# Eradication Efficacy of Modified Dual Therapy Compared with Bismuth-Containing Quadruple Therapy as a First-Line Treatment of *Helicobacter pylori*

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OBJECTIVES: **This study assessed the effectiveness, adverse events, patient adherence, and costs of modified dual therapy compared with bismuth-containing quadruple therapy for treating *Helicobacter pylori* infection in Chinese patients. We also sought to determine whether modified dual therapy could be used as an alternative first-line treatment for *H. pylori* infection.**

METHODS: **A total of 232 *H. pylori*-infected, treatment-naive patients were enrolled in this open-label, randomized controlled clinical trial. Patients were randomly allocated into 2 groups: the 14-day modified dual therapy group and the bismuth-containing quadruple therapy group. Eradication rates, drug-related adverse events, patient compliance, and drug costs were compared between the 2 groups.**

RESULTS: **The modified dual therapy group achieved eradication rates of 87.9%, 91.1%, and 91.1% as determined by the intention-to-treat, per-protocol, and modified intention-to-treat analyses, respectively. The eradication rates were similar compared with the bismuth-containing quadruple therapy group: 89.7%, 91.2%, and 90.4%. In addition, modified dual therapy ameliorated variations in the CYP2C19, IL-1B-511, and *H. pylori* VacA genotypes. There were no significant differences in the compliance rates between the 2 groups. The modified dual therapy group exhibited significantly less overall side effects compared with the bismuth-containing quadruple therapy group ($P < 0.001$). Furthermore, the cost of medications in the modified dual therapy was lower compared with that in the bismuth-containing quadruple therapy.**

CONCLUSIONS: **Modified dual therapy at high dose and administration frequency is equally effective and safer and less costly compared with bismuth-containing quadruple therapy.**

**SUPPLEMENTARY MATERIAL** accompanies this paper at http://links.lww.com/AJG/A53

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## INTRODUCTION

*Helicobacter pylori* infection is a leading cause of gastrointestinal diseases, including peptic ulcers, chronic active gastritis, gastric mucosa-associated lymphoid tissue lymphoma, and ultimately deadly gastric adenocarcinoma (1). It has been estimated that as high as a half of the world's population has been infected with *H. pylori*, including approximately 700,000,000 individuals in China alone (2,3). The standard triple therapy for *H. pylori*, which consists of a proton pump inhibitor (PPI), clarithromycin, and amoxicillin, has been widely used as the first-line regimen to treat *H. pylori* infection across the world. Unfortunately, increasing resistance to antimicrobial agents has posed challenges for effectively treating *H. pylori* infection and has adversely affected eradication of the pathogen. For instance, the eradication rate of *H. pylori* has markedly declined, from 95% to 80% globally (4) and 89% to 78% in China (5). This decline is mainly attributed to an increase in resistance to clarithromycin, 1 of 3 medications in the standard triple therapy. Accordingly, the guidelines for the management of *H. pylori* infection in the Maastricht V Consensus and Toronto Consensus reports, a 14-day quadruple therapy is highly recommended as the first-line treatment regimen for *H. pylori* infection in patients who reside in countries/regions with a resistance prevalence to clarithromycin greater than 15% (6,7), including China, where resistance rates range from 20% to 50% for clarithromycin, 58% to 100% for metronidazole, and 20% to 45% for levofloxacin (8–10). Bismuth-containing quadruple therapy has therefore been highly recommended as the first-line treatment regimen for *H. pylori* infection in China according to

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the most recent Fifth Chinese National Consensus Report on *H. pylori* infection and management (11–13). Despite improvement in the cure rate, bismuth-containing quadruple therapy has limitations, which include increasing side effects mainly associated with the use of bismuth, poor compliance with medication use, high rates of resistance to clarithromycin and metronidazole, and high drug cost.

In contrast to high levels of *H. pylori* resistance to clarithromycin and metronidazole, resistance to amoxicillin has remained rare in China and other countries in the Asia-Pacific region as previously reported (8–10). Indeed, dual therapy consisting of omeprazole (20 mg, once or twice daily) and amoxicillin (1 g, twice daily) was initially proposed to treat *H. pylori* infection in the late 1980s (14), but this therapy achieved low eradication rates ranging from 55% to 62% (15). Amoxicillin is a pH-dependent (stable at a pH value $>$ 6) and time-dependent (absorbed more rapidly into the plasma and excreted within 6–8 hours after administration) antibiotic. Thus, primary dual therapy was modified by increasing both dosage and frequency of administration (16). According to a multi-center clinical study in Italian patients in 2015, a 10-day dual therapy with omeprazole (40 mg, 3 times daily) and amoxicillin (1 g, 3 times daily) achieved an overall high eradication rate of 87.5% (95% confidence interval [CI]: 78.8%–96.2%). Similarly, a 14-day dual therapy consisting of rabeprazole (20 mg, 4 times daily) and amoxicillin (750 mg, 4 times daily) achieved eradication rates of 95.3% (95% CI: 91.9%–98.8%) in treatment-naive patients and 89.3% (95% CI: 80.9%–97.6%) in those for whom *H. pylori* eradication failed after standard triple therapy, as determined by intention-to-treat (ITT) analysis. These eradication rates were significantly greater compared with the first-line standard treatment regimens regardless of CYP2C19 gene polymorphisms (17). To date, however, there have been inconsistent and conflicting reports on the efficacy of different dual therapies. For example, an ITT analysis conducted in the United States demonstrated that a 14-day dual therapy consisting of esomeprazole (40 mg, 3 times daily) and amoxicillin (750 mg, 3 times daily) had an eradication rate of 72.2% (95% CI: 56%–84%) in treatment-naive patients, the low cure rate was mainly attributed to high frequency of unfavorable CYP2C19 gene polymorphisms (18). In a recent ITT analysis of a 14-day dual therapy with ilaprazole (40 mg, twice daily) and amoxicillin (750 mg, 4 times daily) in Korean patients, the eradication rate in treatment-naive patients was 79.3% (95% CI: 61.6%–90.2%), which was similar to that in a Caucasian population (19). Because CYP2C19 genetic polymorphisms are different among any two populations, the polymorphism is unlikely to directly alter the effectiveness of dual therapy. Therefore, further investigation into how to maximize pharmacodynamics effects is required to determine if modified dual therapy is as effective as bismuth-containing quadruple therapy in different populations.

In this open-label, randomized controlled clinical trial study of *H. pylori*-infected, treatment-naive patients, we assessed the effectiveness, adverse events (AEs), patient adherence, and costs of modified dual therapy compared with bismuth-containing quadruple therapy concordant with variations in the CYP2C19, IL-1B-511, and *H. pylori* VacA genotypes, and we sought to determine if dual therapy could be used as first-line treatment regimen to eradicate *H. pylori* in Chinese patients. The findings presented from this clinical trial provide scientific evidence in support of modified dual therapy as a first-line treatment regimen, which could improve clinical outcomes, avoid unnecessary side effects, and reduce cost associated with *H. pylori* infection.

## PATIENTS AND METHODS

### Patients and study design

Patients aged 18–65 years who were diagnosed with chronic gastritis during gastroscopy and tested positive for *H. pylori* (+) determined by the Rapid Urease Test and $^{13}$C-Urea Breath Test (UBT) were initially screened and enrolled between January 2017 and December 2017 in the Department of Gastroenterology at the Daping Hospital of the Army Medical University. Detailed inclusion criteria were as follows: (i) age ranging from 18 to 65 years; (ii) chronic gastritis with or without healed duodenal or stomach ulcer; (iii) *H. pylori* (+) determined by Rapid Urease Test, UBT, and *H. pylori* culture; and (iv) treatment-naive patients for eradication of *H. pylori* infection. Candidate were eventually excluded from this study based on the following criteria: (i) allergy to medications used in this clinical trial; (ii) use of PPI, histamine H2-receptor antagonists, antibiotics, bismuth, or probiotics 4 weeks before initiating study treatment; (iii) use of adrenocorticosteroids, nonsteroidal anti-inflammatory drugs, and anticoagulants; (iv) alcohol abuse; (v) presence of diseases or clinical conditions, such as liver disease, cardiac vascular disease, lung disease, kidney disease, metabolic disease, mental illness, or malignant tumors, that might interfere with the evaluation of study treatment; (vi) female patients planning pregnancy, as well as pregnant and breastfeeding patients; (vii) previous esophageal or stomach surgical procedures; (viii) participation in other clinical studies within 3 months before enrollment in this clinical study; or (xi) incomplete follow-up or noncompliance with the study treatment. Detailed information about patient selection and study design are presented in Figure 1.

The present clinical trial study was reviewed and approved by the Ethics Committee (No. 20, 2017; equivalent to the Institutional Review Board in the United States) at the Daping Hospital of the Army Medical University. Written informed consent was obtained from each participant before enrollment. In addition, the study was conducted in compliance with the Declaration of Helsinki and other relevant regulations. This single-center, open-label, randomized controlled clinical trial to assess eradication efficacy of modified dual therapy vs bismuth-containing quadruple therapy as a first-line treatment of *H. pylori* infection in Chinese patients was registered at the Chinese Clinical Trial Registry (www.chictr.org.cn); trial registration number is ChiCTR-IPR-17010774, through which the trial protocol can be accessed.

### Treatments and follow-up

In this open-label study, the 232 study subjects were randomly allocated in a 1:1 ratio into two treatment groups with random allocation sequence determined by a computer-generated randomization chart. The 14-day modified dual therapy group received 20 mg esomeprazole sodium enteric-coated tablets (AstraZeneca China, Shanghai, China) and 750 mg amoxicillin tablets (The United Laboratories, Hong Kong, China). Esomeprazole was administrated 4 times daily, 30 minutes before 3 meals and 1 hour before sleep; amoxicillin was administered 30 minutes after 3 meals and 1 hour before sleep. The bismuth-containing quadruple therapy group received 20 mg esomeprazole sodium enteric-coated tablets (AstraZeneca China, Shanghai, China), 1 g bismuth potassium citrate (220 mg of bismuth,

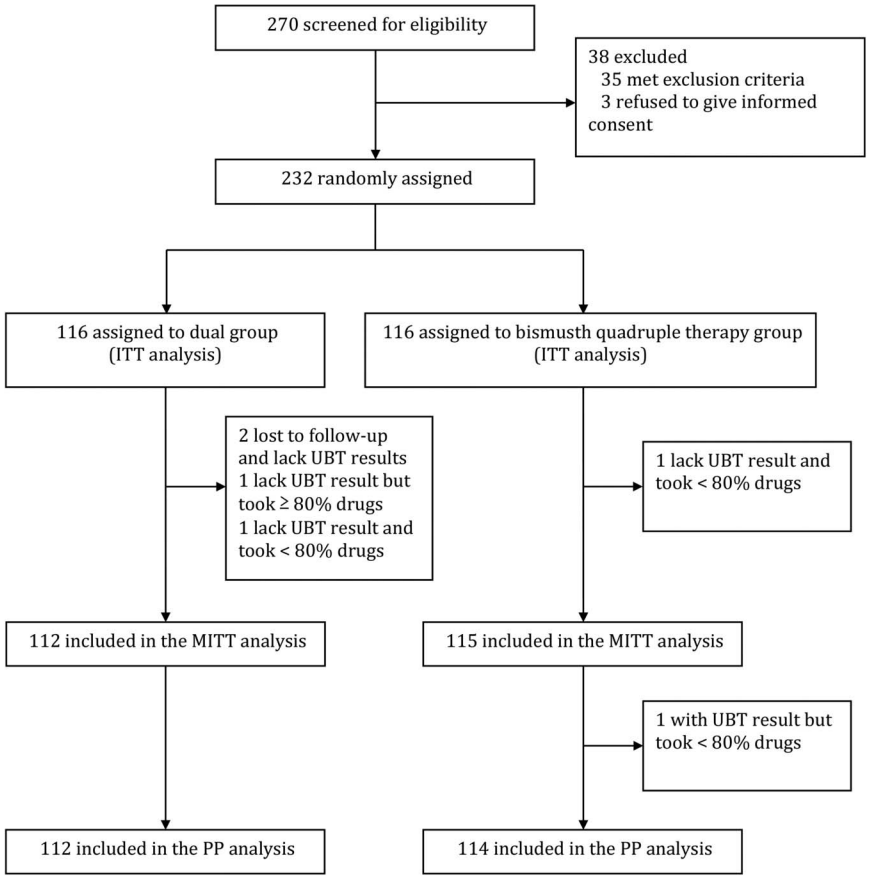


**Figure 1.** Schematic diagram of patient selection and study design. Of the 277 *H. pylori*-infected patients assessed for eligibility, 38 were excluded from this study, 35 were ineligible, and 3 refused. A total of 232 study subjects were successfully randomized and allocated to the modified dual therapy group (n = 116, ITT population) and the bismuth-containing quadruple therapy group (n = 116, ITT population). ITT, intention-to-treat; MITT, modified intention-to-treat; PP, per-protocol; UBT, $^{13}$C-Urea Breath Test.

Livzon Pharmaceutical Group, Zhuhai, China), 1 g amoxicillin (The United Laboratories Ltd., Hong Kong, China), and 500 mg clarithromycin (Abbott Pharmaceutical Co. Ltd., Shanghai, China). The quadruple therapy was administered twice daily at approximately 12-hour intervals. Esomeprazole and bismuth potassium citrate were administered 30 minutes before breakfast and dinner; amoxicillin and clarithromycin were administered 30 minutes after breakfast and dinner.

During the 14-day period of the eradication therapy, all study patients were instructed and required to record their compliance to the medications and AEs. In addition, participating individuals were scheduled to revisit the clinic 4–6 weeks after treatment was completed to determine the efficacy of modified dual therapy compared with bismuth-containing quadruple therapy.

### Outcome measurements

The primary outcome in this study was efficacy of *H. pylori* eradication rates of modified dual therapy compared with bismuth-containing quadruple therapy determined using the $^{13}$C-UBT assay. A cut-off value greater than 2.4 defined *H. pylori* (+) patients and indicated failure of the eradication therapy. Secondary outcomes were (i) medication adherence, which was assessed using the medication possession ratio (MPR) recorded during the 14-day treatment period by the study patients; MPR was defined as the proportion of days within the fixed 14-day treatment that a patient had access to the medication, which was measured by a patient pill count. An MPR $\geq$ 80% was considered good compliance, and an MPR $<$ 80% was defined as poor compliance; (ii) AEs, which were reported by participants as instructed according to the influence of AEs on their daily activities and graded as "mild" (discomfort with no interruption of their daily activities), "moderate" (discomfort affecting their daily activities), and "severe" (severe interruption of their daily activities); and (iii) cost of medications in the modified dual therapy or the bismuth-containing quadruple therapy. The cost of medications in the 2 treatment regimens was calculated according to the 2016 Medication Pricing Catalogue in Chongqing. The prices were expressed in US dollars with Chinese currency converted to US dollars at the exchange rate reported in January 2017: 1.00 USD = 6.87 CNY.

### CYP2C19, IL-1B-511, and VacA genotyping

Genotyping of CYP2C19, IL-1B-511, and *H. pylori* VacA was performed as described previously (17). Detailed information is described in Supplemental Materials (see Supplemental Digital Content, http://links.lww.com/AJG/A53).

### Antibiotic resistance tests

Drug susceptibility testing of *H. pylori* isolates was performed after the agar dilution method, which is described in Supplemental

**Table 1. Baseline demographics and clinical characteristics of the study subjects**

| | Modified dual group (n=116) | Bismuth-containing quadruple group (n=116) | *P* value |
|---|---|---|---|
| Gender | | | 0.410 |
| Male | 44 (37.9) | 38 (32.8) | |
| Female | 72 (62.1) | 78 (67.2) | |
| Age (yr) | 43.3 ± 10.7 | 44.6 ± 11.5 | 0.375 |
| Body mass index (kg/m$^2$) | 21.8 ± 2.1 | 21.6 ± 2.0 | 0.483 |
| Individual living space (m$^2$) | 108.1 ± 23.6 | 108.7 ± 22.3 | 0.844 |
| Place of residence | | | 0.478 |
| Urban area | 99 (85.3) | 95 (81.9) | |
| Suburban area | 17 (14.7) | 21 (18.1) | |
| Marital status | | | 1.000 |
| Married | 105 (90.5) | 105 (90.5) | |
| Single or divorced or widowed | 11 (9.5) | 11 (9.5) | |
| Education status | | | 0.395 |
| High school or less | 77 (66.4) | 83 (71.5) | |
| College or more | 39 (33.6) | 33 (28.5) | |
| Style of dining | | | 0.683 |
| Gather dining | 112 (96.6) | 114 (98.3) | |
| Individual dining | 4 (3.4) | 2 (1.7) | |
| Family population | | | 0.893 |
| >3 | 44 (37.9) | 45 (38.8) | |
| ≤3 | 72 (62.1) | 71 (61.2) | |
| Cigarette smoking | 24 (20.7) | 19 (16.4) | 0.398 |
| Alcohol drinking | 41 (35.3) | 26 (22.4) | 0.030 |
| Drinking water | | | 1.000 |
| Tap water | 116 (100) | 115 (99.1) | |
| Well water | 0 | 1 (0.9) | |
| History of antibiotics use | | | |
| Beta-lactam | 113/114 (99.1) | 113/113 (100) | 1.000 |
| Metronidazole | 0/114 | 2/113 (1.8) | 0.247 |
| Macrolide | 2/114 (1.8) | 0/113 | 0.498 |
| Using with doctor's advice | 19/114 (16.7) | 15/113 (13.3) | 0.474 |
| Family history of gastric carcinoma | 13 (11.2) | 15 (12.9) | 0.687 |
| Atrophy | 4 (3.5) | 3 (2.6) | 1.000 |
| VacA | | | 0.143 |
| m1 strain | 28/81 (34.6) | 38/83 (45.8) | |
| m2 strain | 53/81 (65.4) | 45/83 (54.2) | |
| CYP2C19 | | | 0.926 |
| Poor metabolizer | 16/109 (14.7) | 15/111 (13.5) | |
| Intermediate metabolizer | 42/109 (38.5) | 47/111 (42.3) | |
| Rapid metabolizer | 50/109 (45.9) | 48/111 (43.2) | |
| Extensive metabolizer | 1/109 (0.9) | 1/111 (0.9) | |
| IL-1β-511 | | | 0.207 |
| C/C | 27/109 (24.8) | 30/111 (27.0) | |
| C/T | 61/109 (55.9) | 50/111 (45.1) | |
| T/T | 21/109 (19.3) | 31/111 (27.9) | |

Data are expressed as mean ± s.d.; categorical data are presented as number of subjects and percentage in parentheses.

Materials (see Supplemental Digital Content, http://links.lww.com/AJG/A53).

### Statistical analysis

Statistical analysis was performed using the software SAS version 9.2 (SAS Institute Inc., Cary, NC). Sample size was evaluated on the basis of a previous study using bismuth-containing quadruple therapy. The parameters used to determine sample size were as follows: *H. pylori* eradication rate of 90%, noninferiority margin delta ($\delta$) = −0.1 (−10%), $\alpha$ = 0.025 (one side), 1-$\beta$ = 0.80, $P$ = 90%, and 97.5% CI. We estimated that at least 104 cases were needed in each group for comparative analysis of noninferiority between the 2 groups. In this clinical trial, we enrolled a total of 232 cases, with 116 in the modified dual therapy group and 116 in the bismuth-containing quadruple therapy group. *H. pylori* eradication rate was determined using ITT, modified intention-to-treat (MITT), and a per-protocol (PP) analyses. All enrolled patients were included in the ITT analysis, and those with unproven state of *H. pylori* eradication because of follow-up loss were classified as failure of treatment during ITT analysis. Study patients with unavailable data of *H. pylori* eradication state were excluded in the PP analysis due to loss of follow-up. Baseline characteristics of the study patients were analyzed using chi-square, Fisher exact, and ANOVA tests. Noninferiority was established if the 95% lower confidence boundary for the difference between the modified dual therapy and the traditional bismuth-containing quadruple therapy in eradication rates was >−0.1, with a 1-sided alpha level of 0.025. Outcomes, AEs, and treatment adherence were compared using chi-square and Fisher exact tests. In addition, linear-by-linear association analysis was performed to assess trends in eradication rates. A *P*-value less than 0.05 was considered statistically significant.

## RESULTS

### Baseline demographic and clinical characteristics of the study subjects

The baseline demographics, as well as clinical and laboratory characteristics, of the study patients are summarized in Table 1. Overall, there were no statistically significant differences in patient demographics between the 2 study groups. In addition, there

were no significant differences in CYP2C19 and IL-1B-511 genotypes between the groups. However, the 2 groups differed significantly in history of alcohol abuse ($P < 0.05$), with increased alcohol abuse in the modified dual therapy group (35.3%, 41/116) compared with the bismuth-containing quadruple therapy group (22.4%, 26/116).

### Eradication rates of modified dual therapy compared with bismuth-containing quadruple therapy

We compared the eradication rates in the modified dual therapy group with the bismuth-containing quadruple therapy group using different methods of analysis , including ITT, PP, and MITT. ITT analysis was performed to assess practical efficacy, whereas PP analysis was conducted to examine biological efficacy. ITT analysis showed that eradication rates were 87.9% (102/116; 95% CI 82.0%–93.9%) in the modified dual therapy group and 89.7% (104/116; 95% CI 84.1%–95.2%) in the bismuth-containing quadruple therapy group (Table 2). In the PP analysis, the eradication rates were 91.1% (102/112; 95% CI 85.8%–96.4%) in the modified dual therapy group and 91.2% (104/114; 95% CI 86.0%–96.4%) in the bismuth-containing quadruple therapy group. In the MITT analysis, the eradication rates were 91.1% (102/112; 95% CI 85.8%–96.4%) in the modified dual therapy group and 90.4% (104/115; 95% CI 85.1%–95.8%) in the bismuth-containing quadruple therapy group. There were no significant differences in eradication rates between the 2 groups ($P = 0.677$, $P = 0.967$, and $P = 0.869$ in the ITT, PP, and MITT analysis, respectively). The lower confidence boundary for the difference between the 2 groups in eradication rates was greater than the prespecified noninferiority margin of $-0.1$, and thus the noninferiority of the modified dual therapy to the bismuth-containing quadruple therapy was established ($P = 0.0228$, 0.0028, and 0.0046 in the ITT, MITT, and PP analysis, respectively).

We also evaluated effects of polymorphisms in CYP2C19 (poor metabolizer, intermediate metabolizer, rapid metabolizer, and extensive metabolizer), IL-1B-511 (TT, C/C, and C/T), and *H. pylori* VacA (m1 strain and m2 strain) on eradication rates. We found no significant correlation between eradication rates and differences in the CYP2C19, IL-1B-511, and H. pylori VacA genotypes (Table 3). We also showed that modified dual therapy at high doses and administration frequency ameliorated effects of variations in CYP2C19 and IL-1B-511 genotypes on treatment outcomes (Table 3).

### Antibiotic resistance rates in the modified dual therapy and bismuth-containing quadruple therapy groups

It has been reported that antibiotic resistance is an important factor that adversely affects eradication treatment outcomes. We therefore conducted antibiotic resistance tests. The overall antibiotic resistance rates were 29.7% (69/232) for clarithromycin, 0 (0/232) for amoxicillin, 39.7% (88/232) for levofloxacin, 0 (0/232) for furazolidone, 0 (0/232) for tetracycline, and 96.6% (224/232) for metronidazole. The resistance rates were 29.3% (68/232) and 29.7% (69/232) for clarithromycin and metronidazole, 13.8% (32/232) for clarithromycin/levofloxacin, and 36.2% (94/232) for metronidazole/levofloxacin, whereas the resistance rate to the three antibiotics was 13.4% (31/232) for clarithromycin/metronidazole/levofloxacin. We found that the modified dual therapy group exhibited significantly higher resistance rates to clarithromycin, clarithromycin/metronidazole, clarithromycin/levofloxacin, and clarithromycin/metronidazole/levofloxacin compared with those in the bismuth-containing quadruple therapy group (41.1% vs 18.1%, $P < 0.001$; 40.5% vs 18.1%, $P < 0.001$; 20.7% vs 6.9%, $P = 0.002$; 19.8% vs 6.9%, $P = 0.004$, respectively), whereas there were no significant differences in resistance rates to the remaining antibiotics (Table 4). However, we noticed that the differences in the antibiotic resistance rates did not alter the eradication rates between the two groups in this study (Table 3).

### Drug-induced adverse effects, patient adherence, and drug cost in modified dual therapy compared with bismuth-containing quadruple therapy

The primary AEs that occurred during the eradication treatment included: nausea, diarrhea, dizziness, change in sense of taste, rash, black tongue, black stool, etc. These AEs disappeared shortly after treatment was completed. As shown in Table 5, overall treatment-related AEs were significantly less frequent in the modified dual therapy group (6.3%, 7/112) compared with the bismuth-containing quadruple therapy group (22.8%, 26/114) ($P < 0.001$). In particular, the frequency of change in sense of

**Table 2. Eradication rates of modified dual therapy compared with bismuth-containing quadruple therapy**

| | Modified dual group | Bismuth-containing quadruple group | Difference from quadruple group (adjusted 95% CI for difference) | *P* value for noninferiority[a] | *P* value for difference[b] |
|---|---|---|---|---|---|
| ITT | 87.9% (102/116) | 89.7% (104/116) | −1.72% | 0.0228 | 0.677 |
| 95% CI | 82.0%–93.9% | 84.1%–95.2% | −9.84% to 6.39% | | |
| MITT | 91.1% (102/112) | 90.4% (104/115) | 0.64% | 0.0028 | 0.869 |
| 95% CI | 85.8%–96.4% | 85.1%–95.8% | −6.90% to 8.17% | | |
| PP | 91.1% (102/112) | 91.2% (104/114) | −0.16 % | 0.0046 | 0.967 |
| 95% CI | 85.8%–96.4% | 86.0%–96.4% | −7.56% to 7.25% | | |

CI, confidence interval; ITT, intention-to-treat; MITT, modified intention-to-treat; PP, per-protocol.
[a]The *P* values were obtained from one-sided test comparisons of noninferiority between the modified dual therapy group and bismuth-containing quadruple therapy group.
[b]The *P* values were from two-sided comparisons of differences between the modified dual therapy group and the bismuth-containing quadruple therapy group.

**Table 3. Factors affecting eradication of *H. pylori* infection in modified dual therapy compared with bismuth-containing quadruple therapy**

| | Modified dual group (n = 116) | Bismuth-containing quadruple group (n = 116) |
|---|---|---|
| Gender | *P* = 0.685 | *P* = 0.179 |
| Male | 38/44 (86.4%) | 32/38 (84.2%) |
| Female | 64/72 (88.9%) | 72/78 (92.3%) |
| Cigarette smoking | *P* = 1.000 | *P* = 0.012 |
| No | 81/92 (88.0%) | 90/97 (92.8%) |
| Yes | 21/24 (87.5%) | 14/19 (73.7%) |
| Alcohol drinking | *P* = 0.221 | *P* = 1.000 |
| No | 68/75 (90.7%) | 80/90 (88.9%) |
| Yes | 34/41 (82.9%) | 24/26 (92.3%) |
| Compliance | *P* = 0.001 | *P* = 0.028 |
| Poor | 0/3 | 1/3 (33.3%) |
| Good | 102/113 (90.3%) | 103/113 (91.2%) |
| Clarithromycin resistance (phenotypic) | *P* = 0.485 | *P* = 0.453 |
| Susceptible | 61/68 (89.7%) | 86/95 (90.5%) |
| Resistant | 41/48 (85.4%) | 18/21 (85.7%) |
| Amoxicillin resistance (phenotypic) | NA | NA |
| Susceptible | 102/116 (87.9%) | 104/116 (89.7%) |
| Resistant | 0/0 | 0/0 |
| Metronidazole resistance (phenotypic) | *P* = 0.546 | *P* = 1.000 |
| Susceptible | 5/6 (83.3%) | 2/2 (100%) |
| Resistant | 97/110 (88.2%) | 102/114 (89.5%) |
| Furazolidone resistance (phenotypic) | NA | NA |
| Susceptible | 102/116 (87.9%) | 104/116 (89.7%) |
| Resistant | 0/0 | 0/0 |
| Tetracycline resistance (phenotypic) | NA | NA |
| Susceptible | 102/116 (87.9%) | 104/116 (89.7%) |
| Resistant | 0/0 | 0/0 |
| Levofloxacin resistance (phenotypic) | *P* = 0.202 | *P* = 1.000 |
| Susceptible | 62/68 (91.2%) | 68/76 (89.5%) |
| Resistant | 40/48 (83.3%) | 36/40 (90.0%) |
| IL-1β-511 polymorphism | *P* = 0.202 | *P* = 1.000 |
| C/C & C/T | 80/88 (90.9%) | 71/80 (88.8%) |
| T/T | 19/21 (90.5%) | 30/31 (96.8%) |
| CYP2C19 polymorphism | *P* = 1.000 | *P* = 0.353 |
| Poor metabolizer | 15/16 (93.8%) | 15/15 (100%) |
| Intermediate/rapid/extensive metabolizer | 84/93 (90.3%) | 86/96 (89.6%) |
| VacA | *P* = 0.487 | *P* = 1.000 |
| m1 strain | 26/28 (92.9%) | 34/38 (89.5%) |
| m2 strain | 46/53 (86.8%) | 40/45 (88.9%) |

Data are expressed as number of subjects with percentage included in parentheses.
NA, not applicable.

taste was significantly greater in the bismuth-containing quadruple therapy group compared with the modified dual therapy group (12.3% vs 0%, $P < 0.001$) (Table 5).

Two patients withdrew from the bismuth-containing quadruple therapy group because of serious rash and change in sense of taste, whereas no patients withdrew from the modified dual therapy group. Furthermore, there were no significant differences in treatment adherence between the modified dual therapy group and the bismuth-containing quadruple therapy group (96.6% and 98.3%, respectively).

**Table 4. Antibiotic resistance rates in the modified dual therapy group compared with the bismuth-containing quadruple therapy**

| | Modified dual group (n = 116) | Bismuth-containing quadruple group (n = 116) | *P* value |
|---|---|---|---|
| Clarithromycin resistance (phenotypic) | 48 (41.4) | 21 (18.1) | <0.001 |
| Amoxicillin resistance (phenotypic) | 0 | 0 | NA |
| Metronidazole resistance (phenotypic) | 110 (94.8) | 114 (98.3) | 0.280 |
| Levofloxacin resistance (phenotypic) | 48 (41.4) | 40 (34.5) | 0.279 |
| Tetracycline resistance (phenotypic) | 0 | 0 | NA |
| Furazolidone resistance (phenotypic) | 0 | 0 | NA |
| Dual resistance (phenotypic) | | | |
| CLA-R/MTZ-R | 47 (40.5) | 21 (18.1) | <0.001 |
| CLA-R/LEV-R | 24 (20.7) | 8 (6.9) | 0.002 |
| MTZ-R/LEV-R | 44 (37.9) | 40 (34.5) | 0.585 |
| Triple resistance (phenotypic) | | | |
| CLA-R/MTZ-R/LEV-R | 23 (19.8) | 8 (6.9) | 0.004 |

Data are expressed as number of subjects with percentage included in parentheses.
NA, not applicable.

**Table 5. Drug-induced adverse effects and patient adherence to modified dual therapy compared with bismuth-containing quadruple therapy**

| | Modified dual group | Bismuth-containing quadruple group | *P* value |
|---|---|---|---|
| Adverse events | 6.3% (7/112) | 22.8% (26/114) | <0.001 |
| Nausea | 2.7% (3/112) | 1.8% (2/114) | 0.682 |
| Diarrhea | 0.9% (1/112) | 0.9% (1/114) | 1.000 |
| Dizziness | 0 | 0.9% (1/114) | 1.000 |
| Taste distortion | 0 | 12.3% (14/114) | <0.001 |
| Skin rash | 0 | 0.9% (1/114) | 1.000 |
| Tongue discolouration | 0.9% (1/112) | 2.6% (3/114) | 0.622 |
| Darkened stool | 0 | 2.6% (3/114) | 0.247 |
| Others | 1.8% (2/112) | 0.9% (1/114) | 0.620 |
| Discontinued drugs because of adverse events | 0 | 1.7% (2/116) | 0.498 |
| Compliance | 96.6% (112/116) | 98.3% (114/116) | 0.683 |

Adverse events were assessed in the per protocol (PP) population. Compliance was indicative of patients who took at least 80% of study drugs.
NA, not applicable.

Drug costs were calculated and directly compared between the two groups. The cost for the modified dual therapy group was $113.60 ($97.50 for 56 tablets of esomeprazole plus $16.10 for 168 capsules of amoxicillin), which was less costly compared with $130.10 ($48.80 for 28 tablets of esomeprazole, $1.90 for 28 sachets of bismuth potassium citrate, $10.70 for 112 capsules of amoxicillin, and $68.70 for 56 tablets of clarithromycin) for the bismuth-containing quadruple therapy group.

## DISCUSSION

Dual therapy to eradicate *H. pylori* has not yet been recommended and established as a first-line treatment regimen, which is mainly because of conflicting eradication rates in different populations with respect to efficacy, compared with existing first-line regimens, including bismuth-containing quadruple therapy and standard triple therapy (18–21). To the best of our knowledge, this open-label, randomized controlled clinical trial is the first comparative study to analyze the effectiveness, adverse effects, patient adherence, and costs between 14-day modified dual therapy and bismuth-containing quadruple therapy to treat *H. pylori*-naive patients in a Chinese population. The primary novel findings of this study are summarized as follows: (i) There were no significant differences in eradication rates between the modified dual therapy and the bismuth-containing quadruple therapy groups as determined by ITT, PP, and MITT analyses, indicating that modified dual therapy is as effective as the first-line bismuth-containing quadruple therapy for treating *H. pylori* infection in Chinese patients. (ii) Patient adherence was similar between the modified dual therapy and the bismuth-containing quadruple therapy groups. (iii) Modified dual therapy exhibited significantly less overall side effects compared with bismuth-containing quadruple therapy ($P < 0.001$). (iv) Modified dual therapy was less costly than bismuth-containing quadruple therapy.

In the present study, the 14-day modified dual therapy at a high dose and frequency of administration (esomeprazole 20 mg, 4 times a day; amoxicillin 750 mg, 4 times a day), which achieved a high *H. pylori* eradication rate, was mainly based on the following observations. First, it has been well recognized that *H. pylori* enters into a replicative state at pH > 6, at which the pathogen becomes highly susceptible to amoxicillin (22). Thus, the PPI-induced sufficient and sustainable inhibition of intragastric acid secretion could be helpful in achieving successful eradication of *H. pylori*. Second, amoxicillin has proven to be pH-dependent, which suggests that amoxicillin has higher stability and a lower minimum inhibitory concentration as pH increases (7,23). In addition, amoxicillin's effects are time-dependent, as it is rapidly absorbed, allowing it to circulate in the plasma and be excreted in the urine within a relatively short time. Therefore, a high dose and frequency of drug administration are expected to improve its effectiveness for treating *H. pylori* infection. In this study, the high dose and frequency of drug administration of esomeprazole (20 mg, 4 times daily) and amoxicillin (750 mg, 4 times daily) were used in treatment-naive patients with *H. pylori* infection. These treatment strategies achieved similarly high eradication rates compared with several previous studies, including those with a 14-day dual therapy (rabeprazole 20 mg, 4 times daily; amoxicillin 750 mg, 4 times daily) in Taiwan (17). The eradication rate was as high as 95.3% (ITT analysis, 95% CI: 91.9%–98.8%), independent of CYP2C19 genotypes in the treatment-naive patients and in a dual therapy (rabeprazole 10 mg, 4 times daily; amoxicillin 500 mg, 4 times daily) in Japan (24). In both these studies, the intensity of intragastric acid inhibition appeared sustainable and sufficient. Our eradication rates using the modified dual therapy in the treatment-naive patients were consistent with the above two mentioned studies in Taiwan and Japan. However, conflicting results on the effectiveness of dual therapy from a number of previous studies may be largely attributed to differences in dose and frequency of PPI-amoxicillin. Administration of PPI-amoxicillin at a frequency less than four times a day did not meet expectations and was unacceptable for eradicating *H. pylori* infection (18,25–27). Sugimoto et al. (28) investigated the correlation between the administration frequency of rabeprazole and its inhibitory effect on intragastric acid. They found that the median intragastric pH values during a 24-hour study differed with administration frequencies of 40 mg rabeprazole: 4.8 (3.6–6.4) given once daily, 5.7 (4.1–7.4) given twice daily, and 6 (4.9–8.4) given 4 times daily. As such, the frequency of 2 or 3 times daily administration of PPI-amoxicillin in a dual therapy, as previously recommended, may not be ideal for maximizing pharmacokinetic and pharmacodynamic effects in treating *H. pylori* infection.

Aside from sufficient inhibition of intragastric acid to maintain appropriate gastric pH values, several other factors likely affect the efficacy and success of *H. pylori* treatment. In this study, we evaluated patient compliance, antibiotic resistance, different antibiotic-sensitive strains of *H. pylori*, and polymorphisms in CYP2C19 and IL-1B-511 (29–31). Patient

adherence to the modified dual therapy was high, and the side effects were minimal and mild in this study. In contrast to the bismuth-containing quadruple therapy, the eradication treatment regimen in the modified dual therapy showed significantly less overall side effects. We also determined the effects of different genotypes of CYP2C19 (a poor metabolizer, as well as an intermediate/rapid/extensive metabolizer) and IL-1B-511 (TT, C/C, and C/T) on eradication rates. We found no significant correlation between the treatment outcomes and CYP2C19 and IL-1B-511 genotypes. In agreement with a previous report, our study showed that the modified dual therapy at a high dose and administration frequency ameliorates the influence of different genotypes within both CYP2C19 and IL-1B-511 genes and leads to a higher eradication rate of *H. pylori*. Moreover, the cost of the modified dual therapy was lower than the bismuth-containing quadruple therapy, as determined by the drug cost.

To date, 3 randomized controlled trials, including ours, have demonstrated that high-dose dual therapy with a 4-time daily dosing is highly effective in eradicating *H. pylori* infection in East Asian populations (17,32). In the previous 2 clinical trials (17,32), however, only rabeprazole and esomeprazole were the effective PPI components of the dual therapy regimen regardless of the CYP2C19 genotype. It has remained unclear whether other PPIs, such as omeprazole and lansoprazole, could also attain a suitable pH value for the dual therapy, and the appropriate dosage and frequency of administration of various PPIs should be tested. In addition, vonoprazan, a potassium-competitive acid blocker, was recently approved to treat patients with *H. pylori* infection, which was more potent and long-acting than the traditional PPIs (e.g., omeprazole, esomeprazole, and rabeprazole) (24,33,34). Thus, it would be worthwhile to conduct clinical trials to assess the efficacy of the modified dual therapy by replacing the traditional PPIs with vonoprazan in patients with *H. pylori* infection.

Our clinical trial has a number of limitations. First, we did not examine 24-hour intragastric pH values during the entire course of treatment; therefore, we were unable to directly assess if secretion of intragastric acid was successfully inhibited and if pH values were sustained at values greater than 6. Second, the sample size was relatively small, which may lead to potential sampling selection bias. Further studies are needed to increase the sample size and optimize the dual therapy. Third, the open-label study may raise concerns regarding reporting of AEs. We did consider different types of clinical trials, such as an open-label, single blind, and double blind clinical trial, during study design. We selected an open-label experimental design, as we felt that it was more appropriate for comparing the effectiveness (eradication rate as primary clinical outcome) of the modified dual therapy and the bismuth-containing quadruple therapy. In contrast, the use of other clinical trials, such as a single- or double-blind study, would increase the complexity and cost of drug regimens, potentially leading to missed or mistakenly taken medications, which may in turn adversely affect efficacy and reduce patient compliance to the medications.

Based on the findings of our study and others, we propose that further investigation is required before high-dose dual therapy can be used to supplant the traditional bismuth-containing quadruple therapy as a first-line therapy (35–37). First, a better PPI has to be selected to attain a suitable pH value for dual therapy; a new class of an acid-suppressing drug and a potassium-competitive acid blocker, namely vonoprazan, were recently approved to treat *H. pylori* (24,33,34). Second, an appropriate dosage and frequency of PPI administration must be determined to achieve optimal pH levels for dual therapy. Third, PPI selection has to be tailored based on the patient population that expresses different CYP2C19 and other genotypes, which have been shown to significantly affect the eradication rate of *H. pylori*. Thus, it would be worthwhile to conduct another trial to assess the efficacy of dual therapy by replacing the conventional PPIs (e.g., omeprazole, esomeprazole, or rabeprazole) with vonoprazan in patients with *H. pylori* infection. In addition, it would be interesting to assess whether levels of pepsinogen could affect the response rate in the future study, although our current findings cannot exclude the possible effect.

Taken together, our results demonstrate that modified dual therapy at a high dose and high frequency of administration is similarly effective, less costly, and safer compared with the bismuth-containing quadruple therapy for eradicating *H. pylori* in Chinese treatment-naive patients. The scientific evidence supports a recommendation for modified dual therapy as an alternative first-line treatment regimen for Chinese patients with *H. pylori* infection.

## CONFLICTS OF INTEREST

**Guarantor of the article:** Chun-Hui Lan, MD, PhD.
**Specific author contributions:** The first two authors contributed equally to this work. C.-H.L.: study conceptualization, study design, data interpretation, manuscript editing, and funding acquisition; J.Y.: study design, patient recruitment, acquisition of data, statistical analysis, and manuscript preparation; Y.Z.: study design, patient recruitment, acquisition of data, statistical analysis, and manuscript preparation; L.F.: patient recruitment and acquisition of data; Y.-J.Z. and T.-Y.W.: laboratory studies; X.-W.W.: oversight of the statistical analyses; and D.-F.C.: study supervision and coordination. All authors have read and approved the final manuscript.
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## Study Highlights

### WHAT IS KNOWN

- ✓ Eradication rates of dual therapy for *H. pylori* infection vary in different populations.
- ✓ Bismuth-containing quadruple therapy is the current first-line treatment regimen for Chinese patients with *H. pylori* infection.

### WHAT IS NEW HERE

- ✓ The modified dual therapy is equally effective compared with the bismuth-containing quadruple therapy.
- ✓ The modified dual therapy is safer and less costly than the bismuth-containing quadruple therapy.

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