompting researchers to reassess management strategies for *H. pylori* infection. The World Health Organization (WHO) has made clarithromycin-resistant *H. pylori* infection a top priority for antibiotic resistance research and development [12].

Vonoprazan has a rapid onset of action. It works by binding to the gastric proton pump (H+/K+ ATPase). Consequently, it raises intragastric pH rapidly and sustains it at a stable alkaline pH for a significant duration compared to conventional PPIs [13]. Studies have established that *H. pylori* grows only in the pH range of 6-8 [14]. This has been attributed to enhanced eradication rates of *H. pylori*, because several growth-dependent antibiotics, including amoxicillin, clarithromycin and tetracycline, need active replication of *H. pylori* to produce maximum antimicrobial effects [15]. Vonoprazan, with its rapid onset of action and no food effect [16], keeps gastric pH at a sufficiently alkaline level to maintain bacterial replication. The benefit of vonoprazan over traditional PPIs is that its effect on the gastric pH is evident within 3 h of administration, meaning that the antibacterial drug is able to achieve full efficacy from day 1 of the regimen [17].

Studies suggest that vonoprazan dual therapy (VDT), combining vonoprazan with amoxicillin, leads to faster bacterial elimination and reduced risk of treatment failure due to resistance. A recent network meta-analysis by Rokkas *et al* ranked VDT highly among regimens, supporting its efficacy in randomized controlled trials (RCTs) [18]. Addressed and updated. This systematic review and meta-analysis aimed to consolidate existing evidence, assess the eradication success and safety profile of VDT, and explore its potential as a first-line treatment for *H. pylori* infection.

Materials and methods

This systematic review and meta-analysis included RCTs involving patients with *H. pylori* infection who underwent either VDT or triple/quadruple therapy, ensuring comparability between the 2 groups. Studies had to report at least 1 of the following outcomes: primary (eradication rates at 7 or 14 days) or secondary (adverse effects in 7 days, compliance/adherence rate, and antibiotic resistance).

We excluded studies that compared 2 drug regimens not involving vonoprazan, those not reporting relevant outcomes, and pediatric studies. Additionally, cohort studies, unpublished studies, case reports, editorials, articles not published in English, and expert opinions were excluded, including duplicates. The searches in PubMed, Embase, Scopus, ClinicalTrials.gov and Google Scholar were conducted up to March 2025. The search approach combined Medical Subject Headings (MeSH) terms and free-text keywords. The search terms included- "*Helicobacter pylori*" AND "Vonoprazan" OR "Proton pump inhibitor" AND ("Vonoprazan" AND "Amoxicillin") AND ("Triple therapy" OR "Quadruple therapy"). See Supplementary Table 1 for full search strategy. These terms were applied to the abovementioned databases with appropriate search strings to identify relevant studies based on predefined population, intervention, comparison and outcome criteria. To ensure comprehensive data collection for additional references, a manual search was conducted across bibliographies and gray literature, including conference proceedings, abstracts and pre-prints.

The articles were screened by 2 independent reviewers; in case of conflict decisions were made with the third reviewer,

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Conflict of Interest: None

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using the Rayyan AI tool. Studies were selected based on the following criteria: enrolled patients were ≥18 years of age - with *H. pylori* infection who underwent either VDT or triple/quadruple therapy. Studies conducted in animal models or published in non-peer-reviewed sources were excluded. Baseline data from all the studies is shown in Table 1.

Two independent reviewers (UB, AG) performed the initial screening of titles and abstracts to exclude irrelevant studies. Full-text articles were retrieved for all potentially eligible studies and systematically assessed for inclusion. Initial screening agreement: κ=0.85; conflicts were resolved by a third reviewer (AD).

For each included study, 3 independent reviewers extracted the following data. These included study characteristics, including first author, publication year, country, study design and total sample size. Patient demographics—mean age, sex distribution, body mass index—were also included. The outcomes of interest were subdivided into 2 categories. Primary outcomes included treatment efficacy at 7 days and 14 days, and per protocol (PP) analysis of eradication rate. Pooled estimates used intention-to-treat (ITT) data when available, with PP as sensitivity. Secondary outcomes included adverse effects in 7 days, compliance/adherence rate, and antibiotic resistance. Extracted data were collected in a standardized Excel sheet. Another independent reviewer resolved any discrepancies.

The risk of bias in the data from the extracted RCTs was assessed using the Cochrane Risk-of-Bias tool (RoB 2). This tool evaluates 5 domains defining the risk of bias that can affect the results of RCTs. The domains are: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. For each domain, a series of signaling questions guided the judgment of risk, leading to domain-level ratings of "low risk of bias", "some concerns", or "high risk of bias." An overall risk-of-bias judgment was then derived for each outcome within each study, based on the individual domain ratings: 8 of 11 studies had low risk overall, whereas 3 had some concerns regarding randomization/selection bias. Risk of bias was consistently low and this supports validity of the outcomes.

According to the GRADE approach for assessing evidence quality, confidence in the cumulative evidence was moderate to high. A consistent trend for a lower risk ratio in the experimental group than in the control group was observed in the forest plot. This indicates a positive effect of the intervention on compliance and adherence. The narrow confidence intervals (95%CI) for most studies also suggest a relatively high degree of precision in the estimates. However, the variability in the risk ratios across studies (I^2=65.20%) indicates some heterogeneity, which may slightly reduce confidence in the cumulative

Table 1 Baseline characteristics

Author year [ref.]	Study design	Study objective	Population	Total participants	Number of patients	Age: mean±SD	Males (%)	BMI: Mean±SD
Chen 2024 [29]	RCT	VDT vs. BQT	Patients aged 18-75 years	135 (2arms)*	45 vs. 45	44.87±2.00 vs. 40.78±1.49	44.40 vs. 55.60	-
Cheung 2024 [30]	RCT	VDT vs. BQT	Adults aged between 18 and 75 years	298 (2 arms)*	100 vs. 100	35.9±8.3 vs. 35.0±7.4	45.00 vs. 44.00	23.20±3.70 vs. 22.50±3.30
Chey 2022 [15]	RCT	VDT vs. LTT	Patients older than 18 years	1046 (2 arms)*	349 vs. 697	51.8±13.6 vs. 51.2±13.7	39.50 vs. 36.40	28.70±5.78 vs. 29.00±5.11
Furuta 2019 [36]	RCT	VDT vs. VTT		186 (2 arms)	62 vs. 124	60.2±12.2 vs. 62.5±3	53.22 vs. 63.09	-
Huang 2024 [31]	RCT	VDT vs. BQT	Patients aged 18 to 70 years old	306 (2 arms)*	99 vs. 96	45.69±12.39 vs. 43.84±14.26	45.45 vs. 51.06	-
Li 2023 [17]	RCT	VDT vs. BQT	Patients older than 18 years	224 (2 arms)*	75 vs. 75	45.85±13.97 vs. 42.67±12.61	34.66 vs. 45.33	25.85±4.80 vs. 25.48±3.58
Liu 2025 [32]	RCT	VDT vs. SBIT	Patients aged 18-70 years	240 (2 arm)	120 vs. 120	47.70±12.40 vs. 47.50±11.50	40.80 vs. 45.80	21.90±2.20 vs. 22.40±2.80
Suzuki 2020 [34]	RCT	VDT vs. VTT	Patients aged 20-79 years	335 (2 arms)	168 vs. 167	61.2±11.5 vs. 61.3±10.4	63.09 vs. 61.67	23.90±3.20 vs. 23.90±3.40
Yan 2023 [35]	RCT	VDT vs. BQT	Patients aged 18-70 years	314 (2 arms)	157 vs. 157	38.1±12.37 vs. 38.64±13.60	45.85 vs. 39.49	23.31±3.70 vs. 22.39±3.02
Yang 2023 [33]	RCT	VDT vs. BQT	Patients aged 18 to 80 years	600 (2 arms)*	200 vs. 200	48.70±13.4 vs. 46.01±11.7	47.50 vs. 49.00	22.77±3.37 vs. 21.90±2.69
Zuberi 2022 [25]	RCT	VDT vs. STT	Patients aged 18-75 years	192	96 vs. 96	-	59.80 vs. 62.10	-

*SD, standard deviation; BMI, body mass index; RCT, randomized controlled trial; VDT, vonoprazan-amoxicillin dual therapy; BQT, bismuth quadruple therapy; SBIT, sensitivity based individual therapy; LTT, lansoprazole triple therapy; STT, standard triple therapy; VTT, vonoprazan base triple therapy (including amoxicillin clarithromycin) *These RCTs have three arms but only the total population and the variable counts were mentioned for the two arms that were included in our analysis*

evidence. Overall, the evidence suggests a positive effect of the intervention. Interstudy heterogeneity was addressed using a random-effects model. Heterogeneity across studies was assessed using I^2 statistics: I^2<50% indicates low heterogeneity, I^2=50-75% moderate heterogeneity, and I^2>75% significant heterogeneity. All statistical analyses were performed using Review Manager 5.4.1 (The Cochrane Collaboration), with a P-value <0.05 considered statistically significant.

A statistical approach with a random-effects model was employed, which accounts for variability in treatment effects across the different studies. This type of model is particularly ideal for meta-analysis of this kind, in which studies are heterogeneous, and implies a more conservative estimate of the treatment effect. The pooled estimates derived from this study are expressed in terms of odds ratio (OR), risk ratio (RR) or mean difference, with 95%CI, depending upon the type of outcome data being analyzed.

For the evaluation of potential reporting biases, including publication bias, we visually examined funnel plots. In addition, we conducted Egger's regression test and Begg's rank correlation test to detect small-study effects. We also used trial registries and protocols where available to identify selective outcome reporting. The risk of reporting bias was independently assessed by 2 reviewers, and disagreements were resolved by discussion with a third reviewer. This approach aimed to ensure a comprehensive assessment of biases that could influence the results of the meta-analysis.

This meta-analysis and systematic review followed the PRISMA 2020 guidelines (Fig. 1). The protocol for this study is registered on PROSPERO with ID CRD420251013739.

Results

Only RCTs published in English in the past 5 years (2022-2025) comparing VDT with triple or quadruple therapy were included in this meta-analysis. Primary outcomes included eradication rate at 7 and 14 days, and PP analysis. VDT demonstrated a significantly higher eradication rate compared to control regimens under ITT analysis, with a pooled RR of 1.06 (95%CI 1.00-1.12; P<0.0001). The 7-day treatment

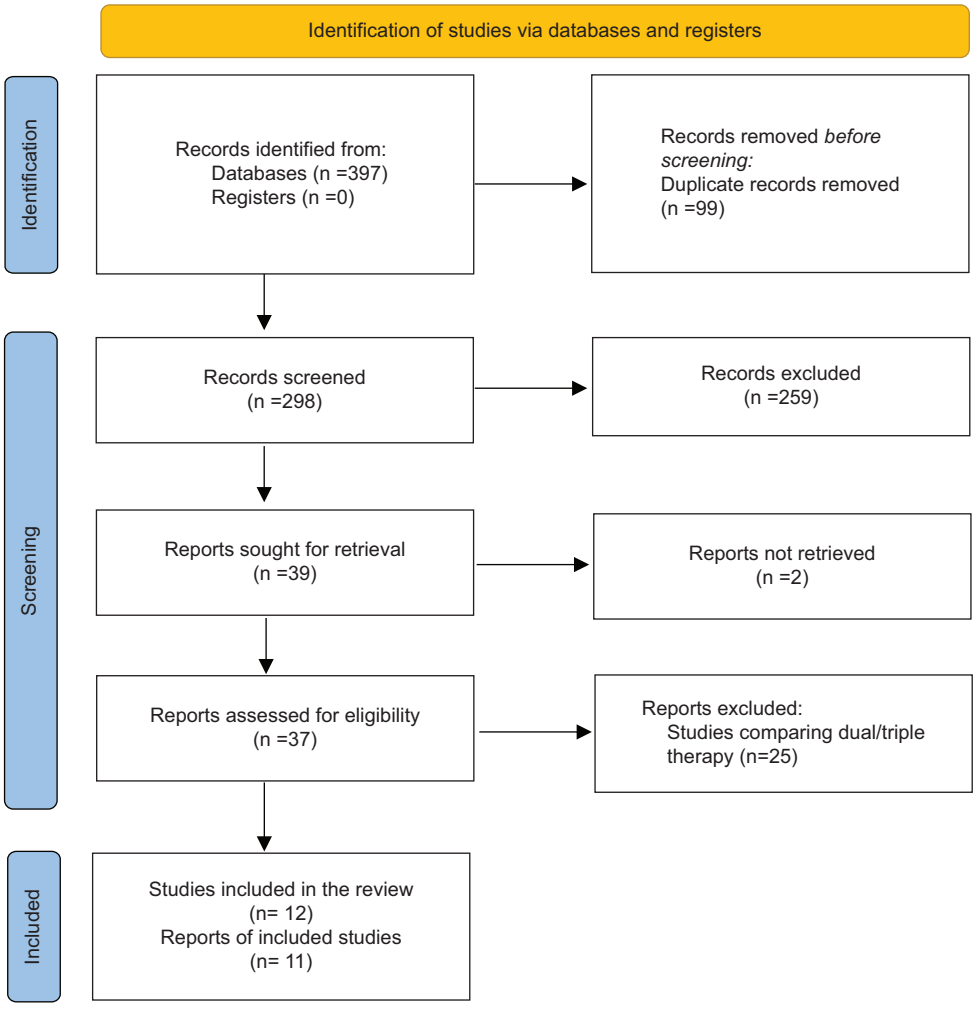

Figure 1 PRISMA flowchart outlining the literature screening process, study selection, and exclusion criteria

subgroup showed RR 0.97 (95%CI 0.91-1.04; P=0.30), with low heterogeneity (I2=8.6%) and subgroup differences (P=0.03), while the 14-day subgroup showed RR 1.08 (95%CI 1.01-1.15; P=0.0001) and I2=74.3%. This suggests that a shorter treatment duration has lesser efficacy (Fig. 2). PP analysis indicated that VDT achieved a slightly higher eradication rate than control therapies, with a pooled RR of 1.02 (95%CI 0.97-1.07; P=0.0001). However, this difference was not statistically significant, suggesting similar efficacy among the treatment groups. Moderate heterogeneity (I2=71.5%) was observed, indicating some variability among the included studies (Fig. 3).

Secondary outcomes, including the rates of adverse effects and treatment compliance, were also evaluated. Adverse effects occurred in both VDT and standard therapy groups across studies. Adverse effects presented in a wide range, from gastrointestinal symptoms to dizziness and skin rashes. VDT was associated with significantly lower rates of adverse events compared to the control group, with a pooled RR of 0.66 (95%CI 0.52-0.84; P=0.001) though the heterogeneity (I2=65.6%) warrants caution. A total of 370 adverse events were reported in the experimental group and 485 in the control group, indicating that vonoprazan-based therapy caused fewer side-effects.

Despite the heterogeneity, the overall results support VDT over standard treatment for the reduction of adverse effects (Fig. 4). Pooled compliance rates determined VDT to be comparable with control therapy, with no statistically significant difference, having a pooled RR of 1.02 (95%CI 0.99-1.05; P=0.03). At the patient level, across studies, the overall levels of adherence matched most of the RR estimates around 1.00, which implies minimal variation between groups. There was study-to-study heterogeneity, however (I2=50.3%), suggesting some difference in patient compliance, treatment tolerance and regimen delivery. The combined effect test (Z=1.55, P=0.12) did not show a statistically significant difference in VDT compliance, indicating that patients were equally likely to complete treatment with either regimen (Fig. 5). Funnel plots showed no evidence of publication bias.

Discussion

Our pooled analysis revealed that VDT had a significantly higher eradication rate compared to standard regimens, with

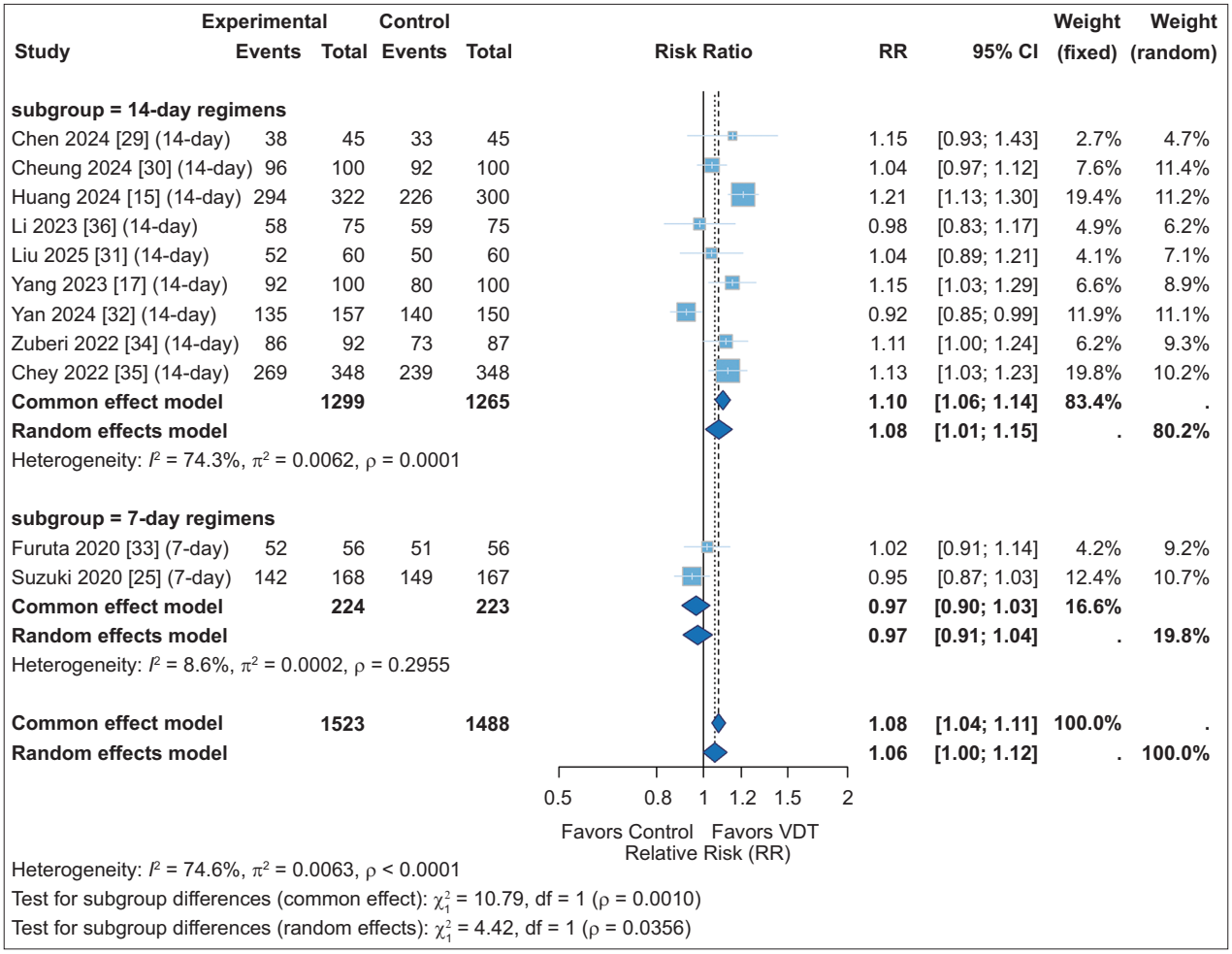

Figure 2 Forest plot comparing the eradication rates in 7 and 14 days
VDT, vonoprazan-amoxicillin dual therapy; RR, relative risk; CI, confidence interval

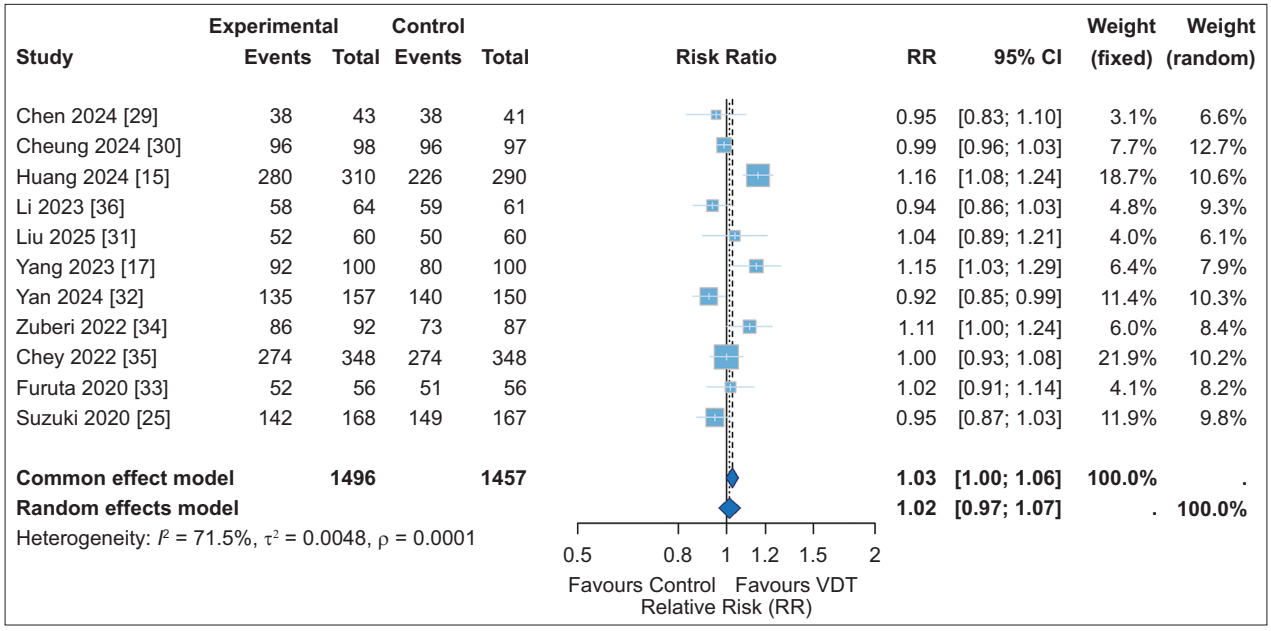

Figure 3 Forest plot comparing eradication rates of *Helicobacter pylori* (per protocol analysis)
VDT, vonoprazan-amoxicillin dual therapy; RR, relative risk; CI, confidence interval

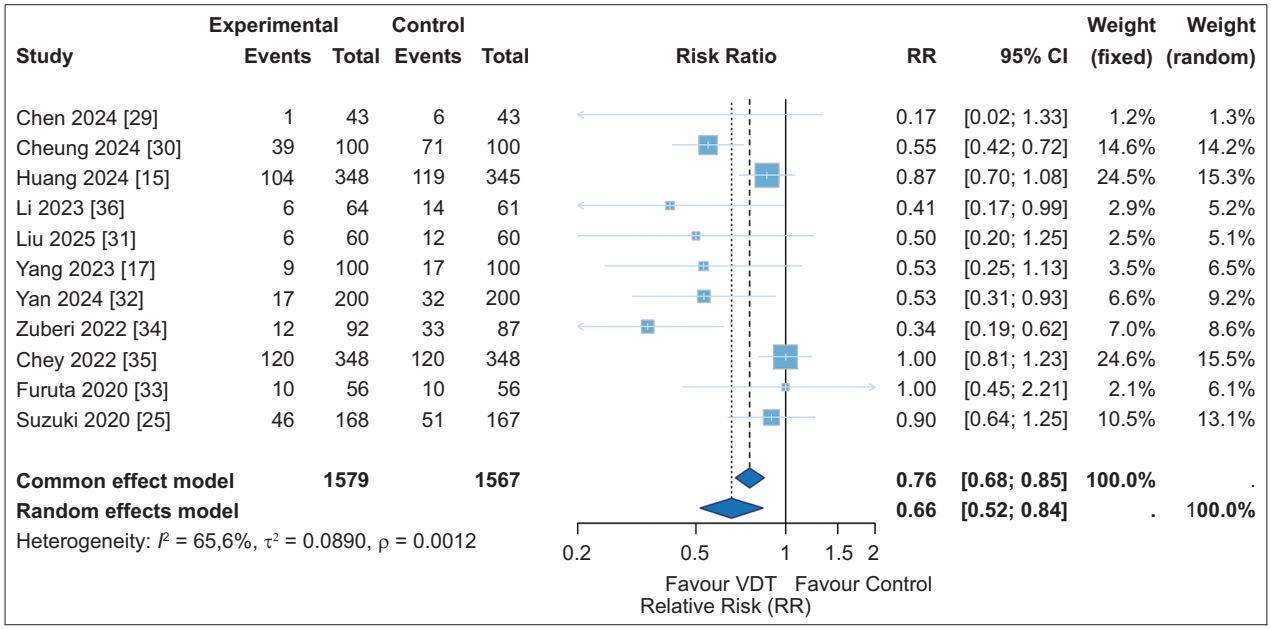

Figure 4 Forest plot comparing adverse effects
VDT, vonoprazan-amoxicillin dual therapy; RR, relative risk; CI, confidence interval

an RR of 1.06 (95%CI 1.00-1.12; P<0.0001). Subgroup analysis revealed that treatment for 14 days had better efficacy rates (RR 1.08, 95%CI 1.01-1.15; P=0.0001) than a 7-day treatment (RR 0.97, 95%CI 0.91-1.04; P=0.30). This finding indicates that a longer duration of treatment improves its efficacy, possibly because of better bacterial clearance and fewer resistance- related failures. Our findings agree with Zhang *et al* [21], who reported that 10-day and 14-day regimens of VDT had eradication rates over 90%, with significantly fewer side effects than standard triple therapy.

Although the PP analysis did reflect a moderately higher eradication rate with vonoprazan dual therapy (RR 1.02, 95%CI 0.97-1.07; P=0.0001), the difference was not statistically significant, and both regimens would be of similar efficacy under

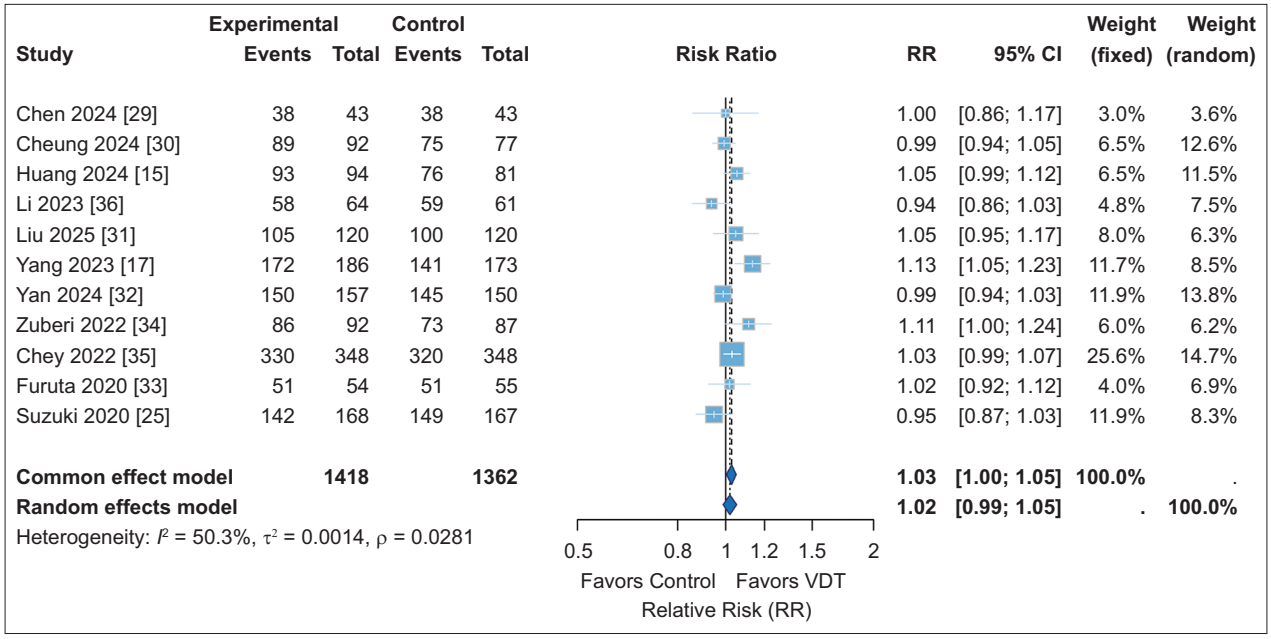

Figure 5 Forest plot comparing compliance rates
VDT, vonoprazan-amoxicillin dual therapy; RR, relative risk; CI, confidence interval

ideal conditions. However, the good ITT success rate indicates that VDT might be more effective under real-world conditions, where resistance and compliance factor in, rather than in ideal situations. ITT analyses better reflect real-world efficacy, accounting for non-compliance, while PP may overestimate in ideal adherence. The modest PP difference suggests that VDT's benefit is robust, but potentially biased by dropout in controls; high compliance (RR 1.02, 95%CI 0.99-1.05) minimizes this. This also agrees with Zhang *et al* [22], who showed that VDT had 85.6% eradication in ITT and 88.5% in PP analysis, with much greater efficacy than standard regimens in treating clarithromycin-resistant strains.

Zhou *et al* [23] however, found that VDT had a lower eradication rate in ITT than vonoprazan triple therapy (RR 0.94, 95%CI 0.88-0.99; P=0.03). Du *et al* [24] showed that, while VDT had a better efficacy than PPI-based triple therapy (82.0% vs. 71.4%, P<0.01), vonoprazan-based quadruple therapy showed a small but significant superiority over VDT (83.1% vs. 93.3%, P=0.02). Low to moderate heterogeneity across 7-day, 14-day and PP-analysis eradication rates (I2=8.6%, 74.3%, 71.5% respectively) could be due to differences in treatment regimens and patient populations.

VDT was much less likely to cause side-effects than control therapies (RR 0.66, 95%CI 0.52-0.84; P=0.001). This dramatic decrease in side-effects is an important benefit, as they are known reasons for therapy discontinuation and non-adherence, which are major issues in H. pylori eradication therapy. This statement is also confirmed by Zuberi *et al* [25] who, in a randomized controlled trial, found that 14-day vonoprazan-amoxicillin therapy had an eradication rate of 93.5%, with fewer side-effects than triple therapy. This result varies from Ouyang *et al* [26], who reported that, while VDT showed lower rates of adverse effects, the difference was not statistically significant (RR 0.75, 95%CI 0.59-1.06; P=0.12).

Pooled compliance rates of included studies in comparison to control therapy determined that VDT had a pooled RR of 1.02 (95%CI 0.99-1.05; P=0.03), indicating that patient adherence was comparable to that of control therapies, with no statistically significant difference. This finding suggests that patients were equally likely to complete treatment with either regimen, which is also suggestive of the feasibility of VDT as a first-line eradication regimen. Zhou *et al* [23] showed similar results, with no significant change in compliance. There was study-to-study heterogeneity, however, in both our study and that of Zhou *et al* (I2=50.3%), suggesting some difference in patient compliance, treatment tolerance and regimen delivery among different populations. Heterogeneity may stem from geographic variation: studies from Japan (lower clarithromycin resistance) showed higher 14-day VDT success (RR>1.10), while Chinese studies (higher resistance) had more variability. Where resistance data were unavailable, this limits interpretation; future RCTs should routinely report local profiles.

One of the strongest aspects of this meta-analysis is that it only analyzed RCTs, guaranteeing the high quality and relevance of the evidence. Observance of the PRISMA 2020 guidelines further validates our results. This meta-analysis also consists of subgroup analyses to provide more information regarding the optimal treatment duration for H. pylori eradication.

Our study, however, also had some limitations: moderate-to-high heterogeneity (I2=50.3-74.6%), possibly from geographic/resistance variations; inclusion of only English- language publications, with possible bias; lack of long-term recurrence data; publication bias (see Results); and no direct vonoprazan triple comparisons in the pooled analysis. While our meta-

analysis focused on VDT versus standard regimens, emerging evidence compares VDT directly to vonoprazan-based triple therapy (vonoprazan + amoxicillin + clarithromycin). This suggests VDT may be preferable in resistance-prevalent settings to minimize unnecessary antibiotic exposure, though head-to-head RCTs are needed for confirmation.

To summarize, VDT is as effective as standard therapies overall, but offers superior efficacy with 14-day regimens, a better safety profile and fewer adverse events. The lack of benefit in 7-day regimens highlights the importance of duration in clinical decision-making.

Antimicrobial stewardship, or the responsible use of antibiotics, is an emerging avenue in healthcare. With increasing levels of antibiotic resistance in communities worldwide, judicious use of narrow spectrum antibiotics and completion of regimens are essential to the eradication of pathogens [27]. In light of this, VDT may prove itself as a feasible alternative to conventional multidrug regimens. Its simplicity and reduced selection pressure make VDT less prone to resistance, helping to avoid the further spread of clarithromycin-resistant H. pylori in the community [28]. VDT aligns with antimicrobial stewardship by using fewer antibiotics (amoxicillin only), reducing selection pressure for resistance compared to clarithromycin-inclusive regimens. This minimizes the community spread of resistant *H. pylori*, supports WHO priorities, and improves adherence via simplicity and fewer adverse events.

Summary Box

What is already known:

- Standard triple and quadruple therapies for *Helicobacter pylori* are challenged by antibiotic resistance
- Vonoprazan offers superior acid suppression compared to proton pump inhibitors
- Prior meta-analyses suggest efficacy for vonoprazan dual therapy (VDT), but updates from recent randomized controlled trials are needed
- 14-day regimens may outperform shorter ones

What the new findings are:

- 14-day VDT improves eradication rates over standard therapies
- VDT has fewer adverse events, with comparable compliance
- No benefit for 7-day VDT, emphasizing importance of duration
- Heterogeneity is linked to regional resistance; VDT supports antimicrobial stewardship

Acknowledgments

This was a multinational Collaboration Study. We thank all the study authors. We thank the founder of the collaboration group Open Frontiers, Dr Ashesh Das for conceptualizing the study and turning this idea into a reality. We also thank him for his valuable mentorship throughout the project.

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Supplementary material

Supplementary Table 1 PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
		TITLE	
Title	1	Identify the report as a systematic review.	1
		ABSTRACT	
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	4
		INTRODUCTION	
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	6-7
Objectives	4	Provide an explicit statement of the objective (s) or question (s) the review addresses.	6-7
		METHODS	
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	8
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	8
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	8
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	9
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	9
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	9
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	10
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool (s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	11-12
Effect measures	12	Specify for each outcome the effect measure (s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	10
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	10
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	10-11
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	10-11
	13d	Describe any methods used to synthesize results and provide a rationale for the choice (s). If meta-analysis was performed, describe the model (s), method (s) to identify the presence and extent of statistical heterogeneity, and software package (s) used.	10-11
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	10-11
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	10-11
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	11-11

(Contd...)

Supplementary Table 1 *(Continued)*

Section and Topic	Item #	Checklist item	Location where item is reported
		METHODS	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	11
		RESULTS	
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	12-13
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	12-13
Study characteristics	17	Cite each included study and present its characteristics.	12-13
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	12-13
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	12-13
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	12-13
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	12-13
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	12-13
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	12-13
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	12-13
		DISCUSSION	
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	13-18
	23b	Discuss any limitations of the evidence included in the review.	13-18
	23c	Discuss any limitations of the review processes used.	13-18
	23d	Discuss implications of the results for practice, policy, and future research.	13-18
		OTHER INFORMATION	
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	11
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	11
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	11
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	18
Competing interests	26	Declare any competing interests of review authors.	18
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	18