Efficacy and safety comparison of Helicobacter pylori eradication between vonoprazan dual therapy versus triple therapy: a systematic review and meta-analysis

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Abstract
Background: As a novel drug, vonoprazan (VPZ) has been developed as a new strategy against Helicobacter pylori (H. pylori) infections. However, whether VPZ + amoxicillin (AMO) dual therapy has a clear advantage is still unclear.
Objective: To review and meta-analyze the available literature investigating the efficacy and safety of H. pylori eradication in VPZ dual therapy.
Design: A systematic review and meta-analysis were conducted.
Data sources and methods: We performed a systematic search in the PubMed, Embase, Elsevier/Science Library, and Cochrane Library databases from 2015 to 2022. Meta-analyses were conducted to evaluate the actual cure rate and the incidence rate of adverse reactions in dual therapy and VPZ + AMO + clarithromycin (CLA) triple therapy; furthermore, eradication rates in CLA-resistant infections and different doses of antibiotics were evaluated in subgroup analysis.
Results: Seven studies with 1490 patients were included in this meta-analysis. According to intention-to-treat analysis, the actual cure rates of VPZ dual and triple therapy were 82.8% and 84.6%, respectively \( p = 0.29 \), odds ratio [OR]: 0.86, 95% confidence interval [CI]: 0.64–1.14]. And in the per-protocol analysis, the actual cure rates of these two therapies were 84.8% and 87.0%, respectively \( p = 0.21 \), OR: 0.80, 95% CI: 0.57–1.13]. The incidence of adverse reactions between VPZ dual and triple therapy was 26.1% versus 29.6% \( p = 0.04 \), OR: 0.78, 95% CI: 0.61–0.99]. In subgroup analysis, the eradication rates in CLA-resistant infections were dual therapy: 85.7% for VPZ versus 71.0% for triple therapy \( p = 0.03 \), OR: 2.36, 95% CI: 1.10–5.05]. And the actual cure rate of VPZ with high-dose antibiotics was lower than with low-dose antibiotics \( p = 0.000 \) in dual therapy; \( p = 0.011 \) in triple therapy.
Conclusion: A combination of VPZ and a low dose of AMO should be prioritized as a treatment option for H. pylori eradication.
Registration: PROSPERO registration number CRD42022346100.

Keywords: dual therapy, eradication therapy, Helicobacter pylori, triple therapy, vonoprazan

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disease in the Maastricht V Consensus report, clinicians focused on the actual cure rates of *H. pylori* infections and adverse reactions rates of its therapies. Proton pump inhibitor (PPI) and two antibiotics, with or without bismuth, are mostly used for the eradication of *H. pylori* infections in Japan, Europe, and America. Although two antibiotics ensure the cure rate of *H. pylori* infections above 90% as much as possible, the actual cure rate of *H. pylori* has decreased owing to increasing antimicrobial resistance, especially clarithromycin (CLA), metronidazole, and levofloxacin. It has been reported that the antimicrobial resistance rate of *H. pylori* to CLA is 20–50%, to metronidazole is 40–70%, and to levofloxacin is 20–50% in China. At the same time, the adverse reactions caused by taking two antibiotics and the higher costs are problems too. So dual therapy composed of a PPI and amoxicillin (AMO) has attracted increasing attention since 1989. Unfortunately, there were many differences in the efficacy of such therapies in previous studies. Kayser et al. reported that the actual cure rate of *H. pylori* was only 23%, but Shirai et al. reported that the actual cure rate was up to 90.9%. These findings may be attributed to the dosage and pharmacokinetics of the drugs; however, they still limited the use of PPI-based dual therapy in clinic.

As a novel potassium-competitive acid blocker, vonoprazan (VPZ) has been developed and gained increasing attention. VPZ noncovalently combines with K+/H+-ATPase through hydrogen and ionic bonds, competing for acting sites of K+ and inhibiting the conformational change of the K+/H+-ATPase, which leads to enzyme inactivation, eventually reducing gastric acid secretion. According to a recent randomized controlled trial (RCT) reported in Japan, VPZ provides a stronger and longer-lasting effect on gastric acid suppression than other PPIs. Therefore, its application in the treatment of *H. pylori* infections is expected to improve the actual cure rate of *H. pylori* infections. A meta-analysis by Jung et al. showed that the actual cure rates of VPZ-containing versus PPI-containing first-line triple therapies were 85.1% versus 68.0% in an intention-to-treat (ITT) analysis, and there was a significant difference between the two groups [relative risk (95% confidence interval), CI = 1.19 (1.15–1.24)]. The safety of VPZ versus PPI for *H. pylori* eradication therapies showed that there was no significant difference [RR (95% CI) = 1.02 (0.78–1.34)]. Therefore, VPZ may be an alternative to PPI as an eradication therapy for *H. pylori* infections.

Obviously, problems such as antimicrobial resistance increased; serious side effects and high costs are also associated with VPZ triple therapy. VPZ provides quicker, stronger, and longer-lasting effects on gastric acid suppression compared to PPIs. Therefore, we expect better efficacy of dual therapy composed of VPZ and AMO. We also expect VPZ dual therapy not to contribute to the development of *H. pylori* antibiotic resistance. However, many studies have reported that the efficacy and safety of VPZ dual therapy were similar to triple therapy, even though VPZ dual therapy was recommended, but with high-dose antibiotics. And only a few studies have reported the actual cure rate of VPZ dual therapy and triple therapy in CLA-resistant infections, so we wanted to perform a meta-analysis to discuss whether the VPZ + AMO dual therapy has a clear advantage over VPZ + AMO + CLA triple therapy.

**Materials and methods**

**Literature search strategy**

This study was conducted according to the PRISMA checklist 2020 for reporting systematic reviews and meta-analyses (Figure 1; Supplemental file). The review protocol was registered in advance on PROSPERO under registration number CRD42022346100 (see https://www.crd.york.ac.uk/prospero). A systematic literature search was conducted using the PubMed, Embase, Elsevier/Science Library, and Cochrane Library databases up to 20 June 2022. We used the following keywords: ‘vonoprazan’ OR ‘potassium-competitive acid blocker’ OR ‘P-CAB’ OR ‘TAK-438’ AND ‘Helicobacter pylori’ OR ‘Helicobacter nemestrinae’ OR ‘Campylobacter pylori’ for retrieval. All of the above works were independently completed by two researchers.

**Study selection criteria**

The inclusion criteria were as follows: (i) The study was a RCT comparing the efficacy and safety of VPZ-based dual therapy and VPZ-based triple therapy; (ii) the study confirmed *H. pylori* infections by rapid urease tests or 13C-urea breath
tests; (iii) the study confirmed *H. pylori* eradication by $^{13}$C-urea breath tests after treatment for 1 month; (iv) the study used 7-day therapies; and (v) the study included more than 30 patients in each group. The study was not included if any of the exclusion criteria were met.

The exclusion criteria were as follows: (i) The study was a meta-analysis, review, letter, or case report; (ii) the study contained incomplete or had unavailable data; (iii) the study did not have the full-text accessible; and (iv) the study focused on healthy people, animals, or other diseases.

**Data extraction**

We read every detail of the included studies carefully and extracted the following information and data from each study: (i) the first author’s name and the study publication year; (ii) the study type and treatment strategy; (iii) the sample size; (iv) the actual cure rate and incidence of adverse reactions to *H. pylori* treatments; and (v) all figures, images, and other data. Whole works were completed by two researchers independently.

**Study quality assessment**

According to the Cochrane Review Handbook (Version 6.2), we conducted a quality assessment on every RCT included in the study. The following items of each RCT were evaluated: (i) the methods of random allocation; (ii) whether and how the participants and researchers were blinded; (iii) whether and how the outcome assessors were blinded; (iv) whether there were missing data and how to deal with missing data; (v) whether there was a protocol deviation and how to deal with it and (vi) whether there were other biases.

**Statistical analysis**

Review Manager 5.4.1 (provided by the Cochrane Collaboration, 2020) was used for statistical analysis in our meta-analysis. We compared the following data using a likelihood-ratio $\chi^2$-test, odds ratios (ORs), and 95% CIs: (i) the actual cure rates of VPZ-based dual therapy and VPZ-based triple therapy and (ii) the incidence of adverse reactions between the two groups. We estimated the heterogeneity of each study using the $I^2$ test and considered an $I^2 <$ 25% to indicate that no heterogeneity existed; otherwise, subgroup analysis or a randomized effect model was used. In all analyses, a $p < 0.05$ was considered to indicate significant difference.

**Results**

**Literature search**

The search identified 288 studies that were retrieved from the PubMed, Embase, Elsevier/Science Library, and Cochrane Library databases, of which seven studies$^{19-25}$ were included for analysis (Figure 1). Characteristics of the included studies for meta-analysis are presented in Table 1. All patients were diagnosed as infected by *H. pylori* using a $^{13}$C-urea breath test. Demographic and clinical characteristics were similar between the two groups. In total, in this meta-analysis, there were 686 patients that received VPZ + AMO dual therapy, and 804 patients that received VPZ + AMO + CLA triple therapy. According to the Cochrane Review Handbook, the overall risk of bias assessed by the QUADAS-2 tool was low in the seven included studies, and the details are presented in Figure 2.

**Comparison of actual cure rates between dual and triple therapies**

One retrospective study$^{23}$ used a propensity score matching analysis and considered it to provide an equivalent degree of evidence as an RCT, so we classified it as an RCT. In the ITT analysis, the actual cure rates of *H. pylori* were 82.8% and 84.6% between dual therapy and triple therapy, respectively ($p = 0.29$, OR: 0.86, 95% CI: 0.64–1.14; Table 2(a)). And in a per-protocol (PP) analysis, there was still no statistical differences between the two therapies (84.8% versus 87.0%; $p = 0.21$, OR: 0.80, 95% CI: 0.57–1.13; Table 2(b)).

**Safety comparison between dual and triple therapies**

Only three studies$^{19-21}$ did not provide detailed information about adverse reactions. According to our analysis, the total incidence of adverse reactions was 26.1% for dual therapy and 29.6% for triple therapy, with a corresponding OR of 0.78 (95% CI: 0.61–0.99 $p = 0.04$; Table 2(c)) under the fixed-effect model. Diarrhea was a common adverse reaction in both therapies. And in terms of a single symptom, the incidence of diarrhea was lower in dual therapy, which had a significant difference compared to triple therapy.
Furthermore, there was statistical difference (0.79% versus 2.62%; $p = 0.011$; Table 3) in the patients who discontinued treatment due to severe adverse reactions between two therapies.

Eradication rates in CLA-resistant infections between dual and triple therapies

Only two studies provided detailed information about CLA-resistant infections. In these two studies, the CLA-resistant *H. pylori* infection rates were 19.6% and 22.5% ($p = 0.295$). Eradication rate in CLA-resistant *H. pylori* infections in dual therapy was higher than triple therapy (85.7% versus 71.0%; $p = 0.03$, OR: 2.36, 95% CI: 1.10–5.05 Table 2(d)).

Comparison of actual cure rates between different doses of antibiotics

We further performed a subgroup analysis on antibiotic dosing administration. We defined AMO 1500 mg and CLA 200 mg as low-dose administration and AMO 3000 mg and CLA 500 mg as high-dose administration. After analysis, we found that for dual and triple therapy the actual cure rate of high-dose antibiotics was lower than a low dose of antibiotics ($p = 0.000$ in dual therapy; $p = 0.011$ in triple therapy; Table 4).

Discussion

Many studies have suggested that VPZ is superior to PPI in *H. pylori* eradication treatment. According to Dong et al., the actual cure rate of *H. pylori* infections was 92.6% for VPZ treatment and only 74.1% for PPI treatment, with a significant statistical difference. On one hand, VPZ can ensure a gastric pH above 7, preventing *H. pylori* from colonizing by inhibiting urease activity. Homeless *H. pylori* is more easily killed by antibiotics. On the other hand, VPZ can still inhibit acid secretion without the proton pump activated. This was a great difference from PPI. Through this mechanism, the acid secretion function of gastric epithelial cells can be
Table 1. Characteristics of studies included in meta-analysis.

| First author, year | Journal                                      | Study design          | Diagnostic basis       | Patients number | Eradication regime                      |
|--------------------|----------------------------------------------|-----------------------|------------------------|-----------------|----------------------------------------|
| Furuta et al.19    | American Journal of Gastroenterology         | RCT                   | ¹³C-urea breath test    | 61              | VPZ 20 mg bid + AMO 500 mg tid for 1 week |
|                    |                                               |                       |                        |                 | VPZ 20 mg bid + AMO 750 mg bid + CLA 200 mg for 1 week |
| Furuta et al.20    | Clinical Pharmacology and Therapeutics       | RCT                   | ¹³C-urea breath test    | 32              | VPZ 20 mg bid + AMO 500 mg tid for 1 week |
|                    |                                               |                       |                        |                 | VPZ 20 mg bid + AMO 750 mg bid + CLA 200 mg for 1 week |
| Furuta et al.21    | Gastroenterology                             | RCT                   | ¹³C-urea breath test    | 67              | VPZ 20 mg bid + AMO 500 mg tid for 1 week |
|                    |                                               |                       |                        |                 | VPZ 20 mg bid + AMO 750 mg bid + CLA 200 mg for 1 week |
| Furuta et al.22    | Digestion                                    | RCT                   | ¹³C-urea breath test    | 112             | VPZ 20 mg bid + AMO 500 mg tid for 1 week |
|                    |                                               |                       |                        |                 | VPZ 20 mg bid + AMO 750 mg bid + CLA 200 mg for 1 week |
| Suzuki et al.23    | Gut                                          | RCT                   | ¹³C-urea breath test    | 335             | VPZ 20 mg bid + AMO 750 mg bid for 1 week |
|                    |                                               |                       |                        |                 | VPZ 20 mg bid + AMO 750 mg bid + CLA 200 mg for 1 week |
| Gotoda et al.24    | Japanese Society of Gastroenterology         | Prospective observational study | ¹³C-urea breath test | 221             | VPZ 20 mg bid + AMO 750 mg bid for 1 week |
|                    |                                               |                       |                        |                 | VPZ 20 mg bid + AMO 750 mg bid + CLA 200 mg for 1 week |
| Chey et al.25      | Gastroenterology                             | RCT                   | ¹³C-urea breath test    | 662             | VPZ 20 mg bid + AMO 1 g tid for 1 week   |
|                    |                                               |                       |                        |                 | VPZ 20 mg bid + AMO 1 g bid + CLA 500 mg bid for 1 week |

AMO, amoxicillin; bid, twice a day; CLA, clarithromycin; RCT, randomized controlled trial; tid, three times a day; VPZ, vonoprazan.

Figure 2. Assessment of risk of bias of included studies.
Table 2. Forest plot of efficacy and safety of *H. pylori* eradication between two therapies.

| Study or subgroup | VPZ duplex therapy | VPZ triple therapy | Weight | OR M-H. Random. 95% CI | OR M-H. Random. 95% CI |
|-------------------|--------------------|--------------------|--------|-------------------------|-------------------------|
|                   | Events             | Total              | Events | Total                   |                         |
| Chey *et al.*<sup>25</sup> | 250                | 324                | 273    | 338                     | 58.0%                    | 0.80 (0.55–1.17)          |
| Furuta *et al.*<sup>19</sup> | 15                 | 16                 | 14     | 16                      | 1.3%                     | 2.14 (0.17–26.33)          |
| Furuta *et al.*<sup>20</sup> | 28                 | 30                 | 28     | 31                      | 2.3%                     | 1.50 (0.23–9.68)           |
| Furuta *et al.*<sup>21</sup> | 30                 | 32                 | 33     | 35                      | 2.0%                     | 0.91 (0.12–6.86)           |
| Furuta *et al.*<sup>22</sup> | 52                 | 56                 | 51     | 56                      | 4.3%                     | 1.27 (0.32–5.02)           |
| Gotoda *et al.*<sup>24</sup> | 51                 | 60                 | 132    | 161                     | 12.3%                    | 1.24 (0.55–2.81)           |
| Suzuki *et al.*<sup>23</sup> | 142                | 168                | 149    | 167                     | 19.7%                    | 0.66 (0.35–1.26)           |
| Total (95% CI)    | 686                | 804                | 100.0% | 0.86                    | 0.64–1.14                |

Total events 568 680

Heterogeneity: τ² = 0.00; χ² = 2.74, df = 6 (p = 0.84); I² = 0%

Test for overall effect: Z = 1.05 (p = 0.29)

b.

| Study or subgroup | VPZ duplex therapy | Vomoprazan triple therapy | Weight | OR M-H. Random. 95% CI |
|-------------------|--------------------|---------------------------|--------|-------------------------|
|                   | Events             | Total                     | Events | Total                   |                         |
| Chey *et al.*<sup>25</sup> | 215                | 265                        | 240    | 280                     | 55.5%                    | 0.72 (0.45–1.13)          |
| Furuta *et al.*<sup>22</sup> | 51                 | 54                         | 51     | 55                      | 4.8%                     | 1.33 (0.28–6.26)          |
| Gotoda *et al.*<sup>24</sup> | 51                 | 59                         | 132    | 157                     | 15.6%                    | 1.21 (0.51–2.85)          |
| Suzuki *et al.*<sup>23</sup> | 142                | 163                        | 148    | 164                     | 24.1%                    | 0.73 (0.37–1.46)          |
| Total (95% CI)    | 541                | 656                        | 100.0% | 0.80                    | 0.57–1.13                |

Total events 459 571

Heterogeneity: τ² = 0.00; χ² = 1.59, df = 3 (p = 0.66); I² = 0%

Test for overall effect: Z = 1.26 (p = 0.21)

(Continued)
Table 2. (Continued)

c.

| Study or subgroup | VPZ duplex therapy | Vomoprazan triple therapy | Weight | OR M-H. Random. 95% CI | OR M-H. Random. 95% CI |
|-------------------|--------------------|---------------------------|--------|------------------------|------------------------|
|                   | Events  | Total  | Events  | Total  |                        |                        |
| Chey et al.\textsuperscript{25} | 104    | 348    | 118    | 346    | 59.1%                   | 0.82 (0.60–1.13)       |
| Furuta et al.\textsuperscript{22} | 9      | 56     | 14     | 56     | 6.9%                    | 0.57 (0.23–1.46)       |
| Gotoda et al.\textsuperscript{24} | 6      | 60     | 32     | 157    | 7.0%                    | 0.43 (0.17–1.10)       |
| Suzuki et al.\textsuperscript{23} | 46     | 168    | 51     | 167    | 27.0%                   | 0.86 (0.53–1.38)       |
| Total (95% CI)    | 632    | 726    | 100.0% | 0.78 (0.61–0.99)       |

Total events: 165/215

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.21$, df = 3 ($p = 0.53$); $I^2 = 0$

Test for overall effect: $Z = 2.02$ ($p = 0.04$)

d.

| Study or subgroup | VPZ duplex therapy | VPZ triple therapy | Weight | OR M-H. Random. 95% CI | OR M-H. Random. 95% CI |
|-------------------|--------------------|--------------------|--------|------------------------|------------------------|
|                   | Events  | Total  | Events  | Total  |                        |                        |
| Chey et al.\textsuperscript{25} | 37     | 40     | 32     | 42     | 30.7%                   | 3.85 (0.98–15.23)      |
| Suzuki et al.\textsuperscript{23} | 35     | 44     | 39     | 58     | 69.3%                   | 1.89 (0.76–4.73)       |
| Total (95% CI)    | 84     | 100    | 100.0% | 2.36 (1.10–5.05)      |

Total events: 72/71

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.71$, df = 1 ($p = 0.40$); $I^2 = 0$

Test for overall effect: $Z = 2.21$ ($p = 0.03$)

The squares indicate individual studies. The diamonds represent pooled effect sizes. The dashed lines represent the 95% CIs. a: actual cure rate of \textit{H. pylori} infection in ITT analysis; b: actual cure rate of \textit{H. pylori} infection in PP analysis; c: safety of \textit{H. pylori} eradication between two therapies; d: actual cure rate of \textit{H. pylori} infection in CLA-resistant infections. CI, confidence interval; CLA, clarithromycin; ITT, intention to treat; OR, odds ratio; PP, per protocol; VPZ, vonoprazan.
Inhibited more comprehensively and completely. Last but not least, the potent acid inhibition of VPZ is not influenced by CYP2C19 genotype, which is a well-known factor that failed for patients who eradicate *H. pylori*. Therefore, we suggested that the stronger, faster, and longer-lasting effect of VPZ on gastric acid suppression than PPI that was a crucial factor for VPZ to be a *H. pylori* eradication treatment candidate.

In this meta-analysis, we found that the actual cure rates of VPZ dual therapy and triple therapy were 82.8% versus 84.6% (*p* = 0.29) in ITT analysis and 84.8% versus 87.0% (*p* = 0.21) in PP analysis. This results are consistent with previous studies. However, we noticed that the actual cure rate of *H. pylori* infections with dual therapy was not more than 90%, which indicates low efficacy in the clinical setting according to the guidelines.4,28,29 When we exclude the population from Europe and the United States, the actual cure rate of *H. pylori* infections was 90.0%, that meets the high efficacy standard recommended by the guidelines. We attributed this result to differences in the study population and suggested the VPZ is metabolized differently in different populations. The actual cure rates of *H. pylori* infections were not seen in Japanese trials with VPZ-based regimens of 90% or higher according to many studies. A non-randomized study30 from Brown University showed that the most effective *H. pylori* eradication treatment only achieved a cure rate of 87%. And Chey et al.25 wrote in his study that ‘in recent practice in the US, eradication rates of 90% or greater have been unattainable’. In clinical practice, doctors always increase the drug dosage to ensure the eradication rate. Then we further performed subgroup analysis on antibiotics dose administration. In our study, we noticed that the actual cure rate of low-dose antibiotics treatment

| Table 3. Incidences of adverse events observed in the duplex or triple therapy groups [n (%)]. |
|-----------------------------------------------|------------------|------------------|-------------------|
| Adverse events                        | Duplex therapy (n=632) | Triple therapy (n=726) | *p* Value |
|-----------------------------------------------|------------------|------------------|-------------------|
| Diarrhea                                | 47 (7.4)          | 80 (11.0)        | 0.026*            |
| Bloating                                | 20 (3.2)          | 14 (1.9)         | 0.141             |
| Constipation                            | 11 (1.7)          | 8 (1.1)          | 0.312             |
| Skin rush                               | 12 (1.9)          | 12 (1.7)         | 0.721             |
| Abdominal pains                         | 14 (2.2)          | 9 (1.2)          | 0.161             |
| Nausea                                  | 11 (1.7)          | 14 (1.9)         | 0.808             |
| Treatment discontinuations              | 5 (0.8)           | 19 (2.6)         | 0.011*            |
| Others                                  | 45 (7.1)          | 59 (8.1)         | 0.505             |

*p < 0.05.

| Table 4. Comparison of different dose antibiotics administration to *H. pylori* eradication [n (%)]. |
|-----------------------------------------------|------------------|------------------|-------------------|
| Therapy strategies | Dose of antibiotics | Eradicated | Eradicated (+)/% | *p* Value |
|-----------------------------------------------|------------------|------------------|-------------------|
| Duplex therapy                               | Low              | 318              | 44                | 87.8%    | 0.000***|
|                                              | High             | 250              | 74                | 77.2%    |          |
| Triple therapy                               | Low              | 407              | 59                | 87.3%    | 0.011*  |
|                                              | High             | 273              | 65                | 80.8%    |          |

*p < 0.05; ***p < 0.001.
was higher than that of high-dose antibiotics treatment in both dual and triple therapies. We considered AMO to be a time-dependent drug, reasonably increasing the frequency but not dose, which allows plasma concentration above the minimum inhibitory concentration and can ensure the efficacy of the drug to a greater extent. On the contrary, high-dose antibiotics increased adverse reactions that caused treatment discontinuations. This has also been demonstrated in our research.

At present, the antibiotic resistance of \textit{H. pylori} is one of the non-negligible factors affecting the actual cure rate of \textit{H. pylori} infections, especially for CLA. In 2017, the WHO\textsuperscript{31} published its first-ever list of antibiotic resistance ‘priority pathogens’, and CLA-resistant \textit{H. pylori} was categorized as a high-priority bacterium, in the same tier as methicillin-resistant \textit{Staphylococcus aureus} and vancomycin-resistant \textit{Enterococcus faecium}. In our meta-analysis, CLA resistance rates were 19.6\% and 22.5\% in dual and triple therapies, respectively. And the treatment strategy in CLA-resistant \textit{H. pylori} infection in our study suggested that VPZ dual therapy had a higher eradication rate. The \textit{H. pylori} resistant to CLA mechanism was mutations in 23 SrRNA variable region genes. This leads to ribosome allostery, which reduced the affinity of the CLA binding site.\textsuperscript{32} For CLA-resistant \textit{H. pylori}, frequent exposure to CLA increased the chance of gene mutation. This may increase the probability of mutations in genes encoding penicillin-binding proteins. Thus, that will decrease the efficacy of triple therapy. This needs further research to be proved, but does not significantly affect our conclusions.

Different from previous studies, we found that there was a statistical difference in adverse reaction rate between two therapies and even in triple therapy more patients discontinued treatment due to severe adverse reactions. Further research in terms of a single symptom, the highest incidence of adverse reactions, was for diarrhea. Macrolides, which stimulate increased intestinal motility, could explain the statistical difference and the incidence of diarrhea being the highest. Apart from this, that may be related to the effects of antibiotics on the gut microbiota. Many studies\textsuperscript{33–35} have shown that the use of multiple antibiotics in \textit{H. pylori} eradication therapy could lead to changes in the intestinal microbiology, and the use of probiotics was recommended to alleviate this side effect. Although we did not analyze the difference in gut microbiota after treatment by the two therapies, this did not affect our affirmation of dual therapy efficacy. Besides, CLA not only causes gastrointestinal reactions, but also prolongs the QT interval and increases the risk of arrhythmia.

In conclusion, a combination of VPZ and a low dose of AMO administration indeed increased the actual cure rate of \textit{H. pylori} infection, which may be a new breakthrough in improving the actual cure rate of \textit{H. pylori}. We suggest that dual therapy, especially with a low dose of AMO administration, should be given priority. Although a previous study performed by Ouyang\textsuperscript{36} has done similar work to ours, the antibiotic resistance of \textit{H. pylori} was either not reported or limited by geography. However, our study results have the following limitations: (i) the actual cure rate was not more than 90\%, which may limit its promotion in western countries and (ii) there was a retrospective study, although it used propensity score matching analysis. All of these limitations would have an effect on the results.

Overall, we suggest a combination of VPZ and low-dose AMO as a prioritized strategy for \textit{H. pylori} eradication.

**Declarations**

*Ethics approval and consent to participate*
Not applicable.

*Consent for publication*
Not applicable.

*Author contribution(s)*
Zheyu Wang: Writing – original draft.
Fen Wang: Writing – review & editing.

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Competing interests
The authors declare that there is no conflict of interest.

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

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Supplemental material
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