ORIGINAL PAPER

DOI: http://dx.doi.org/10.15403/jgld-6183

Vonoprazan-containing Dual and Triple Therapies are Non-inferior to Bismuth-quadruple Therapy for *Helicobacter pylori* Eradication: A Single-center, Prospective, Open-label, Real-World Study

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Received: 03.03.2025
Accepted: 04.03.2025

ABSTRACT

Background & Aims: Vonoprazan (Vo) and amoxicillin (Amx) dual therapy has shown promising results for *Helicobacter pylori* (*H. pylori*) eradication. However, its efficacy needs to be verified in an area with a high prevalence of both *H. pylori* and gastric cancer. It is also unknown if the modified Vo-Amx plus bismuth (Bis) regimen might increase the eradication rate. We aimed to investigate the efficacy and safety of Vo-Amx and Vo-Amx-Bis regimens, compared to bismuth-containing quadruple therapy (BQT) for *H. pylori* eradication, as well as factors that affect the curing rate.

Methods: A total of 342 treatment-naïve *H. pylori*-infected patients were screened and 255 were enrolled and randomized into Vo-Amx, Vo-Amx-Bis, and BQT groups for treatment. *H. pylori* infection status was determined by ^{13}C-urea breath test. The eradication rate and incidence of adverse events were assessed, and factors that might affect the curing rate were also analyzed.

Results: In per-protocol (PP) analysis, *H. pylori* eradication rates in Vo-Amx, Vo-Amx-Bis, and BQT groups were 95.1%, 92.7%, and 90.4%, respectively (p>0.05). In intention-to-treat (ITT) analysis, eradication rates in Vo-Amx, Vo-Amx-Bis, and BQT groups were 91.8%, 89.4%, and 88.2%, respectively (p>0.05). The eradication efficacy of Vo-Amx and Vo-Amx-Bis groups was non-inferior to that of BQT group, and the incidence of side effects (including nausea, vomiting, anorexia, abdominal pain, diarrhea, palpitation, dizziness, and debilitation) was lower than that of BQT group (6.1% and 4.9%, vs 45.8%, respectively, p<0.001). Successful eradication was associated with lower body surface area (BSA) in BQT group (p<0.05), but not in Vo-Amx and Vo-Amx-Bis groups. Gender, cigarette smoking, alcohol drinking, side effects, education level, body mass index, infection status of family members, and the frequency of dining out did not affect the curing rate in all three groups (p> 0.05).

Conclusions: Efficacy of the two Vo-containing regimens was comparable and non-inferior to the BQT in this region, and could serve as the first-line regimen for *H. pylori* eradication, and reduced use of one antibiotic per each patient treatment in real-world clinical application.

Key words: *Helicobacter pylori* – vonoprazan – bismuth – amoxicillin – dual therapy – side effects.

Abbreviations: Amx: amoxicillin; Bis: bismuth; BQT: bismuth-containing quadruple therapy; BMI: body mass index, BSA: body surface area; *H pylori: Helicobacter pylori;* ITT: intention-to-treat; P-Cab: potassium channel blocker; PP: per protocol; PPI: proton pump inhibitor; Vo: vonoprazan.

INTRODUCTION

Helicobacter pylori (H. pylori) drug resistance has increased alarmingly following its massive eradication in China and globally in recent years. Reports have indicated that *H. pylori* drug-resistance rate to metronidazole has reached 60-90% and 20% to 40% to clarithromycin and levofloxacin respectively [1]. The antibiotics resistance rate to amoxicillin (Amx) and furazolidone, which has long been thought to be very low, is also starting to increase; the resistance rate to Amx and furazolidone has reached to 9.3%, and 10.1% respectively in some areas in China [2]. This will increase the probability of *H. pylori* treatment failure and reduce the effectiveness of eradication [3]. Therefore, optimizing the treatment regimens to reduce drug resistance is of great significance [4, 5].

Recently emerged high-dose proton pump inhibitor (PPI) or potassium channel blocker (P-Cab) plus Amx dual therapies have shown promising results with the eradication rates ranging from 87.5% [6] to 94.1% [7] in China, and non-inferior to PPI

based regimens [8-12]. These regimens have been recommended as first-line therapy for *H. pylori* eradication in 2022 Chinese national clinical practice guideline [1]. Vonoprazan (Vo) is a novel P-CAB type antisecretory agent that reversibly inhibits gastric H^+/K^+-ATPase, which has been shown to be effective in several clinical trials for *H. pylori* eradication. For example, the latest study in 2024 [11] comprising 298 subjects in Southern China, where primary resistance rates of clarithromycin and levofloxacin are >30%, showed that Vo-Amx dual (Vo 20 mg, b.i.d. and Amx 1 g, t.i.d.) and Vo-Amx triple therapies (Vo 20 mg, amoxicillin 1 g, clarithromycin 500 mg, b.i.d.) are highly effective and noninferior to bismuth-containing quadruple therapy (BQT) (96.0%, 95.9% vs 92.0%). One 2024 meta-analysis [9] including 13 trials mainly in Asia found that Vo-based therapy is superior to PPI-based therapy for *H. pylori* eradication, especially in patients with clarithromycin-resistant patients. Another 2024 meta-analysis [8] which included 5,815 patients reported that the 2-week Vo-based triple regimen has a higher eradication rate (94.7%) and could be the preferred choice for *H. pylori* eradication. Additionally, one 2022 study [12] in the United States and Europe involving 1,046 patients also reported that the Vo dual and triple therapy regimens were superior to lansoprazole triple therapy, both in patients who had a clarithromycin-resistant *H. pylori* strain (Vo triple therapy 65.8%, dual therapy 69.6%, vs lansoprazole triple therapy 31.9%) and in the overall population. These results indicated that Vo-containing regimens are promising regimens, but their efficacies varied by different regions.

The bactericidal effect of Amx is time and pH dependent, a combined application of acid inhibitors which raise the 24-hour pH above 6 in the stomach is critical for its bioavailability and activity [13]. It is desirable to use less frequent but effective drug concentrations during the treatment. Previous studies on Vo triple therapy often includes Vo plus two antibiotics [11, 14]; however, few studies have tested whether adding bismuth (Bis) to Vo dual therapy can reduce the amoxicillin dosage and frequency, and if the three times daily dose of Amx in Vo dual therapy is as effective as BQT in this region. Previous reports have indicated that adding Bis to the regimen could increase the eradication rate by around 30-40% [15], but no report is available on the role of Bis in Vo-dual regimens.

Henan province is a high-risk area for both *H. pylori* infection and gastric cancer with a population near 100 million [16]. Recent epidemiologic survey [17, 18] have shown its *H. pylori* household infection rates range from 70.11 to 87.23%, and individual infection rates are at 37.13-54.27%. The incidence of gastric cancer is 36.12/100,000 in this region, which ranks second in malignant tumors [19, 20]. The drug resistance rate of *H. pylori* to clarithromycin (74.3%) is also high, followed by levofloxacin (50.4%), but drug resistance rate to Amx (18.5%) and furazolidone (7.95%) is lower [2]. Therefore, optimizing treatment regimens will be important to reduce *H. pylori* regional infection rate for related disease prevention.

In this work, we compared the efficacy and safety of Vo-Amx dual, Vo-Amx-Bis triple therapy as well as the commonly applied BQT for *H. pylori* eradication. We investigated the relevant influencing factors in order to optimize *H. pylori* eradication regimen and to promote antibiotic stewardship and to reduce drug resistance.

METHODS

Subjects and Study Design

This single-center, prospective, open-label, real-world study was conducted at People's Hospital of Zhengzhou University, in Zhengzhou, Henan, China. From August 2021 to June 2023, a total of 342 treatment-naïve patients were screened from outpatient clinics and inpatient wards, but only 255 patients were finally enrolled and randomized. Written informed consent was obtained from all enrolled subjects.

Detailed inclusion criteria were as follows: 1) patients diagnosed with *H. pylori* infection by positive ^{13}C-urea breath test (UBT) either with or without immunohistochemical examinations; 2) adult patients aged between 18 and 70 years who were willing to participate. Patients were excluded if they met the following criteria: 1) recent use of PPIs, Bis, or antibiotics one month before initiating the treatment; 2) previous surgical history of upper gastrointestinal diseases; 3) pregnancy or lactation; 4) presence of severe diseases, such as mental illness, respiratory, heart, liver, lung or kidney diseases, malignant tumors, and other critical diseases.

This study followed the CONSORT statement requirement for the quality of reporting randomized control trials and was registered in the Chinese Clinical Trials Registry (www.chictr.org.cn) with registration number: ChiCTR2400087205, where research protocol is freely available. The study protocol was approved by the Hospital Ethics Committee (No.114,2022).

Drugs and Treatment Regimens

Drugs included Vo (Takeda Pharmaceutical Co. Ltd., Tianjin, China), rabeprazole (Haosen Pharmaceutical Co. Ltd., Jiangsu, China), Amx (Tongda Pharmaceutical Co. Ltd., Shanxi province, China), furazolidone (Yunpeng Pharmaceutical Co. Ltd., Shanxi, China) and Bis potassium citrate (Lizhu Pharmaceutical Factory Co. Ltd., Zhuhai, Guangdong, China). All drugs were certified and routinely prescribed in hospital pharmacy. Eligible patients with *H. pylori* infection were randomly assigned to three groups as follows:

(1) Vo-Amx: vonoprazan 20 mg b.i.d. and amoxicillin 1000 mg t.i.d. for 14 days; (2) Vo-Amx-Bis: vonoprazan 20 mg, amoxicillin 1000 mg and Bis potassium citrate 220 mg, b.i.d. for 14 days; (3) BQT: rabeprazole 20 mg, Bis potassium citrate 220 mg, Amx 1000 mg, and furazolidone 100 mg, b.i.d. for 14 days.

All patients taking amoxicillin and furazolidone were required to avoid alcohol and tyramine-rich foods during the treatment period and 1 week after discontinuation of drugs. If a serious allergic reaction occurred during the treatment period, intervention was terminated promptly, and appropriate medical measures were taken. If the patient requested withdrawal, the intervention was terminated accordingly.

Study Outcomes

Primary study endpoint was *H. pylori* eradication rate of the three treatment groups. A successful eradication was determined if ^{13}C-UBT (HY-IREXC 16 channel, Huayou Mingkang Photoelectric Technology Co. Ltd, Guangzhou, China) showed data over baseline (DOB) value<4.0 after 14 days of regulated dosing and 1 month after drug withdrawal. If UBT results fall into the marginal value (e.g., when ^{13}C-UBT values were around

4-6, local cutoff value is 0-4), ^{13}C-UBT reexamination will be performed to confirm the presence of infection; when a value is at 2 times higher than the upper limit of the reference range, it will be judged as failed eradication, and will be re-treated with different regimens later. The eradication rate was considered to be acceptable if the eradication rate was >85%.

The secondary study outcome was the incidence of adverse events and medication adherence, as well as factors that might affect the eradication rates. Patients were followed up through either telephone calls or face-to-face interviews. The severity of adverse events was graded 1–4 following the Common Terminology Criteria for Adverse Events (CTCAE) V5.0.10 criteria [21]: 1) Grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; 2) Grade 2: moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living; 3) Grade 3: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living; 4) Grade 4: life-threatening consequences; urgent intervention indicated. Medication adherence was defined as good when more than 90% of the prescribed medications were taken.

Statistical Analyses

Data were analyzed using SPSS software (Version 25, IBM Corp, New York, NY). *H. pylori* eradication rates were assessed by intention-to-treat (ITT) and per protocol (PP) analyses. Intention-to-treat analysis included patients who were lost during follow-up and with poor adherence; PP analysis included patients who took medication regularly and completed the full treatment course. Continuous variables were expressed as mean ± standard deviation and evaluated using one-way ANOVA test, and categorical variables using Pearson chi-square or Fisher's exact test; qualitative data were expressed as ratio (%) with a test level of α=0.05 (two-side). A "*p*" value less than 0.05 was considered as statistically significant.

RESULTS

Baseline Characteristics

During the 10-months study period, a total of 342 *H. pylori* infected patients were screened, and 255 patients who met the inclusion criteria were randomly allocated to Vo-Amx, Vo-Amx-Bis, and BQT groups (Fig. 1). In Vo-Amx, Vo-Amx-Bis, and BQT groups, 85, 85, and 85 patients completed ITT analysis; and 82, 82, and 83 patients completed PP analysis. There were no significant differences in age, gender, body mass index (BMI), body surface area (BSA), education level, smoking habits, drinking habits, family member infection, dining out variables, presence of diseases such as hypertension, and diabetes among the 3 groups (Table I).

***H. pylori* Eradication Rates and Influencing Factors**

In Vo-Amx, Vo-Amx-Bis, and BQT groups, *H. pylori* eradication rates by ITT analysis were 91.8% (78/85, 95%CI: 85.8-97.7%), 89.4% (76/85, 95%CI: 87.0-98.0%), and 88.2% (75/85, 95%CI: 81.2–95.2%), respectively (Table II). By PP analysis, the eradication rates were 95.1% (78/82, 95% CI 90.4-99.9%), 92.7% (76/82, 95% CI 87.0-98.0%), and 90.4% (75/83, 95% CI 83.9-96.8%), respectively. There was no significant difference in the eradication rate among the 3 regimens in both ITT and PP analysis (p>0.05). The eradication efficacy of Vo-Amx and Vo-Amx-Bis groups was non-inferior to that of the BQT group (p>0.05).

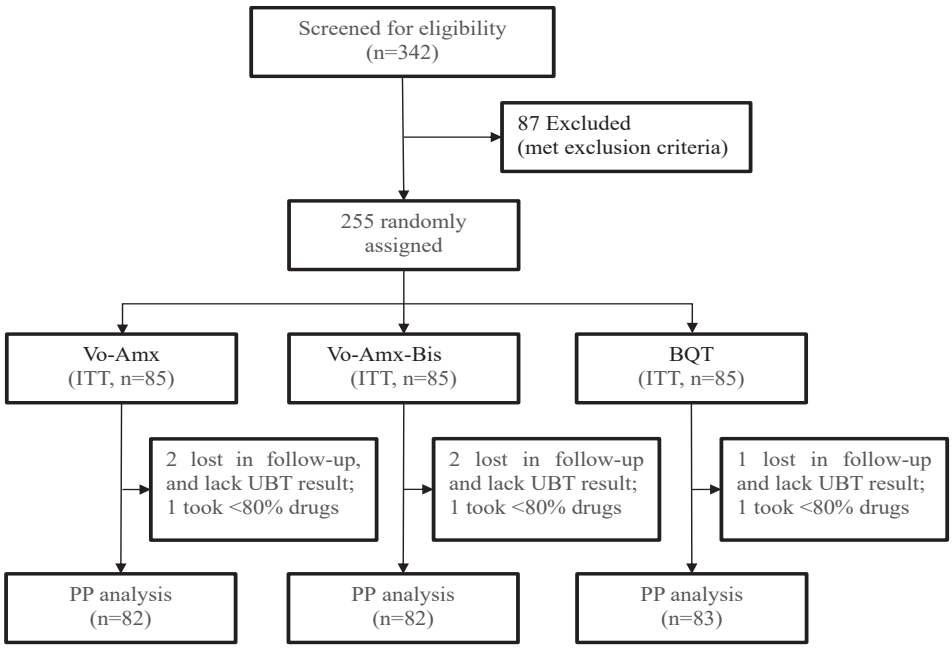

Fig. 1. Flow diagram of patient enrollment and study design. Vo-Amx: vonoprazan plus amoxicillin; Vo-Amx-Bis: vonoprazan plus amoxicillin and bismuth compound; BQT: bismuth-containing quadruple therapy; n: patient number; ITT: intention-to-treat; PP: per-protocol; UBT: ^{13}C-urea breath test.

Table I. Demographic and clinical data of enrolled patients

Variables/groups	Vo-Amx	Vo-Amx-Bis	BQT	p
Patient number (n)	85	85	85	
Age (years, mean±SD)	40.2±12.9	43.0±13.4	44.2±12.3	0.111
Gender (male/female)	44/41	39/46	45/40	0.615
BMI (kg/m^2, mean±SD)	23.2±3.2	23.8±3.1	23.2±2.9	0.314
BSA (m^2, mean±SD)	1.83±0.2	1.81±0.2	1.81±0.2	0.711
Education level				0.055
Junior or below	16	23	22	
Senior	7	12	18	
University or above	62	50	45	
Cigarette smoking	15	15	14	0.973
Alcohol drinking	23	21	16	0.427
Family member infection				0.102
no	40	35	31	
yes	23	20	34	
unclear	22	30	20	
Dining out (≥3/week or not)	36	24	29	0.152
Patients' diagnosis and endoscopy information				
^{13}C-UBT positive during health checkup	59(0)	42(0)	18(4)	0.000 a
Gastritis	22(22)	38(38)	61(46)	0.000 a
Gastroduodenal ulcer	4(4)	5(5)	6(6)	0.809
Hypertension	7	2	5	0.238
Diabetes	0	3	2	0.376
Loss of follow-up	3	3	2	>0.999
Adherence[b]	84	84	84	>0.999

Vo-Amx: vonoprazan plus amoxicillin; Vo-Amx-Bis: vonoprazan plus amoxicillin combined with bismuth; BQT: bismuth-containing quadruple therapy; BMI: body mass index; BSA: body surface area; Endo: number of patients examined by endoscopy; SD: standard deviation. [a] p<0.001, when patients showed ^{13}C-UBT positive during health checkup and diagnosed as gastritis were compared among the three groups; [b]Adherence, taken >80% of regimens.

Factors that may affect the treatment efficacy of the 3 regimens were presented in Table III. Successful eradication was associated with lower BSA in the BQT group (97.4% vs 84.4%, p<0.05). Gender, cigarette smoking, alcohol drinking, education level, BMI, family members infection status, the frequency of dining out, and side effects did not affect the curing rate in all three groups (p > 0.05).

Side Effects

The incidences of side effects in Vo-Amx, Vo-Amx-Bis, and BQT groups were at 6.1% (5/82), 4.9% (4/82), and 45.8% (38/83) respectively, and were lower in Vo-Amx and Vo-Amx-Bis groups compared with BQT group (p<0.001), especially in moderate and severe grade (p<0.001). The most common adverse reaction

Table II. *H. pylori* eradication rate in different treatment groups

Regimens	Vo-Amx	Vo-Amx-Bis	BQT	p
ITT analysis				
Eradication rate % (eradicated/n; 95%CI)	91.8 (78/85; 85.8-97.7)	89.4 (76/85; 87.0-98.0)	88.2 (75/85; 81.2-95.2)	>0.05
Difference from BQT group (adjusted 90% CI for difference)	3.53% (−4.03 to 11.09%)	1.18% (−6.77 to 9.12%)	_	
P value for difference[a]	0.443	0.808	_	
P value for non-inferiority[b]	0.0016	0.0104	_	
PP analysis				
Eradication rate % (eradicated/n; 95%CI)	95.1 (78/82; 90.4-99.9)	92.7 (76/82; 87.0-98.0)	90.4 (75/83; 83.9-96.8)	>0.05
Difference from BQT group (adjusted 90% CI for difference)	4.76% (−1.85 to 11.37%)	2.32% (− 4.8 to 9.45%)	_	
P value for difference[a]	0.239	0.592	_	
P value for non-inferiority[b]	0.0001	0.0022	_	

CI: confidence interval; ITT: intention-to-treat; PP: per-protocol. For the rest of abbreviations see Table I. [a] P values were from two-side comparisons the differences among Vo-Amx or Vo-Amx-Bis and BQT groups. [b] P values were obtained from one-side test comparisons of non-inferiority among Vo-Amx or Vo-Amx-Bis and BQT groups.

Table III. Factors affecting *H. pylori* eradication rates by PP analysis

Eradication rate in subgroups	Vo-Amx %(eradicated/n)	Vo-Amx-Bis %(eradicated/n)	BQT %(eradicated/n)
Patient number (n)	82	82	83
Gender			
Male	95.5 (42/44)	91.9 (34/37)	88.9 (40/45)
Female	94.7 (36/38)	93.3 (42/45)	92.1 (35/38)
p	0.635	0.564	0.456
Cigarette smoking			
Yes	86.7 (13/15)	100 (14/14)	78.6 (11/14)
No	97.0 (65/67)	91.2 (62/68)	92.8 (64/69)
p	0.151	0.313	0.128
Alcohol drinking			
Yes	91.3 (21/23)	100 (21/21)	81.3 (13/16)
No	96.6 (57/59)	90.2 (55/61)	92.5 (62/67)
p	0.312	0.159	0.178
Education level			
Senior high school or less	100 (20/20)	88.6 (31/35)	87.5 (35/40)
University or above	93.5 (58/62)	95.7 (45/47)	93.0 (40/43)
p	0.319	0.210	0.316
BMI, kg/m^2			
<23	95.2 (40/42)	97.2 (35/36)	97.1 (34/35)
≥23	95.0 (38/40)	89.1 (41/46)	85.4 (41/48)
p	0.673	0.168	0.075
BSA, m^2			
<1.81	94.1 (32/34)	93.0 (40/43)	97.4 (37/38)
≥1.81	95.8 (46/48)	92.3 (36/39)	84.4 (38/45)
p	0.553	0.614	0.049*
Infections in family members			
Yes	95.7 (22/23)	84.2 (16/19)	85.3 (29/34)
No	97.4 (37/38)	95.2 (60/63)	93.3 (28/30)
p value	0.616	0.134	0.268
Dining out (≥3/per week)			
Yes	94.4 (34/36)	91.3 (21/23)	82.8 (24/29)
No	95.7 (44/46)	93.2 (55/59)	94.4 (51/54)
p	0.594	0.542	0.094
Side effects			
Yes	100 (5/5)	100 (4/4)	92.1 (35/38)
No	94.8 (73/77)	92.3 (72/78)	88.9 (40/45)
p	0.774	0.734	0.456

For abbreviations see Table I. P was obtained from comparison within each Vo-Amx, Vo-Amx-Bis, and BQT groups. * P<0.05, when eradication rates were compared between higher BSA index (≥1.81) and lower BSA index (<1.81) in BQT group.

in BQT therapy was nausea (36.5%, 19/52, Table IV). In multiple hypothesis correction tests, there was no statistical difference in the frequency of nausea among these subgroups (Table IV).

In Vo-Amx group, the overall incidence of adverse events was 6.1%, with only 5 patients experiencing mild adverse events (CTCAE grade 1). The overall adverse event rate in Vo-Amx-Bis group was 4.9%, with only 2 patients experiencingmild adverse event (CTCAE grade 1) and 2 patients experiencingsevere adverse event (CTCAE grade 3). In the BQT group, the overall adverse events rate was 45.8%, with 27 patients experiencing mild adverse events (CTCAE grade 1), 9 patients experiencing moderate adverse events (CTCAE grade 2), and 2 patients experienced severe adverse events (CTCAE grade 3); and 1 patient withdrew from the trial due to adverse effects (Table IV). No patient experienced a severe adverse event (CTCAE grades 4).

Table IV. Drug adverse events in different treatment groups

Variables	Vo-Amx % (n/N)	Vo-Amx-Bis % (n/N)	BQT % (n/N)	p
Total	6.1 (5/82)	4.9 (4/82)	45.8 (38/83)	< 0.001*
Grade of Adverse event				
Mild	5	2	27	
Moderate	0	0	9	
Severe	0	2	2	
Moderate + severe	0	2	11	< 0.001*
Type of Adverse events				
Nausea	4	0	19	
Vomiting	0	0	5	
Anorexia	1	0	6	
Abdominal pain	0	0	4	
Diarrhea	0	0	3	
Skin rash	0	0	0	
Palpitation	0	0	4	
Dizziness	0	2	6	
Debilitation	0	2	5	
Dropout due to side effects	0	0	1	0.658

For abbreviations see Table I. *p < 0.001, when the incidences of drug adverse events and their grades in Vo-Amx group and Vo-Amx-Bis group were compared with BQT group.

DISCUSSION

Helicobacter pylori related drug resistance has emerged as an important issue for its eradication worldwide. Optimizing the eradication regimen is critical to reduce drug resistance. Our previous work [22] in 2022 on 292 patients has shown that the eradication rate of high dose dual therapy of rabeprazole-Amx regimen (rabeprazole 20 mg b.i.d. plus Amx 1000 mg t.i.d. for 14 days) achieved 89.6% eradication rate by PP analysis in central China. In current work, we further evaluated the efficiency and side effects of Vo-Amo, Vo-Amx-Bis, and BQT regimens in the treatment of native *H. pylori* infected patients. The result showed that the efficacy of vonoprazan-containing regimens was non-inferior to traditional BQT, and is safe, which provides an alternative choice for *H. pylori* eradication in this region.

Vonoprazan binds to cellular H^+/K^+-ATPase regardless of whether the enzyme is in an active or inactive state [23, 24], which works through a noncovalent and reversible manner, blocking potassium binding through competitive inhibition, causing rapid, profound, and sustained suppression of gastric acid secretion which results in the elevation of intragastric pH [25, 26], and improves the stability of antibiotics used in *H. pylori* treatment [27, 28]. In addition, the elevated intragastric pH also helps to promote *H. pylori* replication, increasing its susceptibility to antibacterial agents [13, 28]. Notably, an external pH in the narrow range of pH 6 to 7 is required for optimal *H. pylori* sensitivity to growth-dependent antibiotics such as Amx, clarithromycin, and tetracycline [29].

Vonoprazan-containing regimens are effective in *H. pylori* eradication similar to BQT therapy [22, 30-32]. However, several conditions remain to be optimized, including their duration, dosage, and frequency of antibiotics intake. For example, one study in 2022 in Nanjing, China on 375 individuals showed that 10-day Vo-Amx dual therapy (vonoprazan 20 mg b.i.d. plus amoxicillin 750 mg q.i.d.) provided eradication rates of >90%, with fewer adverse events, and similar adherence rate comparable to BQT regimen, but the twice daily regimen of Vo-Amx dual therapy had less satisfactory results (85.1%), indicating the less frequent drug intake may not be the optimal regimen [30]. One 2023 survey on 690 individuals in Wuhan, China reported that the eradication rate of 10-day Vo-Amx regimen achieved 91.4% by PP analysis [31]. Another multicenter study also found that Vo 20 mg twice a day plus Amx 750 mg 4 times a day all provide satisfactory efficacy (90.9% vs 94.5%) in both 10- and 14-days regimens [32]. These results demonstrate that higher dosage and more frequency of the Amx administration may achieve better treatment results.

The present work using Vo twice a day and Amx three times dosage provides more convenient and efficient treatment, and the efficacy is comparable to other studies [33, 34]. Further, the current work also showed fewer side effects compared to the standard BQT regimen. One study in 2024 in Hainan, China on 135 patients showed that the incidence of adverse effects was significantly lower in Vo dual therapy compared to Vo- and PPI-quadruple regimens [33]. Another study in 2023 in Beijing on 151 individuals also revealed that the efficacy of Vo-Amx dual therapy (Vo 20 mg twice daily and Amx 750 mg four times daily, for 14 days) is non-inferior to rabeprazole-BQT 14 day therapy with fewer adverse reactions [34]. These results indicate one advantage that using fewer antibiotics can maintain similar efficacy and have fewer drug side effects.

Bismuth plays a crucial role in *H. pylori* eradication. It is a chemical element with the symbol Bi (atomic number 83), and it is not an antibiotic [35]; Bis subsalicylate and Bis subnitrate have been used to treat peptic ulcers. Furthermore, it has antimicrobial activity, especially for *H. pylori* infection. The most striking point is that *H. pylori* strains that are resistant to Bis have not been reported, and bismuth is safe and effective in treating patient with drug resistance to other antibiotics [36, 37], and has a synergistic effect with antibiotics and may overcome clarithromycin and levofloxacin resistance [38].

One 2022 meta-analysis in China including eight studies and 340 individuals has shown that bismuth significantly increased the eradication rates of clarithromycin-, metronidazole-, and dual-resistant strains by 40%, 26%, and 59%, respectively [40]. Furthermore, addition of Bis can improve eradication rates, and Bis-containing regimens were better than non-Bis regimens, and increased the eradication rate by 3.5 times, and the incidence of total side effects was insignificant [15, 40]. Another study in 2013 in Shanghai which included 152 patients indicated that Bis was able to maintain treatment effectiveness in patients even with fluoroquinolone resistance rate as high as 25%; among 152 of 161 enrolled patients who completed treatment course, the eradication rate by PP analysis were 94.6% (70/74) with Bis, but only 85.9% without Bis (p=0.07) [41]. These results suggested that adding Bis to the regimen was able to improve the *H. pylori* eradication efficacy.

However, in present work, Vo-Amx-Bis regimen did not significantly increase the eradication rate and side effects over Vo-Amx treatment, which is an unexpected result. The explanation might be due to the reduction in the frequency of Amx from thrice to twice daily dosage. Additionally, it might also be that the Vo-Amx regimen has achieved eradication rates of 95.1% by PP and 91.8% by ITT analysis, which are already very high eradication rates, and adding one more compound might not be able to show additive effects to this regimen. Future large-scale studies are warranted to confirm these results.

Regarding the adverse effects, in Vo-Amx-Bis and BQT groups, aside from vonoprazan and PPI, the dosage and frequency of Amx and Bis were the same; therefore, furazolidone may be responsible for these adverse events (4.9%, vs 45.8%). Furazolidone is a nitrofuran antibiotic that is effectively against both gram-negative and gram-positive bacteria [42], which has shown high potency and safety for *H. pylori* eradication especially when used together with bismuth compounds [43]. A 2018 meta-analysis report which included 18 articles mainly in China and Iran indicated that the incidence of some adverse effects, such as fever, weakness, and anorexia, was higher in the furazolidone group than those in other antibiotic-containing groups, but the overall incidences of total side effects and severe side effects showed no differences between these groups [42]. In addition, our previous report in 2022 found that PPI-furazolidone dual therapy was less effective than the traditional BQT regimen [22].

Body surface area is an important part of antibiotic pharmacokinetics, closely related to basal human metabolism, and usually determines the course of treatment and the dose administrated. One recent study from 2023 including 385 naive patients shown that BSA (≥1.69 m^2), but not BMI, was an independent predictor that impacted on *H. pylori* eradication failure [44]. Our results are similar, we noted that low BSA patients have a higher eradication rate than those of high BSA patients in the BQT group, but this effect was not observed in the Vo-Amx and Vo-Amx-Bis groups (Table III). The explanations for the lower eradication rate in high BSA patients may be due to the lower Amx blood concentration and bioavailability than that in patients with low BSA levels. For example, one 2021 study from Japan including 163 patients showed that successful *H. pylori* eradication with Vo-Amx dual therapy was associated with the patient's small body size (90.8% in patients with BSA <1.723 vs. 79.6% in those with BSA ≥1.723; p=0.045) [45], which is in line with the current results. Therefore, a higher dose of antibiotics might be required to achieve maximal therapeutic effects in high BSA patients.

In current work, Vo-Amx therapy contains thrice the amoxicillin doses, and Vo-Amx-Bis contains an additional bismuth compound, these regimens contained Vo collectively may overcome the reduced effects observed in the BQT regimen related to BSA and BMI, the results could also be one unrevealed advantage of Vo-Amx-Bis regimen that Bis can compensate for the low frequency of Amx dosage in *H. pylori* eradication, but future studies will be necessary for a stratified analysis on drug doses and body size to achieve maximum therapeutic effects.

Despite these novel points, the current study has limitations. First, *H. pylori* culture, drug sensitivity, and measurement of intragastric pH level were not performed, as these assays require sophisticated equipment, biopsy samples, and laboratory accessibility. Future studies will be required to confirm the effects. Second, this study is a single center trial, aimed to investigate the eradication efficacy in central China, which is a clarithromycin highly resistant area, and the result may be improved with multi-center analysis. Third, this regimen may not be suitable for patients who are allergic to Amx, and other drugs such as tetracycline and cefuroxime will need to be tested. However, even with these limitations, the results have shown advantages of Vo-Amx dual and triple therapies for antibiotic stewardships, especially for *H. pylori* and gastric cancer prevalent areas.

CONCLUSIONS

Vonoprazan-containing regimens are effective and safe in *H. pylori* eradication in central China region and can be used clinically as first-line treatment. Future work is required to optimize antibiotic application, and to test the dual regimens with antibiotic other than Amx, such as tetracycline or cefuroxime, and help to reduce the antibiotic resistance during *H. pylori* eradication.

Conflicts of interest: None to declare.

Authors' contributions: Y.B.Q., X.T.L., L.D.Z., and S.Z.D. conceived and designed the study. Y.B.Q., X.T.L., X.H.F., and Q.Q.S. searched and screened related literature. Y.B.Q., X.T.L., L.X., W.J.Z., S.B.S., Q.N.Y., S.Y.S., C.Z., R.B.H., J.M., and W.X. performed data extraction. K.L., and T.T.L. performed quality assessment. Y.B.Q., X.T.L., A.M., and Q.Q.S. analyzed the data. Y.B.Q., X.T.L., Q.Q.S., and S.Z.D. wrote

the manuscript. S.Z.D. was responsible for funding and resource. All authors critically revised and approved the final version of the manuscript.

Acknowledgements: This work was supported by grants from the National Natural Science Foundation of China, NO U1604174; Health Commission of Henan Province-Province and Ministry Co-construction Project: NO. 20170123. I would like to thank all the collaborators and team members who participated in this study, whose professional knowledge provided an important guarantee for the smooth development of this study.

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