10-Day versus 14-day bismuth quadruple therapy for first-line eradication of *Helicobacter pylori* infection: a randomised, open-label, non-inferiority trial

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Summary

Background Bismuth quadruple therapy is currently consensus recommendation for first-line *Helicobacter pylori* (*H. pylori*) treatment; however, the optimal duration is unknown. We compared the efficacy of 10-day bismuth quadruple therapy with that of 14-day bismuth quadruple therapy for first-line eradication.

Methods For our multicentre, parallel randomised, open-label, and non-inferiority study, we recruited *H. pylori* treatment-naïve patients from one medical centre and one teaching hospital in Taiwan. Patients were randomly assigned (1:1) to receive 10-day (PBMT-10) or 14-day (PBMT-14) bismuth quadruple therapy. The primary outcome was the eradication rate as determined by intention-to-treat (ITT) and per-protocol (PP) analyses. The eradication rates between the two groups were compared using a one-sided α value of 0.025 and a non-inferiority margin of 7%. The secondary outcomes were the rate of adverse effects. The trial is registered with ClincialTrials.gov (NCT04527055).

Findings From August 3, 2020 to April 28, 2023, 313 *H. pylori* treatment-naïve patients (PBMT-10 = 157; PBMT-14 = 156) were enrolled. 35 patients were excluded from PP analyses. The eradication rates (95% CI) for PBMT-10 and PBMT-14 were respectively 92.4% (88.2%–96.5%) and 92.9% (88.9%–97.0%) by ITT analyses, and 97.9% (95.5%–100.0%) and 99.3% (97.8%–100.0%) by PP analyses. The eradication rates for PBMT-10 were non-inferior to those for PBMT-14 (absolute difference [lower boundary of the one-sided 97.5% CI] −0.6% [−6.7%], P_{NI} = 0.020 in ITT analyses, −1.4% [−5.8%], P_{NI} = 0.007 in PP analyses). The rates of overall adverse effects (54.1% versus 57.1%, P = 0.604) were similar between the two groups; nevertheless, the rates of dizziness (18.5% versus 34.0%, P = 0.003) and vomiting (4.5% versus 12.8%, P = 0.008) were lower in PBMT-10 than in PBMT-14.

Interpretation The 10-day bismuth quadruple therapy was non-inferior to the 14-day therapy as a first-line treatment for eradicating *H. pylori* infection and had no different rates of overall adverse effects, but less serious adverse events in terms of dizziness and vomiting.

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Keywords: *Helicobacter pylori*; Bismuth quadruple therapy; First-line eradication; Non-inferiority trial

Research in context

Evidence before this study

PubMed and Embase were searched from their inception to September 20, 2023, without language restrictions, using the search terms "bismuth quadruple therapy" or "bismuth-containing quadruple therapy" in the title. Only one study conducted a head-to-head comparison of the first-line *Helicobacter pylori* (*H. pylori*) eradication rate of 10- and 14-day bismuth quadruple therapy, which consists of proton pump inhibitor (PPI), bismuth, tetracycline, and metronidazole. This study found similar eradication rates for the two regimens; however, the regimens were designed as twice-a-day regimens and the paper was published more than a decade ago. Two meta-analyses of bismuth-containing quadruple therapy, which consisted of PPI, bismuth, and two antibiotics (various types), also showed no significant difference in eradication rate between 10- and 14-day regimens. The Toronto Consensus and the Maastricht VI guidelines recommend 14-day standard bismuth quadruple therapy for first-line *H. pylori* eradication in regions with a high or unknown prevalence rate of clarithromycin-resistant strains; however, the quality of evidence for the optimal treatment duration is very low. It is still unclear whether extending bismuth quadruple therapy from 10 days to 14 days would increase *H. pylori* eradication rates.

Added value of this study

The efficacy of 10-day bismuth quadruple therapy was found to be non-inferior to that of 14-day bismuth quadruple therapy as a first-line anti-*H. pylori* treatment, as determined by intention-to-treat or per-protocol analyses. Both regimens achieved optimal eradication rates. Our study found that extending bismuth quadruple therapy from 10 days to 14 days did neither affect medication adherence nor have overall adverse effects; nevertheless, 10-day bismuth quadruple therapy had lower rates of dizziness and vomiting.

Implications of all the available evidence

Shortening the duration of bismuth quadruple therapy reduces the incidence of specific side effects and the cost of treatment. Accordingly, 10 days is an appropriate duration for bismuth quadruple therapy in first-line treatment in regions without high-level metronidazole resistance of *H. pylori*.

Introduction

Helicobacter pylori (*H. pylori*) causes dyspeptic symptoms, peptic ulcer disease, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma.[1] *H. pylori* eradication therapy reduces the risk of gastric adenocarcinoma and recurrent peptic ulcer disease. *H. pylori* eradication rates have been falling in most regions of the world due to the rise in antimicrobial resistance rates.[2] Bismuth quadruple therapy, which consists of proton pump inhibitor (PPI), bismuth, tetracycline, and metronidazole, is currently the recommended first-line therapy for *H. pylori* infection. However, the optimum duration is unknown. The level of evidence for treatment duration is very low.[1,3,4] Longer treatment duration of *H. pylori* eradication achieves higher cure rates.[5] Sequential therapy extending from 10 days to 14 days potentially had better eradication efficacy.[6] Nevertheless, previous studies found that 10-day standard bismuth quadruple therapy achieved high efficacy for first-line *H. pylori* eradication, as determined by intention-to-treat (ITT) analyses (≥90%) and per-protocol (PP) analyses (≥95%)[7–9]; thus, extending bismuth quadruple therapy from 10 days to 14 days might have a limited effect on the eradication rate. However, females have higher antibiotic resistance rates in *H. pylori* infection than males do.[10] It is uncertain whether shorter antibiotic courses have differences by sex in eradication efficacy. In addition, there are concerns that a longer duration would result in more adverse events, poorer medication adherence, and higher cost. There are also some emerging considerations for prolonged antibiotics, including antibiotics resistance and alteration of gut microbiota.[11] The aim of our study was to compare 10- and 14-day bismuth quadruple therapy in patients with *H. pylori* treatment-naïve in terms of efficacy and side effects.

Methods

Study design and participants

This was a randomised, open-label, and non-inferiority study conducted in two hospitals, namely National Cheng Kung University Hospital and Tainan Hospital, Ministry of Health and Welfare, Tainan, Taiwan. National Cheng Kung University Hospital is a medical centre, which provides general and specific medical services and conducts a variety of education programs and research projects. Tainan hospital is a regional teaching hospital, which provides general medical services and performs a variety of tasks in public affairs. A schematic diagram of the study protocol is shown in Fig. 1.

Patients, who were 18 years old or older and confirmed to be *H. pylori*-infected, were enrolled in the study from August 3, 2020 to April 28, 2023. Females and males, defined by biological attributes based on external body characteristics, were enrolled randomly.

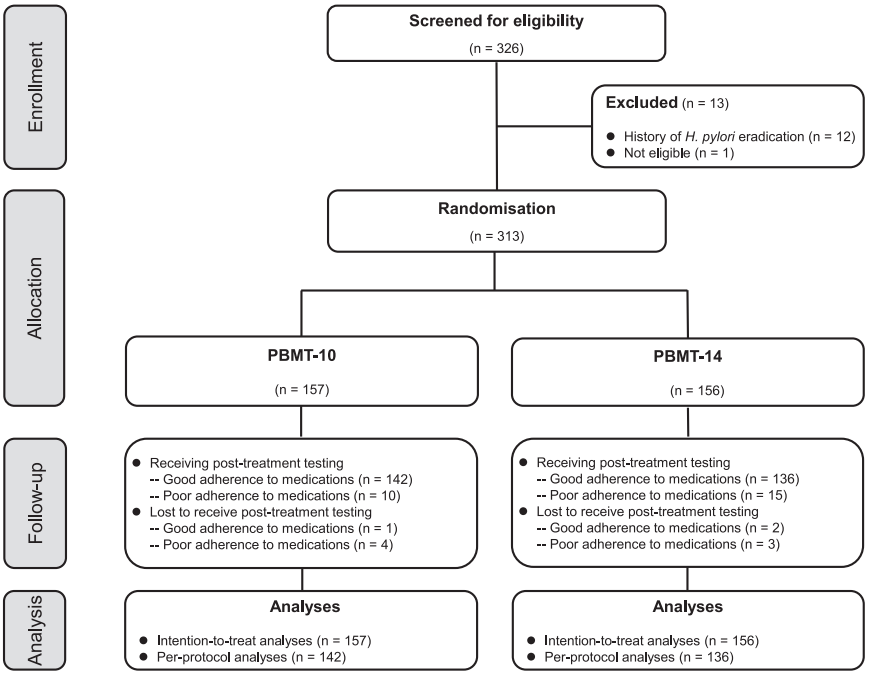

Fig. 1: CONSORT Flow chart of participants. Abbreviations: *H. pylori*, *Helicobacter pylori*; PBMT-10, 10-day proton pump inhibitor-bismuth-metronidazole-tetracycline (bismuth quadruple therapy); PBMT-14, 14-day bismuth quadruple therapy.

The presence of pre-treatment *H. pylori* infection was identified by one or more of the following tests: (1) histological evidence of *H. pylori* infection from gastric biopsy, (2) a positive rapid urease test, and (3) a positive ^{13}C-urea breath test. Patients were excluded if they had previously received *H. pylori* eradication therapy, had previous allergic reactions to any drugs in the bismuth quadruple therapy, had severe comorbidities, or were pregnant or breastfeeding women.

The regimen of bismuth quadruple therapy included esomeprazole (40 mg twice daily), colloidal bismuth subcitrate (120 mg four times daily), metronidazole (500 mg thrice daily), and tetracycline (500 mg four times daily) for a total of 10 days (PBMT-10) or 14 days (PBMT-14). The recent use of PPI was recorded and defined as PPI usage within two weeks preceding the administration of bismuth quadruple therapy.

Ethics

The trial protocol was approved by the National Cheng Kung University Hospital Institutional Review Board (approval number: B-BR-109-012). The registration identifier on ClinicalTrials.gov is NCT04527055. After the research staff explained the study purpose and obtained written informed consent, the participants were enrolled.

Outcomes

The primary endpoint of the study was the eradication rate of *H. pylori*. Successful eradication was defined as a negative ^{13}C-urea breath test or a negative *H. pylori* stool antigen test at least four weeks after the completion of *H. pylori* eradication. The staff assessing the ^{13}C-urea breath test or the *H. pylori* stool antigen test was blinded to the group allocation. The eradication rates were evaluated by ITT and PP analyses. All enrolled participants were included in the ITT analysis; those who were lost to follow-up, took less than 80% of the study medications, or had any protocol violation were excluded from the PP analysis. The ITT analysis was the prespecified primary approach to ensure the maintenance of randomisation features, which balance confounding factors, and represent real-world clinical practice. Secondary endpoints were the rates of adverse events and medication adherence. Adverse events and medication adherence were assessed by a physician and a format questionnaire survey after the end of treatment. Serious adverse events were defined as daily activities restricted or participant unable to work.

Randomisation and masking

In this study, the physicians enrolled the participants; then, the research assistants allocated them to interventions. The study participants from National Cheng Kung University Hospital and Tainan Hospital joined in the randomisation. They were randomly assigned into 10- or 14-day bismuth quadruple therapy with a 1:1 allocation ratio. The randomisation procedure was carried out by the research assistants with drawing a sealed opaque envelope from a box. Each envelope had a

code that assigned the patient to either the 10- or 14-day group. Once we have accumulated 100 patient cases, we replenished the box with another set of 100 envelopes. Each new envelope contained the code. This process continued iteratively. By implementing the randomisation process at every 100-case interval, we were able to ensure a balanced distribution of patients between two groups.

Statistics

Previous studies showed that the *H. pylori* eradication rates of 10- or 14-day bismuth quadruple therapy were ~97%.[7,12] We attempted to identify a non-inferiority margin of 7% between the 10- and 14-day bismuth quadruple therapy because the target of the *H. pylori* eradication rate is 90%, which is currently the consensus recommendation.[1,13] We used a one-sided α value of 0.025 and a statistical power of 90% for the non-inferiority testing of eradication rates between the two groups; thus, the estimated sample size was at least 125 in each group.[14] Under the assumption of a dropout rate of ~20%, at least 156 participants were needed for each group. The non-inferiority comparison of eradication rates was evaluated using the Farrington and Manning test with a one-sided confidence interval (CI) of 97.5% for the group risk difference and a non-inferiority margin of 7%. The null hypothesis assumed that the difference in eradication rate between the 10- and 14-day bismuth quadruple therapy was less than or equal to –7%. The null hypothesis was rejected if the non-inferiority *P* value was less than 0.025. P_{NI} was employed to represent the non-inferiority *P* value.

Categorical variables were compared and tested using either Pearson's χ^2 test or Fisher's exact test as appropriate for the participant's characteristics and the adverse effect of medication. Continuous variables were compared and tested using Student's *t*-test. Because post-treatment *H. pylori* status was unknown for participants who lost to receive post-treatment testing, we assumed that *H. pylori* eradication was successfully for all of them (the best-case scenario) or that it failed for all of them (the worst-case scenario). A complete case analysis was conducted only for the participants who had results of the ^{13}C-urea breath test or the *H. pylori* stool antigen test after *H. pylori* treatment. The eradication rates for the best-case/worst-case scenario and complete case analyses were also calculated with the noninferiority test. SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA) and SPSS software (SPSS Statistics 17.0, IBM Corp., Armonk, NY, USA) were used for the statistical analyses.

Role of the funding source

The funding source had no role in the study design, data collection, data analysis, data interpretation, patient recruitment, or writing of this report. We have not been paid to write this article by any pharmaceutical company or agency. All authors had full access to all the data in the study and accept responsibility to submit the manuscript for publication.

Results

Demographic characteristics of patients

A total of 326 patients with *H. pylori* infection were screened for eligibility in the study. Among them, 13 patients were excluded, including 12 patients who had previous history of *H. pylori* eradication and one patient with advanced terminal cancer and life-threatening infection. The remaining 313 participants were randomly assigned to the PBMT-10 (n = 157) and PBMT-14 (n = 156) groups. Among them, 136 (86.6%) participants in the PBMT-10 group and 136 (87.2%) ones in the PBMT-14 group were enrolled from National Cheng Kung University Hospital. The others were enrolled from Tainan hospital. The characteristics of the two groups were not significantly different in terms of female sex, age, body weight, body mass index, recent use of PPI, cigarette smoking, alcohol drinking, gastric ulcer, and duodenal ulcer (Table 1). In the PBMT-10 group, 152 participants received post-treatment testing, with 142 of them having good adherence to medications (≥80% of medications taken). Moreover, five patients lost to receive post-treatment testing and only one of them had good adherence to medications. In the PBMT-14 group, 151 participants received post-treatment testing, with 136 of them having good adherence to medications. Moreover, five patients lost to receive post-treatment testing and two of them had good adherence to medications (Fig. 1). The rates of lost to receive post-treatment testing were similar between the PBMT-10 and PBMT-14 groups (5/157 [3.2%] versus 5/156 [3.2%], $P > 0.99$).

N (%), mean ± SD	PBMT-10 (n = 157)	PBMT-14 (n = 156)
Female sex	74 (47.1%)	89 (57.1%)
Age (years)	55.0 ± 14.6	55.0 ± 13.0
Weight (kg)	65.0 ± 12.9	63.3 ± 12.3
Body mass index	24.0 ± 3.4	23.9 ± 4.0
Recent use of PPI	32 (20.4%)	41 (26.3%)
Cigarette smoking	20 (12.7%)	20 (12.8%)
Alcohol drinking	23 (14.6%)	14 (9.0%)
Gastric ulcer	32 (20.4%)	42 (26.9%)
Duodenal ulcer	20 (12.7%)	31 (19.9%)

PBMT, proton pump inhibitor-bismuth-metronidazole-tetracycline (bismuth quadruple therapy); PBMT-10, 10-day bismuth quadruple therapy; PBMT-14, 14-day bismuth quadruple therapy; PPI, proton pump inhibitor; SD, standard deviation.

Table 1: **Demographic characteristics of participants in 10- and 14-day therapy groups.**

Rates of *H. pylori* eradication

The *H. pylori* eradication rates in the PBMT-10 and PBMT-14 groups were respectively 92.4% (145/157, 95% CI: 88.2%–96.5%) and 92.9% (145/156, 95% CI: 88.9%–97.0%), as determined by ITT analyses, and 97.9% (139/142, 95% CI: 95.5%–100.0%) and 99.3% (135/136, 95% CI: 97.8%–100.0%), as determined by PP analyses. The eradication rates in the PBMT-10 group were non-inferior to those in the PBMT-14 group, as determined by ITT analyses (absolute difference: –0.6%, lower boundary of the one-sided 97.5% CI: –6.7%, P_{NI} = 0.020) and PP analyses (absolute difference: –1.4%, lower boundary of the one-sided 97.5% CI: –5.8%, P_{NI} = 0.007, Table 2).

Sensitivity analyses were conducted with the best- and worst-case scenarios and a complete case for missing eradication outcomes. The eradication rates obtained from the best-case analysis were 95.5% (150/157, 95% CI: 92.3%–98.8%) in the PBMT-10 group and 96.2% (150/156, 95% CI: 93.1%–99.2%) in the PBMT-14 group (P_{NI} = 0.008). The eradication rates obtained from the worst-case analysis were 92.4% (145/157, 95% CI: 88.2%–96.5%) in the PBMT-10 group and 92.9% (145/156, 95% CI: 88.9%–97.0%) in the PBMT-14 group (P_{NI} = 0.020). The eradication rates obtained from the complete case analysis were 95.4% (145/152, 95% CI: 92.1%–98.7%) in the PBMT-10 group and 96.0% (145/151, 95% CI: 92.9%–99.1%) in the PBMT-14 group (P_{NI} = 0.009, Table 2). All of the above analyses demonstrate that the eradication rates in the PBMT-10 group were non-inferior to those in the PMBT-14 group.

Among the participants enrolled from National Cheng Kung University Hospital, the *H. pylori* eradication rates in the PBMT-10 and PBMT-14 groups were analysed. The results were comparable with the overall population. However, the limited sample size among the participants enrolled from Tainan Hospital posed a challenge to interpret the result (Supplementary Table S1).

Sex-based analyses were conducted. Among the males, the eradication rates in the PBMT-10 group were non-inferior to those in the PBMT-14 group, as determined by ITT analyses (absolute difference: 1.2%, lower boundary of the one-sided 97.5% CI: –6.8%, P_{NI} = 0.022) and PP analyses (absolute difference: 0.4%, lower boundary of the one-sided 97.5% CI: –5.9%, P_{NI} = 0.011). In contrast, among the females, the lower boundary of absolute difference in the eradication rates between the PBMT-10 and PBMT-14 groups were less than –7.0; thus, it failed to reject the null hypothesis (by ITT analyses, absolute difference: –3.0%, lower boundary of the one-sided 97.5% CI: –12.3%, P_{NI} = 0.198; by PP analyses, absolute difference: –3.1%, lower boundary of the one-sided 97.5% CI: –9.4%, P_{NI} = 0.112, Supplementary Table S2).

Adverse effects and adherence to medications

The most common adverse effect in both groups was dizziness. The frequencies of overall adverse effects were not significantly different between the PBMT-10 and PBMT-14 groups (54.1% [85/157] versus 57.1% [89/156]; absolute difference –2.91% [95% CI: –13.74%–8.01%], P = 0.604), but the frequencies of dizziness and vomiting were significantly lower in the PBMT-10 group. The frequency of dizziness was 18.5% (29/157) and 34.0% (53/156) between the PBMT-10 and PBMT-14 groups, and the absolute difference was –15.50% (95% CI: –24.88% to –5.77%, P = 0.003). The frequency of vomiting was 4.5% (7/157) and 12.8% (20/156) between the PBMT-10 and PBMT-14 groups, and the absolute difference was –8.36% (95% CI: –14.92% to –2.12%, P = 0.008, Table 3).

The frequency of serious adverse events was not significantly different between the two groups (3.8% [6/157] versus 2.6% [4/156]; absolute difference 1.26 [95% CI: –3.10 to 5.80], P = 0.750); moreover, the proportion of patients who discontinued treatment because of adverse effects in the PBMT-10 group was not significantly different from that in the PBMT-14 group (4.5% [7/157] versus 5.1% [8/156]; absolute difference –0.67% [95% CI: –5.86% to 4.44%], P = 0.782). One patient presented with anaphylactic shock caused by esomeprazole. The rates of good adherence to medications (≥80% of medications taken) were comparable between the two groups (PBMT-10 versus PBMT-14: 91.1% [143/157] versus 88.5% [138/156]; absolute difference 2.62% [95% CI: –4.24% to 9.55%], P = 0.444).

	PBMT-10	PBMT-14	Absolute difference	P_{NI} value[b]
	N, % (95% CI)	N, % (95% CI)	% (97.5% CI[a])	
Intention-to-treat	145/157, 92.4 (88.2–96.5)	145/156, 92.9 (88.9–97.0)	–0.6 (–6.7)	0.020[c]
Per-protocol	139/142, 97.9 (95.5–100.0)	135/136, 99.3 (97.8–100.0)	–1.4 (–5.8)	0.007[c]
Best-case	150/157, 95.5 (92.3–98.8)	150/156, 96.2 (93.1–99.2)	–0.6 (–5.8)	0.008[c]
Worst-case	145/157, 92.4 (88.2–96.5)	145/156, 92.9 (88.9–97.0)	–0.6 (–6.7)	0.020[c]
Complete case	145/152, 95.4 (92.1–98.7)	145/151, 96.0 (92.9–99.1)	–0.6 (–5.9)	0.009[c]

CI, confidence interval; PBMT, proton pump inhibitor-bismuth-metronidazole-tetracycline (bismuth quadruple therapy); PBMT-10, 10-day bismuth quadruple therapy; PBMT-14, 14-day bismuth quadruple therapy. [a]Lower boundary of one-sided 97.5% confidence interval. [b]Non-inferiority test with Farrington and Manning test and difference in eradication rate with margin of 7%. [c]Alpha level = 0.025.

Table 2: **Comparison of eradication rates between 10- and 14-day therapy groups.**

N (%)	PBMT-10 (n = 157)	PBMT-14 (n = 156)	Absolute difference % (95.0% CI)	*P* value
Dizziness	29 (18.5)	53 (34.0)	−15.50 (−24.88, −5.77)	0.003
Skin rash	10 (6.4)	10 (6.4)	−0.04 (−5.80, 5.70)	0.988
Headache	18 (11.5)	27 (17.3)	−5.84 (−13.69, 2.00)	0.141
Unpleasant taste	19 (12.1)	31 (19.9)	−7.77 (−15.90, 0.39)	0.061
Abdominal pain	20 (12.7)	16 (10.3)	2.48 (−4.72, 9.71)	0.491
Nausea	37 (23.6)	49 (31.4)	−7.84 (−17.54, 2.05)	0.120
Vomiting	7 (4.5)	20 (12.8)	−8.36 (−14.92, −2.12)	0.008
Diarrhea	20 (12.7)	31 (19.9)	−7.13 (−15.33, 1.10)	0.088
Constipation	10 (6.4)	7 (4.5)	1.88 (−3.44, 7.35)	0.463
Abdominal fullness	27 (17.2)	35 (22.4)	−5.24 (−14.03, 3.62)	0.245
Glossitis	13 (8.3)	19 (12.2)	−3.90 (−10.84, 2.94)	0.255
Darkened stool	54 (34.4)	63 (40.4)	−5.99 (−16.49, 4.69)	0.274
Fatigue	33 (21.0)	47 (30.1)	−9.11 (−18.58, 0.57)	0.065
Anorexia	22 (14.0)	33 (21.2)	−7.14 (−15.55, 1.33)	0.097

PBMT, proton pump inhibitor-bismuth-metronidazole-tetracycline (bismuth quadruple therapy); PBMT-10, 10-day bismuth quadruple therapy; PBMT-14, 14-day bismuth quadruple therapy.

Table 3: **Adverse event profile in 10- and 14-day therapy groups.**

Discussion

This study found that the efficacy of 10-day bismuth quadruple therapy was non-inferior to that of 14-day bismuth quadruple therapy as a first-line anti-*H. pylori* treatment, as determined by ITT and PP analyses. The efficacy was confirmed by best-case, worst-case, and complete case analyses. The participants who received 10-day therapy had a lower incidence of dizziness and vomiting than those who received 14-day therapy; however, neither the rate of discontinued treatment due to adverse effects nor the overall medication adherence was significantly different between the two groups.

The participants in this study were enrolled from a medical centre and a regional hospital. Medical centres provide medical services for emergency, intensive care, refractory diseases, rare diseases, and others. Regional hospitals perform tasks of public health. Based on outpatient medical benefit claims of National Health Insurance, the rates of outpatient medical visits were ∼30% for medical centres, ∼40% for regional hospitals, and ∼30% for district hospitals in Taiwan.[15] Accordingly, our participants were representative of ∼70% of outpatient medical visits and those who accessed healthcare with various medical backgrounds and social class divisions. In this open-label clinical trial, ascertainment bias may exist. However, the un-blinded nature had a limited impact on the assessment of efficacy because both the ^{13}C-urea breath test and the *H. pylori* stool antigen test are inherently objective and assessed by a staff unaware of the group allocation. Nevertheless, the assessment of adverse events was subjective and potentially influenced by lack of blinding. As for the best-case and worst-case scenario, we conducted an analysis in a scenario of worst-case for 10-day therapy and best-case for 14-day therapy (Supplementary Table S3). The results did not conclusively establish non-inferiority; however, it is noteworthy that the probability of encountering such an extreme situation was very low.

The European Registry on *Helicobacter pylori* management (Hp-EuReg), an international multicentre prospective non-interventionist registry, reported that prolonging treatment duration was observed in Europe from 2013 to 2018.[5] Moreover, the eradication rates in 10-day and 14-day bismuth quadruple therapy for first-line empirical treatments were respectively 93% and 88%, as determined by both PP and modified ITT analyses.[5] Our study is the first randomised trial to demonstrate that 10- and 14-day bismuth quadruple therapy with standard doses have similar eradication efficacy as a first-line anti-*H. pylori* treatment. Although 10-day therapy provided a smaller amount of medication than 14-day therapy did, the eradication efficacy was non-inferior. Both regimens achieved high efficacy of *H. pylori* eradication. Few studies have conducted head-to-head comparisons of the efficacy of 10- and 14-day bismuth quadruple therapy. Previous systematic review and meta-analyses found that there is no significant difference in eradication rate between the regimens with different treatment durations.[16,17] However, neither the antibiotics nor doses were consistent in these studies; moreover, most studies were not conducted on patients with treatment-naïve. Patients with treatment-naïve and those with a history of treatment failure have distinct characteristics. The observed trend in second-line treatment may not be applicable to first-line treatment. To our best knowledge, only one study compared the efficacy between 10- and 14-day therapy for first-line treatment; however, it used a twice-daily regimen rather than a standard one.[18] Twice-daily bismuth quadruple therapy is not generally applicable because the dose of metronidazole should be 500 mg thrice a day to overcome metronidazole-resistant strains.[19] Using a standard dose is currently the consensus recommendation.[3,4] For example, the Toronto Consensus recommends that the metronidazole dose should be at least 1500 mg daily because of the concern about rising metronidazole resistance.[3] Thus, an updated head-to-head comparison of the efficacy and safety between 10- and 14-day bismuth quadruple therapy with a standard dose for first-line *H. pylori* eradication is needed.

Resistance to antibiotics is an important factor in *H. pylori* eradication failure.[19,20] Clarithromycin resistance is associated with treatment failure in 10- or 14-day sequential therapy, 10-day concomitant therapy, and 14-day triple therapy.[7,8] Bismuth quadruple therapy could overcome clarithromycin-resistant strains,[20] in which 10-day bismuth quadruple therapy had better eradication efficacy than both 10-day concomitant therapy and 14-day sequential therapy did.[7,8] Thus, bismuth quadruple therapy could be an effective alternative to concomitant therapy or sequential therapy in areas with

high clarithromycin resistance. However, the efficacy of bismuth quadruple therapy was reduced by 9% in a population with a metronidazole resistance prevalence rate of >40% as compared with that for a rate of ≤40%.[20] In addition, the duration of bismuth quadruple therapy is a crucial predictor of *H. pylori* eradication for patients with metronidazole resistance.[19] Ten-day bismuth quadruple therapy could achieve an eradication rate of 85% for adherent patients that harbor metronidazole-resistant strains.[21] The estimated rate of *H. pylori* eradication is >90% for bismuth quadruple therapy that lasts 10 days or long in a region where the rate of metronidazole resistance is <40%.[22] In Europe, the prevalence rate of metronidazole-resistant *H. pylori* was the highest in the east region, at 38%; nevertheless, the eradication rate was 92% with bismuth quadruple therapy in this region, as determined by modified ITT analyses.[5] Our study provides direct evidence that this eradication rate can be achieved with either 10- or 14-day bismuth quadruple therapy for first-line *H. pylori* eradication. The prevalence rates of metronidazole resistance of *H. pylori* are below 40% in most countries and regions, including Europe.[2,5,23] Therefore, the results of this study could be generalisable to clinical practice worldwide. The next issue is whether the treatment duration could be reduced or not. A recent study showed that 7-day bismuth quadruple therapy is promising if standard- or high-dose PPI, but not low-dose PPI, is used.[24]

Female sex is a factor of eradication failure with concomitant therapy or sequential therapy,[25] but not of 10-day bismuth quadruple therapy.[7–9] In this study, sex-based analyses confirmed that the efficacy of 10-day bismuth quadruple therapy was non-inferior to that of 14-day therapy in male sex. However, the issue regarding whether 10-day therapy is non-inferior in female sex is inconclusive because our study was not designed to test this hypothesis. The statistical power is insufficient in the subgroup analysis. Future studies focusing on the sex effect are needed.

Poor adherence to medications is another predictor for eradication failure with bismuth quadruple therapy.[7,8] Bismuth quadruple therapy has a high pill burden and a complex treatment course; thus, medication tolerability and adherence should be considered. In this study, adverse events were assessed by a physician and a format questionnaire after the end of treatment; however, the questionnaire could not accurately determine the timing of adverse effect occurrence. The incidence of adverse effects seems to be correlated with the treatment dose and the duration of bismuth quadruple therapy.[26,27] Fourteen-day bismuth quadruple therapy had a higher incidence of adverse effects as compared with 7- or 10-day therapy. Nevertheless, medication adherence was not significantly affected by adverse effects.[16,27] Our study also showed that both 10- and 14-day bismuth quadruple therapy have high medication adherence rates, which are consistent with previous studies.[7,8,12] Moreover, both therapies achieved a good eradication rate (≥90% treatment success, as determined by ITT analyses), even though they had a high incidence of adverse events (Table 3). The good adherence to medications may be due to the severity of the adverse events being not serious and the study design of the clinical trial having structured counselling. The 10-day bismuth quadruple therapy had a lower incidence of dizziness and vomiting than that for the 14-day therapy. It is thus reasonable to conclude that 10-day bismuth quadruple therapy is an appropriate regimen as a first-line *H. pylori* treatment.

This study had some limitations. First, not all enrolled patients had antibiotics susceptibility tests of *H. pylori*. However, a recent meta-analysis demonstrated that the eradication rate achieved by empiric quadruple therapy was similar to that achieved by susceptibility-guided therapy for first-line *H. pylori* treatment.[28] The prevalence rates of primary antibiotic resistance to metronidazole, tetracycline, and clarithromycin are about 35%, 0%, and 20% in Taiwan, respectively.[9,29,30] It is justifiable to suggest 10-day bismuth quadruple therapy for first-line *H. pylori* eradication because it achieves adequate efficacy in geographic regions without high-level metronidazole resistance and its results are similar to estimated results.[22] Nevertheless, the efficacy of 10-day standard bismuth quadruple therapy may not be applicable to geographic regions where the prevalence of metronidazole-resistant *H. pylori* is >40%.[20] The resistance of *Helicobacter pylori* varies in different countries and regions. In the future, it requires a large-scale prospective multicentre study in different countries and regions or where the prevalence rate of metronidazole-resistance *H. pylori* is >40%. Second, the adherence to medications might be suboptimal in the real world[25]; thus, the high efficacy for *H. pylori* treatment in a clinical trial may not be reflected in real-world practice. Third, considering multiple comparisons across adverse events, only the frequencies of dizziness but not vomiting were significantly different between the two groups after Bonferroni correction (Bonferroni corrected alpha level 0.0036). Therefore, the inference that PBMT-10 had a lower incidence of vomiting in contrast to PBMT-14 should be taken with caution. Fourth, the aim of this study was to compare the efficacy of first-line eradication; thus, we did not enroll patients with prior treatment experience. *H. pylori* strains in second-line therapy tend to carry more resistance compared to those in first-line therapy. Therefore, the results in this study were not applicable to second-line treatment. Fifth, while this was a multicentre study, the participants were enrolled predominantly from a single hospital. Thus, this limited the external representativeness of the findings.

In conclusion, our study found that the efficacy of 10-day bismuth quadruple therapy was non-inferior to that of 14-day therapy, with both therapies achieving

adequate efficacy of *H. pylori* eradication; however, the limitation of generalisability should be noted. Shortening the duration of bismuth quadruple therapy reduced the incidence of specific adverse effects and the cost of treatment. Accordingly, 10-day is an appropriate duration for bismuth quadruple therapy for first-line *H. pylori* eradication in regions without high-level metronidazole-resistant strains.

Contributors

The first draft of the manuscript was written by Er-Hsiang Yang. All authors commented on previous versions of the manuscript and had read and approved the final manuscript. Er-Hsiang Yang, Wei-Ying Chen, Hsueh-Chien Chiang, Chung-Hao Li, I-Hsuan Wu, Po-Jun Chen, Chung-Tai Wu, Yu-Ching Tsai, Wei-Chun Cheng, Chien-Jui Huang, Bor-Shyang Sheu, and Hsiu-Chi Cheng had full access to all the data in the study and accept responsibility to submit the manuscript for publication.

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Data sharing statement

Data underlying the results presented in this paper are not publicly available at this time but may be obtained from the authors upon reasonable request.

Declaration of interests

All authors declare no potential conflicts, including financial, professional, or personal, that are relevant to the manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102529.

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