

Efficacy and safety of vonoprazan–amoxicillin dual therapy for *Helicobacter pylori* first-line treatment: a single-center, randomized, controlled trial

Xiaolei Wang , Guigen Teng, Xinhong Dong, Yun Dai and Weihong Wang

Abstract

Background: With the increase in antibiotic resistance, the success rate of *Helicobacter pylori* (*H. pylori*) eradication therapy has declined in recent years. Vonoprazan–amoxicillin (VA) dual therapy has been reported to be a promising regimen.

Objectives: To compare the efficacy and safety of VA dual therapy and bismuth quadruple therapy containing amoxicillin and clarithromycin for *H. pylori* first-line eradication, and to further analyze the effects of clarithromycin resistance on eradication rate.

Design: This study was a single-center, open-label, randomized controlled trial.

Methods: Treatment-naïve *H. pylori*-infected patients were randomly allocated 1:1 to the VA group (vonoprazan 20 mg twice daily and amoxicillin 750 mg four times daily, for 14 days) or the RBAC group (rabeprazole 10 mg, bismuth potassium citrate 220 mg, amoxicillin 1000 mg and clarithromycin 500 mg twice daily, for 14 days). *H. pylori* clarithromycin resistance and CYP2C19 gene polymorphisms were detected with real-time polymerase chain reaction (PCR) technique. The eradication rates and adverse events were analyzed.

Results: A total of 151 patients were enrolled. The intention-to-treat (ITT), modified intention-to-treat (mITT), and per-protocol (PP) eradication rates and their 95% confidence intervals (95% CIs) were 94.6% (86.0–98.3%), 98.6% (91.3–99.9%), and 98.5% (90.9–99.9%) for VA group and 87.0% (77.0–93.3%), 91.8% (82.3–96.6%), and 93% (83.7–97.4%) for RBAC group. The eradication rate of the VA group was noninferior to the RBAC group in ITT, mITT, and PP analyses ($p < 0.0001$). In patients infected with strains of clarithromycin resistance point mutation, the eradication rate of the RBAC group decreased to lower than 90%, but the difference from the VA group did not achieve statistical significance (ITT eradication rate: 81.5% in the RBAC group and 96.2% in the VA group, $p = 0.192$). The incidence of adverse events in the VA group was 39.2%, which was significantly lower than that in the RBAC group (79.2%, $p = 0.000$).

Conclusion: The efficacy of VA dual therapy is noninferior to RBAC in *H. pylori* first-line eradication, with fewer adverse reactions.

Registration: This study was registered at the Chinese Clinical Trial Registry (ChiCTR2100052550) on 30 October 2021.

Keywords: bismuth quadruple therapy, clarithromycin resistance, eradication treatment, *Helicobacter pylori*, vonoprazan–amoxicillin dual therapy

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Correspondence to:

Weihong Wang
Department of
Gastroenterology, Peking
University First Hospital,
No.8 Xishiku Street,
Beijing 100034, China.
wangweihong2581@163.com;
weihongwang03829@pkufh.com

Xiaolei Wang
Guigen Teng
Xinhong Dong
Yun Dai
Department of
Gastroenterology, Peking
University First Hospital,
Beijing, China

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Introduction

Helicobacter pylori (*H. pylori*) is one of the major causes of gastrointestinal diseases such as peptic ulcer, chronic active gastritis, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer.¹ Eradication of *H. pylori* is recommended by consensus to prevent and treat the associated diseases.^{2,3} However, with the increase in antibiotic resistance, the success rate of *H. pylori* eradication therapy has declined in recent years.⁴ It has been reported that the primary resistance rate of *H. pylori* to clarithromycin is over 15% in all WHO regions except the Americas and South-East Asia region and over 30% in the Western Pacific region.⁵ Resistance of clarithromycin is significantly associated with the failure of clarithromycin-containing regimens, causing huge public health and social impacts.⁶ In most parts of the world, the eradication rate of standard triple therapy containing amoxicillin and clarithromycin has decreased to unacceptable levels. As the addition of bismuth salts to standard triple therapy increases the success rate in resistant *H. pylori* eradication by 30–40%,⁷ multiple main consensuses recommend the use of bismuth-containing quadruple therapy in areas of high clarithromycin resistance to achieve an acceptable eradication rate.^{3,8} The major disadvantages of bismuth-containing quadruple therapy are complexity and side effects, which result in reduced compliance.^{9,10} Incomplete adherence to antibiotic therapy may cause the selection of resistant mutants and induce antibiotic resistance to *H. pylori*. In addition, the combination of broad-spectrum antibiotics increases the risk of intestinal microbiota dysbiosis.¹¹ Therefore, it is of considerable practical significance to explore new regimens that include fewer antibiotics, higher convenience, and fewer side effects.

Since the primary resistance and acquired resistance of *H. pylori* to amoxicillin are both rare,^{5,12} there has been a constant interest in proton pump inhibitors (PPIs) and amoxicillin dual therapy. Recently, high-dose PPI (3–4 times/day) plus amoxicillin (3000 mg/day) dual therapy (HDDT) for 14 days was reported to be not inferior to bismuth quadruple therapy containing amoxicillin and clarithromycin in initial *H. pylori* eradication.^{13,14} In this regimen, the enhanced acid inhibition provided by high-dose and high-frequency use of PPI is one of the key factors for successful eradication.¹⁵ Vonoprazan (VPZ), a novel

potassium-competitive acid blocker (P-CAB), produces more rapid, profound, and durable suppression of gastric acidity than PPIs.¹⁶ These properties are believed to contribute to achieve higher success rates in *H. pylori* eradication therapies.¹⁷ Meta-analyses from Japan demonstrated that replacement of PPI with VPZ (20 mg twice daily) in standard triple therapy significantly improved eradication rates without increasing the incidence of adverse events in both first-line and second-line regimens.¹⁸ We therefore speculated that the replacement of PPI with VPZ in HDDT may also achieve a more satisfactory eradication rate.

As a first-line regimen, low-dose Vonoprazan–amoxicillin dual therapy (VA dual therapy) (VPZ 20 mg twice daily and amoxicillin 1500 mg/day) has been reported to reach an eradication rate of nearly 90% in Japan.¹⁹ In China, 10 days of high-dose VA dual therapy (VPZ 20 mg twice daily and amoxicillin 750 mg four times daily) demonstrated an eradication rate of 93.4%.²⁰ However, although the eradication rate of VA dual therapy (77.2%) was not inferior to standard triple therapy in the United States and Europe in treatment-naïve patients,²¹ it was substantially lower than that in East Asia, suggesting that the effectiveness of VA dual therapy may be of regional and/or ethnic differences. Unfortunately, few studies to date have provided background data on *H. pylori* antibiotic resistance or polymorphism of drug metabolism of participants to enable further analysis of the difference.

In this study, we investigated the efficacy and safety of high-dose VA dual therapy for 14 days as first-line treatment for *H. pylori* eradication in Northern China by comparing it with bismuth quadruple therapy containing amoxicillin and clarithromycin, and further analyzed the effects of *H. pylori* clarithromycin resistance on eradication rate.

Materials and methods

Study design

Our study was designed as a single-center, open-label, randomized controlled trial and conducted according to the CONSORT statement. The study was in accordance with the Declaration of Helsinki.

Study population

This study was conducted at the Department of Gastroenterology of Peking University First Hospital during the period from 30 October 2021 to 1 November 2022. The inclusion criteria were as follows: (1) treatment-naïve patients aged 18–70 and (2) *H. pylori* positive, diagnosed by a positive ¹³C-UBT test within 1 month. The subjects were excluded if they were (1) allergic to any of the study drugs; (2) with the history of gastrointestinal surgery; (3) in clinical conditions that could affect the evaluation of the treatment: hepatic/renal/cardiac dysfunction, malignancy, or mental diseases; (5) administered with PPIs, antibiotics, anticoagulants, or steroids within 8 weeks, or concomitant use of these drugs; (6) pregnancy or lactation; and (7) body weight below 40 kg.

Randomization and intervention

The simple randomization was carried out using random numbers generated with the SPSS 25.0 software. The sealed envelope method was used for allocation concealment. Participants were randomly assigned 1:1 to the open-label VA group (VPZ-amoxicillin dual therapy group) or RBAC group (bismuth quadruple therapy containing amoxicillin and clarithromycin). The VA group received VPZ (Takeda Pharmaceutical Co, Osaka, Japan) 20 mg twice daily and amoxicillin capsules (Kangenbei Pharmaceuticals Ltd, Jinhua, China) 750 mg four times daily. The RBAC group received rabeprazole (Eisai Co. Ltd., Tokyo, Japan) 10 mg twice daily, bismuth potassium citrate (Livzon Pharmaceutical Group, Inc., Zhuhai, China) 220 mg twice daily, amoxicillin (Kangenbei Pharmaceuticals Ltd, Jinhua, China) 1000 mg twice daily, and clarithromycin (Abbott Laboratories Ltd., Shanghai, China) 500 mg twice daily. The treatment lasted for 14 days. All participants were requested to refrain from alcohol consumption during and within 1 week after the treatment.

Procedures

Upon enrollment, detailed records of demographic information, past medical history, and drug medication were recorded. Participants underwent upper gastroscopy prior to medication, and one mucosa sample was taken from the antrum of the stomach to determine point mutations conferring clarithromycin resistance and

CYP2C19 polymorphism. VA or RBAC regimen was prescribed according to the randomized allocation. Compliance information and adverse events during treatment were collected within 1 week after the end of medication via an online questionnaire survey. ¹³C-UBT was repeated 4–6 weeks after the last dose of the study drug to evaluate the therapeutic outcome.

Determination of clarithromycin resistance point mutation and CYP2C19 gene polymorphism

Total DNA was extracted from biopsy specimens using a QIAamp DNA FFPE Tissue kit (QIAGEN, Germany) according to the manufacturer's instructions and stored at –80°C until analysis. The 2142 and 2143 locus of *H. pylori* genome DNA encoding 23S rRNA were amplified and the mutations of A2143G, A2142G, and A2142C were detected using a real-time fluorescent probe PCR assay (*H. pylori* Antibiotic Resistance Gene Mutation Detection Kit, the NewGLife, China). Mutations were indicated by FAM-labeled fluorescent probes, while *H. pylori* 16S rRNA genes were indicated by HEX/VIC-labeled fluorescent probes. If the difference between $C_{t_{FAM}}$ and $C_{t_{HEX/VIC}}$ is less than 9, mutations in two sites of the 23S rRNA gene were considered to be present, that is, clarithromycin resistance. CYP2C19 genetic polymorphism was detected with real-time PCR technique (CYP2C19 Gene Polymorphism Detection Kit, the NewGLife, China). The metabolic types of patients were divided as extensive metabolizer (EM, CYP2C19 *1/*1), intermediate metabolizer (IM, CYP2C19*1/*2 or *1/*3), or poor metabolizer (PM, CYP2C19*2/*2, *3/*3 or *2/*3), according to their CYP2C19 genotypes.

Sample size

This study was a noninferiority trial. According to previous studies, the eradication rate of VA dual therapy could reach 92.9%.²² While in recent meta-analyses, the eradication rate of bismuth-containing quadruple therapy containing amoxicillin and clarithromycin was 89%.⁴ The inspection level α was set as 0.025 (unilateral), the power $1-\beta$ as 0.80, and the non-inferiority margin as 10%. Based on the sample size calculation formula

$$n = \left\{ (z_{1-\alpha} + z_{1-\beta})^2 \left[p_1(1-p_1)/k + p_2(1-p_2) \right] \right\} / (\delta - \Delta)^2,$$

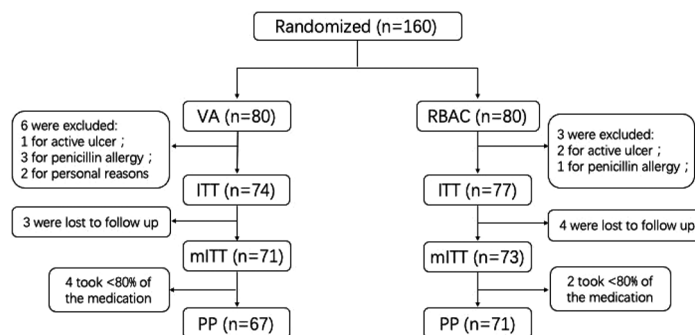


Figure 1. Flowchart of patient selection and grouping.
ITT, intent-to-treat; mITT, modified intention-to-treat; PP, per-protocol.

a minimum of 66 patients were required in each group. With a lost-to-follow-up rate of 10%, a sample size of 73 in each group was determined.

Outcome assessment

The primary end point of this study was the eradication rate in each group. Successful eradication was defined as a negative result of ^{13}C -UBT (Fisher Analysen instruments GmbH, Leipzig, Germany) 4–6 weeks after the treatment period. The secondary end points were the incidence of adverse events, medication adherence, and the comparison of the eradication rate between the two groups according to point mutations of clarithromycin resistance. Good adherence was defined as taking at least 80% of the prescribed study medication.

Statistical analysis

Eradication rates were evaluated using intention to treat (ITT), modified ITT (mITT), and per-protocol (PP) analysis. ITT analysis was based on the full analysis set, which included participants enrolled following the inclusion and exclusion criteria and received at least one dose of the study medication. Participants who received at least one dose of study medication and completed the final follow-up were included in the mITT analysis. Patients who received over 80% of the study medication and completed the final follow-up were included in the PP analysis. The Wilson method with continuous correction was used to calculate 95% CI of the eradication rate. The differences between the eradication rates and their 95% CI were calculated using the normal approximation method. The noninferiority

hypothesis was tested using a one-sided μ -test with a noninferiority margin of 10%.

Statistical analyses were performed using SPSS (version 25.0; SPSS, Inc., Chicago, IL, USA) and SAS (version 9.4; SAS Institute, Inc., Cary, NC, USA). Student's t -test was used to compare the quantitative data conforming to a normal distribution, and Mann–Whitney U test was performed for those not conforming. Classified data were reported as percentages and compared by χ^2 test. $p < 0.05$ was considered statistically significant.

Results

Subject characteristics

From 1 November 2021 to 1 November 2022, a total of 160 treatment-naïve *H. pylori*-infected patients were randomized, 80 to the VA group and 80 to the RBAC group. During the screening process, three patients were excluded for active peptic ulcer, four for penicillin allergy, and two refused to participate for personal reasons. A total of 151 people were included in the study. Of which, 74 were in the VA group and 77 in the RBAC group. In the VA group, three patients were lost to follow-up and four received less than 80% of the medication. In the RBAC group, four patients were lost to follow-up and two received less than 80% of the medication (Figure 1). The final follow-up was completed on 15 January 2023.

The demographic characteristics and clinical information of the participants are shown in Table 1. No significant differences were found in baseline characteristics between the groups.

Table 1. Baseline characteristics and demographics of the included patients.

Characteristic	Total (n=151)	VA (n=74)	RBAC (n=77)	p Value (chi-square)
Age, year, (mean $\pm$ SD)	44.3 $\pm$ 9.8	44.2 $\pm$ 10.8	44.5 $\pm$ 8.8	0.844
Gender (female %)	53.6	51.4	55.8	0.580
BMI (median (IQR))	23.2 (5.0)	23.5 (5.4)	23.1 (4.6)	0.596
Smoking (%)	9.9	6.8	13	0.201
Alcohol consumption (%)	31.8	33.8	29.9	0.606
Family history of gastric malignancy (%)	11.9	9.5	14.3	0.360
CYP2C19 gene polymorphism				
EM (%)	39.1	43.2	35.1	0.303
IM (%)	48.3	44.6	51.9	0.366
PM (%)	12.6	12.2	13.0	0.879
Gastroscopy diagnosis				
Non-atrophic gastritis (%)	58.3	55.4	61.0	0.483
Atrophic gastritis (%)	41.7	44.6	39.0	0.483
Peptic ulcer (non-acute phase) (%)	19.9	23.0	16.9	0.348
Reflux esophagitis (%)	6.0	4.1	7.8	0.332
BMI, body mass index; IQR, interquartile range; SD, standard deviation.				

H. pylori eradication rate

ITT analysis was performed based on the full analysis set. *H. pylori* was successfully eradicated in 70 of 74 patients in the VA group, with an eradication rate of 94.6% (95% CI: 86.0–98.3%). In all, 67 of 77 patients in the RBAC group got *H. pylori* successfully eradicated, with an eradication rate of 87.0% (95% CI: 77.0–93.3%) (Figure 2). The difference in eradication rate between the two groups was 7.6% (95% CI: –1.5% to 16.7%).

After excluding patients who did not complete the final follow-up, mITT analysis was performed. The mITT eradication rate was 98.6% (95% CI: 91.3–99.9%) in the VA group and 91.8% (95% CI: 82.3–96.6%) in the RBAC group. The difference in eradication rate was 6.8% (95% CI: –0.1% to 13.7%).

PP analysis was performed after further exclusion of the patients taking less than 80% of the

medication. The PP eradication rate was 98.5% (95% CI: 90.9–99.9%) in the VA group and 93.0% (95% CI: 83.7–97.4%) in the RBAC group. The difference in eradication rate was 5.6% (95% CI: –1.1% to 12.2%).

Noninferiority analyses revealed that the eradication rate of *H. pylori* in VA group was statistically not inferior to RBAC group ($Z=3.78$, $p<0.0001$ in ITT; $Z=4.80$, $p<0.0001$ in mITT and $Z=4.60$, $p<0.0001$ in PP analysis).

The effects of clarithromycin resistance point mutations

23S rRNA gene point mutations associated with clarithromycin resistance were detected in 53 patients. In which 26 patients were in the VA group and 27 in the RBAC group. The total clarithromycin resistance rate was 35.1% (53/151), which was consistence with previous reports.⁵

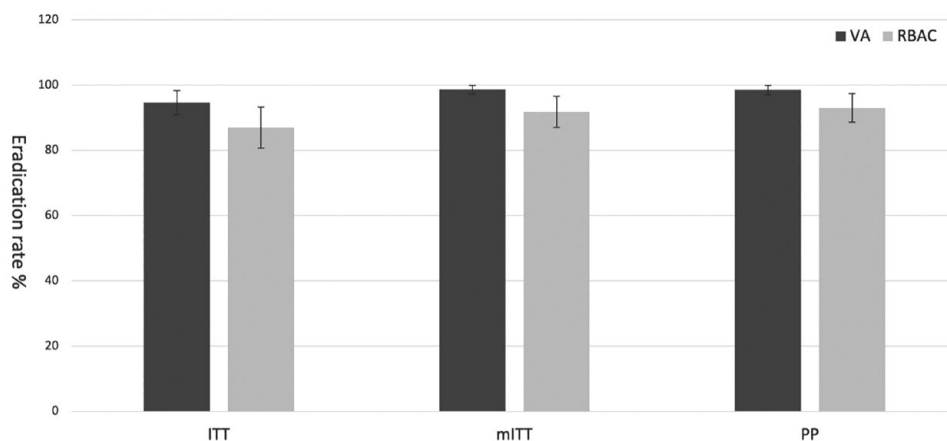


Figure 2. Comparison of the eradication rates between VA and RBAC groups. ITT, intent-to-treat; mITT, modified intention-to-treat; PP, per-protocol.

Table 2. Comparison of the eradication rates according to 23S rRNA point mutation in each group.

Clarithromycin resistance point mutation	ITT (% 95% CI)		<i>p</i> Value	PP (% 95% CI)		<i>p</i> Value
	VA	RBAC		VA	RBAC	
Wild strain	93.8 [81.8–98.4]	90.0 [77.4–96.3]	0.498	100	93.8 [81.8–98.4]	0.243
Mutant strain	96.2 [78.4–99.8]	81.5 [61.3–93.0]	0.192	96.2 [78.4–99.8]	88.0 [67.7–96.9]	0.350
<i>p</i> Value	0.662	0.289		0.188	0.406	

In the VA group, similarly, high eradication rates were achieved in patients infected with wild or mutant strains (ITT eradication rate: 93.8% for wild strain and 96.2% for mutant strains; PP eradication rate: 100% for wild strain and 96.2% for mutant strains), suggesting that the efficacy of VA dual therapy was not affected by clarithromycin resistance. In the RBAC group, a decreasing tendency was demonstrated for the eradication rate in patients infected with mutant strains (ITT eradication rate: 90.0% for wild strain and 81.5% for mutant strains; PP eradication rate: 93.8% for wild strain and 88.0% for mutant strains), but the difference was not statistically significant.

In patients infected with wild strain, the eradication rates were similar between VA and RBAC groups (ITT eradication rate: 93.8% in the VA group and 90.0% in the RBAC group; PP eradication rate: 100% in the VA group and 93.8% in the RBAC group). In patients infected with mutant strains, VA dual therapy maintained a high eradication rate (ITT and PP eradication

rates were both 96.2%), while the eradication rate of RBAC group decreased to lower than 90% (ITT: 81.5%, PP 88%). But the difference did not achieve statistical significance ($p=0.192$, 0.350, respectively). Detailed information is shown in Table 2.

Adverse events and compliance

Totally, 29 patients (39.2%, 95% CI: 27.8–50.6%) in the VA group and 61 patients (79.2%, 95% CI: 70.0–88.5%) in the RBAC group reported adverse events, with statistically significant differences ($p=0.000$). In VA group, the most common adverse events were diarrhea (20.3%), epigastric discomfort (20.3%), and skin rash (6.8%). In the RBAC group, the most common adverse events were bitter mouth (67.5%), diarrhea (22.1%), and epigastric discomfort (11.7%; Table 3).

In the VA group, one patient discontinued the therapy on day 7 for epigastric discomfort. One

Table 3. Adverse events.

Symptom	VA <i>n</i> (%)	RBAC <i>n</i> (%)	<i>p</i> Value (chi-square)
Diarrhea	15 (20.3)	17 (22.1)	0.786
Epigastric discomfort	15 (20.3)	9 (11.7)	0.149
Skin rash	5 (6.8)	8 (10.4)	0.565
Bitter mouth	2 (2.7)	52 (67.5)	0.000*
Deepened urine color	4 (5.4)	8 (10.4)	0.369
Insomnia	0 (0)	1 (1.3)	1.000
Regurgitation	0 (0)	1 (1.3)	1.000
Total adverse events	29 (39.2)	61 (79.2)	0.000*

*The incidence of bitter mouth and total adverse events in VA group was significantly lower than that in RBAC group.

was discontinued on day 7 for skin rash and one on day 11 for personal reasons. In the RBAC group, two patients discontinued on day 5 and day 9 for skin rash. All adverse events were manageable and reversible. Five patients took oral antiallergics for skin rash and recovered.

In all, 67 patients in the VA group and 71 in the RBAC group completed at least 80% of the study drugs. There was no significant difference in medication compliance between the two groups ($p = 0.358$).

Discussion

Our present study indicated that high-dose VA dual therapy achieved a good eradication rate in first-line treatment of *H. pylori* infection, which was not inferior to bismuth quadruple therapy containing amoxicillin and clarithromycin, with a lower frequency of adverse events. VA dual therapy was a simple, effective, and safe eradication regimen, which was not affected by clarithromycin resistance.

As one of the most prescribed antibiotics in *H. pylori* eradication, amoxicillin interferes with peptidoglycan synthesis and damages bacterial cell walls to achieve a bactericidal effect by binding to penicillin-binding proteins (PBPs). Resistance of *H. pylori* to amoxicillin is mainly mediated by mutations of PBPs-related genes. In most cases, single amino acid substitution mediates only low to moderate levels of resistance, while accumulation of multiple point mutations leads to

higher resistance levels.²³ Since the accumulation of point mutations is not an easy task, the primary resistance and acquired resistance of *H. pylori* to amoxicillin are both rare.^{5,12} On the other hand, pharmacokinetic studies have shown that amoxicillin is a time-dependent antibiotic. Increasing the dosing frequency to 600–750 mg per 6 h can maintain the mucosal concentration above the minimum inhibitory concentration for as long as possible so that the bactericidal activity of amoxicillin can be maximized.¹⁴ Meanwhile, the stability of amoxicillin is pH dependent. It is unstable in an acidic environment and achieves maximum stabilization when pH is near 6.0.²⁴ In addition, when the intragastric pH is over 6, *H. pylori* enters the replicative state where they become more susceptible to amoxicillin.¹³ These factors together determine that amoxicillin is an effective antibiotic for *H. pylori* eradication and that intragastric pH has a highly significant impact on the effectiveness of amoxicillin.

HDDT, in which high doses of PPIs are administered to increase the intragastric pH, has been shown to have acceptable eradication rates. The advent of P-CAB has made inhibition of gastric acid easier and more effective. P-CAB inhibits both active and resting H^+ , K^+ -ATPase by reversible K^+ -competitive binding,²⁵ to more strongly inhibit gastric acid secretion. Pharmacodynamic data showed that the intragastric pH was above 4.0 at 4 h after the first administration of VPZ 20 mg and sustained for up to 24 h. Administration of VPZ (20 mg twice daily) for seven consecutive days could maintain the intragastric pH above 5

for almost the whole day.²⁶ These properties have a favorable synergistic effect with the bactericidal mechanism of amoxicillin so that VA dual therapy can achieve a relatively satisfactory eradication rate.

VA dual therapy has aroused considerable concern worldwide and has been reported by many studies in recent years. Recently, several studies have explored the dosage and course of VA dual therapy.^{27–29} Overall, the eradication rate was positively correlated with the dose of amoxicillin, the frequency of administration, and the duration of treatment. A course of ≥ 10 days, a daily dosage of > 3 g/days, and a dosing frequency of ≥ 3 times daily may be necessary for achieving a satisfactory eradication rate of over 90%. Several studies compared VA dual therapy with standard triple therapy^{30,31} or bismuth-containing quadruple therapy²⁰ and demonstrated the noninferiority and safety for the former. However, there have been few studies investigating the effect of VA dual therapy on antibiotic-resistant *H. pylori* strains so far. Only one study from Japan³¹ reported that VA dual therapy was superior to VA-clarithromycin triple therapy in clarithromycin-resistant strains.

The resistance rate of *H. pylori* to clarithromycin is considerably high and has led to a decline in the eradication rates of conventional regimens. In patients infected with clarithromycin-resistant strains, the eradication rate of 14-day triple therapy was barely 46.2%.³² The addition of bismuth salts increased the success rate in resistant *H. pylori* to 84.6%,³³ which was in accordance with our study, but increased the variety of drugs and adverse events. Clarithromycin-resistant *H. pylori* has been listed as one of the high priority pathogens for the development of new drugs by the World Health Organization.⁶ Therefore, the eradication rate of clarithromycin-resistant strains is of great value in evaluating new first-line regimens. Traditionally, the detection of antibiotic-resistant *H. pylori* has relied on culture and antimicrobial susceptibility testing. But this method is technically demanding, time-consuming, and with a low success rate, which limits its clinical use.³⁴ Clarithromycin inhibits bacterial growth by targeting the 50S subunits of the ribosome. The 50S subunit of *H. pylori* is encoded by 23S rRNA. Mutations at key sites in its V region can alter the spatial conformation of the bacterial ribosome, weakening its affinity for

clarithromycin and leading to drug resistance. Of these, the most common point mutations are A2146C, A2146G, and A2147G. Detection of the above three mutations using molecular biological approaches can identify about 85% of clarithromycin-resistant strains,^{34,35} which can meet clinical needs. In our study, we detected *H. pylori* 23S rRNA mutations associated with clarithromycin resistance (A2142–43G, A2142C) using real-time PCR technique and analyzed the effect of clarithromycin resistance on the eradication rates of VA dual therapy. It was found that VA dual therapy provided a stably high eradication rate in both wild and mutant strains. Moreover, the eradication rate of VA dual therapy tended to be higher than the RBAC regimen in clarithromycin-resistant strain. But due to the relatively small sample size, the difference did not reach statistical significance.

In addition to antibiotic resistance, CYP2C19 gene polymorphism is another essential factor associated with *H. pylori* eradication failure.³⁶ CYP2C19 is responsible for the primary metabolism of many drugs, including the earlier-generation PPIs. So that when the regimen includes PPIs that are heavily metabolized by CYP2C19, the enhanced metabolic phenotype of CYP2C19 is associated with higher rates of treatment failure.³⁷ The dependent degree of various PPIs metabolism on CYP2C19 is different. Of which, the main metabolic pathway of rabeprazole has been reported to be mainly via a non-enzyme metabolism (approximately 85%), with only minor involvement of CYP2C19 so that its acid inhibition effect is not easily affected by CYP2C19 gene polymorphism.³⁸ As for VPZ, it is metabolized by a variety of enzymes including CYP3A4, CYP2C19, and sulfotransferase, among which the contribution of CYP2C19 is considered to be of little importance.³⁹ In our study, both groups were treated with acid suppressants that were not affected by CYP2C19 gene polymorphism, thereby reducing the impact of confounders on eradication rates. The results indicated that there was no difference in eradication rates between different metabolizers (EM *versus* IM/PM), either in VA or in RBAC groups (Supplemental Table S1).

Currently, the RBAC regimen has been recommended as the first-line eradication regimen in areas of high antibiotic resistance, with an acceptable eradication rate. However, adverse events are common due to the presence of bismuth and

two broad-spectrum antibiotics. The most frequently reported adverse events are bitter mouth and black stool. Although these symptoms are mild and reversible, they affect patients' willingness to continue the therapy and lead to poor compliance. The fact that PPI should be taken 30 min before meals also makes it difficult to take the medicine on time in real life. Compared with the RBAC regimen, VA dual therapy eliminates the bismuth and one antibiotic, and presents a significantly lower incidence of adverse effects. Moreover, since the absorption rate and acid-suppressive effect of VPZ are not affected by meals,⁴⁰ VPZ can be taken together with amoxicillin after meals, which also improves convenience and compliance. It should be noted that, instead of by telephone or outpatient follow-up, we collected adverse event data using an online questionnaire to allow patients to choose from a series of symptoms listed in advance, which might remind patients to recall mild symptoms. Therefore, in our study, the incidence of adverse events in both VA and RBAC groups seemed higher than previous reports,⁴¹ but the trend of difference between the two groups was the same as before.

There were some limitations in the present study. First, published data showed that eradication rates of vonoprazan-containing regimens differed greatly among countries and regions.^{16,21,27,30} The reasons are still unclear. Our study was a single-center study with most of the patients coming from Beijing and surrounding areas. Whether the results of this study can be generalized to other regions remains to be further determined. Second, in our study, clarithromycin resistance was detected by a molecular biological approach. A small proportion of clarithromycin-resistant strains caused by rare mutations might be missed, which could potentially underestimate the eradication rate in patients infected with clarithromycin-susceptible strains. Third, this study was a noninferior study with a relatively small sample size so the superiority test failed to reach statistical significance, especially in clarithromycin-resistant strains. Well-designed, multicenter clinical trials with larger sample sizes are needed to verify the efficacy of VA regimens in the future.

Conclusion

Our study demonstrated that high-dose VA dual therapy may be a promising new regimen with

noninferior efficacy and fewer adverse reactions compared with bismuth quadruple therapy containing amoxicillin and clarithromycin.

Declarations

Ethics approval and consent to participate

The research was approved by the Ethics Committee of Peking University First Hospital (Scientific Research No. 2021-374) and registered at the Chinese Clinical Trial Registry (ChiCTR2100052550) on 30 October 2021. Written informed consent was obtained from all patients.

Consent for publication

Not applicable.

Author contributions

Xiaolei Wang: Conceptualization; Data curation; Investigation; Methodology; Project administration; Writing – original draft; Writing – review & editing.

Guigen Teng: Investigation; Writing – original draft.

Xinhong Dong: Investigation; Writing – original draft.

Yun Dai: Investigation; Writing – original draft.

Weihong Wang: Conceptualization; Data curation; Investigation; Methodology; Writing – original draft; 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 relevant to the study were included in the article. Further inquiries can be directed to the corresponding author.

ORCID iD

Xiaolei Wang  <https://orcid.org/0000-0002-6568-2394>

Supplemental material

Supplemental material for this article is available online.

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