# Concomitant, bismuth quadruple, and 14-day triple therapy in the first-line treatment of *Helicobacter pylori*: a multicentre, open-label, randomised trial

*Jyh-Ming Liou, Yu-Jen Fang*, Chieh-Chang Chen*, Ming-Jong Bair, Chi-Yang Chang, Yi-Chia Lee, Mei-Jyh Chen, Chien-Chuan Chen, Cheng-Hao Tseng, Yao-Chun Hsu, Ji-Yuh Lee, Tsung-Hua Yang, Jiing-Chyuan Luo, Chun-Chao Chang, Chi-Yi Chen, Po-Yueh Chen, Chia-Tung Shun, Wen-Feng Hsu, Wen-Hao Hu, Yen-Nien Chen, Bor-Shyang Sheu, Jaw-Town Lin, Jeng-Yih Wu†, Emad M El-Omar, Ming-Shiang Wu†, for the Taiwan Gastrointestinal Disease and Helicobacter Consortium‡*

## Summary

**Background** Whether concomitant therapy is superior to bismuth quadruple therapy or 14-day triple therapy for the first-line treatment of *Helicobacter pylori* infection remains poorly understood. We aimed to compare the efficacy and safety of 10-day concomitant therapy, 10-day bismuth quadruple therapy, and 14-day triple therapy in the first-line treatment of *H pylori*.

**Methods** In this multicentre, open-label, randomised trial, we recruited adult patients (aged >20 years) with *H pylori* infection from nine medical centres in Taiwan. Patients who had at least two positive tests from the rapid urease test, histology, culture, or serology or who had a single positive $^{13}$C-urea breath test for gastric cancer screening were eligible for enrolment. Patients were randomly assigned (1:1:1) to either concomitant therapy (lansoprazole 30 mg, amoxicillin 1 g, clarithromycin 500 mg, and metronidazole 500 mg, all given twice daily) for 10 days; bismuth quadruple therapy (bismuth tripotassium dicitrate 300 mg four times a day, lansoprazole 30 mg twice daily, tetracycline 500 mg four times a day, and metronidazole 500 mg three times a day) for 10 days; or triple therapy (lansoprazole 30 mg, amoxicillin 1 g, and clarithromycin 500 mg, all given twice daily) for 14 days. A computer-generated permuted block randomisation sequence with a block size of 6 was used for randomisation, and the sequence was concealed in an opaque envelope until the intervention was assigned. Investigators were masked to treatment allocation. The primary outcome was the eradication frequency of *H pylori* with first-line therapy assessed in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, number NCT01906879.

**Findings** Between July 17, 2013, and April 20, 2016, 5454 patients were screened for eligibility. Of these, 1620 patients were randomly assigned in this study. The eradication frequencies were 90·4% (488/540 [95% CI 87·6–92·6]) for 10-day bismuth quadruple therapy, 85·9% (464/540 [82·7–88·6]) for 10-day concomitant therapy, and 83·7% (452/540 [80·4–86·6]) for 14-day triple therapy in the intention-to-treat analysis. 10-day bismuth quadruple therapy was superior to 14-day triple therapy (difference 6·7% [95% CI 2·7–10·7], p=0·001), but not 10-day concomitant therapy. 10-day concomitant therapy was not superior to 14-day triple therapy. The frequency of adverse events was 67% (358/533) in patients treated with 10-day bismuth quadruple therapy, 58% (309/535) in patients treated with 10-day concomitant therapy, and 47% (252/535) in patients treated with 14-day triple therapy.

**Interpretation** Bismuth quadruple therapy is preferable to 14-day triple therapy in the first-line treatment in the face of rising prevalence of clarithromycin resistance. Concomitant therapy given for 10 days might not be optimum and a longer treatment length should be considered.

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## Introduction

Emerging evidence has shown that eradication of *Helicobacter pylori* might reduce the risk of gastric cancer.[1–3] However, the eradication frequency of standard triple therapy has fallen to lower than 80% in many countries because of the rising prevalence of antibiotic resistance.[4–6] Extension of the treatment length of triple therapy to 14 days or the use of four drug regimens (bismuth quadruple therapy, concomitant therapy, or sequential therapy) have been shown to increase the eradication frequency in first-line treatment.[7–14] In the past two decades, bismuth quadruple therapy was usually reserved as rescue therapy in second-line or third-line treatment because of its complexity and high frequency of adverse effects.[15,16] However, a large randomised trial[9] has shown that a new capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline given with omeprazole was more effective than 7-day triple therapy in Europe. Concomitant therapy (also termed non-bismuth quadruple therapy), containing a proton-pump inhibitor, amoxicillin, clarithromycin, and metronidazole (or tinidazole), given twice daily for 5–10 days was shown to be more effective than the 7-day or 10-day triple therapy.[17] Concomitant therapy is less

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*†Contributed equally

‡Members listed at end of paper

**Department of Internal Medicine** (J-M Liou MD, Chieh-C Chen MD, Prof Y-C Lee MD, M-J Chen MD, Chien-C Chen MD, Prof J-T Lin MD, Prof M-S Wu MD) **and Department of Pathology** (Prof C-T Shun MD), **National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan; Department of Internal Medicine, National Taiwan University Hospital, Yun-Lin Branch, National Taiwan University College of Medicine, Yun-Lin, Taiwan** (Y-J Fang MD, J-Y Lee MD, T-H Yang MD); **Division of Gastroenterology, Department of Internal Medicine, Mackay Memorial Hospital, Taitung Branch, Taitung, Taiwan** (M-J Bair MD); **Department of Nursing, Meiho University, Pingtung, Taiwan** (M-J Bair); **Department of Internal Medicine, E-DA Hospital and I-Shou University, Kaohsiung County, Taiwan** (C-Y Chang MD, C-H Tseng MD, Y-C Hsu MD); **Department of Medicine, National Yang-Ming University, School of Medicine, and Taipei Veterans General Hospital, Taipei, Taiwan** (Prof J-C Luo MD); **Division of Gastroenterology and Hepatology, Department of Internal Medicine, Taipei Medical University Hospital and School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan** (C-C Chang MD); **Division of**

**Gastroenterology and Hepatology, Department of Internal Medicine, Chia-Yi Christian Hospital, Chia-Yi, Taiwan** (C-Y Chen MD, P-Y Chen MD)**; Department of Internal Medicine, National Taiwan University Hospital, Hsin-Chu Branch, Hsin-Chu, Taiwan** (W-F Hsu MD, W-H Hu MD, Y-N Chen MD)**; Department of Internal Medicine, National Cheng Kung University Hospital, and National Cheng Kung University Medical Center, Tainan, Taiwan** (Prof B-S Sheu MD)**; School of Medicine, Fu Jen Catholic University, New Taipei City, Taiwan** (Prof J-T Lin)**; Department of Internal Medicine, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan** (J-Y Wu MD)**; and Department of Medicine, St George & Sutherland Clinical School, University of New South Wales, Sydney, Australia** (Prof E M El-Omar MD)

Correspondence to:
Prof Ming-Shiang Wu, Department of Internal Medicine and Primary Care Medicine, National Taiwan University Hospital, Taipei, Taiwan
**mingshiang@ntu.edu.tw**

## Research in context

### Evidence before this study

Before we initiated this trial in 2013, we did a search of ClinicalTrials.gov and PubMed between Jan 1, 1990, and Dec 31, 2012, without language restrictions. Our search did not reveal any published, ongoing, or planned randomised trials comparing the efficacy of 10-day concomitant therapy with 10-day bismuth quadruple therapy or 14-day triple therapy in the first-line treatment of *Helicobacter pylori*. After completion of the trial, we again searched PubMed for articles published between Jan 1, 1990, and June 30, 2016. We searched specifically for randomised trials comparing the efficacy of two of bismuth quadruple therapy, concomitant therapy, or 14-day triple therapy in the first-line treatment of *H pylori* in adults. Since 14 days was the current recommended treatment length by the Maastricht V and the Toronto Consensus Reports, trials that used 7-day or 10-day triple therapy as comparison groups were excluded.

When we used the search terms "*H pylori*" and "concomitant therapy" and "quadruple therapy" and limited the search to randomised controlled trials, we identified only one trial comparing bismuth quadruple therapy and concomitant therapy. When we used the search terms of "*H pylori*" and "concomitant therapy" and "triple therapy" and limited the search to randomised controlled trials, we identified ten trials comparing concomitant therapy and triple therapy. However, only one trial compared 5-day concomitant therapy and 14-day triple therapy. The other trials compared concomitant therapy to 5-day triple therapy (n=2), 7-day triple therapy (n=8), or 10-day triple therapy (n=7). In trials that used the 7-day or 10-day triple therapy as the comparison group, concomitant therapy was superior to 7-day or 10-day triple therapy. However, 5-day concomitant therapy was reported to be inferior to 14-day triple therapy. None of these trials compared 10-day concomitant therapy with 14-day triple therapy.

A recent systematic review and meta-analysis of randomised trials identified 12 trials comparing bismuth quadruple therapy and triple therapy between January, 1995, and November, 2011. Meta-analysis showed that bismuth quadruple therapy and triple therapy yielded similar eradication frequencies. Yet, only four of the 12 trials provided information about antibiotic resistance. Only two of the 12 trials compared bismuth quadruple therapy to "14-day" triple therapy. We further searched PubMed using the search terms "*H pylori*" and "quadruple therapy" and "triple therapy" and "bismuth" and limited the search to randomised controlled trials published between Jan 1, 2011, and June 30, 2016, and identified no other trials comparing bismuth quadruple therapy and 14-day triple therapy. To identify the causes of the discrepant results regarding the efficacy of concomitant therapy in clarithromycin and metronidazole resistant strains in the scientific literature, we did a systematic review and meta-analysis using the search terms "*H pylori*" and "concomitant therapy" in PubMed between Jan 1, 1990, and June 30, 2016.

In summary, few previous trials have compared concomitant therapy with bismuth quadruple therapy or with 14-day triple therapy. More importantly, none of the three identified trials provided information about antibiotic resistance

### Added value of this study

We showed that 10-day bismuth quadruple therapy was more efficacious than 14-day triple therapy in the first-line therapy for *H pylori* infection with clarithromycin and metronidazole resistance prevalence of about 15% and 25–30%, respectively. However, 10-day concomitant therapy was not superior to 14-day triple therapy. The result indicated that concomitant therapy given for 10 days was not long enough and increasing the length to 14 days as suggested in the updated Toronto and Maastricht/Florence Consensus conferences should be considered.

### Implications of all the available evidence

The findings from this trial, taken together with all the available evidence, show that bismuth quadruple therapy is preferable to 14-day triple therapy in the first-line treatment in the face of the rising prevalence of clarithromycin resistance. Concomitant therapy given for 10 days might not be optimum and a longer treatment length should be considered.

complex than traditional bismuth quadruple therapy and therefore has the potential to become the standard first-line treatment for *H pylori* infection.[17] Consensus reports[18–20] recommend that both bismuth quadruple therapy and concomitant therapy can be used as the first-line treatment in regions with either low or high clarithromycin resistance.

However, several concerns need to be resolved before concomitant therapy or bismuth quadruple therapy can be used as the standard first-line therapy. First, whether concomitant therapy is superior to bismuth quadruple therapy has not been reported. Therefore, the Toronto Consensus Report[20] has suggested that head-to-head randomised trials are warranted to compare the efficacy of concomitant therapy and bismuth quadruple therapy. Second, although several randomised trials showed that concomitant therapy given for 5–10 days was superior to 7-day or 10-day triple therapy,[17] only one trial used 14-day triple therapy as the comparison group.[8] In a multicentre randomised trial in Latin America, Greenberg and colleagues[8] showed that 5-day concomitant therapy was inferior to 14-day triple therapy. However, none of the previous trials compared the efficacy of 10-day concomitant therapy with 14-day triple therapy. Third, although meta-analysis of randomised trials showed that bismuth quadruple therapy was not superior to triple therapy, significant heterogeneity was observed among these trials and information about antibiotic resistance was not available in most of these trials.[21,22] Only two randomised trials[23,24] directly compared the

efficacy of bismuth quadruple therapy with that of 14-day triple therapy. These two trials showed higher eradication rates of bismuth quadruple therapy than 14-day triple therapy in the per-protocol analysis, but not in the intention-to-treat analysis.[23,24] Of note, susceptibility testing was not done in most of the previous clinical trials, which limited the generalisation of the results to other geographic regions. Finally, little is known about how to re-treat patients who did not clear *H pylori* infection with bismuth quadruple therapy or concomitant therapy.

We designed this randomised controlled trial to compare the efficacy of 10-day concomitant therapy, 10-day bismuth quadruple therapy, and 14-day triple therapy as first-line therapy. Factors that might affect the eradication frequencies, including antibiotic resistance, CYP2C19 polymorphism, and bacterial virulence factors (CagA and VacA) were extensively assessed. We also assessed the efficacy of bismuth quadruple therapy in patients that did not respond well to concomitant therapy and triple therapy and the efficacy of concomitant therapy as rescue therapy in patients that did not respond well to bismuth quadruple therapy. Finally, we constructed a prediction model to estimate the efficacy of the three regimens in regions with different prevalence of antibiotic resistance.

## Methods

### Study design and patients

We did a multicentre, open-label, randomised trial of adult patients (aged >20 years) with symptoms suggestive of upper gastrointestinal tract disorders who underwent oesophagogastroduodenoscopy due to dyspepsia or had other symptoms, as well as asymptomatic individuals with a single positive $^{13}$C-urea breath test for gastric cancer screening, from nine medical centres in Taiwan. Recruited individuals were invited to an *H pylori* screening programme. Those who had at least two positive tests from the rapid urease test, histology, culture, or serology were eligible for enrolment. Study research staff recruited potential participants and explained the purpose and eligibility requirements of the study. Patients with any one of the following criteria were excluded from the study: people younger than 20 years; previous eradication therapy for *H pylori*; history of gastrectomy; severe concurrent diseases or malignancy; pregnant or lactating women; contraindication or previous allergic reactions to the study drugs; or patients who could not give informed consent by themselves. This study was approved by the Institutional Review Board of each participating hospital. Written informed consent was obtained from all patients before enrolment. The protocol is available online.

### Randomisation and masking

Eligible patients were randomly assigned to receive one of the following regimens: triple therapy for 14 days (lansoprazole 30 mg, amoxicillin 1 g, and clarithromycin 500 mg, all given twice daily); concomitant therapy for 10 days (lansoprazole 30 mg, amoxicillin 1 g, clarithromycin 500 mg, and metronidazole 500 mg, all given twice daily); or bismuth quadruple therapy for 10 days (lansoprazole 30 mg twice daily, bismuth tripotassium dicitrate 300 mg [KCB FC Tablets, Swiss Pharm, Taiwan] four times a day, tetracycline 500 mg four times a day, and metronidazole 500 mg three times a day). A computer-generated permuted block randomisation sequence with a block size of six was used for randomisation, and the sequence was concealed in an opaque envelope until the intervention was assigned. An independent research assistant (Miss Yu-Chung Huang, National Taiwan University Hospital, Taiwan) kept this envelope. All investigators were masked to treatment allocation. After the written informed consent was obtained from eligible patients, the study nurses from each centre contacted the independent assistant at National Taiwan University Hospital to obtain the next allocation number by phone to ensure adequate allocation concealment. Patients who remained positive for *H pylori* after 14-day triple therapy or 10-day concomitant therapy were re-treated with 10-day bismuth quadruple therapy, whereas those who remained positive for *H pylori* after 10-day bismuth quadruple therapy were re-treated with 10-day concomitant therapy. The dose and frequency of each regimen were the same as that of first-line treatment.

### Procedures

The $^{13}$C-urea breath test was used to determine the *H pylori* status of patients at least 6 weeks after completion of treatment. All patients were asked to stop proton-pump inhibitors and histamine-2 blockers for at least 2 weeks before the $^{13}$C-urea breath test. The urea kit containing 75 mg $^{13}$C-urea was dissolved in water and mixed with orange juice. Baseline and 30 min breath samples were assayed with an infrared spectrometer that produced computer-generated results (Taipei Institute of Pathology, Taipei, Taiwan). A δ value of 4 or more units was defined as positive for *H pylori* infection as in our previous studies.[10,25] Patients were informed of the common side-effects of the drugs studied before therapy. They were also asked to record these symptoms during treatment. A standardised interview at the outpatient clinic at the end of treatment was also arranged.

The minimum inhibitory concentrations were determined by agar dilution test with Brucella chocolate agar with 7% sheep blood and incubated for 7 days under microaerobic conditions in the central laboratory in the National Taiwan University Hospital.[26] The resistance breakpoints were 0·5 mg/L or more for amoxicillin, 1 mg/L or more for clarithromycin, 8 mg/L or more for metronidazole, more than 0·5 mg/L for tetracycline, and more than 1 mg/L for levofloxacin.[26] PCR followed by direct sequencing with an automatic sequencer was used to genotype the *gyrA* and 23S rRNA mutations (ABI

For the **protocol** see https://clinicaltrials.gov/ct2/show/NCT01906879

PRISM 3100 Genetic Analyzer, Applied Biosystems, CA, USA).[26,27] PCR was also used to detect the CagA gene and to genotype the VacA signal region (s1/2) and midregion (m1/2) mosaics as described previously.[10,27] CYP2C19 polymorphism was genotyped with the SEQUENOM MassARRAY system (SEQUENOM, CA, USA) in the National Genotyping Center.[10,11] Commercially available kits (Eiken Chemical, Tokyo, Japan) were used to determine pepsinogen I and II concentrations. Fasting serum collected at the time of study entry were centrifuged and stored at –80°C until used. The serological atrophic gastric phenotype was defined as a pepsinogen I concentration of 70 ng/mL or less and a pepsinogen I:II ratio of 3 or less.[28] The severity of gastritis was graded by the updated Sydney Classification (where a score of 0 indicated no gastritis, 1 indicated slight gastritis, 2 indicated moderate gastritis, and 3 indicated marked gastritis) among those who underwent oesophagogastroduodenoscopy and had biopsy samples taken for histological examination.

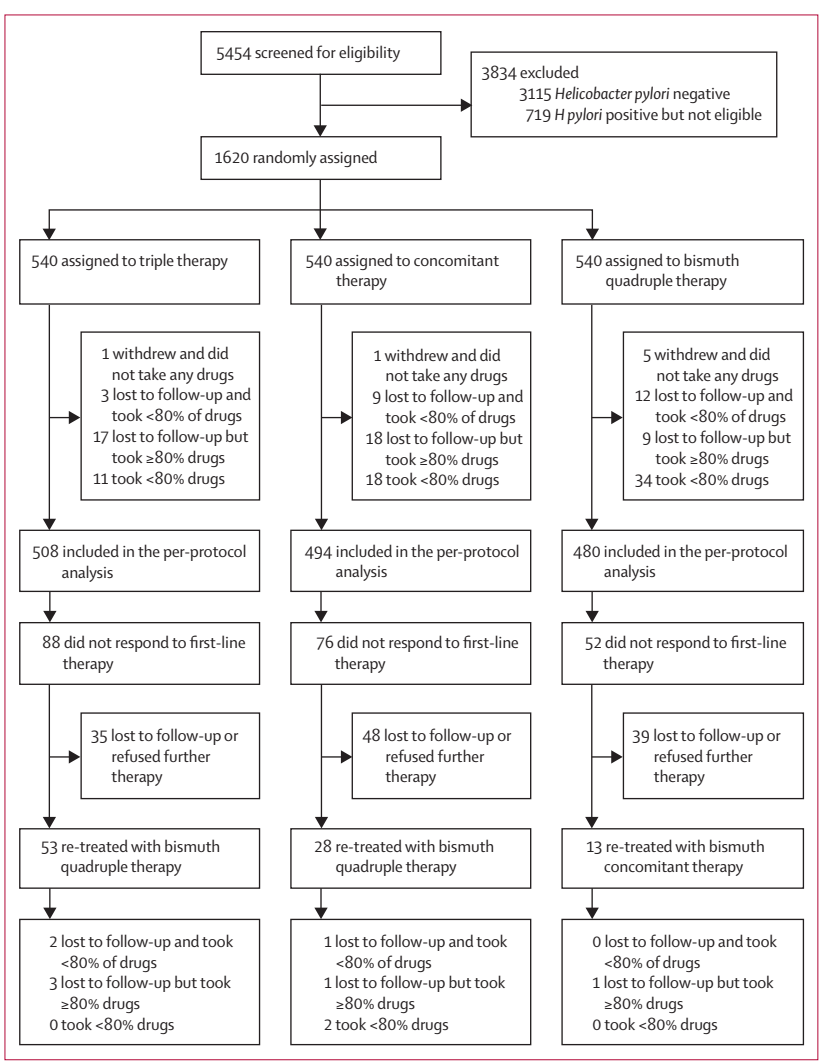


*Figure 1:* **Trial profile**

## Outcomes

The primary endpoint of the study was the eradication frequency of *H pylori* with first-line therapy assessed with the $^{13}$C-urea breath test measured at least 6 weeks after the end of first-line therapy. Secondary endpoints were the frequency of adverse events and the compliance to each regimen. Adverse events and compliance were assessed by research staff with a predefined case report form. The pills not taken by patients were also counted. Compliance was considered low when less than 80% of pills were taken.

## Statistical analysis

We assumed that the eradication frequency of triple therapy was 83%, according to our previous trial and estimated a sample size of at least 400 in each group to detect a 7% difference in the eradication frequency to give a statistical power of 80% (1–β) at an α level of 5% significance on a two-sided test, with an assumed loss to follow-up of 7%.[10,11] Following an interim analysis of the preliminary data of 600 patients, we increased the sample size to a conservative estimate of 540 for each group to give a statistical power of 80% (1–β) at an α level of 5% significance on a two-sided test, with an assumed loss to follow-up of 7% on the basis of preliminary eradication frequencies of 90·5% for bismuth quadruple therapy and 84% for triple therapy in participants from the interim analysis. The primary endpoint was assessed in the intention-to-treat population. All individuals who violated protocol, such as patients who did not take at least 80% of treatment drugs, or those with unknown post-treatment *H pylori* status were excluded from the per-protocol analysis. Patients with missing safety data were not included in the per-protocol analysis. Safety outcomes were assessed in the per-protocol population. The $\chi^2$ test or Fisher's exact test were used to analyse categorical data. Student's *t* test was used to analyse continuous data and was expressed as mean (SD). The 95% CI of the eradication frequency of each regimen was calculated. For the primary endpoint, adjustment for multiple comparisons was made by setting a Bonferroni-corrected α level of 0·015. For secondary variables, exploratory analyses were done by setting an α level of 0·05 without adjustment for multiple comparisons.

Multiple logistic regression analyses with the following predictors of interest were used to assess factors affecting the eradication frequencies: clarithromycin resistance, metronidazole resistance, amoxicillin resistance, age, sex, peptic ulcer disease, VacA genotype, and smoking. Patients with missing data were excluded from the regression analyses. We also constructed a model to predict the efficacies of the three regimens in regions with different prevalence of clarithromycin resistance according to our previous reports.[11,29,30] The data required for model generation were based on the eradication frequencies of bismuth quadruple therapy, concomitant therapy, and triple therapy, according to the antibiotic

resistance in the intention-to-treat analysis, which was obtained from this study. Assuming the eradication frequency in strains susceptible to clarithromycin to be A and those resistant to clarithromycin to be B, the predicted eradication frequency of that regimen would be $A \times (1-p) + B\,p$, where the prevalence of clarithromycin (p) was between 0 and 1. The predicted efficacies of bismuth quadruple therapy, concomitant therapy, and triple therapy according to the prevalence of clarithromycin resistance were plotted with Excel. SPSS statistical software, version 21 for Windows, was used for the statistical analyses. This trial was registered with Clinical Trial.gov, number NCT01906879.

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Between July 17, 2013, and April 20, 2016, 5454 patients were screened for eligibility. Of these, 1620 patients were randomly assigned in this study (figure 1). Biopsy samples for culture were taken from 1225 patients who underwent endoscopy because of upper gastrointestinal symptoms. *H pylori* was isolated in 1022 patients and antibiotic susceptibility data were available in 999 patients. Characteristics were similar across the three randomised groups (table 1, appendix).

With first-line therapy, the eradication frequencies were 90·4% (488/540 [95% CI 87·6–92·6%]) for 10-day bismuth quadruple therapy, 85·9% (464/540 [82·7–88·6]) for 10-day concomitant therapy, and 83·7% (452/540 [80·4–86·6]) for 14-day triple therapy in the intention-to-treat analysis. In the per-protocol population, eradication frequencies were 96% (461/480 [93·9–97·5]) for 10-day bismuth quadruple therapy, 91·7% (453/494 [88·9–93·8%]) for 10-day concomitant therapy, and 87·8% (446/508 [84·7–90·4]) for 14-day triple therapy (table 2). Bismuth quadruple therapy was superior to triple therapy in the intention-to-treat analysis (difference 6·7% [95% CI 2·7–10·7] p=0·001) and per-protocol analysis (difference 8·2% [4·9–11·5]; figure 2). Bismuth quadruple therapy was not superior to concomitant therapy in the intention-to-treat analysis, although a 4·3% (95% CI 1·3–7·3) higher eradication frequency was observed with bismuth quadruple therapy than with concomitant therapy in the per-protocol analysis. Concomitant therapy was not superior to triple therapy in both the intention-to-treat and per-protocol analysis. With second-line therapy, the eradication frequency of bismuth quadruple for patients who did not respond well to triple therapy was 86·8% and for patients who did not respond well to concomitant therapy was 75%; the eradication frequency of concomitant therapy for patients whose treatment with bismuth quadruple therapy did not clear the *H pylori* infection was 84·6% (table 2). After two courses of antibiotic treatment, no significant difference in the overall eradication frequencies between three algorithms of triple therapy and bismuth quadruple therapy, concomitant therapy and bismuth quadruple therapy, and bismuth quadruple therapy and concomitant therapy was noted in both the intention-to-treat and per-protocol analyses (table 2, figure 2).

The frequency of any adverse effects was 67% (358/533) in patients treated with bismuth quadruple therapy, 58% (309/535) in those treated with concomitant therapy, and 47% (252/535) in those treated with triple therapy (table 3; bismuth quadruple therapy *vs* concomitant therapy, p=0·001; bismuth quadruple therapy *vs* triple therapy, p<0·0001; concomitant therapy *vs* triple therapy, p<0·0001). The frequencies of dizziness, headache, nausea, vomiting, and darkened stool were significantly higher in patients treated with bismuth quadruple therapy than in those treated with triple therapy (table 3). However, the frequencies of diarrhoea and taste

| | Triple therapy (n=540) | Concomitant therapy (n=540) | Bismuth quadruple therapy (n=540) |
|---|---|---|---|
| Had at least two positive tests at recruitment* | 480 (89%) | 476 (88%) | 470 (87%) |
| Sex | | | |
| Male | 267 (49%) | 255 (47%) | 279 (52%) |
| Female | 273 (51%) | 285 (53%) | 261 (48%) |
| Age (years) | 53·5 (13·0) | 53·3 (11·8) | 53·3 (12·5) |
| Cigarette smoking | 54 (10%) | 58 (11%) | 59 (11%) |
| Alcohol drinking | 45 (8%) | 46 (9%) | 47 (9%) |
| Gastric ulcer disease | 204 (38%) | 216 (40%) | 215 (40%) |
| Duodenal ulcer | 140 (26%) | 118 (22%) | 141 (26%) |
| CYP2C19 poor metaboliser | 69/517(13%) | 66/511 (13%) | 67/509 (13%) |
| Body-mass index | 24·2 (3·7) | 24·5 (3·7) | 24·5 (3·9) |
| Bodyweight | 63·9 (12·6) | 64·5 (11·7) | 65·3 (12·7) |
| *23S rRNA* mutation | 39/332 (12%) | 41/339 (12%) | 50/328 (15%) |
| *GyrA* mutation | 50/327 (15%) | 47/327 (14%) | 54/319 (17%) |
| Clarithromycin resistance | 48/334 (14%) | 58/339 (17%) | 54/326 (17%) |
| Metronidazole resistance | 97/334 (29%) | 93/339 (27%) | 95/326 (29%) |
| Amoxicillin resistance | 7/334 (2%) | 5/339 (1%) | 7/326 (2%) |
| Levofloxacin resistance | 61/334 (18%) | 62/339 (18%) | 56/326 (17%) |
| Tetracycline resistance | 10/334 (3%) | 8/339 (2%) | 6/326 (2%) |
| *Helicobacter pylori* test positive | | | |
| Serology | 495/507 (98%) | 480/495 (97%) | 470/490 (96%) |
| Rapid urease test | 411/452 (91%) | 422/455 (93%) | 420/458 (92%) |
| Histology | 432/467 (93%) | 452/474 (95%) | 414/450 (92%) |
| Culture | 344/406 (85%) | 346/416 (83%) | 332/403 (82%) |
| Urea breath test | 106/106 (100%) | 110/110 (100%) | 114/114 (100%) |
| Corpus atrophy† | 66/505 (13%) | 54/505 (11%) | 45/502 (9%) |

Data are n (%), mean (SD), or n/N (%). *Two of the following tests needed to be positive: rapid urease test, histology, culture, or serology. †Defined as pepsinogen I concentration lower than 70 ng/mL and a pepsinogen I:II ratio of 3 or less.

***Table 1*: Baseline characteristics and prevalence of antibiotic resistance**

See Online for appendix

| | Triple therapy (n=540) | | Concomitant therapy (n=540) | | Bismuth quadruple therapy (n=540) | | p value |
|---|---|---|---|---|---|---|---|
| | n (%) or n/N (%) | 95% CI | n (%) or n/N (%) | 95% CI | n (%) or n/N (%) | 95% CI | |
| **Eradication frequency with first-line therapy** | | | | | | | |
| Intention-to-treat analysis | 452 (84%)* | 80·4–86·6 | 464 (86%) | 82·7–88·6 | 488 (90%)* | 87·6–92·6 | 0·005 |
| Per-protocol analysis | 446/508 (88%)†‡ | 84·7–90·4 | 453/494 (92%)‡§ | 88·9–93·8 | 461/480 (96%)†§ | 93·9–97·5 | <0·0001 |
| **Eradication frequency with second-line therapy** | | | | | | | |
| Intention-to-treat analysis | 46/53 (87%) | 75·2–93·5 | 21/28 (75%) | 56·6–87·3 | 11/13 (85%) | 57·8–95·7 | 0·40 |
| Per-protocol analysis | 47/48 (98%) | 89·1–99·6 | 20/24 (83%) | 64·1–93·3 | 11/12 (92%) | 64·6–98·5 | 0·08 |
| **Overall eradication frequency after two treatments** | | | | | | | |
| Intention-to-treat analysis | 499 (92%) | 89·9–94·4 | 485/540 (90%) | 87–92·1 | 499 (92%) | 89·9–94·4 | 0·21 |
| Per-protocol analysis | 493/494 (100%) | 98·9–100 | 472/476 (99%) | 97·9–99·7 | 472/473 (100%) | 98·8–100 | 0·21 |

Of the patients who took less than 80% of the study drugs, *Helicobacter pylori* was successfully eradicated in six (55%) of 11 in the triple therapy group , 11 (61%) of 18 in the concomitant therapy group, and 27 (79%) of 34 in the bismuth quadruple therapy group. However, these individuals were excluded from per-protocol analysis according to our protocol. *p=0·001 for bismuth quadruple therapy versus triple therapy in the intention-to-treat analysis. †p<0·0001 for bismuth quadruple therapy versus triple therapy in the per protocol analysis. ‡p=0·042 for concomitant therapy versus triple therapy in the per-protocol analysis. §p=0·024 for bismuth quadruple therapy versus concomitant therapy in the per-protocol analysis.

***Table 2*: Eradication frequencies with first-line and second-line therapies**

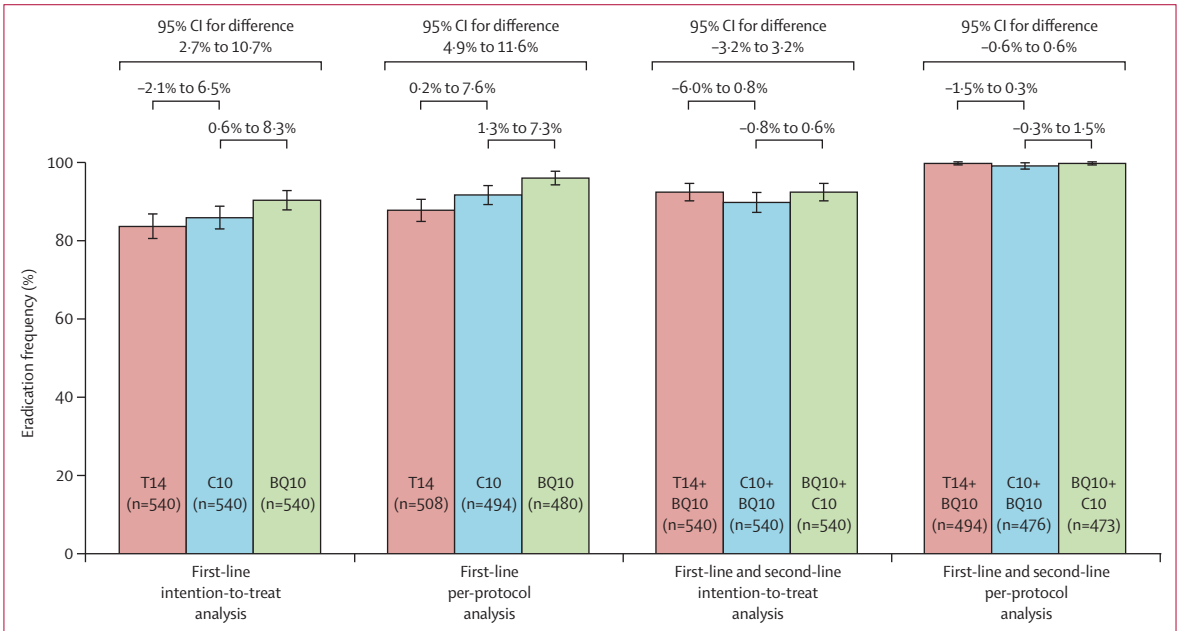


***Figure 2*: Efficacies of first-line and second-line anti-*Helicobacter pylori* treatments**
T14=triple therapy for 14 days. C10=concomitant therapy for 10 days. BQ10=bismuth quadruple therapy for 10 days.

distortion were higher in patients treated with triple therapy and concomitant therapy than in those treated with bismuth quadruple therapy (table 3). Compliance was significantly better in patients treated with triple therapy than in patients treated with concomitant therapy or bismuth quadruple therapy (table 3). The frequency of adverse events in second-line treatment is shown in the appendix.

The eradication frequencies of triple therapy and concomitant therapy were significantly affected by clarithromycin resistance in the intention-to-treat analysis (table 4). Odds ratios (ORs) and 95% CI in the univariate analysis and the eradication frequency according to antibiotic resistance in the per-protocol analysis are shown in the appendix. The results were consistent with the use of different methods (genotypic and phenotypic resistance) to detect the clarithromycin resistance. The eradication frequency of triple therapy also appeared to be lower in the presence of amoxicillin resistance and in strains with the VacA m1 genotype. The efficacy of bismuth quadruple therapy was not affected by clarithromycin or metronidazole resistance. The

| | Triple therapy (n=540) | Concomitant therapy (n=540) | Bismuth quadruple therapy (n=540) |
|---|---|---|---|
| Any adverse events | 252/535 (47%) | 309/535 (58%) | 358/533 (67%) |
| Dizziness | 40/534 (7%) | 63/535 (12%) | 118/531 (22%) |
| Skin rash | 23/534 (4%) | 23/535 (4%) | 13/533 (2%) |
| Headache | 17/534 (3%) | 39/535 (7%) | 43/533 (8%) |
| Taste distortion | 91/534 (17%) | 99/535 (19%) | 63/533 (12%) |
| Abdominal pain | 52/534 (10%) | 54/535 (10%) | 56/533 (11%) |
| Nausea | 31/534 (6%) | 70/535 (13%) | 135/533 (25%) |
| Diarrhoea | 92/533 (17%) | 104/535 (19%) | 45/533 (8%) |
| Constipation | 22/534 (4%) | 12/535 (2%) | 21/533 (4%) |
| Bloating | 35/533 (7%) | 47/535 (9%) | 53/533 (10%) |
| Vomiting | 14/535 (3%) | 21/535 (4%) | 55/533 (10%) |
| Tongue discolouration | 5/534 (1%) | 9/535 (2%) | 13/533 (2%) |
| Darkened stool | 18/533 (3%) | 35/535 (7%) | 146/533 (27%) |
| Discontinued drugs because of adverse events | 19/535 (4%) | 40/536 (7%) | 52/534 (10%) |
| Took less than 80% of drugs | 15/536 (3%) | 28/537 (5%) | 51/540 (9%) |

*Table 3:* **Adverse events with first-line therapy**

efficacies of triple therapy, concomitant therapy, and bismuth quadruple therapy were similarly efficacious for strains susceptible to both clarithromycin and metronidazole. However, the efficacy of bismuth quadruple therapy was higher than triple therapy or concomitant therapy in the presence of clarithromycin resistance. The eradication frequencies of triple therapy, concomitant therapy, and bismuth quadruple therapy were all significantly affected by compliance but not obesity, age, sex, peptic ulcer disease, host CYP2C19 polymorphism, or bacterial virulence factors. 999 patients with drug susceptibility data were included in the multiple logistic regression analyses. Multiple regression analyses showed that the efficacy of triple therapy was significantly affected by compliance, clarithromycin resistance, amoxicillin resistance, and VacA genotype (table 4). The efficacy of concomitant therapy was affected by compliance and clarithromycin resistance, whereas that of bismuth quadruple therapy was only affected by compliance.

The predicted efficacies of bismuth quadruple therapy, concomitant therapy, and triple therapy according to the prevalence of clarithromycin resistance are shown in the appendix. The eradication frequencies of bismuth quadruple therapy, concomitant therapy, and triple therapy in strains susceptible and resistant to clarithromycin were used for the prediction (table 4). Bismuth quadruple therapy appeared to be more effective than concomitant therapy and triple therapy, especially in regions with high clarithromycin resistance. Similarly, concomitant therapy appeared to be more effective than triple therapy in regions with high clarithromycin resistance.

| | Triple therapy (n=540) | Concomitant therapy (n=540) | Bismuth quadruple therapy (n=540) |
|---|---|---|---|
| **23S rRNA mutation (genotypic)** | | | |
| No | 257/293 (88%) | 265/298 (89%) | 254/278 (91%) |
| Yes | 14/39 (36%) | 25/41 (61%) | 47/50 (94%) |
| **Clarithromycin resistance (phenotypic)** | | | |
| Susceptible | 252/286 (88% ) | 251/281 (89%) | 251/272 (92%) |
| Resistant | 21/48 (44%) | 39/58 (67%) | 49/54 (91%) |
| **Metronidazole resistance (phenotypic)** | | | |
| Susceptible | 200/237 (84%) | 214/246 (87%) | 211/231 (91%) |
| Resistant | 73/97 (75%) | 76/93 (82%) | 89/95 (94%) |
| **Amoxicillin resistance (phenotypic)** | | | |
| Susceptible | 271/327 (83%) | 287/334 (86%) | 293/319 (92%) |
| Resistant | 2/7 (29%) | 3/5 (60%) | 7/7 (100%) |
| **Clarithromycin and metronidazole resistance (phenotypic)** | | | |
| Clarithromycin susceptible and metronidazole susceptible | 186/209 (89%) | 189/211 (90%) | 180/196 (92%) |
| Clarithromycin susceptible and metronidazole resistant | 66/77 (86%) | 61/69 (88%) | 71/76 (93%) |
| Clarithromycin resistant and metronidazole susceptible | 14/29 (48%) | 26/36 (72%) | 33/37 (89%) |
| Clarithromycin resistant and metronidazole resistant | 7/19 (37%) | 13/22 (59%) | 16/17 (94%) |
| **Compliance (took at least 80% of the drugs)** | | | |
| Yes | 445/521 (85%) | 452/509 (89%) | 461/489 (94%) |
| No | 6/15 (40%) | 11/28 (39%) | 27/51 (53%) |
| **Gastric ulcer** | | | |
| Yes | 172/204 (84%) | 281/324 (87%) | 296/325 (91%) |
| No | 280/336 (83%) | 183/216 (85%) | 192/215 (89%) |
| **Duodenal ulcer** | | | |
| Yes | 121/140 (86%) | 103/118 (87%) | 128/141 (91%) |
| No | 331/400 (83%) | 361/422 (86%) | 360/399 (90%) |
| **CYP2C19 polymorphism** | | | |
| Poor metaboliser | 60/69 (87%) | 54/66 (82%) | 63/67 (94%) |
| Intermediate metaboliser/ extensive metaboliser | 370/448 (83%) | 388/445 (87%) | 400/442 (90%) |
| **VacA** | | | |
| m1 strain | 81/110 (74%) | 104/120 (87%) | 104/110 (95%) |
| m2 strain | 188/220 (85% ) | 185/218 (85%) | 195/216 (90%) |
| **Multivariate analyses*** | | | |
| Compliance | 5·3 (1·3–21) | 11·6 (4·1–32·8) | 12·7 (4·7–34·0) |
| Poor *vs* good | 0·018 | <0·0001 | <0·0001 |
| Clarithromycin | 9·3 (4·5–19·5) | 5·0 (2·4–10·8) | 1·2 (0·4–3·6) |
| Resistance *vs* no resistance | <0·0001 | <0·0001 | 0·80 |
| Metronidazole | 1·4 (0·7–2·9) | 1·3 (0·6–2·8) | 0·7 (0·2–1·9) |
| Resistance *vs* no resistance | 0·33 | 0·43 | 0·46 |
| Amoxicillin | 17·5 (2·4–129·5) | 4·1 (0·5–30·3) | .. |
| Resistance *vs* no resistance | 0·005 | 0·17 | .. |
| VacA | 0·5 (0·3–1·0) | 1·2 (0·6–2·6) | 1·0 (0·4–3·0) |
| m2 *vs* m1 strains | 0·06 | 0·55 | 0·95 |

*Data are adjusted odds ratio (95% CI), p value; odds ratios in the multiple logistic regression models were adjusted for clarithromycin resistance, metronidazole resistance, amoxicillin resistance, compliance, Vac A genotype, age, sex, gastric ulcer, and duodenal ulcer.

*Table 4:* **Factors affecting eradication frequencies in first-line therapy in the intention-to-treat population**

The resistance determined by the genotypic and phenotypic methods correlated well for both clarithromycin and levofloxacin (appendix). The characteristics among patients recruited according to criteria 1 and 2 were similar and among patients with and without susceptibility tests were also similar (appendix). The minimum inhibitory concentrations of the strains with amoxicillin resistance ranged from 0·5 to 2, whereas that of tetracycline resistant strains ranged from 1 to 4 (appendix). Our prediction model showed that the estimated sample sizes for future randomised trials would be larger in regions with low clarithromycin resistance (appendix). The multivariate logistic regression model including treatment groups confirmed that bismuth quadruple therapy was superior to triple therapy (appendix). Systematic review and meta-analyses of trials comparing concomitant therapy and triple therapy showed that 5–10 day concomitant therapy was superior to 7–10 day triple therapy, but was not superior to 14-day triple therapy (appendix). Systematic review and meta-analysis of trials (appendix) reporting the efficacy of concomitant therapy in resistant strains showed that the eradication frequency of concomitant therapy was 68·9% (95% CI 56·7–79) in clarithromycin and metronidazole dual resistant strains (appendix).

## Discussion

This study had several novel findings. First, this is the first large randomised trial to show that 10-day bismuth quadruple therapy was more effective than 14-day triple therapy. However, 10-day bismuth quadruple therapy was not superior to 10-day concomitant therapy and 10-day concomitant therapy was not superior to 14-day triple therapy. Second, by thorough assessment of the antibiotic susceptibility in 999 patients within this randomised trial, we confirmed that 10-day bismuth quadruple therapy was more effective than 14-day triple therapy and 10-day concomitant therapy in the presence of clarithromycin resistant *H pylori* strains. The results allowed us to estimate the efficacies of the three regimens in regions with different prevalence of clarithromycin resistance. Third, we found that bismuth quadruple therapy was effective as a rescue therapy for patients who did not respond to 14-day triple therapy. Concomitant therapy was also effective for those who did not respond to bismuth quadruple therapy. Finally, the frequencies of adverse effects were higher in patients treated with 10-day bismuth quadruple therapy and 10-day concomitant therapy than in those treated with 14-day triple therapy.

The Maastricht[18] and the Toronto Consensus Reports[20] recommended that bismuth quadruple therapy or concomitant therapy might be used as alternative therapy to triple therapy in regions with low clarithromycin resistance. Yet, little is known about whether concomitant therapy is equivalent or superior to bismuth quadruple therapy or 14-day triple therapy. The results from this study provided evidence that bismuth quadruple therapy is more effective than 14-day triple therapy in a country with a clarithromycin resistance of about 15%. The advantage of bismuth quadruple therapy was that its efficacy was not significantly affected by antibiotic resistance.[16,31] The eradication frequency of bismuth quadruple therapy in the intention-to-treat analysis was 90·4% (488/540) and in the per-protocol analysis was 96% (461/480), and bismuth quadruple therapy was classified as grade B regimen (90–95% eradication) according to the report card of *H pylori* eradication.[32]

The optimum length of concomitant therapy and bismuth quadruple therapy is also an important issue. Although concomitant therapy was shown to be more effective than the 7-day or 10-day triple therapy in the first-line treatment of *H pylori*, a large randomised trial[8] showed that 5-day concomitant therapy was inferior to 14-day triple therapy in Latin America. In a non-randomised prospective trial, Molina-Infante and colleagues[33] showed that 14-day concomitant therapy was superior to 14-day triple therapy. Since Wu and colleagues[34] showed a high eradication frequency of 10-day concomitant therapy in Taiwan, we did this randomised trial to assess whether the treatment length of concomitant therapy could be shortened to 10 days. However, our result showed that 10-day concomitant therapy was not superior to 14-day triple therapy, indicating that concomitant therapy given for 10 days was not enough. Although 10-day bismuth quadruple therapy appeared to be superior to 10-day concomitant therapy by 4·3% in the per-protocol analysis, the difference was not observed in the intention-to-treat analysis. Besides, the 4·3% difference is of doubtful clinical relevance. The difference is likely to have been narrowed by increasing the length of concomitant therapy to 14 days. These findings collectively indicated that the optimum duration of concomitant therapy is 14 days as recommended in the updated Toronto and Maastricht/Florence Consensus conferences. The eradication frequency of 10-day bismuth quadruple therapy was higher than 95% in Taiwan where metronidazole resistance remained low. Further trials are warranted to assess whether extending its length to 14 days would further increase the eradication frequency. Nevertheless, better results would probably have been achieved with a 14-day duration in countries with *H pylori* strains with a high metronidazole resistance than with regimens given for a shorter duration.

The appropriate dose and frequencies of drugs included in the regimen are also important to achieve higher eradication frequency. Studies[35] have shown that the use of high dose dual therapy containing rabeprazole 20 mg plus amoxicillin 750 mg four times a day was more effective than 7-day triple therapy or 10-day sequential therapy.[35] The use of lansoprazole 30 mg twice daily might be an explanation for the lower eradication frequency of the 10-day concomitant therapy and the 14-day triple therapy (non-optimised) than of bismuth

quadruple therapy. A non-randomised study[33] from Spain showed that concomitant therapy containing high dose esomeprazole (40 mg) twice daily achieved a higher eradication frequency than 14-day triple therapy. The use of a high dose of proton-pump inhibitors and the 14-day treatment length might contribute to the high (>90%) eradication frequency of concomitant therapy in Spain and Greece where the clarithromycin resistance rates were 18% and 40%, respectively.[33,36] In this trial, we used a higher dose of metronidazole and tetracycline in bismuth quadruple therapy than the doses used in previous studies because a recent trial from Hong Kong reported a high eradication frequency (92·7%, 166/179) of 10-day quadruple therapy containing metronidazole 400 mg four times a day and tetracycline 500 mg four times a day.[37] The higher dose of tetracycline (1500 mg per day) and metronidazole (2000 mg per day) might contribute to the high eradication frequency and the higher frequency of adverse events. The all in one capsule used in the European study is less complex and might be easier for adherence.[9] Future trials are warranted to compare the efficacies and adverse events of the traditional bismuth quadruple regimen and the all in one capsule in the treatment of *H pylori* infection. Whether bismuth enhanced triple therapy (proton-pump inhibitor, bismuth, clarithromycin, and amoxicillin) would be more effective than 14-day triple therapy or bismuth quadruple therapy containing a proton-pump inhibitor, bismuth, metronidazole, and tetracycline is important to assess in the future.[31]

An important message from this trial was that the eradication frequency of concomitant therapy in strains with dual clarithromycin and metronidazole resistance were only 59% (13/22) in the intention-to-treat analysis, which was not as high as earlier reports (appendix). Meta-analysis of the data showed that the eradication frequency of concomitant therapy was 68·9% (95% CI 56·7–79) in dual resistant strains (appendix). The discrepancies might be attributed to the low number of patients within this subgroup of patients, the dose of proton-pump inhibitors, the test used for minimum inhibitory concentration determination, and probably the ethnic differences. The metronidazole resistance might be overestimated by the epsilometer test which was used in previous trials, whereas the agar dilution test was used in this study. The misclassification of metronidazole susceptible strains in the group with dual resistance might overestimate the efficacy of concomitant therapy in dual clarithromycin and metronidazole resistant strains. In this study, the minimum inhibitory concentrations determined by the agar dilution test correlated well with genotypic resistance (appendix)

The efficacy of a therapy is currently the most important factor in deciding the optimum eradication regimen in the consensus reports. However, other issues deserve our investigation, including the emergence of antibiotic resistance and the manipulation of gut microbiota after ingestion of different types of antibiotics and regimens. Metagenomic analysis of faecal samples before, at the end of treatment, 6 weeks after treatment, and 1 year after treatment will be done to investigate the long-term (1-year) effect of different eradication regimens on the gut microbiota, which is one of the secondary outcomes of this trial.

The strength of this study included the large sample size, the extensive analysis of factors that might affect the efficacy of the three regimens, and the assessment of the efficacy of bismuth quadruple therapy and concomitant therapy in second-line rescue therapy. This trial provides evidence that bismuth quadruple therapy is superior to 14-day triple therapy in a country with clarithromycin resistance higher than 15%. More importantly, the determination of the minimum inhibitory concentration in 999 strains allowed us to construct a model to predict the performance of the three regimens in regions with different prevalence of clarithromycin resistance. Although further randomised trials from regions with high clarithromycin resistance can provide direct evidence for this region, such trials are still small in number from a PubMed search and a search of ClinicalTrials.gov. In the absence of randomised trials in these regions, policy makers might choose appropriate regimens according to our prediction model through the surveillance of the antibiotic resistance.

This study has some limitations. First, this trial was not a double-blind placebo-controlled trial in which the detection bias was minimised. However, the $^{13}$C-urea breath test used to assess the primary outcome is objective and the technicians who did the infrared measurement were not aware of the treatment groups. Furthermore, the use of placebo in patients treated with 14-day triple therapy would increase the complexity of the trial and might underestimate the actual efficacy of triple therapy and lead to bias away from the null hypothesis as the eradication frequency might be decreased, resulting in an observed difference between bismuth quadruple therapy and triple therapy that might be larger than the actual difference. Second, the use of envolopes for allocation concealment might not be as ideal for web-based patient randomisation. Yet, the opaque envelope was kept by one independent assistant in the call centre of National Taiwan University Hospital and all investigators were masked to the randomisation sequence. The demographic characteristics were also similarly distributed, indicating that our allocation concealment was adequate. Third, the use of two different criteria to enrol participants might have also led to selection bias. However, the proportions of enrolled patients on the basis of the two criteria were similar among the three treatment groups through the adequate randomisation (table 1, appendix). Fourth, the minimum inhibitory concentration was not determined in 37% of study participants because cultures were not assessed in 395 patients (24%) and the culture frequency (1022 [83%] of 1225) was less than perfect. However, the

demographic characteristics and the eradication frequencies in those with and without a minimum inhibitory concentration test in the three treatment groups were not significantly different, indicating that the confounding effect was minimal (appendix). Therefore, we did a prespecified case analysis of available data with multivariate logistic regression analysis rather than multiple imputation. Our results could, however, be extrapolated to non-Taiwanese individuals based on the prediction model we constructed using information about antibiotic resistance (appendix). Finally, although the prediction model could more confidently be extrapolated to areas with high clarithromycin resistance, it could not be extrapolated to regions with a clarithromycin resistance rate lower than that in this study (about 15%) because a larger sample size would be needed in these regions (appendix).

Overall, 10-day bismuth quadruple therapy was superior to 14-day triple therapy in first-line therapy for *H pylori* infection. However, 10-day bismuth quadruple therapy was not superior to 10-day concomitant therapy in the intention-to-treat analysis (compliant and non-compliant patients). 10-day concomitant therapy was not superior to 14-day triple therapy. The result indicated that concomitant therapy given for 10 days was not long enough and increasing the length to 14 days as suggested in the updated Toronto and Maastricht/Florence Consensus[18,20] conferences should be considered. The findings from this trial taken together with all available evidence showed that bismuth quadruple therapy is preferable to 14-day triple therapy in the first-line treatment in the face of the rising prevalence of clarithromycin resistance. Concomitant therapy given for 10 days might not be optimum and a longer treatment length should be considered.

#### Contributors

J-ML, M-SW, J-YW, and EME-O conceived the study, with input from all the other listed contributors from the Taiwan Helicobacter Consortium. J-ML designed the study and wrote the protocol. J-ML, Y-JF, Chieh-CC, M-JB, C-YCha, Y-CL, M-JC, Chien-CC, C-HT, Y-CH, J-YL, T-HY, J-CL, C-CCha, C-YChe, P-YC, W-FH, W-HH, Y-NC, J-TL, and M-SW recruited patients to the study. C-TS contributed to the histological assessment. J-ML prepared the statistical analyses. J-ML drafted the Article which was critically revised by M-SW, J-YW, B-SS, J-TL, and EME-O. All authors commented on drafts and approved the final version.

#### The Taiwan Gastrointestinal Disease and Helicobacter Consortium

*Steering Committee:* J-M Liou, J-T Lin, C-Y Wu, J-Y Wu, C-C Chen, C-H Lin, Y-R Fang, M-J Bair, J-C Luo, and M-S Wu.
*Others investigators:* T-Y Cheng, P-H Tseng, C-C Yu, M-C Chiu, Y-N Chen, W-H Hu, C-K Chou, C-M Tai, C-T Lee, W-L Wang, Y-C Wang, and W-S Chang.

#### Declaration of interests

We declare no competing interests.

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