

ORIGINAL ARTICLE

Effectiveness and Safety of First-Line Non-Bismuth Quadruple Concomitant Therapy Versus Single-Capsule Bismuth Quadruple Therapy

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ABSTRACT

Background: The V Spanish Consensus Conference on *Helicobacter pylori* recommended either a 14-day non-bismuth quadruple concomitant therapy (CT: proton pump inhibitor [PPI], clarithromycin, amoxicillin, and metronidazole) or a 10-day bismuth-containing quadruple therapy (Sc-BQT: PPI, bismuth, tetracycline, and metronidazole in a single capsule). The relative advantages of each remain uncertain.

Aim: To compare the effectiveness and safety of first-line empirical CT versus Sc-BQT in Spain.

Methods: We analysed data from treatment-naïve patients enrolled in the European Registry on *H. pylori* Management (Hp-EuReg; 2013–2024). Multivariate logistic regression with propensity score weighting and bootstrap analysis (10,000 replicas) estimated modified intention-to-treat effectiveness and safety.

Results: We evaluated 13,787 treatments: 7234 (52%) with CT—10 and 14 days, and 6553 (48%) with Sc-BQT—every 6 and 8 h. Sc-BQT showed greater effectiveness than 14-day CT (94% vs. 91%; $p < 0.001$). However, 14-day CT with standard-dose

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PPI (93%) outperformed Sc-BQT every 6 h with low-dose PPI (90%) ($p = 0.043$). Sc-BQT every 8 h with high-dose PPI achieved the highest eradication (98%) ($p = 0.015$). Adherence was similar with Sc-BQT (94%) and 14-day CT (93%), being highly associated with eradication success ($p < 0.001$). Sc-BQT, particularly with low- or standard-dose PPI, had a better safety profile ($p < 0.001$).

Conclusion: Sc-BQT is more effective, better tolerated, and more broadly applicable than 14-day CT. Both regimens achieved $\geq 90\%$ success, but Sc-BQT's stewardship-friendly profile further supports its use as first-line therapy for *H. pylori* eradication.

1 | Introduction

Helicobacter pylori (*H. pylori*), a gram-negative bacterium, infects approximately half of the global population. It is identified as the primary factor behind conditions, such as gastritis, peptic ulcer disease, and gastric cancer [1]. However, nowadays the appropriate treatment of choice is still unclear.

The Maastricht VI/Florence consensus defines effective *H. pylori* eradication therapy as achieving cure rates of $\geq 90\%$ [1], emphasising the importance of tailoring drug combinations, dosages, and acid suppression for success [2]. In Europe, bismuth-containing quadruple therapy (BQT) is the recommended first-line treatment due to widespread clarithromycin resistance [3], while non-bismuth quadruple therapy (CT) is an alternative [4], except in regions with high dual resistance to clarithromycin and metronidazole [5–7]. Both regimens demonstrate high efficacy when appropriately applied.

The 2022 Spanish consensus on *H. pylori* highlighted advancements in treatment, recommending both quadruple therapies (CT and BQT) as first-line options with similar evidence levels [8]. While the classical BQT is limited by the unavailability of tetracycline and bismuth, the introduction of a single-capsule BQT (Sc-BQT, Pylera) has simplified administration. Sc-BQT has shown excellent efficacy as both first-line and rescue therapy, even in cases of dual resistance to clarithromycin and metronidazole [9–11]. Additionally, in Spain, this Sc-BQT has proven more effective when prescribed every 6 h, that is three capsules four times a day (off-label) as compared to the official prescription, that is every 8 h with four capsules three times a day (as per the technical sheet) [12].

Data from the European Registry on *H. pylori* Management (Hp-EuReg) show a shift in first-line empirical prescription practices in Spain, likely driven by recent clinical consensus guidelines. From 2013 to 2018, triple therapies (primarily standard triple therapy with amoxicillin and clarithromycin) or non-bismuth CT were used in about half of the Spanish Hp-EuReg population. However, from 2019 to 2024, CT or Sc-BQT became the preferred treatment choice (Figure S1), probably to avoid clarithromycin use given the resistance prevalence of this antibiotic in Spain is above 15% [3, 13].

To compare two different treatments, it is essential to evaluate their effectiveness, safety, compliance, impact of local bacterial antibiotic resistance (especially to clarithromycin), cost-effectiveness, and market availability. Currently, there is a lack of studies directly comparing CT and Sc-BQT, as most

previous literature has focused on comparing CT with classic BQT [14, 15].

Therefore, the objective of the current study was to compare the effectiveness, safety, and compliance of the two most frequently prescribed first-line empirical therapies in Spain: CT and Sc-BQT.

2 | Methods

The “European Registry on *H. pylori* Management” (Hp-EuReg) is an international multicentre prospective non-interventional registry recording information of *H. pylori* infection management since May 2013. Detailed information can be found in the published protocol [16].

Current study data were recorded in an Electronic Case Report Form (e-CRF) using the collaborative research platform REDCap hosted at “Asociación Española de Gastroenterología” (AEG; www.aegastro.es), a non-profit Scientific and Medical Society focused on Gastroenterology research [17, 18]. Data were anonymised. Written, informed consent was obtained from all patients included in the study.

To analyse data from Spain's 17 autonomous communities, four geographic regions were grouped based on sample size: North, North-East, Centre, and South. Region was included solely as a possible confounder variable to account for differences in prescription patterns across Spain, rather than variations in the prevalence of bacterial resistance.

Treatment regimens included 10- and 14-day CT and a 10-day Sc-BQT, with Sc-BQT evaluated using two schedules: the one following the technical sheet [every 6 h (three capsules, four times daily)], and the off-label prescription [every 8 h (four capsules, three times daily; usually with meals, that is, with breakfast, lunch and dinner)].

Patients with a known allergy to penicillin were not prescribed CT, as this regimen includes amoxicillin. Consequently, current study design reflects real-life prescribing patterns rather than a randomised allocation, and the CT group inherently excludes individuals with penicillin allergy. In contrast, Sc-BQT (which does not contain penicillin) is suitable for such patients and could be used in this subgroup.

Proton pump inhibitor (PPI) dosages were standardised using omeprazole equivalents (OE), categorised into low (ranging

from 4.5 to 27 mg OE), standard (ranging from 32 to 40 mg OE), and high doses (ranging from 54 to 128 mg OE) to ensure comparability, as reported by Graham et al. [19] and Kirchheiner et al. [20] (Table S1). Adverse events (AEs) were classified by severity. Compliance was defined as taking $\geq 90\%$ of prescribed medication.

Statistical analysis: Univariate and multivariate analyses were conducted to evaluate modified intention-to-treat (mITT) treatment effectiveness and safety (AEs incidence) across variables, such as treatment regimens and durations, PPI dose and compliance, using Chi-square and Kruskal-Wallis tests for group comparisons.

Propensity score (PS) weighting, using Standardised Mortality Ratio Weighting (SMRW), addressed confounder imbalances [21, 22]. For mITT analysis of varying treatment durations, a generalised boosted model (GBM) with the Average Treatment Effect (ATE) estimated PS and outcomes, implemented via the *weightit* package [23].

Logistic regression models with 10,000 bootstraps, using the *car* [24], *boot.pval* [25] and *bayestestR* [26] packages, enhanced robustness. Odds ratios (ORs) with 95% confidence intervals (CIs) identified factors influencing eradication success and AEs incidence, with statistical significance set at $p < 0.05$.

Detailed information on the categorisation of variables and the statistical analyses conducted is available in File S2.

3 | Results

3.1 | Baseline Characteristics

This study evaluated the Spanish cohort of the Hp-EuReg (Figure S2), analysing 13,787 cases. The study population had a mean age of 52 (± 15) years, with 60% female patients, predominantly treated for non-investigated dyspepsia (33%) or dyspepsia with normal endoscopy findings (37%). *H. pylori* diagnosis was primarily made by histology (47%), followed by the ^{13}C -urea breath test (29%), rapid urease test (18%), and stool antigen test (13%).

3.2 | Prescriptions

Among the patients assessed, 7234 (52%) were prescribed non-bismuth quadruple therapy (CT), while 6553 (48%) received single-capsule bismuth quadruple therapy (Sc-BQT). The most frequent prescription schedules were 14-day CT (34%) and Sc-BQT every 6 h (29%), followed by 10-day CT (19%) and Sc-BQT every 8 h (19%). Both 10- and 14-day CT, as well as Sc-BQT every 6 h, were predominantly prescribed with low-dose PPIs (45% and 55%, respectively). Conversely, Sc-BQT every 8 h was often administered with standard or high-dose PPIs, each in about one-third of cases. All treatments in our cohort included a PPI administered twice daily, rather than once or three times daily. All CT regimens followed the same antibiotic dosing schedule: 500 mg of clarithromycin, 1000 mg of amoxicillin, and 500 mg of metronidazole, each taken twice daily

(i.e., every 12 h), as recommended by the Spanish consensus guidelines. In the case of Sc-BQT, both the on-label regimen (as per the product's technical sheet) and the off-label schedule included 140 mg of bismuth subcitrate potassium, 125 mg of metronidazole, and 125 mg of tetracycline per capsule.

All Spanish geographical regions showed balanced prescriptions for each of the four treatment groups; however, in the Centre, Sc-BQT every 8 h was the most prescribed (43%), whereas in the South, Sc-BQT every 6 h (31%) and 14-day CT (34%) were most common, as was the case in the North (21% and 22%, respectively).

Baseline patient characteristics for each treatment group—10- and 14-day CT and 10-day Sc-BQT every 6 and 8 h—are detailed in Table 1, with variables analysed before and after propensity score matching (data not shown).

3.3 | Effectiveness

First-line empirical treatment effectiveness was significantly lower ($p < 0.001$) for 10-day CT (89% by PP and 88% by mITT) compared to 14-day CT (92% and 91%, respectively). Similarly, Sc-BQT administered every 6 h showed, in the overall analysis, lower ($p < 0.001$) effectiveness (93% for both PP and mITT) than Sc-BQT every 8 h (95% for both).

Cure rates varied based on the PPI dose prescribed (Table S2). For example, mITT effectiveness exceeding 90% was observed for 10-day CT only when combined with a high-dose PPI (92%), for 14-day CT with either standard- or high-dose PPI (both 93%), and for Sc-BQT, regardless of prescription type or PPI dosage. However, statistically significant ($p < 0.001$) higher cure rates were achieved for Sc-BQT administered every 6 h combined with either standard- or high-dose PPI (both 96%) or every 8 h with high-dose PPI (96%) compared to other Sc-BQT regimens.

Therapeutic groups, defined by varying treatment durations and PPI doses, were evaluated through multivariate analysis using different methods adjusted by PS, as detailed in the sections below.

3.4 | Concomitant Therapy

The first analysis compared the two CT prescriptions (evaluating the different combinations in terms of duration and PPI dose). The reference category was a 14-day course of CT administered with a standard-dose PPI, and all other prescription combinations were compared against this baseline. This analysis showed that 14-day CT with low-dose PPI (the most frequent CT combination used in the studied cohort) (OR 0.82; 0.72–0.92; $p < 0.001$), 10-day CT with low-dose PPI (OR 0.59; 0.52–0.56; $p < 0.001$), and 10-day CT with standard-dose PPI (OR 0.45; 0.40–0.50; $p < 0.001$) were significantly associated with lower mITT effectiveness. On the other hand, when 10-day CT was prescribed with high-dose PPI, significantly higher effectiveness was achieved compared with 14-day CT with standard-dose PPI. Additionally, 14-day CT with

TABLE 1 | Baseline characteristics and prescriptions after propensity score adjustment.

Prescriptions, N (% ^c)	CT		Sc-BQT	
	10 days	14 days	Every 6 h	Every 8 h
CT	2600 (36%)	4634 (64%)	NA	NA
Sc-BQT	NA	NA	3999 (61%)	2554 (39%)
<i>Dose of PPI^a</i>				
Low	1587 (61%)	1682 (36%)	2196 (55%)	751 (29%)
Standard	603 (23%)	997 (22%)	1026 (26%)	801 (31%)
High	398 (15%)	1937 (42%)	759 (19%)	995 (39%)
<i>Recruitment years</i>				
2013–2019	2381 (92%)	1872 (40%)	1229 (31%)	551 (22%)
2020–2024	219 (8.4%)	2762 (60%)	2770 (69%)	2003 (78%)
<i>Gender</i>				
Female	1616 (62%)	2703 (58%)	2477 (62%)	1552 (61%)
Male	983 (38%)	1922 (42%)	1520 (38%)	1001 (39%)
Age, Median (IQR)	50 (40, 61)	56 (44, 67)	55 (43, 67)	53 (41, 63)
Age 18–30	281 (11%)	406 (8.8%)	324 (8.1%)	254 (9.9%)
Age 31–50	1066 (41%)	1578 (34%)	1358 (34%)	952 (37%)
Age 51–70	1030 (40%)	2039 (44%)	1750 (44%)	1095 (43%)
Age 71-highest	223 (8.6%)	611 (13%)	567 (14%)	253 (9.9%)
<i>Indications for H. pylori investigation</i>				
Dyspepsia and others	2006 (84%)	3416 (80%)	3001 (82%)	2060 (89%)
Ulcer (gastric and duodenal)	393 (16%)	849 (20%)	650 (18%)	264 (1%)
<i>Geographical region^b</i>				
Centre	463 (18%)	1601 (35%)	943 (24%)	1096 (43%)
Northeast	841 (32%)	1131 (24%)	980 (25%)	577 (23%)
North	403 (16%)	1034 (22%)	836 (21%)	249 (9.8%)
South	893 (34%)	857 (19%)	1229 (31%)	631 (25%)

Abbreviations: A, amoxicillin; AE, adverse event; B, bismuth salts; C, clarithromycin; CT, concomitant therapy; IQR, interquartile range; ITT, intention-to-treat; M, metronidazole; mITT, modified intention-to-treat; NA, not applicable; PP, per protocol; PPI, proton pump inhibitor; Sc-BQT, single capsule bismuth quadruple therapy; Tc, tetracycline.

^aLow dose PPI: 4.5 to 27 mg OE b.i.d.; standard dose PPI: 32 to 40 mg OE b.i.d.; high dose PPI: 54 to 128 mg OE b.i.d.

^bNorth: Cantabria, Navarra, Galicia, La Rioja, País Vasco, Asturias; North-East: Aragón, Cataluña, Valencia, Baleares; Centre: Castilla León, Castilla la Mancha, Madrid, Extremadura; South: Andalucía, Murcia, Canarias.

^cThe percentage provided corresponds to the number of cases within each treatment group (i.e., either CT or Sc-BQT). After propensity score, *p*-values for region, age and recruitment years were: 0.31; 0.99 and 0.71; respectively.

high-dose PPI exhibited significantly higher effectiveness (OR 1.31; 1.15–1.49; $p < 0.001$) than 14-day CT with standard-dose PPI (Figure S3A,B).

Additionally, the effect of PPI dosage was evaluated using an analysis of predicted probabilities of effectiveness. The results showed that high-dose PPI provided a better probability of effectiveness than standard-dose PPI when prescribed with 14-day CT. The differences were even greater with 10-day CT (Figure S4), confirming the findings of the abovementioned multivariate analysis.

3.5 | Single Capsule Bismuth Quadruple Therapy

All prescriptions in this comparison were for 10-day regimens. The baseline for this analysis was Sc-BQT administered every 6 h with standard-dose PPI. Compared to this baseline, Sc-BQT every 6 h with low-dose PPI was the only group that was associated with significantly lower effectiveness (OR 0.64; 0.55–0.74; $p < 0.001$).

Conversely, Sc-BQT every 6 h with high-dose PPI (OR 1.35; 1.14–1.59; $p = 0.001$), Sc-BQT every 8 h with low-dose PPI (OR

1.25; 1.06–1.47; $p=0.008$), and Sc-BQT every 8 h with standard-dose PPI (OR 2.64; 2.16–3.25; $p=0.001$) were all associated with significantly higher effectiveness compared to the baseline. Finally, Sc-BQT administered every 8 h with high-dose PPI demonstrated similar results to the reference category (OR 1.00; 0.85–1.17; $p=0.97$) (Figure S5A,B).

The analysis of predicted probabilities confirmed the findings of the multivariate analysis, showing that effectiveness was higher for Sc-BQT every 6 h when combined with high-dose PPI and with Sc-BQT every 8 h regardless of the PPI dose used. Nonetheless, the highest values were observed with the off-label prescription, that is, with Sc-BQT every 8 h with standard-dose PPIs (Figure S6).

3.6 | Importance of Treatment Duration and PPI Dose in Prescriptions

As a first step, CT and Sc-BQT were compared regardless of treatment duration or PPI dosage. The multivariate analysis confirmed that Sc-BQT was significantly associated with higher eradication success compared to CT (OR 1.55; 1.35–1.77; $p<0.001$). These findings were also further validated by the bootstrap analysis (Table S3).

Secondly, CT and Sc-BQT were compared taking into account varying durations and regimen schedules. The baseline category was 14-day CT. The final model showed that 10-day CT was significantly associated with a lower mITT cure rate (OR 0.75; 0.69–0.82; $p<0.001$), whereas significantly higher effectiveness was observed for both Sc-BQT every 6 h and every 8 h (OR 1.45; 1.31–1.59 and OR 1.88; 1.69–20.9; respectively, both $p<0.001$) (Table S4).

Lastly, the effectiveness of all different Sc-BQT combinations was evaluated. This analysis considered various treatment durations and PPI dosages, controlling for CT groups and other independent variables within the PS-matched Spanish cohort. The baseline was 14-day CT with standard-dose PPI, and all other therapeutic groups were compared against it.

The analysis found that 10-day CT with either low- or standard-dose PPI was associated with significantly lower effectiveness compared to the baseline (OR 0.54; 0.38–0.75; $p<0.001$ for low-dose PPI; OR 0.44; 0.29–0.68; $p<0.001$ for standard-dose PPI). Similarly, 14-day CT with low-dose PPI (OR 0.59; 0.45–0.77; $p<0.001$) and Sc-BQT administered every 6 h with low-dose PPI (OR 0.75; 95% CI 0.56–0.99; $p=0.04$) showed lower effectiveness.

In contrast, 10- and 14-day CT with high-dose PPI, Sc-BQT every 6 h with high-dose PPI, and Sc-BQT every 8 h with either low- or standard-dose PPI showed similar effectiveness to the baseline, with no statistically significant differences. However, Sc-BQT every 6 h with standard-dose PPI (OR 1.61; 1.08–2.46; $p=0.02$) and Sc-BQT every 8 h with high-dose PPI (OR 1.66; 1.11–2.52; $p=0.015$) were associated with significantly higher effectiveness than the baseline. These results were also confirmed by the bootstrap analysis (Table 2 and Figure S7A,B).

The analysis of predicted probabilities confirmed the abovementioned multivariate findings. Among Sc-BQT regimens, those

administered every 6 h with standard-dose PPI and every 8 h with high-dose PPI achieved the highest mITT cure rates, all exceeding 95% effectiveness (Figure S8).

3.7 | Safety

Overall, 3753 (27%) patients experienced at least one AE. Among these, 650 (25%) cases occurred in the 10-day CT group, 1476 (32%) in the 14-day CT group, 1017 (26%) in the Sc-BQT every 6 h group, and 610 (24%) in the Sc-BQT every 8 h group. Significant differences ($p<0.001$) were observed in the univariate analysis between the 10- and 14-day CT groups; however, no significant differences were found between the two Sc-BQT schedules.

Conversely, significant differences were observed based on the PPI dose used in the regimen. The highest rates were reported for 14-day CT groups, regardless of whether standard- or high-dose PPI was used (38% and 41%, respectively; $p<0.001$). Similarly, high-dose PPI was associated with the highest rates when prescribed within the Sc-BQT regimen every 6 h (49%) or every 8 h (34%; both $p<0.001$) (Table S5).

Regarding the types of AEs experienced, the most frequent were diarrhoea, nausea, and asthenia in all treatments groups with a limited duration between 1 and 10 days, and most of them (80% of the cases) exhibited mild intensity.

Additionally, among all treated cases, 16 (0.12%) reported a serious AE: 2 were experienced with 10-day CT, 7 with 14-day CT, 5 with Sc-BQT every 6 h, and 2 with Sc-BQT every 8 h. All of them were associated with hospitalisations due to the following causes: abdominal pain (14-day CT group), amoxicillin hypersensitivity (14-day CT group), pseudomembranous colitis (Sc-BQT every 6 h group), *Clostridioides difficile* infection causing diarrhoea (Sc-BQT every 6 and every 8 h groups), severe diarrhoea of unknown causes (10-day CT group), hypertension (Sc-BQT every 6 h group), oedematous-ascitic decompensation (14-day CT group), intestinal subocclusion (10-day CT group), dizziness and vomits (Sc-BQT every 6 h group), oedema, vomiting and papuloerythematous lesions (14-day CT group), oral mycosis and oesophageal candidiasis (14-day CT group), biliary pancreatitis, and acute cholecystitis (14-day CT group). Treatment was interrupted due to an AE in 254 (1.8%) patients.

The multivariate analysis of safety (Table 3) considered all therapeutic groups, taking into account treatment duration, regimen schedule, and PPI dose, using 14-day CT with a standard-dose PPI as the baseline reference category. The analysis revealed that, when combined with a low-dose PPI, all regimens—regardless of the CT duration or Sc-BQT schedule—were significantly ($p<0.001$) associated with a lower incidence of AE compared to the baseline.

For standard-dose PPI, Sc-BQT every 8 h was likewise associated with a decrease in AE incidence (OR 0.42; 0.32–0.55; $p<0.001$), while Sc-BQT every 6 h showed a similar safety profile (OR 0.96; 0.78–1.18; $p=0.71$).

In contrast, when all groups were combined with a high-dose PPI, a significantly higher AE incidence was observed, except

TABLE 2 | Multivariate analysis of the propensity score-matched Spanish cohort in the evaluation of first-line empirical effectiveness of concomitant and single capsule bismuth quadruple therapies according to varying duration and proton pump inhibitor dose.

Multivariate analysis adjusted by standardised mortality ratio (SMR) weighting propensity score				Bootstrap replicas		
				R = 10,000		
Dependent variable: mITT effectiveness						
Characteristics	OR ^b	95% CIOR ^b	p	OR ^b	95% CIOR ^b	p
Prescription						
14-day CT standard-dose PPI						
14-day CT low-dose PPI	0.59	0.45–0.77	<0.001	0.59	0.42–0.85	0.0018
14-day CT high-dose PPI	0.99	0.71–1.36	0.94	0.98	0.67–1.49	0.9312
10-day CT low-dose PPI	0.54	0.38–0.75	<0.001	0.53	0.36–0.8	0.001
10-day CT standard-dose PPI	0.44	0.29–0.68	<0.001	0.44	0.27–0.72	0.0004
10-day CT high-dose PPI	0.96	0.52–1.91	0.896	0.96	0.51–1.77	0.9072
Sc-BQT every 6 h standard-dose PPI	0.75	0.56–0.99	0.043	0.74	0.53–1.07	0.0762
Sc-BQT every 6 h low-dose PPI	1.62	1.08–2.46	0.021	1.62	1.02–2.54	0.0334
Sc-BQT every 6 h high-dose PPI	1.51	0.96–2.44	0.082	1.52	0.9–2.49	0.0964
Sc-BQT every 8 h low-dose PPI	1.33	0.90–2.01	0.162	1.33	0.84–2.11	0.2152
Sc-BQT every 8 h standard-dose PPI	1.17	0.79–1.75	0.431	1.17	0.75–1.84	0.4958
Sc-BQT every 8 h high-dose PPI	1.66	1.11–2.52	0.015	1.66	1.06–2.61	0.0268
Gender						
Female						
Male	0.94	0.82–1.09	0.412	0.94	0.81–1.1	0.4444
Age (years)						
18–30	0.88	0.69–1.13	0.325	0.88	0.68–1.16	0.3614
31–50	0.94	0.73–1.19	0.615	0.94	0.72–1.24	0.6392
51–70	1.02	0.75–1.39	0.904	1.02	0.71–1.46	0.9088
71-highest						
Compliance						
No (<90% drug intake)						
Yes (>90% drug intake)	7.72	5.72–10.40	<0.001	7.79	5.42–10.84	0
Treatment indication						
Dyspepsia and others						
Ulcer	1.23	1.00–1.54	0.058	1.24	0.98–1.55	0.0628
Geographical region ^a						
Centre						
North-east	0.54	0.45–0.64	<0.001	0.54	0.45–0.65	0
North	1.24	0.96–1.61	0.102	1.24	0.94–1.62	0.1132
South	0.98	0.81–1.20	0.854	0.98	0.78–1.23	0.8844
Recruitment years						
2013–2018						
2019–2023	0.85	0.72–1.02	0.078	0.85	0.72–1.02	0.0634

Note: CT: concomitant therapy; Sc-BQT: single capsule bismuth quadruple therapy; mITT: modified intention-to-treat; PPI: proton pump inhibitor; Low dose PPI: 4.5 to 27 mg OE b.i.d; standard dose PPI: 32 to 40 mg OE b.i.d; high dose PPI: 54 to 128 mg OE b.i.d. Bold values indicate statistical significance at $p < 0.05$.

^aNorth: Cantabria, Navarra, Galicia, La Rioja, País Vasco, Asturias; North-East: Aragón, Cataluña, Valencia, Baleares; Centre: Castilla León, Castilla la Mancha, Madrid, Extremadura; South: Andalucía, Murcia, Canarias.

^bObservations: 12.261; R^2 Tjur 0.043.

TABLE 3 | Multivariate analysis of the propensity score-matched Spanish cohort in the evaluation of safety of first-line empirical concomitant and single capsule bismuth quadruple therapies according to varying duration and proton pump inhibitor dose.

Multivariate analysis adjusted by standardised mortality ratio (SMR) weighting propensity score				Bootstrap replications		
				R = 10,000		
Dependent variable: incidence of at least one adverse event						
Reference category: 14-day CT with standard-dose PPI						
Characteristics	OR ^b	95% CI ^b	p	^b	95% CI ^b	p
Prescription						
14-day CT standard-dose PPI	—	—		—	—	
14-day CT low-dose PPI	0.44	0.37–0.54	< 0.001	0.44	0.36–0.56	0
14-day CT high-dose PPI	1.42	1.19–1.70	< 0.001	1.42	1.17–1.73	0
10-day CT low-dose PPI	0.7	0.55–0.88	0.003	0.70	0.55–0.89	0.003
10-day CT standard-dose PPI	1.79	1.30–2.44	< 0.001	1.79	1.32–2.41	0
10-day CT high-dose PPI	0.42	0.25–0.67	< 0.001	0.42	0.25–0.75	0.001
Sc-BQT every 6 h low-dose PPI	0.45	0.37–0.54	< 0.001	0.45	0.37–0.55	0
Sc-BQT every 6 h standard-dose PPI	0.96	0.78–1.18	0.71	0.96	0.78–1.19	0.7248
Sc-BQT every 6 h high-dose PPI	1.8	1.45–2.24	< 0.001	1.81	1.46–2.23	0
Sc-BQT every 8 h low-dose PPI	0.64	0.51–0.81	< 0.001	0.64	0.5–0.83	0.001
Sc-BQT every 8 h standard-dose PPI	0.42	0.32–0.55	< 0.001	0.42	0.31–0.56	0
Sc-BQT every 8 h high-dose PPI	1.3	1.06–1.59	0.013	1.30	1.03–1.63	0.03
Gender						
Female						
Male	0.7	0.63–0.77	< 0.001	0.70	0.63–0.77	0
Age (years)						
18–30						
31–50	0.86	0.73–1.02	0.082	0.86	0.71–1.04	0.127
51–70	0.92	0.78–1.09	0.322	0.92	0.76–1.1	0.386
71-highest	1.38	1.14–1.68	0.001	1.38	1.12–1.69	0.002
Compliance						
No (< 90% drug intake)						
Yes (> 90% drug intake)	0.07	0.05–0.09	< 0.001	0.07	0.05–0.1	0
Treatment indication						
Dyspepsia and other						
Ulcer	1.22	1.08–1.39	0.002	1.22	1.08–1.38	0.001
Geographical region ^a						
Centre						
North-east	0.84	0.74–0.96	0.01	0.84	0.73–0.97	0.019
North	2.72	2.38–3.10	< 0.001	2.72	2.36–3.11	0
South	0.27	0.23–0.31	< 0.001	0.27	0.23–0.32	0
Recruitment years						
2013–2018						
2019–2023	0.75	0.67–0.85	< 0.001	0.75	0.67–0.85	0

Note: CT: concomitant therapy; Sc-BQT: single capsule bismuth quadruple therapy; mITT: modified intention-to-treat; PPI: proton pump inhibitor; low dose PPI: 4.5 to 27 mg OE b.i.d; standard dose PPI: 32 to 40 mg OE b.i.d; high dose PPI: 54 to 128 mg OE b.i.d. Bold values indicate statistical significance at $p < 0.05$.

^aNorth: Cantabria, Navarra, Galicia, La Rioja, País Vasco, Asturias; North-East: Aragón, Cataluña, Valencia, Baleares; Centre: Castilla León, Castilla la Mancha, Madrid, Extremadura; South: Andalucía, Murcia, Canarias.

^bObservations: 12,432; R^2 Tjur 0.144.

for the 10-day CT group, which showed a better safety profile than the baseline (OR 0.42; 0.25–0.67; $p < 0.001$) (Figure S9A,B).

The analysis of predicted probabilities corroborated the multivariate findings, showing a higher probability of AEs in all groups when combined with a high-dose PPI, except for 10-day CT and Sc-BQT every 8 h (Figure S10).

3.8 | Compliance

Overall, patients adhered to treatment in 97% of cases. Adherence was higher in Sc-BQT (every 6 h, 94%; and every 8 h, 95%) than in 14-day CT (93%), although the differences were not statistically significant.

When analysed alongside other independent factors potentially associated with higher eradication success, compliance was the variable with the strongest and most significant impact on treatment outcome (OR 7.72; 5.72–10.4; $p < 0.001$ (Table 2).

4 | Discussion

This study compared the effectiveness, safety, and compliance of CT and Sc-BQT, both recommended as first-line empirical *H. pylori* eradication therapies in Spain, where clarithromycin resistance exceeds 15% and metronidazole resistance is below 40% [8].

Both 10- or 14-day CT and 10-day Sc-BQT (every 6 or 8 h) achieved over 90% effectiveness, with Sc-BQT showing higher eradication rates overall. The best CT outcomes occurred with 14-day treatment and at least a standard-dose PPI, while Sc-BQT performed optimally with standard-dose PPI (every 6 or 8 h) or high-dose PPI (every 8 h). Notably, the every-8-h Sc-BQT regimen demonstrated superior safety compared to every-6-h Sc-BQT and 14-day CT.

The choice of first-line treatment in each country will depend primarily on the rate of resistance of *H. pylori* to the different antibiotics [3, 13, 27–30]. In Spain, CT has been widely used for *H. pylori* eradication due to its high success rates and comprehensive treatment regimen. This strategy involves administering a PPI along with three antibiotics—clarithromycin, amoxicillin, and metronidazole—over 10–14 days to target the pathogen through different mechanisms and address resistance issues [4, 31]. Clinical data indicate that CT achieves eradication rates often exceeding 90% when dual (both to clarithromycin and metronidazole) resistance is below 15%, which is typically the case in our setting, and maintains an acceptable safety profile with manageable side effects [1, 4]. However, the use of clarithromycin without prior susceptibility testing is generally not recommended due to growing concerns over antibiotic resistance and its reduced efficacy in eradication therapies. In many cases, clarithromycin may be unnecessary due to resistance, leading to what is referred to as the prescription of large amounts of this antibiotic without benefit [29]. This overuse can contribute to the broader problem of antimicrobial resistance, threatening the effectiveness of treatments not only for *H. pylori* but also for other infections where clarithromycin remains a key

therapeutic option. Thus, current international guidelines recommend avoiding the empiric use of this antibiotic if the local resistance prevalence is above 15%, as it is the case in Spain. In such regions, regimens without clarithromycin, mainly including bismuth-based quadruple therapies, are now preferred [1, 32]. However, if non-bismuth quadruple CT has to be administered, it is more effective when given for 14 days, compared to 10 or 7 days, and is likely more effective with higher PPI doses (it is recommended to use at least omeprazole 40 mg/12 h or its equivalent [2, 8, 33]).

The Sc-BQT formulation, marketed as Pylera, has been endorsed in the latest V Spanish Consensus as an effective first-line alternative to CT [8]. Sc-BQT combines bismuth subcitrate, tetracycline, and metronidazole, which work synergistically to overcome *H. pylori* antibiotic resistance and improve eradication rates. Clinical experience has shown that Sc-BQT, when used together with a PPI, can achieve high effectiveness, often exceeding 95% in first-line treatment [10], around the 90% threshold in subsequent rescue lines [34, 35], and also in the presence of single clarithromycin or dual clarithromycin-metronidazole antibiotic resistance [10]. Furthermore, Sc-BQT has also been positioned as a recommended first-line treatment in patients allergic to penicillin [8, 36]. This distinction is clinically important, as it impacts the interpretation of the mITT analysis: Sc-BQT can be prescribed to virtually all patients, whereas CT cannot. Therefore, even though a direct statistical comparison between CT and Sc-BQT was performed using propensity score-adjusted data, the generalisability of CT is intrinsically limited by its contraindication in penicillin-allergic patients. This factor, alongside the observed higher eradication rates, strengthens the case for Sc-BQT as a preferred first-line therapy.

Given Sc-BQT's superior clinical versatility and high effectiveness—including its applicability in penicillin-allergic patients—its comparative performance against CT has been widely studied [11] since its European Medicines Agency (EMA) approval in 2006. To gain further insight into the results of our study for these two therapies compared to other non-Hp-EuReg studies, a mapping review was conducted (File S3). The selected studies compared CT and Sc-BQT and were from Italy, Greece, Lebanon, and Spain—all countries with similar prevalence of bacterial resistance to clarithromycin and metronidazole, two key antibiotics used in CT [3, 28]. In these studies (Table S6), ITT efficacy for CT varied widely from 77% to 96%, while that of Sc-BQT ranged from 82% to 100%. The meta-analysis was initially conducted without considering CT duration (Figure S1A,B) and later included a comparison of 14-day CT versus Sc-BQT to address the study question (Figure S12A,B). This comparison showed no difference in the ITT analysis, with a similar cure rate for Sc-BQT compared to 14-day CT (88% vs. 89%, respectively; risk difference -0.01 ; -0.07 to 0.05 , $p = 0.79$; 6 studies, $I^2 = 78\%$). In the PP analysis, slightly better cure rates were observed with Sc-BQT compared to 14-day CT (93% vs. 95.5%, respectively; risk difference -0.000 ; 95% CI, -0.03 to 0.02 ; $p = 0.81$; 6 studies, $I^2 = 27\%$), though, again, the difference was not statistically significant.

Although the efficacy results from our mapping review showed lower cure rates for both therapies compared to the Hp-EuReg outcomes—likely due to the high level of commitment of the

gastroenterologists participating in the registry—the overall comparison results were consistent with those of the current study. This alignment enhances the robustness and reliability of the findings of the present Hp-EuReg study, showing an approximate effectiveness increase of 2%–4% with Sc-BQT compared to 14-day CT. This result represents a small improvement consistent with the findings of the mapping review. Furthermore, several systematic reviews and meta-analyses conducted in the world regions evaluating the efficacy of BQT (encompassing both the single capsule formulation and the classic regimen with antibiotics administered separately) versus CT also confirmed the aforementioned conclusions [15, 37, 38]. While these studies consistently report a slight improvement in efficacy for BQT, this difference might not be clinically relevant, as the improvement in eradication rates is small and may not translate into significant differences in patient outcomes. Therefore, despite the statistical significance, the choice between these regimens should also consider other factors, such as cost, patient compliance, or local resistance patterns, which may ultimately have a greater impact on clinical practice.

Higher PPI doses significantly improved the effectiveness of both therapies, aligning with findings from a recent Hp-EuReg study [39]. While 14-day CT with sufficient PPI dosing (≥ 40 mg omeprazole equivalents twice daily) outperformed Sc-BQT with low-dose PPI, increasing PPI doses in Sc-BQT every 6 h showed no added benefit. This underscores the critical role of sufficient PPI dosing in any prescribed regimen. Notably, Sc-BQT administered every 6 h with high-dose PPI did not yield better results compared to the same schedule with standard-dose PPI, suggesting no further advantage from increased acid inhibition within this regimen. Only Sc-BQT every 8 h with high-dose PPI emerged as the most effective Sc-BQT combination, surpassing all other regimens, including 14-day CT with standard-dose PPI.

Regarding therapy adherence, CT presents an advantage over Sc-BQT, because it was administered every 12 h, whereas Sc-BQT was taken, as per our data cohort, most frequently, every 6 h. However, compliance with CT (regardless of duration) was significantly lower than that with Sc-BQT, as reported in a previously published study from Hp-EuReg, where the CT regimen was among the therapies with the lowest adherence [40]. This is likely because the Sc-BQT formulation as a single-capsule treatment reduces the nuisance of taking multiple separate medications, unlike CT, which requires taking three different antibiotics separately. This advantage would potentially enhance patient adherence and subsequently efficacy, especially when the treatment is prescribed three times a day as compared to the traditional four times a day schedule, according to a recent study [12]. Finally, we emphasise the critical role of patient adherence in achieving optimal outcomes. Even highly effective regimens, such as CT and Sc-BQT can yield suboptimal results if adherence is not ensured through adequate patient education and support.

It is also worth mentioning that Sc-BQT is typically prescribed for 10 days, which is considered sufficient and does not require 14 days, whereas CT for 14 days is generally preferred over 10 days. In this context, shorter treatment durations have been consistently associated with a lower incidence of AEs, as shown

in our study, where the 14-day CT group exhibited the highest incidence of AEs (32%). In this regard, although only one serious AE related to penicillin allergy was reported, it is likely that minor hypersensitivity reactions (e.g., rash, pruritus) occurred more frequently in the CT group. Due to the retrospective nature of the registry and variability in AE reporting across centres, these events may have been underreported. This limitation further underscores again the advantage of Sc-BQT, which does not include penicillin and is suitable for a broader range of patients, including those with known β -lactam allergies.

In terms of cost, calculated from the official website of the Spanish Ministry of Health (<https://www.sanidad.gob.es/profesionales/nomenclador.do>), the cost of 14-day CT (€60) and 10-day Sc-BQT (€66), both with standard-dose PPI, is similar. However, Sc-BQT is significantly more expensive in countries like the U.S. (\$300–\$1100 depending on the pharmacy; www.drugs.com, accessed 11/12/2024). Finally, CT has better global availability, as Sc-BQT and its components, bismuth and tetracycline, are less accessible in many regions.

Our study has several limitations, including its retrospective design and the heterogeneity among regions and centres from a unique country, Spain. This variability extends beyond the management of infection and therapeutic accessibility or costs to differing rates of bacterial antibiotic resistance, making it challenging to generalise the results in the studied country, to Europe or globally. In addition, since no cultures were performed in our study, we do not have information on antibiotic resistances. In light of the global rise in antimicrobial resistance, antibiotic stewardship has become an essential principle in the selection of eradication regimens. CT, which combines three key antibiotics—clarithromycin, amoxicillin, and metronidazole—deviates from the core tenets of prudent antibiotic use. This broad-spectrum approach may promote the development of multidrug resistance in both gastric and intestinal microbiota. In contrast, Sc-BQT includes tetracycline—an antibiotic with minimal current clinical use outside *H. pylori* treatment—thereby posing a lower risk of contributing to future resistance. From a stewardship perspective, Sc-BQT aligns more closely with responsible prescribing practices and should be considered a more sustainable first-line option. The importance of integrating antimicrobial stewardship principles into clinical decision-making should be reflected in treatment guidelines and emphasised in the interpretation of therapeutic efficacy. That said, while resistance testing may be ideal, the high success rates of Sc-BQT make it less essential.

Among the strengths of our study are its large sample size, the largest to date evaluating these two therapies, and the comprehensive 12-year time span analysed, which adds robustness to the findings. Although this is an observational study, comparisons were performed using data from a uniform geographical setting with consistent resistance rates, and PS analysis was employed (thus, reducing confounding bias, by creating comparable groups with similar baseline characteristics).

To summarise, if CT is selected, a 14-day regimen is more effective than 10-day prescriptions; however, its effectiveness depends on being combined with at least a standard-dose PPI, with high-dose PPI being preferable to maximise eradication

rates. On the other hand, both Sc-BQT (every 6 h and 8 h), when prescribed with at least standard-dose PPIs, demonstrated small (2%–4%) but statistically significant higher cure rates compared to 14-day CT. Sc-BQT also showed a better safety profile in terms of tolerance, although the clinical relevance of these differences in both efficacy and safety may be limited. Regarding compliance, Sc-BQT had slightly better outcomes than 14-day CT. Both treatments were similarly priced in our setting, though this may vary in other countries. Finally, recent international guidelines recommend, as first-line regimens, bismuth-based quadruple therapies that do not contain clarithromycin.

In conclusion, both 14-day CT and Sc-BQT regimens—administered every 6 or 8 h and combined with standard or high-dose PPIs—demonstrated high eradication rates and maintained acceptable safety profiles, confirming their effectiveness as first-line treatments for *H. pylori*. Among these, Sc-BQT prescribed every 8 h (four capsules, three times daily) outperformed the traditional every-6-h schedule, offering more simplicity and warranting further investigation. Notably, the combination of Sc-BQT every 8 h with a high-dose PPI emerged as the most effective regimen, offering superior tolerability and stronger alignment with current international guidelines. Finally, beyond clinical efficacy, Sc-BQT offers broader applicability, including for penicillin-allergic patients, and reflects a more sustainable, antibiotic-sparing strategy aligned with principles of antimicrobial stewardship.

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Ethics Statement

The Hp-EuReg protocol was approved by the Ethics Committee Hospital Universitario de la Princesa (Madrid, SPAIN), which acted as a reference Institutional Review Board (20 December 2012) (Ethics approval code: Hp-EuReg). This research was conducted according to the guidelines of the Declaration of Helsinki, classified by the Spanish Agency for Medicines and Medical Devices, and prospectively registered at Clinical Trials.gov under the code NCT02328131.

Conflicts of Interest

Olga P. Nyssen has served as a speaker or has received research funding from Allergan, Mayoly Spindler, Richen, Biocodex, and Juvisé. Javier P. Gisbert has served as speaker, consultant, and advisory member for or has received research funding from Mayoly, Allergan/Abbvie, Diasorin, Richen, Juvisé, and Biocodex. The remaining authors declare no conflicts of interest.

Data Availability Statement

All data relevant to the study are included in the article or uploaded as supplementary information. However, previously published data from

the Hp-EuReg study, or de-identified raw data referring to the current study, as well as further information on the methods used to explore the data, may be shared with no particular time constraint. Individual participant data will not be shared.

References

1. P. Malfertheiner, F. Megraud, T. Rokkas, et al., "Management of *Helicobacter pylori* Infection: The Maastricht VI/Florence Consensus Report," *Gut* 71 (2022): 1724–1762.
2. J. P. Gisbert and A. G. McNicholl, "Optimization Strategies Aimed to Increase the Efficacy of *H. pylori* Eradication Therapies," *Helicobacter* 22 (2017): e12392.
3. F. Megraud, R. Bruyndonckx, S. Coenen, et al., "*Helicobacter pylori* Resistance to Antibiotics in Europe in 2018 and Its Relationship to Antibiotic Consumption in the Community," *Gut* 70, no. 10 (2021): 1815–1822.
4. J. P. Gisbert and X. Calvet, "Review Article: Non-Bismuth Quadruple (Concomitant) Therapy for Eradication of *Helicobacter pylori*," *Alimentary Pharmacology & Therapeutics* 34, no. 6 (2011): 604–617.
5. O. P. Nyssen, D. Bordin, B. Tepes, et al., "European Registry on *Helicobacter pylori* Management (Hp-EuReg): Patterns and Trends in First-Line Empirical Eradication Prescription and Outcomes of 5 Years and 21 533 Patients," *Gut* 70, no. 1 (2021): 40–54.
6. Z. Kaouah, J. M. Buyck, M. Pichon, et al., "In Vitro Efficacy of Combinations of Antibiotics Used in Clinical Practice on Clinical Isolates of *Helicobacter pylori*," *Helicobacter* 29, no. 3 (2024): e13081.
7. M. Caldas, A. Perez-Aisa, M. Castro-Fernandez, et al., "European Registry on *Helicobacter pylori* Management: Effectiveness of First and Second-Line Treatment in Spain," *Antibiotics (Basel)* 10, no. 1 (2020): 13.
8. J. P. Gisbert, J. Alcedo, J. Amador, et al., "V Spanish Consensus Conference on *Helicobacter pylori* Infection Treatment," *Gastroenterología y Hepatología* 45, no. 5 (2022): 392–417.
9. O. P. Nyssen, A. Perez-Aisa, M. Castro-Fernandez, et al., "European Registry on *Helicobacter pylori* Management: Single-Capsule Bismuth Quadruple Therapy Is Effective in Real-World Clinical Practice," *United European Gastroenterology Journal* 9, no. 1 (2021): 38–46.
10. O. P. Nyssen, A. G. McNicholl, and J. P. Gisbert, "Meta-Analysis of Three-In-One Single Capsule Bismuth-Containing Quadruple Therapy for the Eradication of *Helicobacter pylori*," *Helicobacter* 24, no. 2 (2019): e12570.
11. P. Malfertheiner, F. Bazzoli, J. C. Delchier, et al., "*Helicobacter pylori* Eradication With a Capsule Containing Bismuth Subcitrate Potassium, Metronidazole, and Tetracycline Given With Omeprazole Versus Clarithromycin-Based Triple Therapy: A Randomised, Open-Label, Non-Inferiority, Phase 3 Trial," *Lancet* 377, no. 9769 (2011): 905–913.
12. A. Perez-Aisa, O. P. Nyssen, A. Keco-Huerta, et al., "Bismuth Quadruple Three-In-One Single Capsule Three Times a Day Increases Effectiveness Compared With the Usual Four Times a Day Schedule: Results From the European Registry on *Helicobacter pylori* Management (Hp-EuReg)," *Gut* 72, no. 11 (2023): 2031–2038.
13. L. Bujanda, O. P. Nyssen, D. Vaira, et al., "Antibiotic Resistance Prevalence and Trends in Patients Infected With *Helicobacter pylori* in the Period 2013–2020: Results of the European Registry on *H. pylori* Management (Hp-EuReg)," *Antibiotics (Basel)* 10, no. 9 (2021): 1058.
14. G. Losurdo, A. V. Borraccino, A. Aloisio, et al., "Concomitant and Bismuth Quadruple Therapy for *Helicobacter pylori* Eradication in Southern Italy: Preliminary Data From a Randomized Clinical Trial," *Antibiotics (Basel)* 13, no. 4 (2024): 348.
15. R. M. Zagari, E. Dajti, A. Cominardi, et al., "Standard Bismuth Quadruple Therapy Versus Concomitant Therapy for the First-Line Treatment of *Helicobacter pylori* Infection: A Systematic Review and

- Meta-Analysis of Randomized Controlled Trials,” *Journal of Clinical Medicine* 12, no. 9 (2023): 3258.
16. A. G. McNicholl, C. A. O’Morain, F. Megraud, and J. P. Gisbert, “As Scientific Committee of the hp-Eureg on Behalf of the National C. Protocol of the European Registry on the Management of *Helicobacter pylori* Infection (Hp-EuReg),” *Helicobacter* 24, no. 5 (2019): e12630.
17. P. A. Harris, R. Taylor, R. Thielke, J. Payne, N. Gonzalez, and J. G. Conde, “Research Electronic Data Capture (REDCap)—A Metadata-Driven Methodology and Workflow Process for Providing Translational Research Informatics Support,” *Journal of Biomedical Informatics* 42, no. 2 (2009): 377–381.
18. P. A. Harris, R. Taylor, B. L. Minor, et al., “The REDCap Consortium: Building an International Community of Software Platform Partners,” *Journal of Biomedical Informatics* 95 (2019): 103208.
19. D. Y. Graham, H. Lu, and M. P. Dore, “Relative Potency of Proton-Pump Inhibitors, *Helicobacter pylori* Therapy Cure Rates, and Meaning of Double-Dose PPI,” *Helicobacter* 24, no. 1 (2019): e12554.
20. J. Kirchheiner, S. Glatt, U. Fuhr, et al., “Relative Potency of Proton-Pump Inhibitors-Comparison of Effects on Intragastric pH,” *European Journal of Clinical Pharmacology* 65, no. 1 (2009): 19–31.
21. T. Sturmer, K. J. Rothman, and R. J. Glynn, “Insights Into Different Results From Different Causal Contrasts in the Presence of Effect-Measure Modification,” *Pharmacoepidemiology and Drug Safety* 15, no. 10 (2006): 698–709.
22. T. Kurth, A. M. Walker, R. J. Glynn, et al., “Results of Multivariable Logistic Regression, Propensity Matching, Propensity Adjustment, and Propensity-Based Weighting Under Conditions of Nonuniform Effect,” *American Journal of Epidemiology* 163, no. 3 (2006): 262–270.
23. N. Greifer, “WeightIt: Weighting for Covariate Balance in Observational Studies. R Package Version 1.3.2.9000,” (2024), <https://github.com/ngreifer/weightit>.
24. J. Fox and S. Weisberg, *An R Companion to Applied Regression, Third Edition* (Sage, 2019), <https://www.john-fox.ca/Companion/>.
25. M. Thulin, “_boot.pval: Bootstrap p-Values_. R Package Version 0.5,” (2023).
26. D. Makowski, M. S. Ben-Shacar, and D. Lüdtke, “bayestestR: Describing Effects and Their Uncertainty, Existence and Significance Within the Bayesian Framework,” *Journal of Open Source Software* 4, no. 40 (2019): 1541.
27. L. Bujanda, O. P. Nyssen, J. Ramos, et al., “Effectiveness of *Helicobacter pylori* Treatments According to Antibiotic Resistance,” *American Journal of Gastroenterology* 119, no. 4 (2024): 646–654.
28. A. Savoldi, E. Carrara, D. Y. Graham, M. Conti, and E. Tacconelli, “Prevalence of Antibiotic Resistance in *Helicobacter pylori*: A Systematic Review and Meta-Analysis in World Health Organization Regions,” *Gastroenterology* 155, no. 5 (2018): 1372–1382.e17.
29. D. Y. Graham and J. M. Liou, “Primer for Development of Guidelines for *Helicobacter pylori* Therapy Using Antimicrobial Stewardship,” *Clinical Gastroenterology and Hepatology* 20, no. 5 (2022): 973–983.e1.
30. Y. Yu, J. Xue, F. Lin, et al., “Global Primary Antibiotic Resistance Rate of *Helicobacter pylori* in Recent 10 Years: A Systematic Review and Meta-Analysis,” *Helicobacter* 29, no. 3 (2024): e13103.
31. A. G. McNicholl, A. C. Marin, J. Molina-Infante, et al., “Randomised Clinical Trial Comparing Sequential and Concomitant Therapies for *Helicobacter pylori* Eradication in Routine Clinical Practice,” *Gut* 63, no. 2 (2014): 244–249.
32. L. Olmedo, X. Calvet, E. Gené, et al., “Evolution of the Use, Effectiveness and Safety of Bismuth-Containing Quadruple Therapy for *Helicobacter pylori* Infection Between 2013 and 2021: Results From the European Registry on *H. pylori* Management (Hp-EuReg),” *Gut* 74, no. 1 (2024): 15–25.
33. G. G. Ciota, G. Marasco, T. Russo, et al., “Optimum Duration of Non Bismuth (Concomitant) Quadruple Therapy for *Helicobacter pylori* Eradication: A Systematic Review and Meta-Analysis,” *Digestive and Liver Disease* 52 (2020): S73.
34. O. P. Nyssen, A. Perez-Aisa, L. Rodrigo, et al., “Bismuth Quadruple Regimen With Tetracycline or Doxycycline Versus Three-In-One Single Capsule as Third-Line Rescue Therapy for *Helicobacter pylori* Infection: Spanish Data of the European *Helicobacter pylori* Registry (Hp-EuReg),” *Helicobacter* 25, no. 5 (2020): e12722.
35. D. Burgos-Santamaria, O. P. Nyssen, A. Gasbarrini, et al., “Empirical Rescue Treatment of *Helicobacter pylori* Infection in Third and Subsequent Lines: 8-Year Experience in 2144 Patients From the European Registry on *H. pylori* Management (Hp-EuReg),” *Gut* 72 (2023): 1054–1072.
36. O. P. Nyssen, A. Perez-Aisa, B. Tepes, et al., “*Helicobacter pylori* First-Line and Rescue Treatments in Patients Allergic to Penicillin: Experience From the European Registry on *H. pylori* Management (Hp-EuReg),” *Helicobacter* 25, no. 3 (2020): e12686.
37. A. Cominardi, G. Marasco, T. Russo, et al., “Bismuth vs Non-Bismuth (Concomitant) Quadruple Therapy for First-Line *Helicobacter pylori* Eradication: A Systematic Review and Meta-Analysis of Randomized Controlled Trials,” *Digestive and Liver Disease* 52 (2020): S13.
38. E. Dajti, A. Cominardi, L. Frazzoni, et al., “Bismuth Quadruple Therapy Versus Concomitant Therapy for the First-Line Treatment of *Helicobacter pylori* Infection: Systematic Review and Meta-Analysis,” *Digestive and Liver Disease* 55 (2023): S173–S174.
39. M. Pabon-Carrasco, A. Keco-Huerta, M. Castro-Fernandez, et al., “Role of Proton Pump Inhibitors Dosage and Duration in *Helicobacter pylori* Eradication Treatment: Results From the European Registry on *H. pylori* Management. United European,” *Gastroenterologisches Journal* 12, no. 1 (2024): 122–138.
40. J. M. Huguet, L. Ferrer-Barcelo, P. Suarez, et al., “Role of Compliance in *Helicobacter pylori* Eradication Treatment: Results of the European Registry on *H. pylori* Management. United European,” *Gastroenterologisches Journal* 12, no. 6 (2024): 691–704.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.