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Role of compliance in *Helicobacter pylori* eradication treatment: Results of the European Registry on *H. pylori* management

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Abstract

Background: Adherence to *Helicobacter pylori (H. pylori)* eradication treatment is a cornerstone for achieving adequate treatment efficacy.

Objective: To determine which factors influence compliance with treatment.

Methods: A systematic prospective non-interventional registry (Hp-EuReg) of the clinical practice of European gastroenterologists. Compliance was considered adequate if ≥90% drug intake. Data were collected until September 2021 using the AEG-REDCap e-CRF and were subjected to quality control. Modified

The remaining list of authors, their affiliations, and contributions are listed in Supplementary File 1. Hp-EuReg Investigators.

intention-to-treat analyses were performed. Multivariate analysis carried out the factors associated with the effectiveness of treatment and compliance.

Results: Compliance was inadequate in 646 (1.7%) of 38,698 patients. The non-compliance rate was higher in patients prescribed longer regimens (10-, 14-days) and rescue treatments, patients with uninvestigated dyspepsia/functional dyspepsia, and patients reporting adverse effects. Prevalence of non-adherence was lower for first-line treatment than for rescue treatment (1.5% vs. 2.2%; $p < 0.001$). Differences in non-adherence in the three most frequent first-line treatments were shown: 1.1% with proton pump inhibitor + clarithromycin + amoxicillin; 2.3% with proton pump inhibitor clarithromycin amoxicillin metronidazole; and 1.8% with bismuth quadruple therapy. These treatments were significantly more effective in compliant than in non-compliant patients: 86% versus 44%, 90% versus 71%, and 93% versus 64%, respectively ($p < 0.001$). In the multivariate analysis, the variable most significantly associated with higher effectiveness was adequate compliance (odds ratio, 6.3 [95%CI, 5.2–7.7]; $p < 0.001$).

Conclusions: Compliance with *Helicobacter pylori* eradication treatment is very good. Factors associated with poor compliance include uninvestigated/functional dyspepsia, rescue-treatment, prolonged treatment regimens, the presence of adverse events, and the use of non-bismuth sequential and concomitant treatment. Adequate treatment compliance was the variable most closely associated with successful eradication.

KEYWORDS
adherence, adverse effects, bismuth, dyspepsia, effectiveness, efficacy, first line, rate, regimens, rescue

INTRODUCTION

Helicobacter pylori (H. pylori) selectively infects the stomach in humans and is the most prevalent cause of chronic infection worldwide. *H. pylori* infection is the main cause of gastritis, peptic ulcer, and gastric cancer as well as an acknowledged etiology for iron deficiency anaemia, vitamin B12 deficiency and idiopathic (immune) thrombocytopenic purpura.[1–3]

Consensus conferences on the eradication of *H. pylori* infection recommend using treatments that achieve a minimal cure rate of 90%, as none of the available therapies to date reaches 100% effectiveness.[3]

Lack of adherence to pharmacological treatment, or therapeutic non-compliance, is a prevalent and relevant problem in clinical practice. In 2003, the World Health Organization warned of this problem, especially in long-term therapies and because of aging of the world's population.[4] Non-compliance has been clearly associated with the efficacy of treatment in various diseases, including arterial hypertension,[5] asthma,[6] and diabetes mellitus.[7] It has also been linked to polypharmacy.[8,9]

Rates of compliance with *H. pylori* eradication treatment vary according to country, age group (pediatrics vs. adults), type of study (real-life vs. clinical trial), and duration of therapy[10,11,12,13,14] days.

Key summary

Established knowledge on this subject

- Poor adherence to pharmacologic treatments is a prevalent and relevant problem in clinical practice that also affects Helicobacter pylori eradication treatment.

What are the significant and/or new findings of this study?

- Helicobacter pylori eradication treatment has high adherence rates in real clinical practice (1.7% non-compliance).
- The factors associated with low compliance were the indication of treatment for functional dyspepsia, rescue treatment, longer prescriptions, adverse events, and receiving sequential or concomitant treatment.
- Appropriate compliance was the variable that was most closely associated with successful eradication.

The plethora of variable factors associated with a lack of adherence include complexity of treatment, duration of treatment, the motivation and attitude of the physician, the information received by the

patient (about the disease and risks and benefits of treatment), and the associated adverse events (AEs).[15] However, the factors that might negatively influence adherence in large cohorts of patients receiving different treatment regimens have not been well elucidated. Similarly, the probability that lack of adherence affects the efficacy of treatment has not been sufficiently evaluated.

The "European Registry on *Helicobacter pylori* management" (Hp-EuReg) is a database that systematically collects data from routine clinical practice in Europe on the management of *H. pylori* infection and currently includes around 60,000 patients.[16] Hp-EuReg provides a robust geographic picture of the current management of *H. pylori*, thus enabling not only a continuous evaluation of the implementation of clinical recommendations based on medical consensus, but also improvements in health care strategies.

Therefore, the objectives of this study were to evaluate adherence to *H. pylori* eradication treatment in Europe, to identify the factors that could influence compliance, and to assess how compliance could influence the effectiveness of treatment.

METHODS

European Registry on *Helicobacter pylori* management

This analysis focused on Hp-EuReg, an international multicenter prospective non-interventional registry that was launched in 2013 and sponsored by the European *Helicobacter* and Microbiota Study Group (www.helicobacter.org). Currently, 32 countries are represented.

The Hp-EuReg protocol[16] was approved by the Ethics Committee of La Princesa University Hospital (Madrid, Spain), which acted as a reference Institutional Review Board. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's human research committee. The study was classified by the Spanish Agency for Medicines and Medical Devices and registered at ClinicalTrials.gov (NCT02328131). Written informed consent was obtained from each patient included in the study.

The objectives of the current Hp-EuReg sub-study were as follows:

1. To evaluate compliance with the *H. pylori* eradication treatments most frequently prescribed by European gastroenterologists in clinical practice
2. To identify those factors that could influence the completion of treatment
3. To assess how compliance influences the effectiveness of eradication

Patient and public involvement

Patients and the public were not involved in the design and conduct of this study.

Participants

The criteria for country selection, national coordinators, and gastroenterologists recruiting investigators were detailed in the protocol.[16] The inclusion criteria were as follows: adult patients (age ≥18 years) infected with *H. pylori* for whom validated tests were used to confirm eradication. In addition, patients had to have received a therapeutic regimen in any line (first-line or rescue therapy). Cases were managed and registered according to the participants' routine clinical practice.

Data were recorded in an electronic case report form managed using the web-based application designed to support data capture for research studies (REDCap) hosted at Asociación Espaola de Gastroenterologa (www.aegastro.es),[17] a non-profit scientific and medical society focusing on gastroenterology research. The list of variables and outcomes can be found in the protocol.[16]

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 collected correctly, thus ensuring that the study was conducted according to the highest scientific and ethical standards. Discordances were resolved by querying the investigators and through group emailing.

Data collected from 2013 to September 2021 were evaluated.

Statistical analysis

Categorization and definition of variables

In current analysis, in order to compare the different PPIs prescribed (omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole), it was decided to calculate the different PPI dosages by standardising PPI potency, in terms of the duration of intragastric pH > 4/24 h (pH4-time) to rank PPIs, where relative potency varied from 4.5 mg omeprazole equivalents (20 mg pantoprazole) to 72 mg omeprazole equivalents (40 mg rabeprazole). Such standardisation allows the interchangeable use of PPIs based on relative potency, and so, following this method, the different PPIs schedules and types were grouped into the three categories used in analyses (low, standard, and high).[18,19]

Likewise, the duration of treatment was categorized as 7, 10, or 14 days to ease interpretation. For the multivariate analysis, the three most frequently used treatments were considered, both in the first-line and in rescue lines.

AEs and compliance were evaluated by asking patients open-ended questions and administering a predefined questionnaire during face-to-face interviews[20] (Supplementary Table S1). The incidence of AEs was defined as having experienced at least one of the most frequent AEs, namely, dysgeusia, diarrhea, nausea, vomiting,

dyspepsia, heartburn, abdominal pain, asthenia, and anorexia. AEs were classified depending on the intensity of symptoms based on the evaluation of the corresponding physician as mild (not interfering with daily routine), moderate (affecting daily routine), intense/severe (preventing normal daily routine), and serious (causing death, hospitalization, disability, congenital anomaly, and/or requiring intervention to prevent permanent damage).

Compliance was defined as having taken at least 90% of the drugs prescribed.

The eradication treatments used in the analysis were as follows:

(1) Triple therapy with a PPI, clarithromycin, and amoxicillin (PPI + C + A); (2) quadruple concomitant therapy with clarithromycin, amoxicillin, and metronidazole (Conco-PPI + C + A + M); (3) bismuth quadruple therapy with metronidazole and tetracycline prescribed in a three-in-one single capsule (marketed as Pylera®) (ScBQT); (4) sequential quadruple therapy with clarithromycin, amoxicillin, and metronidazole (Seq-PPI + C + A + M; (5) bismuth quadruple therapy with clarithromycin and amoxicillin (PPI + C + A + B); (6) triple therapy with clarithromycin and levofloxacin (PPI + A + L); (7) sequential quadruple therapy with clarithromycin, amoxicillin, and tinidazole (Seq-PPI + C + A + T); (8) triple therapy with clarithromycin and metronidazole (PPI + C + M); (9) triple therapy with amoxicillin and metronidazole (PPI + A + M); (10) quadruple therapy with amoxicillin, levofloxacin, and bismuth (PPI + A + L + B); (11) quadruple therapy with metronidazole, tetracycline, and bismuth (PPI + M + Tc + B); (12) quadruple therapy with amoxicillin, bismuth, and another drug (PPI + A + B + Other); (13) quadruple therapy with clarithromycin, amoxicillin, and tinidazole (PPI + C + A + T); (14) triple therapy with amoxicillin and rifabutin (PPI + A + R); (15) hybrid therapy with clarithromycin, amoxicillin, and metronidazole (Hyb-PPI + C + A + M); (16) quadruple therapy with amoxicillin, metronidazole, and bismuth (PPI + A + M + B); (17) quadruple therapy with metronidazole, doxycycline, and bismuth (PPI + M + D + B); (18) triple therapy with amoxicillin and moxifloxacin (PPI + A + Mx); (19) triple therapy with clarithromycin and levofloxacin (PPI + C + L); (20) quadruple therapy with amoxicillin, tetracycline, and bismuth (PPI + A + Tc + B).

Continuous variables were summarized using the arithmetic mean and respective standard deviation (SD). Qualitative variables were summarized using percentages and 95% confidence intervals (CI). Statistical significance was set at $p < 0.05$, two-tailed. The sociodemographic and clinical characteristics of the patients were compared using the chi-squared (χ^2) test for qualitative variables and the *t* test for quantitative variables.

Data analysis

Effectiveness was studied in three sets of patients. First, the intention-to-treat (ITT) set, which included all patients registered up to September 2021 to allow at least a 6-month follow-up and considered patients lost to follow-up as treatment failures. Second, the per-protocol (PP) set, which included all compliant patients (i.e., had taken ≥90% of the prescribed drugs) who had completed follow-up. And third, a modified ITT (mITT) set, which, in the current study, was defined as the main effectiveness analysis for interpretation of the data, reflecting the results closest to those obtained in clinical practice. Therefore, the mITT included all patients who had completed follow-up (a confirmatory test indicating success or failure was available after eradication treatment), regardless of compliance.

The results of the ITT and PP analyses are included in the tables for methodological reasons and comparison only; however, they were not used for data evaluation. Effectiveness was considered optimal when the cure rate was ≥90%, as reported in clinical guidelines.[3]

Two multivariate logistic regression models were run: one that assumed compliance as the dependent variable, and another with mITT as the dependent variable.

In the first instance, the multivariate logistic regression analysis considered compliance as the dependent variable and the following covariates: AEs (yes [reference] vs. no), duration of treatment (7, 10, 14 [reference] days), dose of PPI (low [reference], standard, high), indication of treatment (peptic ulcer vs. dyspepsia [reference]), line of treatment (naive vs. rescue [reference]), and sex (female [reference] vs. male). Multivariate analysis was also carried out with the three most frequent treatments and the same variables to determine which factors influenced compliance with these treatments.

A further multivariate logistic regression analysis was performed using the mITT as the dependent variable comprised the naive treatments and included the following covariates: compliance (no [<90% drug intake, reference] vs. yes (≥90%]), treatment regimen (PPI + C + A) [reference], Seq-PPI + C + A + M, Seq-PPI + C + A + T, Conco-PPI + C + A + M, PPI + C + A + T, ScBQT, PPI + C + A + B, others), PPI acid inhibition effect (low [reference], standard, high), duration of treatment (7 [reference], 10, 14 days), sex (female [reference] vs. male), and indication for treatment (peptic ulcer vs. dyspepsia [reference]).

All these variables were entered using the backward stepwise strategy (entry criterion, $p < 0.05$; and exit criterion, $p > 0.1$). The odds ratios (OR) with their respective 95% CIs were reported.

RESULTS

Baseline characteristics

A total of 38,732 prescribed treatments were analysed. The mean age of the patients was 51 years, and 61% were women. The most frequent ethnic group was Caucasian (90% of the prescriptions). Eighty percent of the patients were treatment-naïve, and the most frequent previous concurrent treatment was PPI in 58%. A total of 4.4% of the patients were allergic to at least one of the drugs used in

the regimens analysed, most frequently to penicillin (3.6%). The indication for treatment was functional dyspepsia (dyspepsia with normal endoscopy) in 4 out of 10 cases (Table 1).

Regarding participation in the study, Spain was the country with the most cases included (45%), followed by Russia (16%) and Italy (10%) (Supplementary Table S2 and Supplementary Figure S1).

Overall compliance rates

Among the total number of treated patients, 646 (1.7% [95%CI 1.5–1.8]) did not complete the treatment. Table 2 summarizes the percentages of lack of compliance with the main therapeutic regimens analysed, with the highest non-compliance reported among patients who received Seq-PPI + C + A + M (5.5%), followed by quadruple therapy with PPI + M + D + B (3.9%) and PPI + A + L + B (3.1%) ($p < 0.001$).

Most frequently used treatments

Regarding first-line treatments, the most frequently used treatments were PPI + C + A in 9973 (32,8%) of patients (compliance rate of 99%), followed by PPI + C + A + M in 5567 (18,3%) patients (compliance rate of 98%), and ScBQT in 4056 (13.3%) of patients (with a compliance rate of 98%).

TABLE 1 Patients' baseline demographic characteristics.

	Compliance			
	No (<90% of treatment)	Yes (≧90% of treatment)	*p* value	Total
Total number of patients (*N*, %)	646 (1.7)	38,086 (98.3)	-	38,732
Naïve patients (*N*, %)	474 (1.5%)	30,418 (98.5)	<0.001	30,892 (79.8)
Rescue treatment (*N*, %)	172 (2.2)	7629 (97.8)		7840 (20.2)
Age (mean ± SD)	51.5 ± 16.2	50.8 ± 16.4	0.464	50.8 ± 16.4
Sex (*N*, %)			<0.001	
Men	193 (1.3)	14975 (98.7)		15,168 (39.2)
Women	453 (1.9)	23,052 (98.1)		23,505 (60.8)
Ethnicity (*N*, %)			<0.001	
Caucasian	540 (1.6)	34,167 (98.4)		34,707 (89.9)
Black	8 (2.6)	297 (97.4)		305 (0.8)
Asian	7 (1.5)	451 (98.5)		458 (1.2)
Other	30 (1.3)	2269 (98.7)		2299 (6)
Unknown	60 (7.2)	776 (92.8)		836 (2.2)
Concurrent treatment (*N*, %)				12,949 (36.3)
PPI	153 (2.1)	7289 (97.9)	0.005	7442 (57.7)
Acetylsalicylic acid	31 (1.4)	2187 (98.6)	0.232	2218 (17.5)
NSAIDs	38 (1.3)	2899 (98.7)	0.084	2937 (23.1)
Statins	61 (1.7)	3595 (98.3)	0.353	3656 (28.8)
Allergies to any antibiotic (*N*, %)			0.002	
Yes	44 (2.6)	1677 (97.4)		1721 (4.4)
No	602 (1.6)	36,354 (98.4)		36,956 (95.6)
Indication (*N*, %)			<0.001	
Non-investigated dyspepsia	159 (2.2)	707 (97.8)		7236 (18.7)
Functional dyspepsia[a]	222 (1.5)	14,922 (98.5)		15,144 (39.2)
Duodenal ulcer	51 (1.2)	4226 (98.8)		4277 (11.1)
Gastric ulcer	34 (1.7)	1944 (98.3)		1978 (5.1)
Other	180 (1.8)	9850 (98.2)		1030 (2.7)

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

[a]Dyspepsia with normal endoscopy (that is, no cancer, no ulcer, etc.).

TABLE 2 Compliance according to the therapeutic regimen prescribed in the first- and subsequent treatment lines.

	Non-compliance (<90% of treatment) (*n*/*N* (%))		
Therapeutic regimen	**Overall ($p < 0.001$)**	**Naive ($p < 0.001$)**	**Rescue ($p = 0.056$)**
PPI + C + A	113/10,304 (1.1)	105/9973 (1.1)	8/330 (2.4)
PPI + C + A + M	137/5941 (2.3)	127/5567 (2.3)	10/373 (2.7)
ScBQT	106/5718 (1.9)	71/4056 (1.8)	35/1662 (2.1)
PPI + C + A + B	54/3503 (1.5)	44/3326 (1.3)	10/177 (5.6)
PPI + A + L	36/2431 (1.5)	12/500 (2.4)	24/1929 (1.2)
Seq-PPI + C + A + T	16/1764 (0.9)	13/1654 (0.8)	3/110 (2.7)
PPI + C + M	10/1281 (0.8)	7/1222 (0.6)	3/59 (5.1)
PPI + A + M	11/856 (1.3)	7/674 (1)	4/182 (2.2)
PPI + A + L + B	26/847 (3.1)	4/87 (4.6)	22/760 (2.9)
PPI + M + Tc + B	21/753 (2.8)	6/299 (2)	15/454 (3.3)
Seq-PPI + C + A + M	35/639 (5.5)	35/609 (5.7)	0/30 (0)
PPI + A + B + Other	11/466 (2.4)	9/447 (2)	2/19 (10.5)
PPI + C + A + T	7/413 (1.7)	7/363 (1.9)	0/50 (0)
PPI + A + R	7/343 (2)	0/37 (0)	7/306 (2.3)
Hyb-PPI + C + A + M	0/245 (0)	0/241 (0)	0/4 (0)
PPI + A + M + B	5/239 (2.1)	3/195 (1.5)	2/44 (4.5)
PPI + M + D + B	8/207 (3.9)	4/60 (6.7)	4/147 (2.7)
PPI + A + Mx	0/175 (0)	0/12 (0)	0/163 (0)
PPI + C + L	3/140 (2.1)	1/64 (1.6)	2/76 (2.6)
PPI + A + Tc + B	0/101 (0)	0/89 (0)	0/12 (0)
Other	24/1366 (1.8)	15/902 (1.6)	9/464 (1.9)
Total	630/37,732 (1.7)	470/30,377 (1.5)	160/7351 (2.2)

Abbreviations: A, amoxicillin; B, bismuth; C, clarithromycin; D, doxycycline; Hyb, hybrid; L, levofloxacin; M, metronidazole; Mx, moxifloxacin; PPI, proton pump inhibitors; R, rifabutin; ScBQT, three-in-one single capsule containing bismuth, tetracycline, and metronidazole; Seq, sequential; T, tinidazole; Tc, tetracycline.

The most common second- and successive treatment lines were triple with PPI + A + L in 1929 prescriptions (compliance rate of 98.8%), ScBQT in 1662 prescriptions (compliance rate of 97.9%), and quadruple with PPI + A + L + B in 760 prescriptions (compliance rate of 97.1%).

Factors associated with non-compliance

Non-compliance according to patients' baseline characteristics

Non-compliance was higher in rescue treatment than in treatment-naïve patients (2.2% [95% CI 1.9–2.5] vs. 1.5% [95% CI 1.4–1.7]; $p < 0.001$) and in women than in men (1.9% [95% CI 1.6–2.2] vs. 1.3% [95% CI 0.4–1.1]; $p < 0.001$). Non-statistically significant differences were observed between age and adherence. Worse completion rates were observed among Black patients than among Caucasians, Asians, or other ethnic origins (2.6% [95% CI 1.9–5.6] vs. 1.6% [95% CI 1.3–1.8], 1.5% and 1.3% [95% CI 1.1–4.6], respectively; $p < 0.001$). Patients allergic to penicillin presented worse compliance rates than those who did not present this allergy (2.7% [95% CI 1–3.6] vs. 1.6% [95% CI 1.3–1.8]; $p < 0.005$). Among those patients taking concurrent PPIs before an eradication treatment was prescribed, non-adherence to eradication therapy was higher (2.1% [95% CI 1.4–2] vs. 1.4% [95% CI. 1.1–1.7]; $p = 0.005$). As for the reason for eradication, the highest non-compliance rate was recorded among patients with non-investigated dyspepsia than in those with functional dyspepsia, peptic ulcer, and other causes (2.2% [95% CI 1.8–3.1] vs. 1.5% [95% CI 0.9%–1.6%], 1.4% [95% CI 0.1–3.6], and 1.8% [95% CI 1.4%–2.3%], respectively; $p < 0.001$) (Table 1).

Compliance depending on the duration of treatment, PPI dosage, and use of probiotics

Low-dose PPIs were associated with an increase in the lack of adherence than standard- or high-dose PPIs, although no statistically

significant differences were reported (1.8% vs. 1.6% and 1.5%, respectively).

Completion rates were better for the 7-day treatments than for the 10- and 14-day treatments (non-compliance of 0.8% [$N = 32$] vs. 1.8 [$N = 354$] and 1.6% [$N = 232$], respectively; $p < 0.001$).

Lack of adherence was higher in patients who did not take probiotics than in those who did (1.7% [$N = 536$] vs. 1.4% [$N = 110$]; $p = 0.043$).

Compliance according to the treatment line

Overall, non-compliance was lower in first-line treatments than in rescue treatment (1.5% vs. 2.2%; $p < 0.001$).

Non-compliance in the three most frequent treatments used was 1.1% in PPI + C + A, 2.3% in Conco-PPI + C + A + M, and 1.8% in ScBQT ($p < 0.001$).

Regarding first-line treatments, a lack of adherence was observed in 1.1% in PPI + C + A, in 2.3% in Conco-PPI + C + A + M, and in 1.8% in ScBQT ($p < 0.001$). However, the highest non-compliance rates were observed in bismuth quadruple therapies (PPI + M + D + B and PPI + A + L + B) and in Seq-PPI + C + A + M (6.7%, 4.6%, and 5.7%, respectively; $p < 0.001$).

Regarding second and successive treatment lines, non-compliance was reported in 1.2% of patients prescribed PPI + A + L, in 2.1% of those prescribed ScBQT, and in 2.9% of those prescribed PPI + A + L + B, with no significant differences between therapies.

Compliance in relation to the incidence of AEs

Non-compliance was higher among patients who reported at least 1 AE (5%; 464 patients) than in those who did not present any (0.6%; 177 patients), with statistically significant differences between both groups ($p < 0.001$).

Geographical and temporal analysis

The highest rate of non-adherence was observed in Norway (2.8% [95% CI, 1.7–3.9]) and Spain (2.1% [95% CI 1.9–2.3]), and the differences were statistically significant with respect to the remaining participating countries (Supplementary Table S2). Russia and Italy, which were among the countries with the highest participation rate (see above), reported a non-adherence rate of 1.6% each.

In general, non-compliance rates remained largely unchanged over time (Supplementary figure S2).

Influence of compliance on treatment success

Data confirming first-line eradication are available for 30,838 patients. By intention-to-treat analysis, the overall eradication rate was 88%. Eradication was achieved in 89% of patients with appropriate compliance, compared with 58% of those whose compliance was less than <90% ($p < 0.001$).

Similarly, data confirming eradication with second-line treatment were available for 7333 prescriptions, indicating an eradication rate of 82% in compliant patients compared with 60% in non-compliant patients ($p < 0.001$).

The eradication rates of the most frequently used treatments were higher among patients with adequate compliance (Tables 3 and 4, Figures 1 and 2).

Likewise, regarding the compliance rates by country, the effectiveness of treatments was greater in countries with better compliance than in those with poorer compliance, both in first-line and in rescue treatment (Figure 3).

Multivariate analysis

When compliance was considered as the dependent variable, the final model (Supplementary Table S3) revealed that the factors that were statistically associated with greater success in the mITT analysis were as follows: absence of AEs (OR 8.6; 95% CI [7.2–10.3]; $p < 0.001$); 7-day prescriptions (OR 2; 95% CI [1.3–2.9]; $p = 0.001$); the use of high-dose PPI (OR 1.6; 95% CI [1.3–2]; $p < 0.001$); having peptic ulcer (OR 1.5; 95% CI [1.2–2]; $p = 0.001$); being treatment-naïve (OR 1.3; 95% CI [1.1–1.6]; $p = 0.002$); and male sex (OR 1.2; 95% CI [1.02–1.5]; $p = 0.03$).

Analysis of the factors that affected compliance with the 3 most frequently used treatments revealed the following (Supplementary Table S4):

1. For PPI + C + A, the only factor that was related to greater compliance was the absence of AEs (OR 7.5; 95% CI [5–11.3]; $p < 0.001$).
2. For Conco-PPI + C + A + M, the factors that were related to greater compliance were the absence of AEs (OR 12; 95% CI [7.8–18.8]; $p < 0.001$), treatment duration of 7 days (OR 0.2; 95% CI [0.05–0.8]; $p = 0.02$), use of high doses of PPI (OR 1.9; 95% CI [1.2–3]; $p = 0.004$), and indication for peptic ulcer (OR 2.6; 95% CI [1.4–5]; $p = 0.003$).
3. For ScBQT, the factors that were related to greater compliance were the absence of AEs (OR 7.9; 95% CI [5–12.4]; $p = 0.001$) and the use of high doses of PPI (OR 2.1; 95% CI [1.3–3.4]; $p = 0.002$).

When we considered the success of eradication according to the mITT analysis as the dependent variable, the most closely associated variable was correct compliance with treatment (OR 5.9; 95% CI [4.9–7]; $p < 0.001$), although a correlation was also recorded with ScBQT compared with the remaining treatments (OR 1.8; 95% CI [1.6–2]; $p < 0.001$]), high-dose PPIs (OR 1.7; 95% CI [1.5–1.9]; $p < 0.001$), 14-day treatments (OR 1.6; 95% CI [1.5–1.8]; $p < 0.001$), male sex (OR 1.2; 95% CI [1.1–1.3]; $p < 0.001$), peptic ulcer (OR 1.2; 95% CI [1.1–1.3]; $p < 0.001$), and incidence of AEs (OR 1.2; 95% CI [1.1–1.3]; $p < 0.001$) (Supplementary Table S5).

TABLE 3 Rates of eradication with the most frequent first-line treatments.

		Eradication rates (mITT) as a function of compliance			
Therapeutic regimen	**Non-compliance**	**No (<90% treatment)**	**Yes (≧90% treatment)**	***p* value**	**Total**
PPI + C + A	105 (1.1%)	46 (44.2%)	8522 (86.6%)	<0.001	9973
PPI + C + A + M	127 (2.3%)	92 (72.4%)	4909 (90.3%)	<0.001	5567
ScBQT	71 (1.8%)	44 (62.9%)	3743 (94%)	<0.001	4056
PPI + C + A + B	44 (1.3%)	27 (61.4%)	3029 (92.4%)	<0.001	3326
Seq-PPI + C + A + T	13 (0.8%)	5 (38.5%)	1500 (91.4%)	<0.001	1654
PPI + C + M	7 (0.6%)	2 (28.6%)	1021 (84.1%)	0.002	1222
PPI + A + M	7 (1%)	5 (71.4%)	568 (85.3%)	0.279	674
Seq-PPI + C + A + M	35 (5.7%)	21 (60%)	485 (84.5%)	0.001	609
PPI + A + L	12 (2.4%)	9 (75%)	406 (83.2%)	0.334	500
PPI + A + B + Other	9 (2%)	4 (44.4%)	378 (86.5%)	0.004	447
PPI + C + A + T	7 (1.9%)	1 (16.7%)	344 (96.6%)	<0.001	363
PPI + M + Tc + B	6 (2%)	2 (33.3%)	271 (92.5%)	0.001	299
Hyb-PPI + C + A + M	0 (0%)	0 (0%)	227 (100%)	-	241
PPI + A + M + B	3 (1.5%)	1 (33.3%)	173 (90.1%)	0.031	195

Abbreviations: A, amoxicillin; B, bismuth; C, clarithromycin; D, doxycycline; Hyb, hybrid; L, levofloxacin; M, metronidazole; mITT, modified intention-to-treat; Mx, moxifloxacin; PPI, proton pump inhibitors; ScBQT, three-in-one single capsule containing bismuth, tetracycline, and metronidazole; Seq, sequential; T, tinidazole; Tc, tetracycline.

TABLE 4 Eradication rates in second-line and successive treatment for the most frequent regimens.

		Eradication rates (mITT) as a function of compliance			
Therapeutic regimen	**Non-compliance**	**No (<90% treatment)**	**Yes (≧ 90% treatment)**	***p* value**	**Total**
PPI + A + L	24 (1.2%)	12 (50%)	1548 (81.3%)	0.001	1929
ScBQT	35 (2.1%)	23 (65.7%)	1453 (89.4%)	<0.001	1662
PPI + A + L + B	22 (2.9%)	14 (66.7%)	639 (86.6%)	0.018	760
PPI + M + Tc + B	15 (3.3%)	8 (57.1%)	358 (81.7%)	0.033	454
PPI + C + A + M	10 (2.7%)	6 (60%)	288 (79.6%)	0.136	373
PPI + C + A	8 (2.4%)	6 (75%)	245 (77%)	0.584	330
PPI + A + R	7 (2.3%)	2 (28.6%)	224 (75.2%)	0.014	306
PPI + A + M	4 (2.2%)	2 (50%)	119 (66.9%)	0.411	182
PPI + C + A + B	10 (5.6%)	5 (55.6%)	149 (89.2%)	0.015	177
PPI + A + Mx	0 (0%)	-	141 (87%)	-	163
PPI + M + D + B	4 (2.7%)	2 (50%)	94 (65.7%)	0.432	147
Seq-PPI + C + A + T	3 (2.7%)	1 (33.3%)	77 (72%)	0.202	110

Abbreviations: A, amoxicillin; B, bismuth; C, clarithromycin; D, doxycycline; L, levofloxacin; M, metronidazole; mITT, modified intention-to-treat; Mx, moxifloxacin; PPI, proton pump inhibitors; ScBQT, three-in-one single capsule containing bismuth, tetracycline, and metronidazole; Seq, sequential; T, tinidazole; Tc, tetracycline.

DISCUSSION

To the best of our knowledge, this is the largest study to evaluate the rate of compliance and non-compliance in clinical practice. We analysed factors that could potentially influence this lack of adherence, as well as the association between non-compliance and effectiveness of therapy.

The overall rate of non-compliance in Hp-EuReg was only 1.7%. Published non-compliance rates vary widely owing to numerous factors. Thus, non-compliance rates reported in clinical practice

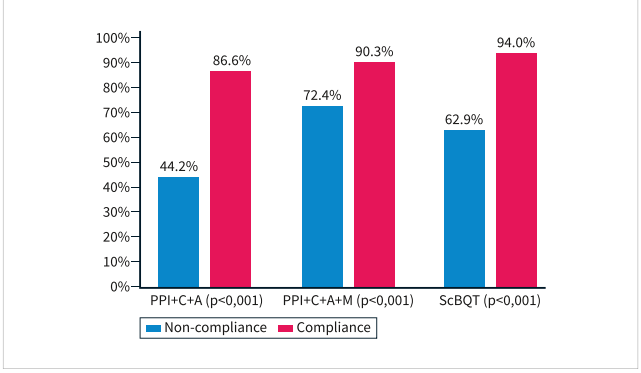

FIGURE 1 Differences in the success of treatment (modified intention-to-treat) based on compliance with the most frequent first-line treatments.

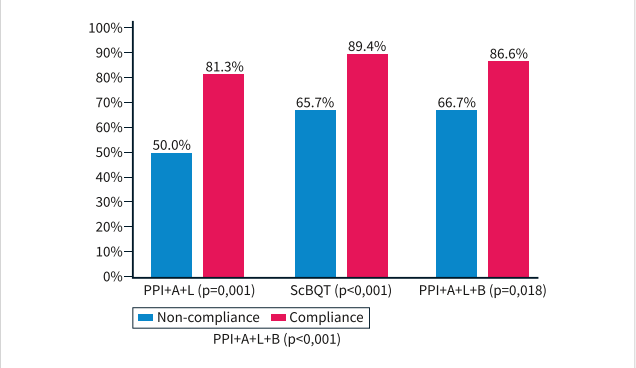

FIGURE 2 Differences in the success of treatment by modified intention-to-treat as a function of compliance in the most frequent rescue treatments.

studies such as ours range from as high as 17.1% in the study by Li et al.[13] to 5% in the study by Romano et al..[21] This variability has also been observed in clinical trials. Rates such as the 18.6% in the HYPER Study[22] were higher than the 10% reported by Sjomina et al.,[23] 8% by de Luo et al.,[24] and 5% by Apostolopoulos et al..[25]

The importance of health care professionals in improving adherence to treatments has been highlighted.[4,8,15] In our study, the participants were gastroenterologists with a special interest in the study and treatment of *H. pylori* who were wholly committed to achieving the highest standards of care, as demonstrated in the high number of patients included and the considerable scientific output generated by the registry.[26] The excellent adherence to treatment we observed could be due, at least in part, to the aforementioned observations. Therefore, the specific approach of our study makes it unlikely that our results could be extrapolated to other populations.

The definition of adequate compliance in the different studies must also be considered. Thus, our study was very demanding in that it determined appropriate compliance in those patients who had completed at least 90% of their treatment course. However, in other studies, compliance was defined as completing more than 80% of the prescribed therapy.[24,25]

The factors associated with greater compliance were the absence of AEs, a 7-day duration of treatment, high doses of PPI, the indication for peptic ulcer, being treatment-naïve, and being male.

AEs have been reported to be one of the main causes of non-compliance with treatment. A recent published study, also derived from the Hp-EuReg, that analysed the AE profile, found that 1.3% of patients had to discontinue treatment because of AEs.[27] In the study by Li et al.,[13] 6.1% of the patients (18/293) discontinued treatment owing to AEs. In a Spanish study, 7 of the 8 discontinuations in non-compliant patients were due to AEs.[10] We observed that adherence was clearly higher among patients without AEs (5% vs. 0.6%). In a study from 2002, it was also suggested that the main reason patients gave for discontinuing treatment was AEs.[27] A more recent study also pointed to AEs as the main cause of non-compliance.[28] However, AEs should not be considered the only explanation for treatment failures.

In our cohort, the duration of treatment affected compliance; we observed that adherence was better when the duration of treatment was shorter, that is, 7 days. However, these findings contrasted with those observed in the study by Zagari et al.,[22] who found no differences in adherence between the 1- and 2-week treatments. However, Apostolopoulos et al.[25] reported adherence to be high in both groups (99.5% for the 10-day treatment vs. 96.2% for the 14-day treatment), although the difference was not statistically significant ($p = 0.067$), probably owing to the small sample size.

In our study, the use of high doses of PPIs was associated with greater compliance, although this aspect has not been adequately evaluated in the medical literature. Thus, the studies in which high doses of PPIs were used did not evaluate whether there were differences in terms of compliance, considering all other possible factors. For example, in the study by Mei et al.,[29] the compliance rates in the esomeprazole high-dose group (20 mg 4 times daily) versus the esomeprazole standard-dose group (20 mg, twice daily) were 97% and 95.9%, respectively, with no statistically significant difference between the 2 groups.

In our study, a lower compliance rate was observed in patients with uninvestigated dyspepsia or functional dyspepsia; this could be due to a lack of importance attributed by physicians or patients.

In our study, sequential treatment and concomitant treatment were associated with a lower compliance rate, in contrast to data reported from studies with smaller sample sizes. Thus, Rakici et al.[30] did not find differences in adherence between the 3 groups analyzed (PPI + C + A 14 days, Seq-PPI + C + A + M 10 days, and triple therapy with PPI + moxifloxacin + metronidazole). Tepes et al[31] recorded very high adherence rates in all 3 treatment arms (PPI + C + A 7 days, Seq-PPI + C + A + M 10 days, and Conco-PPI + C + A + M 7 days), although the differences were not significant.

The countries with the highest non-compliance rates were Norway (2.8%) and Spain (2.1%); the lowest rate was recorded in Portugal (0.4%). Once again, these high rates of treatment could be attributed to the commitment of the participating physicians.[32] Those countries with a relatively low gastric cancer prevalence could have a

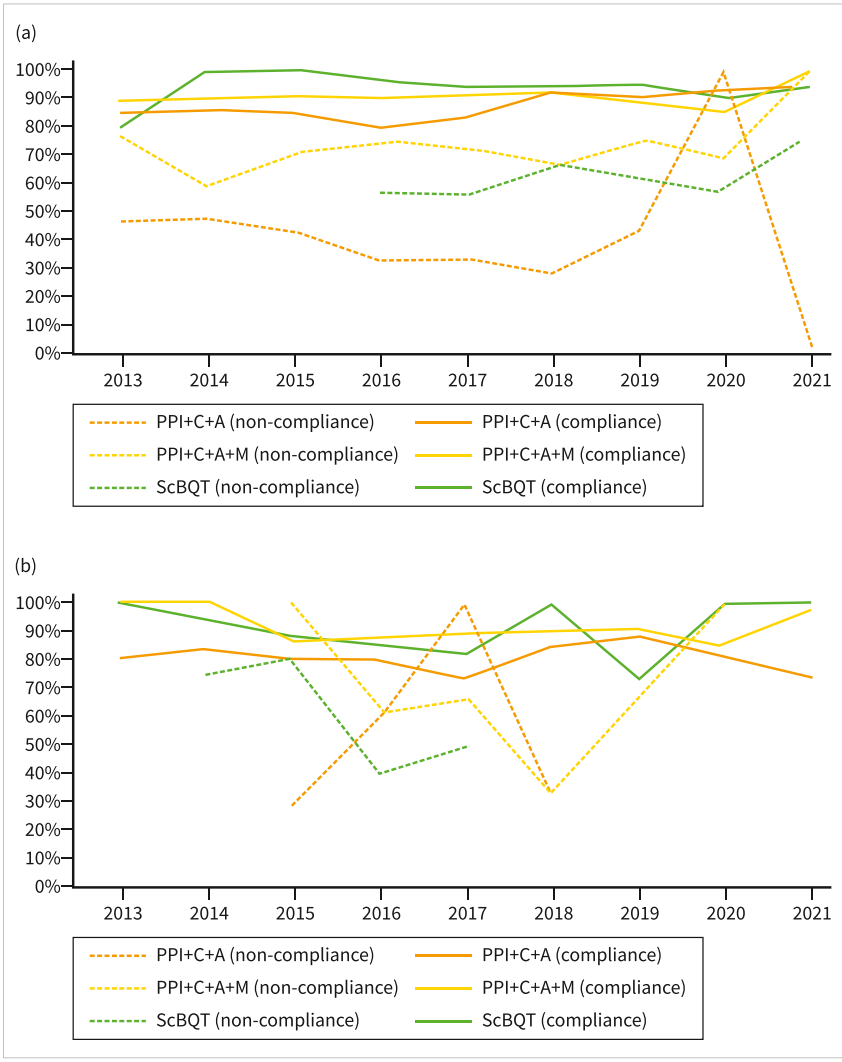

FIGURE 3 Effect of compliance on the modified intention-to-treat effectiveness of the most frequent (a) first-line and (b) rescue treatments over time in Europe.

decrease in treatment adherence, such is the case of Norway and Spain; given either patients or gastroenterologists could potentially pay less attention to treatment intake or explanation, respectively.

Compliance rates clearly affected eradication rates. In our study, we highlight the impact of eradication rates in adherent and non-adherent patients. We observed that in first-line therapy, the eradication rates were 89% and 58% depending on whether patients adhered to the treatment or not. The same occurred in second-line treatment, with eradication rates of 82% for patients who complied compared with 60% for those who did not. These data agree with the findings of the study by Shahbazi et al., who observed that eradication of *H. pylori* was 40 times more successful in patients with good compliance,[11] or in the study by Lan et al.,[33] whose logistic regression analysis showed that therapeutic compliance was an independent factor for the success of eradication. Similarly, in a randomized study,[34] in addition to smoking, poor compliance significantly decreased the effectiveness of the treatment in multiple logistic regression analysis.

Findings from the current cohort should be interpreted cautiously. The Hp-EuReg is not a randomized controlled trial, and treatment comparisons are likely to introduce biases that could affect the primary outcomes, such as compliance in the current case or effectiveness of therapy. For instance, the fact that the participants were gastroenterologists who are highly committed to their task could also have influenced one of the most important variables studied in our cohort, namely, the frequency of adherence to treatment, which is likely to be far higher than in other healthcare settings (this is most likely related to the amount of time and the clear explanation given about the importance of taking the complex treatment, how to take it, the importance of duration, and what to do when feeling uncomfortable or experiencing medication intolerance). Although we used a pre-defined case report form (Supplementary Table S1) to collect data on the type, intensity and duration of adverse events, bias might have occurred during data collection. Additionally, the geographical heterogeneity of the sample might have limited our understanding of the management of this infection

because of socioeconomic constraints, which are not easily taken into account in standard medical-statistical analysis. Such limitations are inherent to our study design, which is based on daily clinical practice.

This said, the design itself brings strengths to the data evaluation. The open inclusion criteria represent the clinical practice of the participating centers, enabling the evaluation of a wide range of treatment choices and patient contexts. Although heterogeneity is a constant feature, the analyses performed to date on the Hp-EuReg, have also demonstrated that the results are consistent and robust.[26] Furthermore, the Registry was launched 10 years ago and now includes over 60,000 patients, thus making it the largest worldwide data series on the management of *H. pylori* and enabling regional and time trend analyses, and also multivariate analyses that are controlled for confounders. Consequently, it serves both as a tool for further clinical studies and as a cornerstone for medical evidence and clinical guidelines.

In view of our results, we consider that following measures should be promoted from the health practitioner perspective in order to increase adherence, mainly in those patients with a priori identifiable risk factors for poor adherence, that is either those receiving longer regimens (10-, 14-days), or rescue treatment and potentially also those patients with uninvestigated dyspepsia or functional dyspepsia: (1) to consider taking time to explain the treatment to the patient by providing handouts; (2) to highlight the fact that side effects might occur but that these are temporary and most often harmless; (3) to potentially improve adherence with e-medicine or with support from a pharmacist, nurse or other health professionals.[35–37]

In summary, compliance with *H. pylori* eradication treatment was very satisfactory in our study. In addition, to the factors that were associated with low compliance included the indication of treatment for functional/non-investigated dyspepsia, rescue treatment, longer prescriptions, AEs, and receiving sequential or concomitant treatment. However, we observed that adequate completion of treatment was the variable that was most closely associated with successful eradication, therefore highlighting the necessity for the prescriber to correctly clarify treatment to the patient and emphasize the vital significance of adherence.

AUTHOR CONTRIBUTIONS

Jose M. Huguet, Luis Ferrer-Barceló and Patricia Suárez planned and coordinated the study, analysed, synthetized, and interpreted the data, wrote the first draft, and approved the submitted manuscript. Susana Barcelo-Cerda analysed the data and approved the submitted manuscript. Olga P. Nyssen, Scientific Director and member of the project's Scientific Committee, planned and coordinated the study, designed and programmed the electronic case report form, extracted and analysed the data, reviewed the drafts and approved the submitted manuscript. Javier Sempere, Ilaria Maria Saracino, Giulia Fiorini, Dino Vaira, Ángeles Pérez-Aísa, Laimas Jonaitis, Bojan Tepes, M. Castro-Fernandez, Manuel Pabón-Carrasco, Alma Keco-Huerga, Irina Voynovan, Alfredo J. Lucendo, Ángel Lanas, Samuel J. Martínez-Domínguez, Enrique Alfaro Almajano, Luis Rodrigo, Ludmila Vologzanina, Dmitry S. Bordin, Antonio Gasbarrini, Gülüstan Babayeva, Frode Lerang, Mārcis Leja, Juozas Kupčinskas, Theodore Rokkas, Ricardo Marcos-Pinto, Antonio Meštrović, Oleksiy Gridnyev, Perminder S Phull, Sinead M. Smith, Doron Boltin, György Miklós Buzás, Lumír Kunovský, Halis Şimşek, Tamara Matysiak-Budnik, Vladimir Milivojevic, Wojciech Marlicz, Marino Venerito, Lyudmila Boyanova, Michael Doulberis and Lisette G. Capelle: acted as recruiters, collected or helped interpreting data, critically reviewed the manuscript drafts, and approved the submitted manuscript. Leticia Moreira, Anna Cano-Català, Olga P. Nyssen, Francis Mégraud, and Colm O'Morain, are members of the project's Scientific Committee, critically reviewed the manuscript drafts and approved the submitted manuscript. Javier P. Gisbert, Director of the project and the project's Scientific Committee, obtained funding, designed the protocol, planned the study, analysed and interpreted the data, enrolled patients, critically reviewed the manuscript drafts, and approved the final submitted manuscript.

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CONFLICT OF INTEREST STATEMENT

Specific Potential competing interests: Dr. Gisbert has served as a speaker, consultant, and advisory board member for or has received research funding from Mayoly, Allergan, Diasorin, Biocodex, Juvisé and Richen. Dr. Nyssen has received research funding from Mayoly, Allergan, Biocodex and Juvisé. The remaining authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data relevant to the study are included in the article or uploaded as supplementary information. The data supporting the conclusions of this study are not publicly available, as their content may compromise the privacy of research participants. 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.

ETHICS STATEMENT

The Hp-EuReg protocol was approved by the Ethics Committee of La Princesa University Hospital (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.

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