

## Nonbismuth concomitant quadruple therapy for *Helicobacter pylori* eradication in Chinese regions: A meta-analysis of randomized controlled trials

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**Author contributions:** Lin LC and Hsu TH contributed equally to this work; Lin LC, Hsu TH and Tam KW acquired, analyzed and interpreted the data, and drafted the article; Tam KW contributed to conception and design of the study; Huang KW critically revised the manuscript; and all authors approved the final version.

**Conflict-of-interest statement:** The authors deny any conflict of interest.

**Data sharing statement:** No additional data are available.

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**Received:** March 15, 2016

**Peer-review started:** March 18, 2016

**First decision:** March 31, 2016

**Revised:** April 8, 2016

**Accepted:** May 4, 2016

**Article in press:** May 4, 2016

**Published online:** June 21, 2016

### Abstract

**AIM:** To evaluate the applicability of nonbismuth concomitant quadruple therapy for *Helicobacter pylori* (*H. pylori*) eradication in Chinese regions.

**METHODS:** A systematic review and meta-analysis of randomized controlled trials was performed to evaluate the efficacy of nonbismuth concomitant quadruple therapy between sequential therapy or triple therapy for *H. pylori* eradication in Chinese regions. The defined Chinese regions include China, Hong Kong, Taiwan, and Singapore. The primary outcome was the *H. pylori* eradication rate; the secondary outcome was the compliance with therapy. The PubMed, Embase, Scopus, and Cochrane databases were searched for studies published in the period up to March 2016 with no language restriction.

**RESULTS:** We reviewed six randomized controlled trials and 1616 patients. In 3 trials comparing concomitant quadruple therapy with triple therapy, the *H. pylori* eradication rate was significantly higher for 7-d

nonbismuth concomitant quadruple therapy than for 7-d triple therapy (91.2% *vs* 77.9%, risk ratio = 1.17, 95%CI: 1.09-1.25). In 3 trials comparing quadruple therapy with sequential therapy, the eradication rate was not significant between groups (86.9% *vs* 86.0%). However, higher compliance was achieved with concomitant therapy than with sequential therapy.

**CONCLUSION:** The *H. pylori* eradication rate was higher for nonbismuth concomitant quadruple therapy than for triple therapy. Moreover, higher compliance was achieved with nonbismuth concomitant quadruple therapy than with sequential therapy. Thus, nonbismuth concomitant quadruple therapy should be the first-line treatment in Chinese regions.

**Key words:** *Helicobacter pylori* eradication; Nonbismuth concomitant quadruple therapy; Peptic ulcer; Chinese region

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**Core tip:** *Helicobacter pylori* (*H. pylori*) infection is highly prevalent in Chinese regions and associated with peptic ulcers. Currently, triple and sequential therapies have been widely used to eradicate *H. pylori*. Nonbismuth concomitant quadruple therapy is an alternative treatment with high efficacy. Our meta-analysis revealed that a higher *H. pylori* eradication rate was achieved with 7-d concomitant therapy than with 7-d triple therapy. The eradication rates of concomitant and sequential therapies were similar. However, the compliance with concomitant therapy was higher. Therefore, nonbismuth concomitant quadruple therapy should be the first-line treatment for *H. pylori* infection.

Lin LC, Hsu TH, Huang KW, Tam KW. Nonbismuth concomitant quadruple therapy for *Helicobacter pylori* eradication in Chinese regions: A meta-analysis of randomized controlled trials. *World J Gastroenterol* 2016; 22(23): 5445-5453 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v22/i23/5445.htm> DOI: <http://dx.doi.org/10.3748/wjg.v22.i23.5445>

## INTRODUCTION

*Helicobacter pylori* (*H. pylori*) infection has been proven to be the major cause of chronic gastritis, gastric and duodenal ulcers, gastric adenocarcinoma, and gastric mucosa-associated lymphoma<sup>[1-3]</sup>. Moreover, *H. pylori* eradication has become the standard and most widely adopted therapy for curing peptic ulcers<sup>[4-6]</sup>.

According to most international guidelines, conventional triple therapy, involving the use of a proton pump inhibitor (PPI) with amoxicillin and clarithromycin for 7-10 d, is the first-line therapy for *H. pylori* eradication<sup>[7-10]</sup>. However, the eradication rate of triple therapy has decreased to 80% in many countries worldwide<sup>[11-14]</sup>.

By contrast, studies have shown a high eradication rate for sequential therapy, which entails administering a PPI and amoxicillin for 5 d, followed by a PPI, clarithromycin, and metronidazole (or tinidazole) for another 5 d<sup>[15-18]</sup>. However, compliance may be poor because of the complexity of sequential therapy<sup>[19]</sup>. In addition, nonbismuth concomitant quadruple therapy, involving the simultaneous administration of a PPI, amoxicillin, clarithromycin, and metronidazole for 7 or 10 d, is more convenient than sequential therapy, although its efficacy is yet to be determined<sup>[20-26]</sup>.

Peptic ulcer is a common disease in Chinese regions. In Taiwan, the overall prevalence of *H. pylori* infection is 54%, and it increases with age<sup>[27]</sup>. However, the infection rate of *H. pylori* is only 31% in Singapore<sup>[28]</sup>. Because antibiotic resistance is a critical reason for *H. pylori* eradication failure, studies on *H. pylori* eradication are needed within specific region<sup>[14]</sup>. However, most meta-analyses of *H. pylori* eradication have been performed in Europe and Korea, and the optimal treatment for *H. pylori* eradication in Chinese regions is still unknown<sup>[29,30]</sup>. Therefore, we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate whether nonbismuth concomitant quadruple therapy is the first-line therapy for *H. pylori* eradication in Chinese regions.

## MATERIALS AND METHODS

### Data sources

The PubMed, Embase, Scopus, and Cochrane databases were searched for studies published in the period up to March 2016 without language restrictions. The following medical search heading terms, words, and combinations of words were used in the systematic search: *Helicobacter pylori* or *H. pylori*, eradication, peptic or gastric or duodenal ulcer, concomitant or quadruple, and China or Chinese or Hong Kong or Taiwan or Singapore. All included studies were also entered into the PubMed "similar articles" function and the science citation index. Moreover, we identified additional studies by manually searching the reference sections of these papers and by contacting known experts in the field. Finally, unpublished trials were retrieved from the ClinicalTrials.gov registry (<http://clinicaltrials.gov/>). The systematic review described herein was accepted by the online PROSPERO international prospective register of systematic reviews of the National Institute for Health Research (CRD42016-032668).

### Study selection

The following studies were selected for analysis: RCTs evaluating the efficacy of nonbismuth concomitant quadruple therapy versus standard triple or sequential for *H. pylori* eradication; those performed in Chinese regions including China, Hong Kong, Taiwan, and Singapore; patients aged 18 years or over; those

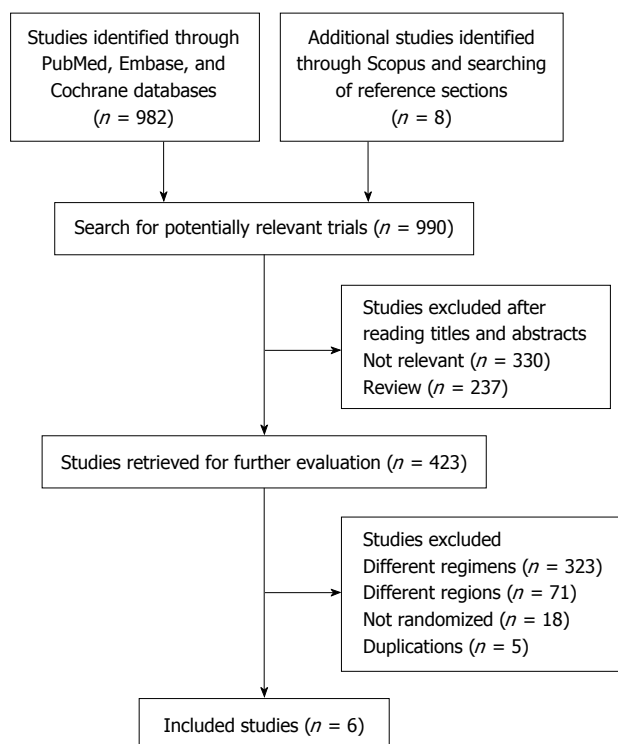


Figure 1 Flowchart for study selection.

clearly describing the inclusion and exclusion criteria used for patient selection; those adequately describing the administration of antibiotics and PPIs; and trials that precisely defined and evaluated *H. pylori* infection. Triple therapy was defined as a PPI plus amoxicillin and clarithromycin given for 7–14 d. Sequential therapy was defined as a PPI plus amoxicillin given for the first 5–7 d, followed by a PPI plus nitroimidazole derivatives and clarithromycin for the next 5–7 d. Nonbismuth concomitant quadruple therapy was defined as a PPI plus amoxicillin, clarithromycin, and nitroimidazole derivatives given for 7–14 d. The Studies were excluded from the analysis if one or both of the following criteria were present: patients enrolled in the trials who were proven to have had previous *H. pylori* infection with a history of bacterial eradication, and an overlap occurred between patient cohorts evaluated in two or more studies.

#### Data extraction and quality assessment

Two independent reviewers (Lin LC and Hsu TH) extracted the data of the trials, including the participants, inclusion and exclusion criteria, administration of experimental drugs, prevalence and assessment of *H. pylori* infection, and complications. Discrepancies and any disagreements were resolved through discussion with a third reviewer (Tam KW). The authors of the studies were contacted for additional information when necessary.

The risk of bias in the included trials was assessed using the following domains: adequacy of the randomization, allocation concealment, blinding, duration of

follow-up, numbers of drop-outs, and performance of intention-to-treat (ITT) analysis.

#### Data synthesis and analysis

The *H. pylori* eradication rate was the primary outcome used to evaluate the efficacy of nonbismuth concomitant quadruple therapy. The occurrence of *H. pylori* infection was determined using assessments of histology, culture, rapid urease tests, or breath tests. The secondary outcome was the compliance with treatment.

The analysis was performed using the statistical package Review Manager, version 5.3 (Cochrane Collaboration, Oxford, England). The meta-analysis was performed according to the recommendations of the PRISMA statement<sup>[31]</sup>. For dichotomous data, the results were summarized as risk ratios (RRs) with 95%CIs. A pooled estimate of the RR was calculated using the DerSimonian and Laird random effect model<sup>[32]</sup>. This approach provides a more appropriate estimate of the average treatment effect when trials are statistically heterogeneous and usually yields wider CIs, thereby resulting in a more conservative statistical claim.  $\chi^2$  statistics tests (*Q* statistics) and the  $I^2$  test were used to test for heterogeneity among controlled trials.

## RESULTS

#### Characteristics of the trials

The review process is outlined in Figure 1. The initial search yielded 990 studies, 567 of which were deemed ineligible through screening of titles and abstracts. Subsequently, the full text of 423 studies was screened. Of these, five did not meet the eligibility criteria because of duplicate publication, 18 were not randomized studies, 71 evaluated *H. pylori* eradication in different regions, and 323 included different comparisons. Thus, only six eligible trials were included in this meta-analysis<sup>[20,22,33–36]</sup>.

The main characteristics of the studies are listed in Table 1. Four of the six studies were performed in Taiwan, and the remaining two were conducted in China and Singapore. The publication dates of the studies were between 2012 and 2015, and the sample sizes ranged from 169 to 462. All trials evaluated patients diagnosed with *H. pylori* infection. In our included studies, three indicated that their patients had gastritis or peptic ulcers<sup>[33–35]</sup>. Only one study did not report the tests for diagnosing *H. pylori* infection<sup>[34]</sup>, and other studies reported the following diagnostic tests: rapid urease test, histology, urea breath test, and culture. The timing of evaluation for the *H. pylori* infection status ranged from 4 to 12 wk after the treatment course. Treatment strategies for *H. pylori* eradication varied among the studies. Regarding the PPIs administered, three studies used esomeprazole<sup>[20,34,35]</sup>, one used pantoprazole<sup>[33]</sup>, one used lansoprazole<sup>[22]</sup>, and one

**Table 1** Characteristics of included studies

Ref.	Inclusion criteria	Region	Diagnostic test	No. of patients (male %)	Age, yr (mean $\pm$ SD)	Intervention
Ang <i>et al</i> <sup>[36]</sup> (2015)	Age > 21 yr	Singapore	RUT, H, UBT	C10: 153 (47.1) S10: 154 (59.7) T10: 155 (58.1)	C10: 46.9 $\pm$ 14.8 S10: 47.5 $\pm$ 12.7 T10: 49.8 $\pm$ 14.6	10-d concomitant therapy 10-d sequential therapy 10-d triple therapy
Hsu <i>et al</i> <sup>[33]</sup> (2014)	Age $\geq$ 20 yr, PU or gastritis	Taiwan	RUT, Cu, H	C7: 102 (59.8) S10: 102 (50.9) T7: 103 (60.2)	C7: 53.9 $\pm$ 12.3 S10: 55.0 $\pm$ 12.0 T7: 56.1 $\pm$ 14.0	7-d concomitant therapy 10-d sequential therapy 7-d triple therapy
Huang <i>et al</i> <sup>[22]</sup> (2012)	Dyspepsia or epigastric discomfort	Taiwan	RUT, Cu, H	C10: 84 (57.1) S10: 85 (56.7)	C10: 53.8 $\pm$ 15.2 S10: 51.3 $\pm$ 15.0	10-d concomitant therapy 10-d sequential therapy
Tai <i>et al</i> <sup>[34]</sup> (2015)	Age $\geq$ 20 yr, PU or gastritis	Taiwan	Not reported	C7: 92 (50.0) T7: 92 (49.0)	C7: 47.8 $\pm$ 11.6 T7: 52.8 $\pm$ 12.8	7-d concomitant therapy 7-d triple therapy
Wang <i>et al</i> <sup>[35]</sup> (2014)	PU and gastritis	China	UBT	C7: 81 (45.7) T7: 82 (42.7) T10: 83 (45.8)	C7: 51 $\pm$ 13 T7: 51 $\pm$ 15 T10: 52 $\pm$ 14	7-d concomitant therapy 7-d triple therapy 10-d triple therapy
Wu <i>et al</i> <sup>[20]</sup> (2010)	Patients visited GI clinics with HP infection	Taiwan	RUT, Cu, H	C10: 115(52.2) S10:117(52.1)	C10: 51.8 $\pm$ 11 S10: 51.7 $\pm$ 12	10-d concomitant therapy 10-d sequential therapy

Concomitant therapy: PPI, amoxicillin, clarithromycin, and metronidazole for 7-10 d; sequential therapy: PPI and amoxicillin for 5 d, followed by PPT, clarithromycin, and metronidazole (or tinidazole) for 5 d; triple therapy: PPI, amoxicillin, and clarithromycin for 7-10 d. PPI: lansoprazole, pantoprazole, or esomeprazole; GI: Gastrointestinal; PU: Peptic ulcer; C7: 7-d concomitant therapy; C10: 10-d concomitant therapy; S10: 10-d sequential therapy; T7: 7-d triple therapy; T10: 10-d triple therapy; Cu: Culture; H: Histology; RUT: Rapid urease test; UBT: Urea breath test.

did not control the choice of the PPI<sup>[36]</sup>. Regarding concomitant and sequential regimens, all studies used metronidazole, except for Wang *et al*<sup>[35]</sup>, who substituted metronidazole with tinidazole. In all included studies, a PPI, amoxicillin, and clarithromycin were administered as triple therapy for 7 d<sup>[33-35]</sup> or 10 d<sup>[35,36]</sup>. Regarding sequential therapy, all treatment regimens entailed administering a PPI and amoxicillin for 5 d, followed by a PPI, clarithromycin, and metronidazole for another 5 d<sup>[20,22,33,36]</sup>. Finally, concomitant therapy involved administering a PPI, clarithromycin, amoxicillin, and metronidazole for 7 d<sup>[33-35]</sup> or 10 d<sup>[20,22,36]</sup>. Huang *et al*<sup>[22]</sup> prolonged PPI maintenance therapy to 10 wk. Baseline characteristics were balanced and similar between groups in the six included RCTs.

Table 2 presents the details of the six included RCTs. The use of random allocation was clearly documented in all studies. The treatment group allocation was concealed from the patients in three studies<sup>[33,34,36]</sup>. Only one reported the blinding of the investigators who assessed the outcomes<sup>[20]</sup>. In all studies, outcomes were evaluated using both ITT and per-protocol analyses. The percentage of patients lost to follow-up was acceptable (< 20%) in all studies. All studies had a bias attributable to insufficient data on antibiotic susceptibility<sup>[20,22,33,36]</sup>.

### *H. pylori* eradication rate

**Nonbismuth concomitant quadruple therapy vs triple therapy:** Three studies compared the *H. pylori* eradication rates of 7-d nonbismuth concomitant quadruple and triple therapies<sup>[33-35]</sup>. The timing of *H. pylori* infection status assessment was different among these studies: 4<sup>[35]</sup>, 6<sup>[33]</sup>, and 8 wk<sup>[34]</sup> after treatment. A significant difference was observed in the overall *H. pylori* eradication rate of nonbismuth concomitant quadruple and triple therapies (91.2% vs 77.9%).

Fewer patients receiving nonbismuth concomitant quadruple therapy experienced *H. pylori* infection after treatment (RR = 1.17, 95%CI: 1.09-1.25) (Figure 2). The results demonstrated low heterogeneity among the studies ( $I^2 = 0\%$ ).

One study compared the *H. pylori* eradication rates of 10-d nonbismuth concomitant quadruple and triple therapies<sup>[36]</sup>. The timing of *H. pylori* infection status assessment was 4 wk after treatment. No significant difference was observed in the *H. pylori* eradication rates of nonbismuth concomitant quadruple and triple therapies (81.7% vs 83.2%, RR = 0.98, 95%CI: 0.89-1.09) (Figure 2).

### **Nonbismuth concomitant quadruple therapy vs sequential therapy:**

Three studies compared the *H. pylori* eradication rate of 10-d nonbismuth concomitant quadruple and sequential therapies<sup>[20,22,36]</sup>. The timing of *H. pylori* infection status assessment was different among the studies: 4<sup>[36]</sup>, 6<sup>[20]</sup>, and 12 wk<sup>[22]</sup> after treatment. No statistically significant difference was observed in the overall *H. pylori* eradication rates of nonbismuth concomitant quadruple and sequential therapies (86.9% vs 86.0%, RR = 1.01, 95%CI: 0.95-1.07) (Figure 2).

### **Compliance**

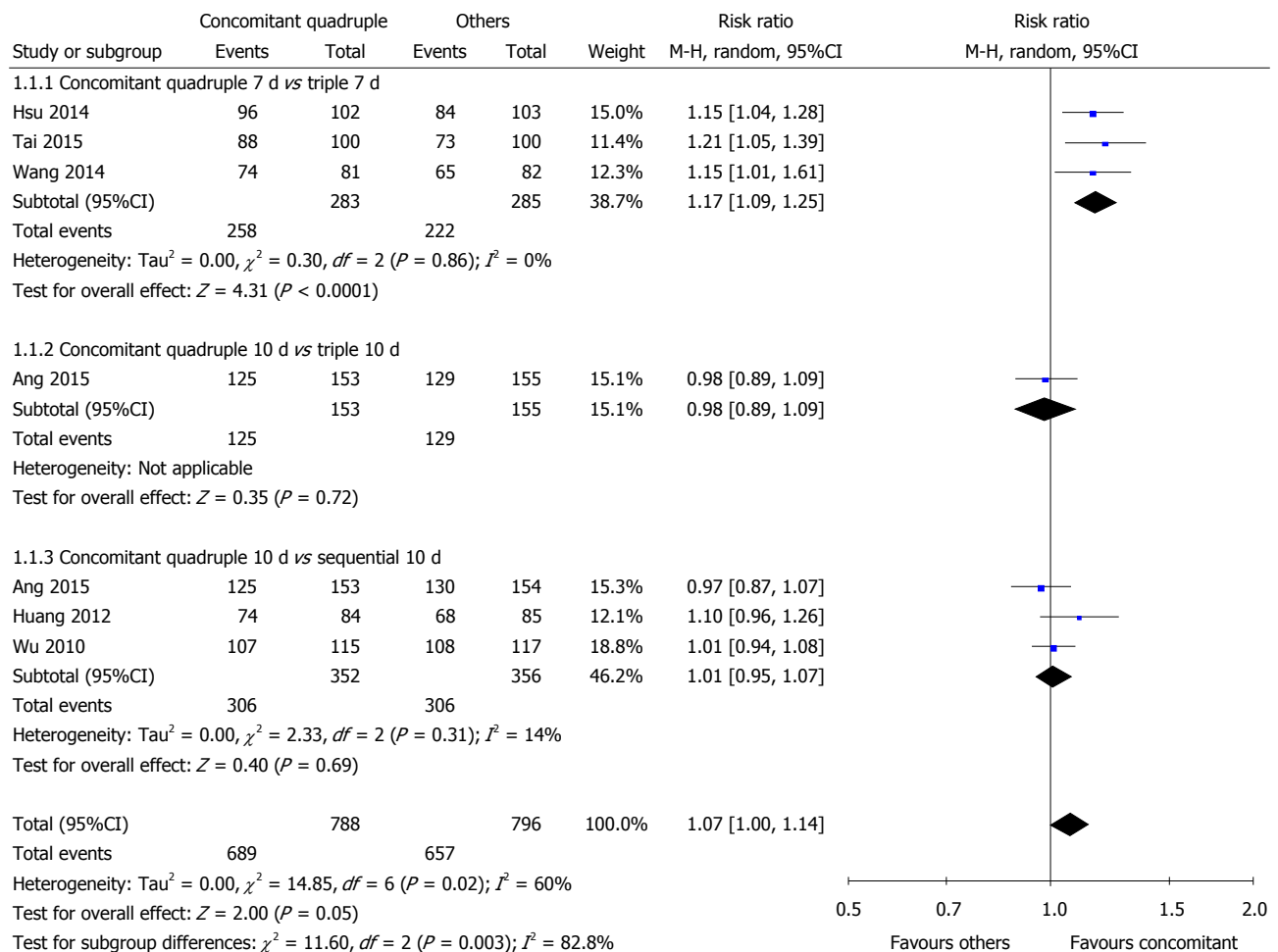
**Nonbismuth concomitant quadruple therapy vs triple therapy:** Three studies compared the compliance with 7-d nonbismuth concomitant quadruple and triple therapies<sup>[33-35]</sup>. No statistically significant difference was observed in the compliance with these therapies (100% vs 99.3%, RR = 1.01, 95%CI: 0.99-1.02) (Figure 3).

**Nonbismuth concomitant quadruple therapy vs sequential therapy:** Three studies compared

**Table 2** Assessment of methodological quality of included studies

Ref.	Region	Allocation generation	Allocation concealment	Blinding of patients and assessors	Data analysis	Loss to follow up	Selective reporting	Other bias
Ang <i>et al</i> <sup>[36]</sup> (2015)	Singapore	Sealed envelope	Adequate	Open-label	ITT/PP	10.0%	Low risk	Not all patients underwent antibiotic susceptibility testing
Hsu <i>et al</i> <sup>[33]</sup> (2014)	Taiwan	Computer generated	Adequate	Open-label	ITT/PP	0.3%	Low risk	Not all patients underwent antibiotic susceptibility testing
Huang <i>et al</i> <sup>[22]</sup> (2012)	Taiwan	Computer generated	Unclear	Open-label	ITT/PP	6.5%	Low risk	No patient underwent antibiotic susceptibility testing
Tai <i>et al</i> <sup>[34]</sup> (2015)	Taiwan	Computer generated	Adequate	Unclear	ITT/PP	8.0%	Low risk	Not all patients underwent antibiotic susceptibility testing
Wang <i>et al</i> <sup>[35]</sup> (2014)	China	Computer generated	Unclear	Unclear	ITT/PP	1.2%	Low risk	No patient underwent antibiotic susceptibility testing
Wu <i>et al</i> <sup>[20]</sup> (2010)	Taiwan	Computer generated	Unclear	Outcome assessor blinded	ITT/PP	0.4%	Low risk	Not all patients underwent antibiotic susceptibility testing

Risk of bias was assessed according to the method recommended by the Cochrane Collaboration. ITT: Intention-to-treat; PP: Per-protocol.

**Figure 2** Forest plot for comparison of concomitant quadruple therapy with other therapies. Outcome: *Helicobacter pylori* eradication rate.



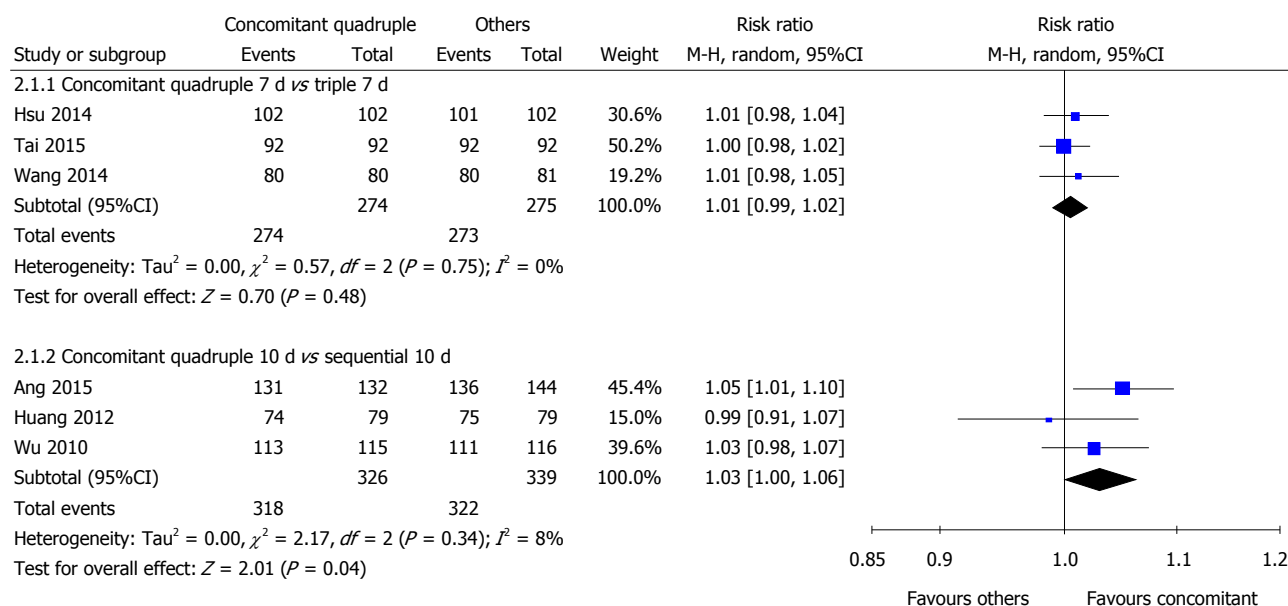


Figure 3 Forest plot for comparison of concomitant quadruple therapy with other therapies. Outcome: Compliance.

the compliance with 10-d nonbismuth concomitant quadruple and sequential therapies<sup>[20,22,36]</sup>. Although no significant difference was observed in the compliance with these therapies (97.5% vs 95.0%, RR = 1.03, 95%CI: 1.00-1.06), more patients tended to comply with nonbismuth concomitant quadruple therapy (Figure 3).

### Adverse events

Two studies compared adverse events including abdominal pain, gastrointestinal disturbance, nausea and vomiting, skin rash, dizziness, and fatigue between 10-d nonbismuth concomitant quadruple and sequential therapies<sup>[20,22]</sup>. Patients receiving these two therapies showed a similar adverse event rate. Moreover, three studies compared the adverse event rate between 7-d nonbismuth concomitant quadruple and triple therapies<sup>[33-35]</sup>. Among two studies, patients receiving these two therapies showed a similar incidence of adverse events<sup>[33,35]</sup>. One study reported more adverse events after 7-d nonbismuth concomitant quadruple therapy than after triple therapy<sup>[34]</sup>. However, these effects were mild and did not markedly interfere with the patients' daily activities.

## DISCUSSION

Because antibiotic resistance is a critical reason for *H. pylori* eradication failure, we conducted a systematic review and meta-analysis of RCTs to evaluate whether nonbismuth concomitant quadruple therapy is the optimal first-line therapy for *H. pylori* eradication in Chinese regions. Our meta-analysis revealed that a higher *H. pylori* eradication rate was achieved with 7-d concomitant therapy than with 7-d triple therapy. The eradication rates of concomitant and sequential

therapies were similar. However, the compliance with concomitant therapy was higher. Therefore, nonbismuth concomitant quadruple therapy should be the first-line treatment for *H. pylori* infection.

Recently, Li *et al*<sup>[37]</sup> conducted a network meta-analysis of treatment for *H. pylori* infection. They showed that nonbismuth concomitant quadruple treatment is effective in *H. pylori* eradication. However, ethnicity and region play pivotal roles in antibacterial treatments; thus, investigating *H. pylori* eradication in different regions is necessary<sup>[38]</sup>. In South Korea, two RCTs showed that a much higher *H. pylori* eradication rate was achieved with nonbismuth concomitant quadruple therapy than with standard triple therapy or sequential therapy<sup>[26,39]</sup>. In Japan, an RCT also reported a higher eradication rate for nonbismuth concomitant quadruple therapy than that for triple therapy<sup>[40]</sup>. Our study revealed a similar outcome in Chinese regions.

Although the included studies used different PPIs, the same PPI was administered to the experimental groups in all studies, except for Ang *et al*<sup>[36]</sup>. Nevertheless, a meta-analysis revealed that different PPI types did not have different efficacies for *H. pylori* eradication<sup>[41]</sup>. Moreover, regarding concomitant therapy, Wang *et al*<sup>[35]</sup> substituted metronidazole with tinidazole; the eradication rate of that study is similar to that of other studies using metronidazole. These results are compatible with the trial that compared the efficacy of tinidazole and metronidazole for *H. pylori* eradication<sup>[42]</sup>.

The optimal dosage of metronidazole remains undetermined. All RCTs used 500 mg of metronidazole twice daily, except for Ang *et al*<sup>[36]</sup>, who used 400 mg twice daily. Nevertheless, Ang *et al*<sup>[36]</sup> still obtained a high eradication rate; this finding indicated that metronidazole doses from 400 to 500 mg are acceptable for *H.*

*pylori* eradication.

To determine the effectiveness of the treatments in practice, we considered the compliance rate. Although the eradication rates of nonbismuth concomitant and sequential therapies were not statistically different, higher compliance was achieved with nonbismuth concomitant therapy than with sequential therapy. Generally, the compliance rate may be higher in RCTs than in clinical settings. Thus, nonbismuth concomitant therapy may be a superior choice for *H. pylori* eradication because higher compliance was achieved with this therapy than with sequential therapy.

The value of  $I^2$  was 0%-14% for each therapy, revealed that mild heterogeneity existed among our selected studies. This could be attributed to heterogeneity among patients' demographics and characteristics and the inclusion and exclusion criteria, dose and route of administration of *H. pylori* treatment, and time of outcome assessment.

Our study has several limitations. First, all our studies were open label, except for the study of Wu *et al.*<sup>[20]</sup>, which was outcome assessor blinded. However, we believe that this is not a major concern because the treatment outcomes were mainly objective. Second, not all trials evaluate antibiotic susceptibility. Third, because China has the highest population globally, more RCTs conducted in China may be required to determine the optimal treatment for *H. pylori* infection in Chinese regions.

In conclusion, the evidence reviewed in the present meta-analysis indicated that nonbismuth concomitant quadruple therapy achieved a higher *H. pylori* eradication rate than that of standard triple therapy and higher compliance than that of sequential therapy. Therefore, nonbismuth concomitant quadruple therapy should be the first-line treatment for *H. pylori* infection in Chinese regions.

## COMMENTS

### Background

Peptic ulcer is a common disease in Chinese regions, and *Helicobacter pylori* (*H. pylori*) eradication has become the standard and most widely adopted therapy. However, eradication rate of standard triple therapy has decreased to 80% in many countries worldwide, and compliance of sequential therapy may be poor due to the complexity. Therefore, there is a need to evaluate whether nonbismuth concomitant quadruple therapy is the first-line therapy for *H. pylori* eradication in Chinese regions.

### Research frontiers

Due to increasing antibiotic resistance, current *H. pylori* eradication therapies may be poor. In this study, the authors compared eradication rate and compliance rate of three different types of therapies in Chinese region.

### Innovations and breakthroughs

This study is the first meta-analysis to compare nonbismuth concomitant quadruple therapy with triple therapy and sequential therapy in Chinese region. Based on this study, nonbismuth concomitant quadruple therapy showed high *H. pylori* eradication rate and good compliance rate in Chinese region.

## Applications

This study showed high efficacy and compliance in nonbismuth concomitant quadruple therapy. Thus, nonbismuth concomitant quadruple therapy is a good choice for first-line *H. pylori* eradication therapy in Chinese region.

## Terminology

Nonbismuth concomitant quadruple therapy consist of proton pump inhibitor plus amoxicillin, clarithromycin, and nitroimidazole derivatives given for 7-14 d. Chinese regions in this study included China, Hong Kong, Taiwan, and Singapore.

## Peer-review

The results of this meta-analysis showed that treatment with nonbismuth concomitant quadruple therapy resulted in high *H. pylori* eradication rate in Chinese region. In addition, good compliance rate and mild adverse effects were also noted in this study. Consequently, the study provided a better choice for first-line eradication therapy of *H. pylori* in Chinese region.

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ISSN 1007-9327



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