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Original research

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)

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ABSTRACT

Background Bismuth quadruple therapies (BQTs) including bismuth, a proton pump inhibitor (PPI) and two antibiotics have been shown to be highly effective for treating *Helicobacter pylori* infection even in areas of high bacterial antibiotic resistance.

Objective To describe the time trends of use, effectiveness and safety of BQT in Europe using the European Registry on *Helicobacter pylori* Management (Hp-EuReg).

Design Patients registered in the Hp-EuReg from 2013 to 2021 who had received BQT were included. The regimens prescribed, the number of eradication attempts, effectiveness, adherence and safety were analysed. The effectiveness was assessed by modified intention to treat (mITT). Time-trend and multivariate analyses were performed to determine variables that predicted treatment success.

Results Of the 49 690 patients included in the Hp-EuReg, 15 582 (31%) had received BQT. BQT use increased from 8.6% of all treatments in 2013 to 39% in 2021. Single-capsule BQT—containing bismuth, metronidazole and tetracycline—plus a PPI (single-capsule BQT, ScBQT) was the most frequent treatment mode (43%). Schemes that obtained an effectiveness above 90% were the 10-day ScBQT and 14-day BQT using tetracycline plus metronidazole, or amoxicillin plus either clarithromycin or metronidazole. Only ScBQT achieved above 90% cure rates in all the geographical areas studied. Using the ScBQT scheme, adherence, the use of standard or high-dose PPIs, 14-day prescriptions and the use of BQT as first-line treatment were significantly associated with higher mITT effectiveness.

Conclusion The use of BQT increased notably in Europe over the study period. A 10-day ScBQT was the scheme that most consistently achieved optimal effectiveness.

Trial registration number NCT02328131.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ *Helicobacter pylori* infection affects billions of people worldwide and is the main cause of chronic gastritis, peptic ulcer disease and gastric cancer.

⇒ In spite of the experience accumulated over more than 30 years, the ideal regimen to treat the infection remains unclear.

⇒ The addition of bismuth to triple therapy increases cure rates without increasing the antibiotic burden.

WHAT THIS STUDY ADDS

⇒ A rate of effectiveness above 90% was obtained with 10-day single-capsule bismuth quadruple therapy containing tetracycline and metronidazole. When antibiotics were prescribed separately, this rate was obtained in different 14-day bismuth quadruple therapies.

⇒ The use of bismuth quadruple therapy in Europe increased from 8.6% in 2013 to 39% in 2021, especially in areas where the single-capsule bismuth quadruple treatment was available.

⇒ The results of this study indicate that 10-day single-capsule bismuth quadruple treatment homogeneously achieves cure rates above 90% in all the geographical areas and is now establishing itself as the preferred treatment in the countries where it is available.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study suggests that bismuth quadruple therapy, and specifically single-capsule bismuth quadruple therapy, is safe and highly effective in many different settings. We recommend that these drug combinations be made available in all regions of Europe.

INTRODUCTION

Helicobacter pylori is a Gram-negative, microaerophilic bacterium that infects more than half of the human population worldwide.[1] *H. pylori* infection causes gastrointestinal diseases, including gastritis, gastroduodenal ulcer disease and gastric cancer as well as iron-deficiency anaemia, vitamin B_{12} deficiency and immune thrombocytopenic purpura.[2] In all these conditions, eradication of the bacterium is considered the best course of action.[3] Treatment of *H. pylori* is challenging, and the treatment schemes currently applied do not achieve 100% cure rates. Furthermore, the success of certain therapies may decline over time due to the increase in antibiotic resistance.[4–6] In this context, expert consensuses have established that any acceptable therapy should achieve a minimal cure rate of 90% for this microbial infection.[7 8]

H. pylori therapies combine antibiotics and adjuvant drugs. The most frequently used schemes comprise triple therapies involving a proton pump inhibitor (PPI) plus two antibiotics or quadruple therapies with an additional antibacterial agent. Triple therapies combining a PPI with clarithromycin and either amoxicillin or metronidazole have classically been the standard of care for *H. pylori* eradication. However, bacterial resistance to clarithromycin markedly reduces *H. pylori* eradication when triple therapy is prescribed. As resistance to clarithromycin has increased steadily in recent years, triple therapy currently fails in more than 20% of cases in most settings.[4] The figures are even more alarming in the case of rescue regimens, due to the high rate of secondary bacterial resistance following accumulation of previous failed attempts.[9–11] For this reason, triple therapies are no longer regarded as acceptable in most settings and quadruple therapies are now considered the new standard of care by consensus conferences.[3 12 13] Quadruple therapies may or may not include bismuth; those that do not (namely sequential, concomitant and hybrid regimens) include three antibiotics plus a PPI, whereas bismuth-based regimens combine a bismuth salt with a PPI and two antibiotics.[14]

Bismuth has been extensively used to treat different gastrointestinal diseases.[15] Its use offers the following advantages: (a) a strong bacteriostatic effect that is not altered by resistances; (b) beneficial synergy when combined with several antibiotics, making it possible to overcome bacterial resistance; (c) a good tolerability and safety profile and (d) a reduction in the antibiotic load and duration of *H. pylori* therapies.[3 16] Bismuth is mainly used in quadruple therapies (bismuth quadruple therapies, BQT). Classical BQT combines bismuth with a PPI, metronidazole and tetracycline. Clinical trials have shown that BQT eradicates *H. pylori* better than standard triple therapies and that its effectiveness is largely unaltered by antibiotic resistances; indeed, BQT is particularly recommended in areas with high rates of antibiotic resistance.[4]

The European Registry on *Helicobacter pylori* Management (Hp-EuReg) was set up in 2013 to collate data regarding the diagnosis and eradication treatments, making it possible to perform time trend evaluations and thus enhance the clinical management of adult infected patients. The Hp-EuReg currently includes more than 70 000 cases from over 300 centres in 38 countries.[17]

The objective of the current study was to analyse the evolution of the use, effectiveness and safety of BQT in the clinical management of *H. pylori* infection in Europe.

METHODS

European registry on *Helicobacter pylori* management

The Hp-EuReg is an international, multicentre, prospective, non-interventionist registry promoted by the European Helicobacter and Microbiota Study Group (www.helicobacter.org) which has been recording information on the management of *H. pylori* infection since 2013.

The Hp-EuReg protocol[17] establishes national coordinators in each of the participating countries, where selected gastroenterologists enter data into the registry. All the investigators are gastroenterologists managing patients infected with *H. pylori* and working at centres with a valid confirmatory testing method.[18 19]

Participants

Patients who had received any treatment scheme containing bismuth in any treatment line, and recruited between June 2013 and December 2021, were included in the current analysis.

Variables and outcomes were recorded using an electronic case report form provided by the collaborative research platform REDCap[20] hosted at 'Asociación Española de Gastroenterología' (www.aegastro.es), a non-profit scientific and medical society focused on gastroenterology research. Data were anonymised and the following variables were recorded: patients' demographics, any previous eradication attempts, treatments used and effectiveness and safety outcomes. Further information on the variables is available in the published protocol.[17] Written, informed consent was obtained from all patients prior to study entry.

Data management

After extracting the data and prior to the statistical analysis, the database was reviewed for inconsistencies and subsequent data cleaning. The data quality review process evaluated whether the study selection criteria had been met and whether data were correctly collected, in order to ensure that the study was conducted according to the highest scientific and ethical standards. Data discordances were resolved by consulting the investigators and through group emailing.

Statistical analysis

Categorisation and definition of variables

The total number of bismuth therapies was determined both for the whole group and separately for each line of treatment,

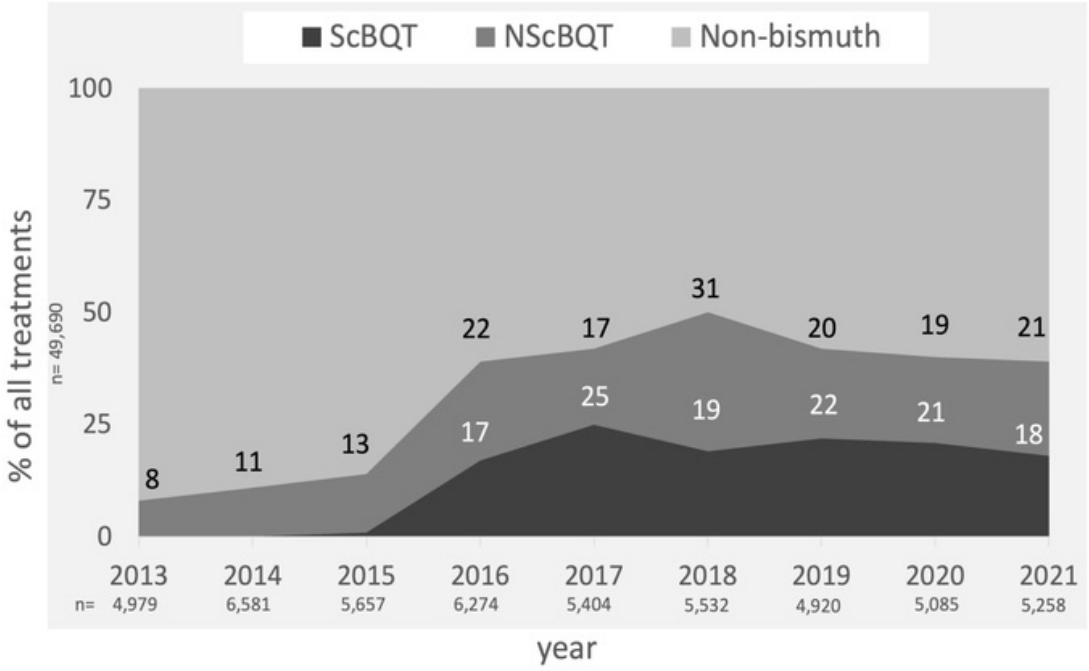

Figure 1 Evolution of all bismuth versus non-bismuth-based prescriptions between 2013 and 2021 in Europe. White numbers represent ScBQT percentage over total treatments. Black numbers represent NScBQT percentage over total treatments; non-bismuth, all regimens without bismuth. NScBQT, non-single-capsule bismuth quadruple therapy; ScBQT, single-capsule BQT.

year and European region. All countries evaluated in the current study were clustered, as in previous studies, in five main regions (East, South-East, South-West, Centre and North) based on their geographical situation and on their gross domestic product per capita (online supplemental files 2 and 3).

In addition, data on effectiveness, adherence and safety were reported for each bismuth-based treatment. Given the diversity of the schemes, some of them applied to only a small number of patients treated, it was decided arbitrarily to include only schemes with 100 or more cases in the treatment analysis. The eight most frequently used treatments (all of them quadruple regimens) were identified and were described as follows: (1) PPI+three-in-one single-capsule containing metronidazole, tetracycline and bismuth (MTB), marketed as Pylera, henceforth referred to as single-capsule BQT (ScBQT); (2) the combination of PPI+CAB (clarithromycin, amoxicillin, bismuth); (3) PPI+MTB; (4) PPI+MDB (metronidazole, doxycycline, bismuth); (5) PPI+TAB (tetracycline, amoxicillin, bismuth); (6) PPI+LAB (levofloxacin, amoxicillin, bismuth); (7) PPI+MAB (metronidazole, amoxicillin, bismuth); (8) PPI+JAB (josamycin, amoxicillin, bismuth).

To compare the different dosage schemes prescribed with the different types of PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole), it was decided to standardise PPI dosages by calculating the PPI potency in terms of duration of intragastric pH>4/24 hours. Using omeprazole as standard, relative potency varied from 4.5 mg omeprazole equivalents (20 mg pantoprazole) to 72 mg omeprazole equivalents (40 mg rabeprazole), as reported by Graham *et al*[21] and Kirchheiner *et al*.[22] According to these authors, this standardisation allows the interchangeable use of PPIs based on their relative potency. Thus, applying this method, the different PPI schemes and types were grouped into three categories: low dose, if the potency of acid inhibition was between 4.5 and 27 mg omeprazole equivalents given two times daily; standard dose, between 32 and 40 mg omeprazole equivalents also given two times daily; and high dose, between 54 and 128 mg omeprazole equivalents two times daily.

In addition, in accordance with the Hp-EuReg, treatment durations were categorised into three levels (7, 10 and 14 days).

With regard to tolerance and safety, the frequency, type, intensity, and duration of adverse events (AEs) and their impact on adherence were assessed. Depending on the intensity of symptoms evaluated by the physician, AEs were classified as follows: mild (not interfering with daily routine), moderate (affecting daily routine), intense/severe (not allowing normal daily routine) and serious (causing death, hospitalisation, disability, congenital anomaly and/or requiring intervention to prevent permanent damage).

AEs and adherence were evaluated in face-to-face interviews with patients using both open-ended questions and a predefined questionnaire. Adherence to treatment was defined as having taken at least 90% of the prescribed drugs.

Missing data in the registry were not substituted in the descriptive analysis. Total numbers, therefore, may vary according to the number of missing values for each of the variables in the different analyses.

Continuous variables are presented as arithmetical means and the respective SDs or as medians and IQRs for variables with a non-normal distribution. Qualitative variables are presented as percentages and absolute frequencies, and 95% CIs were provided. The significance level was established at a $p<0.05$ (two tailed).

Graphical representations were used to show temporal trends in prescriptions.

Data analysis

Univariate subanalyses were performed according to the line of treatment (naïve, second-line and rescue ranging from third to sixth line), treatment duration (7, 10 and 14 days) and PPI doses (low, standard, high). Differences between groups were analysed

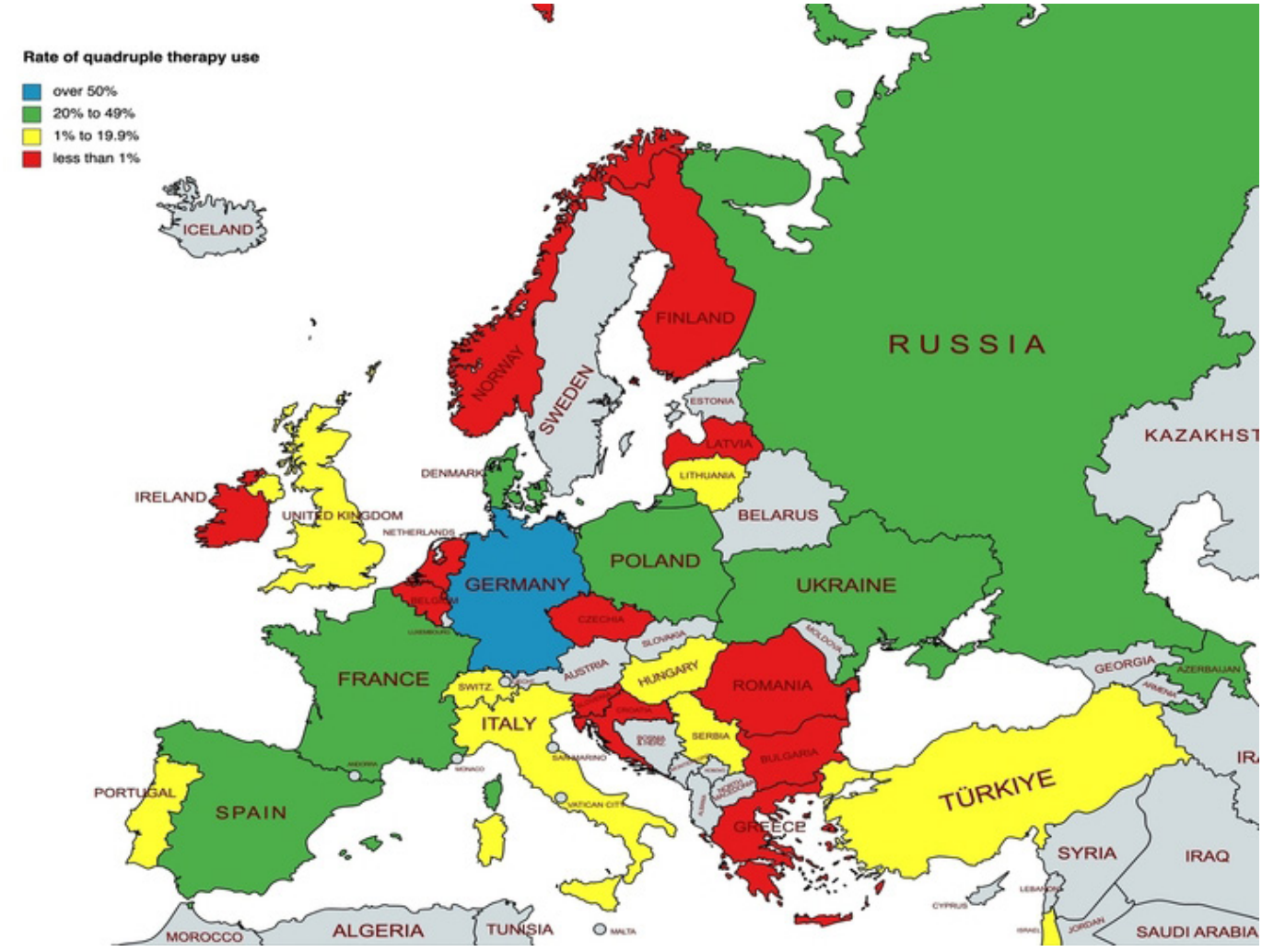

Figure 2 Proportion (%) of bismuth quadruple therapy (over all *Helicobacter pylori* treatments) by European country. Countries in grey did not participate in the registry.

using the χ^2 test. The analysis was also stratified to assess the effect of the different PPI doses (low vs standard or high) used in therapy.

The main outcome was the treatment eradication rate. Treatment effectiveness was studied using the 'modified intention-to-treat' (mITT) analysis. The mITT included all cases that had completed follow-up (ie, a confirmatory test indicating success or failure was available after eradication treatment), regardless of adherence. As recommended by the HP-EuReg scientific committee, the mITT analysis was considered to provide the best reflection of effectiveness in clinical practice and is used to report the effectiveness results in this paper.

Univariate comparisons were performed using the χ^2 test for categorical variables and the t-test or Mann-Whitney test for continuous variables. A multivariate logistic regression was performed using the mITT eradication rate as the dependent variable to determine the factors that might have affected treatment effectiveness. The following independent variables were included a priori in the multivariate analysis: specific BQT scheme, age, gender, length of treatment, PPI dose, line of treatment and adherence. The effect was evaluated by calculating OR and 95% CI. Statistical significance was considered at $p<0.05$.

RESULTS

During the study period, 15 582 (31%) patients out of a total of 49 690 received a bismuth-based treatment. The mean age of patients was 50 years (±17.8), 8897 (62%) were women and the most frequent indications were non-investigated dyspepsia (21%), functional dyspepsia (33%) and peptic ulcer (17%). The most frequently prescribed scheme was ScBQT concomitantly with a PPI, in 6668 cases (43% of all bismuth treatments); the remaining 8914 cases were non-scBQT (NScBQT) using different antibiotic combinations. These NScBQT encompassed 45 different treatment schemes. Of these, 26 were used in fewer than 10 patients and a further 7 were prescribed in more than 100 patients; the latter schemes were selected for further analysis, as described in the Methods section. The most frequently used NScBQTs were PPI+CAB, PPI+LAB and PPI+MTB (online supplemental file 4).

Trends in the use of bismuth-based therapy in Europe

After the commercialisation of ScBQT in Europe in 2013, there was a progressive increase in BQT prescription, especially due to the use of the single-capsule scheme. The use of BQT peaked in 2018 when 50% of the reported treatments were bismuth therapies; thereafter, the rate of bismuth therapies fell slightly with

Figure 3 Most frequently used bismuth quadruple therapies by European country. Countries in grey did not participate in the registry. ALB, amoxicillin, levofloxacin, bismuth; ATB, amoxicillin, tetracycline, bismuth; CAB, clarithromycin, amoxicillin, bismuth; MAB, metronidazole, amoxicillin, bismuth; MTB, metronidazole, tetracycline and bismuth; PPI, proton pump inhibitor; ScBQT, single-capsule bismuth quadruple therapy.

respect to non-bismuth options and remained stable at around 40% in the 2019–2021 period (figure 1).

In 2018, 19% of the treatments were ScBQT and 31% were NScBQT; however, by the end of current study period, the prescription rates of ScBQT and NScBQT were practically the same, representing 17.8% and 21% of all treatments, respectively (figure 1).

Regarding geographical distribution, the greatest increase in BQT prescriptions occurred in Southwestern Europe, accounting for 75% of all treatments in 2018 (online supplemental file 5). ScBQT was the main treatment in this region (60%) (online supplemental file 6), while NScBQT was more frequent in Eastern Europe (60% in 2018 and 40% in 2021).

Both the rate and type of BQT prescriptions ranged widely between European countries (figures 2 and 3, online supplemental file 4).

Use and effectiveness of BQT according to treatment line, length of treatment, PPI dose, European region and year

BQT was used as first-line therapy in 9955 cases (72.3%), as second-line in 2550 (18.5%) and as rescue therapy in 1262 (9.2%). ScBQT was used in 71.7% of cases as first-line therapy, in 18.4% as second-line and in 10% as rescue therapy.

Few schemes achieved an optimal overall effectiveness (above 90%). In first-line therapy, ScBQT, PPI+CAB, PPI+MTB and PPI+MAB achieved mITT cure rates of 93%, 91%, 91% and 90%, respectively (table 1).

According to the length of treatment, only ScBQT lasting 10 days, PPI+CAB for 14 days and PPI+MAB for 14 days achieved overall optimal effectiveness (including all lines of treatment) with rates of 92%, 92% and 91%, respectively (table 2).

Regarding PPI dose, ScBQT using standard or high-dose PPIs (93.5%), PPI+CAB with standard or high-dose PPIs (92.6% and 91.2%, respectively), PPI+MAB with standard and high-dose PPIs (91% and 92.6%, respectively) and PPI+MTB with high-dose PPIs (95.4%) achieved a rate of effectiveness above 90%. No treatment achieved an effectiveness above 90% when combined with a low-dose PPI (table 3).

Effectiveness according to European region is shown in online supplemental file 7. Only ScBQT achieved an effectiveness above 90% in all European regions.

Online supplemental file 8 shows the effectiveness of the treatments by year. The effectiveness of the different BQT remained stable.

Table 1 Modified intention-to-treat effectiveness of bismuth-based quadruple therapy in treatment-naïve and rescue patients in Europe

	Line of therapy			
Schemes	**Naïve**	**Second-line**	**Rescue**	**All lines**
ScBQT				
Cure rate (%)	**93.2**	89.5	85.9	**91.8**
n	4477	1148	623	6248
95% CI	92 to 94	88 to 91	83 to 89	91 to 93
NScBQT schemes				
PPI+CAB				
Cure rate	**91.4**	87.8	77.1	**91.1**
n	3826	181	35	4042
95% CI	91 to 92	82 to 92	59 to 89	90 to 2
PPI-MTB				
Cure rate (%)	**90.9**	84.7	73.2	84.7
n	318	288	190	796
95% CI	87 to 94	80 to 89	66 to 79	82 to 87
PPI+MAB				
Cure rate (%)	**90.2**	79.4	85	88.6
n	245	34	20	299
95% CI	86 to 94	62 to 91	61 to 96	84 to 92
PPI+LAB				
Cure rate (%)	88.8	88.1	75.9	86
n	98	662	158	918
95% CI	80 to 94	85 to 90	68 to 82	84 to 88
PPI+JAB				
Cure rate (%)	86.4	93.5	0	86,7
n	477	31	1	509
95% CI	83 to 89	77 to 99	11 to 95	83 to 90
PPI+TAB				
Cure rate (%)	84.6	72.7	66.7	81.9
n	91	22	3	116
95% CI	75 to 91	50 to 88	13 to 98	73 to 88
PPI+MDB				
Cure rate (%)	77	76.3	62.5	69.2
n	61	38	112	211
95% CI	64 to 86	59 to 88	53 to 71	62 to 75
Overall				
Cure rate (%)	91.4	87.8	78.3	89.5
n	9955	2550	1262	13 767
95% CI	91 to 92	87 to 89	76 to 81	89 to 90

Rescue: third-line therapy and beyond.
Treatment schemes with 90% or more effectiveness are marked in bold.
A, amoxicillin; B, bismuth salts; C, clarithromycin; D, doxycycline; J, josamycin; L, levofloxacin; M, metronidazole; NScBQT, non-single-capsule bismuth quadruple therapy; PPI, proton pump inhibitor; T, tetracycline.

Table 2 Global (all lines of treatment) modified intention-to-treat effectiveness of NScBQT schemes by treatment length

	Length of treatment*		
Scheme	**10 days**	**14 days**	**Total**
PPI+CAB			
Cure rate (%)	86.9	**92.4**	91.1
n	895	3001	3896
95% CI	85 to 89	91 to 93	90 to 92
PPI+MAB			
Cure rate (%)	83.6	**90.7**	88.9
n	61	214	275
95% CI	71 to 91	78 to 88	85 to 92
PPI+MTB			
Cure rate (%)	81.7	89.6	84.4
n	405	346	751
95% CI	78 to 85	86 to 93	82 to 87
PPI+LAB			
Cure rate (%)	84.6	86.1	86
n	52	863	915
95% CI	71 to 93	84 to 88	84 to 88
PPI+JAB			
Cure rate (%)	89.6	86.1	86.6
n	183	302	485
95% CI	84 to 94	82 to 90	83 to 89
PPI+TAB			
Cure rate (%)	76.2	84.3	81.7
n	21	89	110
95% CI	53 to 91	75 to 91	73 to 88
PPI+MDB			
Cure rate (%)	65.4	73	69.2
n	81	122	203
95% CI	54 to 75	64 to 80	62 to 75
Overall			
Cure rate (%)	84.6	90	86.3
n	1698	4937	6635
95% CI	83 to 86	89 to 91	85 to 87

*Number of days of the eradication scheme.
Seven days prescriptions were used in less than 10 cases in most schemes and effectiveness was reported suboptimal in most of the patients.
Treatment schemes with 90% or more effectiveness are marked in bold.
A, amoxicillin; B, bismuth salts; C, clarithromycin; D, doxycycline; J, josamycin; L, levofloxacin; M, metronidazole; NScBQT, non-single-capsule bismuth quadruple therapy; PPI, proton pump inhibitor; T, tetracycline.

Multivariate analysis

Among the variables studied, adherence with treatment (OR: 8.447; 95% CI: 6.46 to 11.038, p<0.000), the use of ScBQT (OR: 1.941; 95% CI: 1.634 to 2.307; p<0.000), the use of 14-day prescriptions (vs 10 days) (OR: 1.396; 95% CI: 1.167 to 1.670 p<0.000) and the combination the BQT with either standard or high-dose PPIs (vs low dose) (OR: 1.696; 95% CI: 1.48 to 1.934, p<0.000) were significantly associated with higher mITT effectiveness. The use of PPI+MDB scheme (OR: 0.435; 95% CI: 0.313 to 0.604; p<0.000) or prescription of BQT as rescue treatment (vs first line) (OR: 0.547; 95% CI: 0.481 to 0.622, p<0.000) were significantly associated with lower effectiveness (table 4).

Adherence and safety

Adherence was above 95% in all BQT (online supplemental file 9).

At least one AE was recorded in 40% of cases. The most frequently reported AEs were taste disturbance, diarrhoea, nausea and abdominal pain (online supplemental file 10). Around 30% of AEs were mild and roughly 6.5% were intense/severe; fewer than 1% were serious. No significant differences were observed in the intensity of AEs between the different BQT schemes.

Treatment was interrupted due to AEs in 10% of cases.

DISCUSSION

Our study shows that one in three treatments prescribed in Europe by the gastroenterologists participating in the Hp-EuReg between 2013 and 2021 was a BQT. BQT has progressively gained popularity; its use rose steadily from 2013 to 2018 and

Table 3 Modified intention-to-treat effectiveness according to the proton pump inhibitor dose

	PPI dose			
Scheme	Low	Standard	High	Total
ScBQT				
Cure rate (%)	89.6	**93.5**	**93.5**	91.8
n	2735	1285	2206	6226
95% CI	88 to 91	92 to 95	92 to 95	92 to 92
PPI+CAB				
Cure rate (%)	87.6	**92.6**	**91.2**	91.1
n	815	1842	1369	4026
95% CI	87 to 88	92 to 93	91 to 91	91 to 91
PPI+MAB				
Cure rate (%)	86	**91**	**92.6**	88.9
n	150	78	68	296
95% CI	83 to 86	86 to 92	86 to 93	88 to 89
PPI+MTB				
Cure rate (%)	79.8	86.3	**95.4**	84.4
n	410	248	131	789
95% CI	79 to 80	85 to 87	92 to 96	84 to 85
PPI+JAB				
Cure rate (%)	82.4	**91.4**	76.5	86.6
n	182	267	51	500
95% CI	80 to 83	90 to 92	70 to 79	86 to 87
PPI+MDB				
Cure rate (%)	67.6	71.4	70.6	69.2
n	111	49	51	211
95% CI	65 to 69	65 to 74	64 to 73	68 to 70
PPI+TAB				
Cure rate (%)	80.6	81.8	**100**	81.7
n	98	11	6	115
95% CI	77 to 82	55 to 87	52 to 99	78 to 82
PPI+LAB				
Cure rate (%)	71.7	87.4	88.2	86
n	113	143	654	910
95% CI	69 to 73	85 to 88	88 to 88	86 to 86
Overall				
Cure rate (%)	86.8	91.9	91.7	90
n	4614	3923	4536	13 073
95% CI	87 to 87	91 to 93	91 to 93	90 to 91

Low PPI dose: 4.5–27 mg omeprazole equivalents, two times per day, standard PPI dose: 32–40 mg omeprazole equivalents, two times per day, high PPI dose: 54–128 omeprazole equivalents, two times per day. Treatment schemes with 90% or more effectiveness are marked in bold.
A, amoxicillin; B, bismuth salts; C, clarithromycin; D, doxycycline; J, josamycin; L, levofloxacin; M, metronidazole; PPI, proton pump inhibitor; ScBQT, single-capsule bismuth quadruple therapy; T, tetracycline.

Table 4 Predictive factors of treatment modified intention-to-treat effectiveness in the multivariate analysis

		95% CI		
	OR	Lower	Upper	Sig.
Adherence over 95% (reference non-adherence)	8.447	6.464	11.038	0.000
PPI+MDB prescription (reference all other BQT schemes)	0.435	0.313	0.604	0.000
ScBQT prescription (reference all other BQT schemes)	1.941	1.634	2.307	0.000
14-day treatment (reference 10 days)	1.396	1.167	1.670	0.000
Rescue treatment (reference first line)	0.547	0.481	0.622	0.000
Standard or high-dose PPI (reference low dose)	1.696	1.488	1.934	0.000

Low PPI dose: 4.5–27 mg omeprazole equivalents, two times per day, standard PPI dose: 32–40 mg omeprazole equivalents, two times per day, high PPI dose: 54–128 omeprazole equivalents, two times per day.
MDB, metronidazole, doxycycline and bismuth salts; PPI, proton pump inhibitor; ScBQT, single-capsule bismuth quadruple therapy.

has remained stable since then. A second noteworthy finding is that there is an extreme heterogeneity in the different BQT schemes prescribed across the different European regions. There are many possible explanations for these findings. The first is the presence of lower bacterial resistance rates in some specific settings (eg, Northern Europe) which allowed triple therapies to achieve good cure rates.[23] Second, the unavailability of ScBQT, tetracycline and/or bismuth salts in many European countries limits the use of BQT. Finally, at the time of the study, European and local consensus reports often recommended other schedules as preferred treatments.[3] The use of BQT has, however, increased steadily in countries where one-in-three ScBQT is available; in most of these countries, ScBQT has become the treatment of choice given its good safety profile and the excellent effectiveness it provides; furthermore, ScBQT is the most widely used treatment in south-western Europe. By contrast, classical BQT, comprising MTB administered separately, might be more laborious and inconvenient for the patient, and these characteristics may have limited its use.

Regarding effectiveness, many of the most frequently prescribed BQT therapies achieved cure rates above 90%. Notably, ScBQT repeatedly achieved cure rates above this figure, regardless of the geographical region or the PPI dose. NScBQT schemes such as PPI+CAB, PPI+MAB and PPI+MTB also achieved optimal results, provided that they were prescribed for 14 days and combined with standard or high-dose PPIs.

Accordingly, the main variables predicting the cure of *H. pylori* infection in the multivariate analysis were the use of ScBQT, administration of NScBQT for 14 days and the use of standard-dose or high-dose PPIs. When PPIs were standardised according to the Hp-EuReg analysis recommendations, the one most frequently prescribed in the low-dose group was omeprazole 20 mg two times per day. The most frequent prescriptions in the standard-dose and high-dose groups were omeprazole 40 mg two times per day and esomeprazole 40 mg two times per day, respectively. Therefore, our study suggests that the PPI dose required for achieving optimal results with any of the BQT should be omeprazole 40 mg or higher two times per day.

Data on the effectiveness of ScBQT were consistent with those of previous studies[24 25] and meta-analyses[26] which also revealed excellent cure rates. In fact, as previously stated, ScBQT was the only treatment to consistently achieve cure rates above 90% in all the European regions. These excellent ScBQT results in spite of the increasing bacterial antibiotic resistance in Europe endorse the Maastricht VI/Florence consensus report's recommendation of BQT as the therapy of choice in areas of high bacterial antibiotic resistance.[13 27] By contrast, since our study showed ScBQT to be highly effective independently of regional antibiotic resistances, our results argue against the recommendation of performing routine antibiotic resistance susceptibility testing for treatment selection. There is no evidence proving that susceptibility-guided treatment may be superior to an adequate empirical treatment[28] and BQT has always been listed

as a therapy that can be given empirically.[29] Therefore, when using empirical ScBQT, the determination of antibiotic resistances would definitively not provide any advantage that might increase effectiveness.

The multivariate analysis results were in line with previous reports: that is, the cure of the infection was related to the use of 10-day ScBQT, prescription of 14 days of therapy in all other NScBQT and administration of standard or high doses of PPIs. Of all BQT, ScBQT was the one most significantly related to greater treatment success and the PPI+MDB combination was the one with the lowest effectiveness.

Finally, we found a wide variety of treatment schemes in use in clinical practice. Although the local patterns of antibiotic resistance may still allow the use of triple therapies in a few privileged areas and may thus explain some of the heterogeneity, the variability in the infection treatments administered remains largely unexplained. As situations of this kind have generally been associated with suboptimal quality of care,[30] the study findings suggest that there may be considerable room for improvement in *H. pylori* treatment.

Adherence to BQT was good overall, and in fact, was better than expected. This may be due to the nature of the registry design, carried out by dedicated gastroenterologists or alternatively may reflect a relatively low sensitivity of the questionnaires used in the registry to detect non-adherence.

The overall incidence of AEs was comparable to that of previous reports, with around 40% of patients presenting at least one AE. The rate of serious AEs, however, was below 1%.[31]

The limitations and strengths related to the use of registry data have been extensively discussed elsewhere.[23 32 33] The limitations include the risk of selection bias, the possible underreporting of AEs and the uncertainty regarding the outcome in patients who do not complete follow-up. To minimise this bias, previous studies have proposed the use of an mITT effectiveness analysis as the most reliable approach.[23] Likewise, the categorisation of the main variables studied, such as the dose of PPIs and the regional analysis aided the interpretation of the great diversity of data and helped to provide more robust conclusions.

The main strength of the study is the large sample size, around 50 000 patients, which gave considerable power to the statistical analysis. In addition, the Hp-EuReg offers a faithful reflection of routine clinical practice and provides data on situations in which randomised trials will probably never be performed.[23]

Our study has important consequences for clinical practice. The results strongly suggest that BQT (and, specifically, ScBQT) should be made available in regions where these therapies are not currently marketed. BQT may be useful either as first-line treatment in areas of high bacterial antibiotic resistance or as rescue therapy in the few regions where standard triple therapy still achieves good results.[24] In a plausible scenario of increasing resistances, BQT (and especially ScBQT) may become the treatment of choice. A second important finding was that none of the treatments achieved an effectiveness above 90% when combined with a low-dose PPI. In fact, the study corroborates the notion that the minimal PPI dose for achieving optimal BQT results should be set to 40 mg omeprazole or an equivalent PPI dose prescribed two times per day. This finding corroborates those of previous studies[34] and suggests that the dose of PPI recommended in the technical specifications of ScBQT—omeprazole 20 mg two times per day—should be updated to 40 mg two times per day. An important related aim for future research will be to determine whether the marked acid suppression obtained by the potassium-competitive acid blockers (P-CABs), in comparison to PPIs, would also increase BQT efficacy.[35] Although P-CABs are not currently available in most European countries, the Hp-EuReg may be key to determining the role of these promising new drugs in increasing the BQT cure rates. A second area that might need further research is whether ScBQT results might be improved by using a 14-day scheme. As this extended ScBQT scheme is currently rarely used in Europe, our study could not provide data regarding this point. Finally, *H. pylori* treatment changed considerably over the course of the study period, a circumstance that highlights the importance of monitoring the trends of both the use and the effectiveness of *H. pylori* eradication therapies.

In conclusion, BQT is one of the most effective *H. pylori* treatments currently available. Specifically, the use of ScBQT homogeneously obtains excellent eradication rates in all areas and its use has increased steadily in the countries in which it is available. This study suggests that expanding the availability of this therapy may reduce the heterogeneity that characterises clinical practice at present and may increase the overall effectiveness of *H. pylori* treatment.

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