Combination of Bismuth and Standard Triple Therapy Eradicates *Helicobacter pylori* Infection in More than 90% of Patients

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BACKGROUND & AIMS: **Due to the poor eradication rates of standard triple therapy, the addition of bismuth salts has been proposed for first-line eradication of *Helicobacter pylori*. We assessed the effectiveness and safety of the combination of bismuth and the standard, clarithromycin-containing triple therapy in eradication of *H pylori* infection, using data from a large multi-center registry.**

METHODS: **We performed an interim analysis of data from the European Registry on *H pylori* Management, a prospective trial registering clinical data and outcomes from infected patients from 27 countries in Europe since 2013. We extracted data on 1141 treatment-naïve patients who received first-line treatment with bismuth salts (240 mg) and a proton pump inhibitor (57% received esomeprazole, 18% received omeprazole, 11% received pantoprazole, and 14% received rabeprazole), amoxicillin (1 g), and clarithromycin (500 mg), all taken twice daily.**

RESULTS: **Intention to treat and per-protocol rates of eradication were 88% and 94%, respectively. Intention to treat eradication increased to 93% in patients who received 14-day treatments.**

Abbreviations used in this paper: Hp-EuReg, European Registry on *Helicobacter pylori* Management; ITT, intention-to-treat; OR, odds ratio; PPI, proton pump inhibitor.

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Adverse events occurred in 36% of patients; 76% of these events were mild, with a mean duration of 6 days. In multivariate analysis, eradication was associated with treatment compliance (odds ratio [OR], 13.0), a double dose (equivalent to 40 mg omeprazole) of proton pump inhibitor (OR, 4.7), and 14-day duration of treatment (OR, 2.0).

CONCLUSIONS: **In an analysis of data from a large multi-center registry, we found the addition of bismuth to 14-day standard triple therapy with clarithromycin and amoxicillin to eradicate *H pylori* infection in more than 90% of patients, based on intention to treat analysis, with an acceptable safety profile and level of adherence. ClinicalTrials.gov no: NCT02328131.**

Keywords: PPI; Bacteria; Optimized Treatment; Antimicrobial; Hp-EuReg; Database.

Helicobacter pylori is a worldwide infection that affects billions of people. This infection is the main known cause of gastritis, gastroduodenal ulcer disease, and gastric cancer.[1] However, after more than 30 years of experience in *H pylori* treatment, the ideal regimen to treat patients without susceptibility testing remains undefined.[2] Large clinical trials and meta-analyses have shown that the most commonly used first-line therapies (a proton pump inhibitor [PPI] plus 2 antibiotics) fail in approximately 20%–30% of patients, and this rate might be even higher in clinical practice.[1,3] Antibiotic resistance to clarithromycin has been identified as 1 of the major factors affecting the ability to cure *H pylori* infection, and the rate of resistance to this antibiotic is steadily increasing in many geographic areas.[4]

The classic bismuth-containing quadruple therapy (PPI, bismuth, tetracycline, and metronidazole) has been recommended as a first-line option in areas with high clarithromycin resistance.[5,6] However, this regimen is relatively complex, and tetracycline is not available in many countries. Additionally, previous meta-analyses have questioned the advantage of this quadruple regimen over standard triple therapy in many contexts.[7–9]

Nonbismuth quadruple sequential and concomitant regimens, including a PPI, amoxicillin, clarithromycin, and a nitroimidazole, are increasingly used as first-line treatments for *H pylori* infection.[5,6,10,11] The concomitant regimen has a higher cure rate than standard triple and sequential therapies in regions with moderate to high clarithromycin resistance.[5,6,11] However, it is impaired by dual metronidazole-clarithromycin resistance.[12]

An acceptable anti–*H pylori* regimen is generally and currently defined as one that reliably offers a cure rate of at least 90%, to meet the existing practice in the field of other common bacterial infectious diseases.[13,14] Because of the frequent lack of susceptibility data in clinical practice, an optimal empiric therapy might be defined as one that reliable achieves high cure rates (eg, $\geq$90%) irrespective of the presence of antimicrobial resistance.

Bismuth is one of the few antimicrobials to which resistance is not developed.[15] In addition, bismuth has an additive or synergistic effect with several antibiotics that is independent of clarithromycin and/or metronidazole resistances.[15,16] Thus, combining bismuth and clarithromycin in the same regimen may be a promising option, as has been tested in previous literature.[17–26]

Therefore, the aim of the present study was to assess the effectiveness and safety of the combination of bismuth plus a standard clarithromycin-containing triple therapy in the eradication of *H pylori* as part of a large prospective multicenter registry.

Methods

European Registry on Helicobacter pylori Management

This manuscript is an interim analysis of the current dataset of the European Registry on *H pylori* Management (Hp-EuReg), an international multicenter prospective noninterventional registry that will last more than 10 years (start date 2013). It has been promoted by the European *Helicobacter* and Microbiota Study Group (www.helicobacter.org). The study protocol is found in Supplementary Appendix 1.

Study Aim

The Hp-EuReg has as 1 of its aims allowing investigators to propose specific subanalyses of data; the present study was performed after approval of the Scientific Committee of the Registry. The aim of this subanalysis was to evaluate the efficacy and safety in the eradication of *H pylori* of a first-line treatment combining bismuth salts with a standard triple therapy including a PPI, amoxicillin, and clarithromycin.

Data Extraction and Management

To perform the present analysis, a programmed data extraction was developed selecting all those cases treated with a combination of a PPI, bismuth salts, clarithromycin, and amoxicillin, registered in Europe up until December 2017. A list of prior data extractions published can be accessed in Supplementary Appendix 2. All

authors had access to the study data and reviewed and approved the final manuscript.

Ethics

The Hp-EuReg protocol was approved by the Ethics Committee of La Princesa University Hospital (Madrid, Spain), which acted as reference Institutional Review Board, was classified by the Spanish Drug and Health Product Agency, and was prospectively registered at ClinicalTrials.gov (NCT02328131). An addendum for a 10-year extension of the project was also approved. Patients were requested to sign an informed consent form, and data were anonymously registered.

Electronic Case Report Form

Study data were prospectively collected and managed using REDCap electronic data capture tools hosted at the Spanish Association of Gastroenterology (Asociación Española de Gastroenterología; www.aegastro.es).[27]

Variables and Outcomes

The electronic case report form registered 290 variables. All personal data were anonymized. Compliance was defined as having taken at least 90% of the prescribed drugs. Adverse events and compliance were evaluated through patient interrogation with both open-end questions and a predefined questionnaire. List of variables and options are shown in Supplementary Appendix 2. Dosages for different PPI molecules were standardized to milligram of omeprazole equivalence.[28] Patients were considered *H pylori*–positive if all validated performed tests by clinical practice were positive. In case of discrepancies between tests, these were noted in the registry and patients were excluded from analyses.

The intention-to-treat (ITT) analysis included all patients that had been registered up to December 2017; lost to follow-up cases were considered treatment failure. Per-protocol analysis included all cases that finished follow-up and took at least 90% of the treatment drugs, as defined in the approved protocol. The database underwent quality and monitoring controls as presented in the supplementary file.

Statistical Analyses

Continuous variables are presented in the manuscript as the arithmetic mean and respective standard deviation. Qualitative variables are presented as percentages and 95% confidence intervals (CIs). Significance was considered at $P < .05$. To evaluate the different factors and covariates that may affect treatment efficacy a logistic regression was performed using ITT eradication as dependent variable. The independent factors were gender, age, country, presence of adverse events, compliance with treatment, PPI type and dose, and length of treatment. Correlation between factors was controlled using covariates.

What You Need to Know

Background

Triple therapy with clarithromycin and amoxicillin provides sub-optimal eradication of *Helicobacter pylori* in clinical practice in Europe (approximately 80%). Non-bismuth quadruple concomitant therapy (adding metronidazole to triple therapy) is challenged by dual clarithromycin and metronidazole resistance. Addition of bismuth to levofloxacin triple therapy has produced promising results.

Findings

Addition of bismuth to triple therapy achieved acceptable intention to treat rates of *H pylori* eradication (approximately 90%). This treatment had an acceptable safety profile, comparable to that of other eradication treatments. Treatments lasting 14-days and including a double dose of proton pump inhibitor (equivalent to 40 mg omeprazole, twice daily) increased efficacy.

Implications for patient care

In regions with moderate to high rates of resistance and no susceptibility analysis in routine clinical practice, addition of bismuth to triple therapy offers an optimal alternative for first-line eradication of *H pylori*.

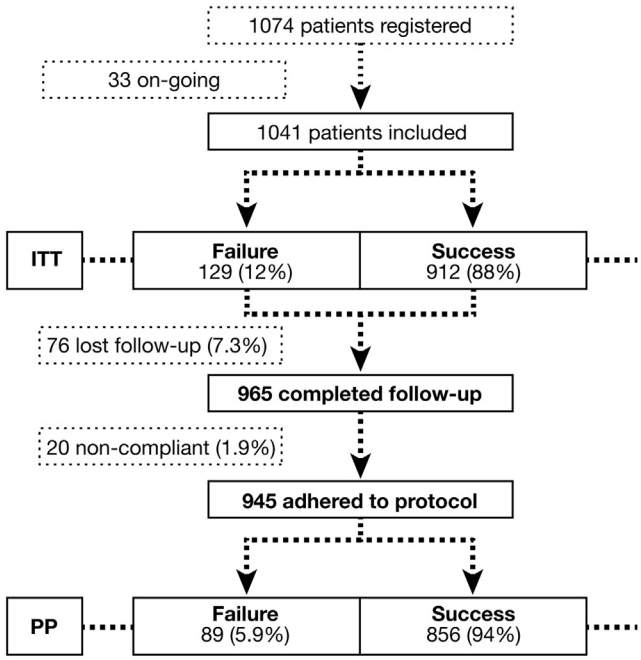

Figure 1. Patient flow chart diagram. PP, per-protocol.

Table 1. Basal Characteristics

			Spain		Russia		Ukraine	
Range	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age								
18–80	48.5	14.57	50.5	14.14	45.6	14.45	47.5	16.23
Group	n	%	n	%	n	%	n	%
Gender								
Females	677	59.4	392	59.2	249	61.9	36	46.8
Males	463	40.6	270	40.8	153	38.1	41	53.2
Ethnicity								
White	939	82.3	632	95.5	230	57.2	77	100.0
Asian	31	2.7	1	0.2	30	7.5	0	0.0
Black	6	0.5	6	0.9	0	0.0	0	0.0
Other	165	14.5	23	3.5	142	35.3	0	0.0
Diagnosis								
Endoscopy	840	73.6	428	64.7	335	83.3	77	100.0
Histology	580	50.8	326	49.2	196	48.8	58	75.3
RUT	327	28.7	153	23.1	155	38.6	19	24.7
Culture	48	4.2	6	0.9	42	10.4	0	0.0
Biochemical	16	1.4	0	0.0	16	4.0	0	0.0
Noninvasive	301	26.4	234	35.3	67	16.7	0	0.0
^{13}C UBT	269	23.6	200	30.2	69	17.2	0	0.0
Serology	20	1.8	1	0.2	18	4.5	1	1.3
Monoclonal SAT	149	13.1	52	7.9	97	24.1	0	0.0
At least 1 validated	1141	100.0	662	100.0	402	100.0	77	100.0
Concurrent drugs								
Any	495	43.4	345	52.1	75	18.7	75	97.4
PPI	311	27.3	202	30.5	34	8.5	75	97.4
Daily	231	20.2	143	21.6	13	3.2	75	97.4
On demand	80	7.0	59	8.9	21	5.2	0	0.0
AAS	78	6.8	43	6.5	35	8.7	0	0.0
Daily	76	6.7	41	6.2	35	8.7	0	0.0
On demand	2	0.2	2	0.3	0	0.0	0	0.0
NSAID	64	5.6	45	6.8	19	4.7	0	0.0
Daily	23	2.0	5	0.8	18	4.5	0	0.0
On demand	41	3.6	40	6.0	1	0.2	0	0.0
Statins	118	10.3	85	12.8	33	8.2	0	0.0
Daily	118	10.3	85	12.8	33	8.2	0	0.0
On demand	0	0.0	0	0.0	0	0.0	0	0.0
Indication								
Dyspepsia	645	56.5	438	66.2	207	51.5	53	68.8
Uninvestigated	206	18.1	176	26.6	30	7.5	53	68.8
Functional	439	38.5	262	39.6	177	44.0	0	0.0
Ulcer	202	17.7	71	10.7	107	26.6	24	31.2
Duodenal	149	13.1	52	7.9	77	19.2	20	26.0
Gastric	53	4.6	19	2.9	30	7.5	4	5.2
Other	294	25.8	153	23.1	88	21.9	0	0.0

AAS, acetylsalicylic acid; ^{13}C UBT, ^{13}C urea breath test; n, number of events; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor; RUT, rapid urease test; SAT, stool antigen test; SD, standard deviation.

Results

Baseline Characteristics

In the Hp-EuReg, 1221 first-line treatments fitting the regimen (bismuth plus standard triple therapy) have been registered, and 1141 were valid for inclusion analysis after monitoring and quality controls (662 from Spain, 402 from Russia, and 77 from Ukraine). Flow chart diagram is shown in Figure 1. Ages ranged from 18 to 86 years old with a mean age of 49 years and a standard deviation of 15; a total of 59% were women. Indications for treatment were: dyspepsia in 57% (uninvestigated 18%, functional 39%); ulcer in 18% (duodenal 13%, gastric 5%); and other in 26%, of which the most common were cancer prevention related, such as first-degree family member of a patient with gastric cancer (6%), and precancerous gastric lesions (6%). A complete description of baseline characteristics is shown in Table 1.

Table 2. Prescription Characteristics

			Spain		Russia		Ukraine	
	n	%	n	%	n	%	n	%
Length of treatment								
10 d	321	28.1	7	1.1	237	59.0	77	100.0
14 d	820	71.9	655	98.9	165	41.0	0	0.0
Proton pump inhibitors								
Omeprazole	208	18.2	100	15.1	92	22.9	16	20.8
20 mg	82	7.2	3	0.5	78	19.4	1	1.3
40 mg	126	11.0	97	14.7	14	3.5	15	19.5
Pantoprazole	122	10.7	13	2.0	48	11.9	61	79.2
20 mg	21	1.8	0	0.0	12	3.0	9	11.7
40 mg	101	8.9	13	2.0	36	9.0	52	67.5
Esomeprazole	647	56.7	548	82.8	99	24.6	0	0.0
20 mg	98	8.6	21	3.2	77	19.2	0	0.0
40 mg	549	48.1	527	79.6	22	5.5	0	0.0
Rabeprazole	164	14.4	1	0.2	163	40.5	0	0.0
20 mg	108	9.5	0	0.0	108	26.9	0	0.0
40 mg	56	4.9	1	0.2	55	13.7	0	0.0
Bismuth subcitrate								
120 mg/6 h	134	11.7	32	4.8	101	25.1	1	1.3
240 mg/12 h	1007	88.3	630	95.2	301	74.9	76	98.7

NOTE. All proton pump inhibitors were prescribed twice daily. Proton pump inhibitor equivalence to 20 mg of omeprazole: 89 mg of pantoprazole, 12.5 mg of esomeprazole, and 11.1 mg of rabeprazole.

Treatment Characteristics

Patients were prescribed this combination lasting 10 days in 321 cases (28%; 95% CI, 25%–30%), and 14 days in 820 cases (72%; 95% CI, 69%–74%). In all cases PPI, amoxicillin, and clarithromycin were prescribed twice daily. Dosing per intake was 1 g of amoxicillin and 500 mg of clarithromycin. Most treatments were prescribed with esomeprazole (647 cases; 57%), omeprazole was prescribed in 208 (18%), pantoprazole in 122 (11%), and rabeprazole in 164 (14%). PPIs were prescribed at half dose (equivalent to approximately 10 mg omeprazole twice daily) in 122 cases (10.7%), standard dose in 82 (7.2%), double dose in 332 (29.1%), or triple or more in 605 (53%; equivalent to more than the equivalent to 50 mg of omeprazole twice daily). Bismuth was prescribed as bismuth subcitrate either in 120-mg dose 4 times daily (134 cases; 12%) or 240 mg twice daily (1007 cases; 88%). Brand names or the generic classification of the pharmaceutical products were not systematically registered and could not be evaluated. A complete description of available prescription characteristics is shown in Table 2.

Efficacy

Of the 1141 included cases, 1002 were cured. ITT eradication efficacy was 88% (95% CI, 85%–92%). Per-protocol analysis achieved a 94% (95% CI, 90%–98%) eradication rate (Table 3). No studied demographic or disease factor was associated with higher or lower eradication rates. No differences in efficacy were found among geographic regions. Higher PPI doses (by omeprazole equivalence) offered higher eradication rates, increasing from 80.9% (95% CI, 76%–87%; n = 204) in 5–10 mg omeprazole-equivalent twice daily, 91% (95% CI, 89%–93%; n = 330) in 20–30 mg, to 92% (95% CI, 80%–94%; n = 604).

When prescribed in 10-day regimens, ITT cure rate was 79% (95% CI, 76%–83%); 14-day ITT eradication rate was higher (92%; 95% CI, 90%–95%). Eradication confirmatory tests were diverse but no difference on efficacy was found among methods, indicating nonexistent or insignificant biases because of potential accuracy differences (Table 4).

Safety and Adherence to Treatment

Adverse reactions to treatment were suffered by 36% (95% CI, 32%–40%) of cases, although most were mild (77%) and of short duration (mean, 6.5 days). No serious adverse reactions were documented. The full list of adverse events is shown in Table 5.

Compliant patients accounted for 98% (95% CI, 97%–100%) of the cases. Seventy-six patients (7.3%) did not return for eradication confirmation testing and were classified as lost to follow-up.

Logistic Regression

A logistic regression was performed to evaluate the effects of gender, age, country, underlying disease (ulcer vs dyspepsia), length of treatment, type and dose of PPI,

Table 3. Outcomes

				Spain			Russia			Ukraine		
	N	n	%	N	n	%	N	n	%	N	n	%
ITT												
Success	1141	1002	87.8	662	617	93.2	402	331	81.9	77	54	70.1
Failure		139	12.2		45	6.8		71	17.6		23	29.9
Positive test		80	7.0		41	6.2		33	8.2		6	7.8
Lost		59	5.2		4	0.6		38	9.4		17	22.1
10-d	321	252	78.8	7	6	85.7	237	192	81.4	77	54	70.1
14-d	820	750	91.6	655	611	93.3	165	139	84.8	0		
Omeprazole	208	181	87.0	100	95	95.0	92	75	81.5	16	11	68.8
20 mg	82	66	80.5	3	2	66.7	78	64	82.1	1	0	0.0
40 mg	126	115	91.3	97	93	95.9	14	11	78.6	15	11	73.3
Pantoprazole	122	84	68.9	13	11	84.6	48	30	62.5	61	43	70.5
20 mg	21	9	42.9	0			12	7	58.3	9	2	22.2
40 mg	101	75	74.3	13	11	84.6	36	23	63.9	52	41	78.8
Esomeprazole	647	598	92.4	548	510	93.1	99	88	88.9	0		
20 mg	98	90	91.8	21	21	100.0	77	69	89.6	0		
40 mg	549	508	92.5	527	489	92.8	22	19	86.4	0		
Rabeprazole	164	139	84.8	1	1	100.0	163	138	84.7	0		
20 mg	108	91	84.3	0			108	91	84.3	0		
40 mg	56	48	85.7	1	1	100.0	55	47	85.5	0		
Bismuth dose												
240 mg bid	1007	879	87.3	630	587	93.2	301	238	79.1	76	54	71.1
120 mg qid	134	123	91.8	32	30	93.8	101	93	92.1	1	0	0.0
Compliance[a]	1141	1119	98.1	662	652	98.5	402	390	96.5	77	77	100.0
10-d	320	314	98.1	7	6	85.7	236	231	97.9	77	77	100.0
14-d	819	803	98.0	655	646	98.6	164	157	95.7	0		
PP												
Success	1068	993	93.0	648	609	94.0	360	330	91.7	60	54	90.0
Failure		75	7.0		39	6.0		30	8.3		6	10.0
10-d	279	252	90.3	6	6	100.0	213	192	90.1	60	54	90.0
14-d	797	741	93.0	642	603	93.9	145	138	95.2	0		
Omeprazole	197	180	91.4	99	94	94.9	86	75	87.2	12	11	91.7
20 mg	169	156	92.3	96	92	95.8	73	64	87.7	0		
40 mg	28	24	85.7	3	2	66.7	13	11	84.6	12	11	91.7
Pantoprazole	93	83	89.2	12	11	91.7	33	29	87.9	48	43	89.6
20 mg	14	9	64.3	0			10	7	70.0	4	2	50.0
40 mg	79	74	93.7	12	11	91.7	23	22	95.7	44	41	93.2
Esomeprazole	627	591	94.3	536	503	93.8	91	88	96.7	0		
20 mg	93	90	96.8	21	21	100.0	72	69	95.8	0		
40 mg	534	501	93.8	515	482	93.6	19	19	100.0	0		
Rabeprazole	151	139	92.1	1	1	100.0	150	138	92.0	0		
20 mg	100	91	91.0	0			100	91	91.0	0		
40 mg	51	48	94.1	1	1	100.0	50	47	94.0	0		
Bismuth dose												
240 mg bid	941	871	92.6	617	580	94.0	264	237	89.8	60	54	90.0
120 mg qid	127	122	96.1	31	29	93.5	96	93	96.9	0		

NOTE. All proton pump inhibitors were prescribed twice daily. Proton pump inhibitor equivalence to 20 mg of omeprazole: 89 mg pantoprazole, 12.5 mg of esomeprazole, and 11.1 mg of rabeprazole.

bid, twice daily; ITT, intention-to-treat; N, number of cases in the category; n, number of cases cured (except in "failure," "positive test," and "lost" rows); PP, per-protocol; qid, four times daily.

[a]Compliance defined as taking >90% of study drugs.

dosing of bismuth, presence of adverse events, and compliance on the likelihood that a patient was cured with treatment.

Compliance was the independent factor more strongly associated with higher eradication rates (odds ratio [OR], 13; 95% CI, 5.3–32). Increasing acid inhibition from a bioequivalent dose of 10 mg of omeprazole (half dose) to 20 mg (standard), or to 40 mg (double) was also associated with higher efficacy; respective ORs were 4.7 (95% CI, 1.8–12) and 9.5 (95% CI, 3.7–24). Longer treatment durations were also associated with higher ITT (OR, 2.0; 95% CI, 1.3–3.2).

A covariate correlation was identified between acid inhibition and length of treatment. This association showed a superiority of 14-day regimens including double-dose PPI than those of 10-day at half doses (OR,

Table 4. Confirmatory Tests

				Spain			Russia			Ukraine		
	N	n	%	N	n	%	N	n	%	N	n	%
Eradication confirmation test	1141			662			402			77		
^{13}C UBT		748	66		643	97		105	26		0	0
Serology		11	0.96		0	0		11	3		0	0
SAT		295	26		9	1		226	56		60	78
Histology		136	12		12	2		124	31		0	0
RUT		12	1.1		2	0		10	2		0	0
Eradication sensitivity analysis by eradication confirmation test[a]												
UBT only	718	672	94	625	590	94	93	82	88			
SAT only	188	169	90	4	3	75	124	112	90	60	54	90
SAT and histology	91	90	99	0			91	90	99			
Histology only	32	30	94	9	9	100	23	21	91			
UBT and SAT	14	13	93	5	4	80	9	9	100			
RUT only	8	4	50	2	1	50	6	3	50			
Serology and histology	8	8	100	0			8	8	100			
UBT and histology	3	2	67	3	2	67						
SAT and RUT	2	2	100	0			2	2	100			
UBT and serology	1	1	100	0			1	1	100			
Histology and RUT	1	0	0	0			1	0	0			
Serology only[b]	2	0	0	0			2	0	0			
No test[b]	59											

^{13}C UBT, ^{13}C urea breath test; N, sample number in the group; n, number of events; RUT, rapid urease test; SAT, stool antigen test.
[a]Because this can only be evaluated in patients that have completed follow-up, it is only performed by per-protocol analysis.
[b]Considered lost to follow-up because of lack of or invalid eradication confirmatory test.

2.4; 95% CI, 1.5–4.0). It also showed that increasing acid inhibition (doubling the dose) had higher impact on 10-day regimens (6.4%–38% relative increase by ITT) than on 14-day (9.5%–16%).

No other factor included in the model was associated with the likelihood of eradication.

Discussion

The present study reports *H pylori* ITT cure rates with bismuth plus PPI therapy around 90% in a large cohort of naive patients mainly from Spain. Of note, mean cure rates for 10-day triple therapy in Spain were recently estimated to be 70%–80%, similar to those reported in the database of the Hp-EuReg.[19] Therefore, addition of bismuth salts to triple therapy in clinical practice resulted in a potential therapeutic gain (10%–20%) in populations with moderate to high clarithromycin resistance.

Several studies have evaluated the effectiveness of adding bismuth to a standard triple therapy in different contexts of resistance, with generally encouraging results (Table 6).[17–25] However, the sample size of these studies has usually been small, and only a few prescribed this quadruple therapy for 14 days.[18,21–24] However, all the previous studies have been conducted in Asia, so the experience in Western countries has been, up to now, inexistent.

In the present study, the treatment was prescribed in 10- or 14-day regimens. Several meta-analyses have

Table 5. Adverse Events to Treatment

Adverse events	n	%	Mild, %	Moderate, %	Severe, %	Length, *d*[a]
Any	377	36	76	23	0.9	6
Metallic taste	147	14	80	20	0.7	7
Diarrhea	105	10	75	24	0.9	5
Nausea	87	8.3	65	32	3.4	9
Vomiting	46	4.4	57	42	0.0	3
Abdominal pain	52	5.0	81	15	3.7	6
Asthenia	23	2.2	75	17	8	5
Heartburn	6	0.6	50	50	10.0	10
Anorexia	5	0.5	40	60	0.0	6
Other	113	10.8				

[a]Mean length of adverse events.

Table 6. Revision From Literature: Efficacy of Standard Triple Therapy (Proton Pump Inhibitor, Clarithromycin, and Amoxicillin) Plus Bismuth as a First-Line Treatment for *Helicobacter pylori* Infection

Author	Year	Country	N	Treatment	Duration (*d*)	Eradication n/N (% ITT)
Ergúl et al[17]	2013	Turkey	97	L 30 mg/12 h A 1 g/12 h C 500 mg/12 h Bi 300 mg/12 h	14	88/97 (91)
Fakheri et al[18]	2001	Iran	55	O 20 mg/12 h A 1 g/12 h C 500 mg/12 h Bi 240 mg/12 h	14	47/55 (85)
Liang et al[19]	2012	China	156	O 20 mg/12 h A 1 g/12 h C 500 mg/12 h Bi 110 mg/12 h	10	106/156 (68)
Mu et al[20]	2007	China	35	L 30 mg/12 h A 1 g/12 h C 250 mg/12 h Bi 220 mg/12 h	7	26/30 (86)
Shavakhi et al[21]	2013	Iran	86	O 20 mg/12 h A 1 g/12 h C 500 mg/12 h Bi 240 mg/12 h	14	70/86 (81)
Srinarong et al[22]	2014	Thailand	24	L 30 mg/12 h A 1 g/12 h C (long-acting) 1 g/12 h Bi 1048 mg/12 h	7	23/25 (92)
Srinarong et al[22]	2014	Thailand	24	L 30 mg/12 h A 1 g/12 h C (long-acting) 1 g/12 h Bi 1048 mg/12 h	14	24/25 (96)
Sun et al[23]	2010	China	80	O 20 mg/12 h A 1 g/12 h C 500 mg/12 h Bi 220 mg/12 h	7	64/80 (80)
Sun et al[23]	2010	China	80	O 20 mg/12 h A 1 g/12 h C 500 mg/12 h Bi 220 mg/12 h	14	75/80 (94)
Zhang et al[24]	2015	China	107	L 30 mg/12 h A 1 g/12 h C 500 mg/12 h Bi 220 mg/12 h	14	95/107 (89)
Zhou et al[25]	2014	China	350	E 20 mg/12 h A 1 g/12 h C 500 mg/12 h Bi 220 mg/12 h	10	271/350 (77)

A, amoxicillin; Bi, bismuth; C, clarithromycin; E, esomeprazole; ITT, intention-to-treat; L, lansoprazole; O, omeprazole.

demonstrated that increasing the duration of PPI-based triple therapy increases *H pylori* eradication rates.[29–33] Consensus conferences have suggested that the treatment duration of PPI-clarithromycin-based triple therapy should be extended to 14 days, a statement that was extensive to all treatment regimens.[5,6]

Sun et al[23] randomized patients to receive a regimen with PPI-clarithromycin-amoxicillin plus bismuth for either 7 or 14 days with higher eradication rate in longer treatments (94% vs 80%). The advantage of the 14-day quadruple therapy was related to higher eradication rates among patients with clarithromycin-resistant *H pylori*, in whom the infection was achieved in 85% of the cases.[23] These results suggest that addition of bismuth and prolonging treatment duration can cure some resistant *H pylori*.[15] In another study, Zhang et al[24] reported a relatively high cure rate (89%) with this 14-day bismuth/clarithromycin-containing regimen despite the high clarithromycin resistance (26%) in their study.

There is indirect and direct evidence that high-dose PPI can improve the cure rates of *H pylori* eradication treatment when eradication rate is low, generally in regions with high antibiotic resistance.[6,34–36] In our study, the use of double-dose PPI (equivalent to 40 mg omeprazole twice daily) was also associated with higher

eradication rates (OR, 4.7), confirming the improvement because of higher acid inhibition.

Adverse events were reported in a high proportion (36%) of our patients. However, most of them were considered clinically irrelevant, such as metallic taste (18%) or mild diarrhea (11%). Thus, in only 1% of the cases were adverse events classified as intense, and none of them was classified as a serious adverse event. Treatment withdrawal because of adverse events occurred in only 1.3% of patients, in agreement with previous studies.[17–25]

In our study, compliance with the bismuth quadruple regimen was excellent, with 98% of patients taking all the medications correctly. Because *H pylori* resistance to bismuth is seldom observed, addition of this antimicrobial agent to a triple standard therapy may be preferred over metronidazole (eg, concomitant therapy) in geographic areas with increasing resistance rates to clarithromycin and metronidazole. Finally, the low cost of the regimen evaluated in the present study is an additional advantage to take into consideration.

This study poses some limitations that should be taken in consideration. As any clinical practice registry in which prescription is decided in the outpatient clinic, there are high risks of bias in the allocation of patients to different treatment strategies. As a clinical practice registry some information is unavailable, such as commercial names of the drugs used, so it is not possible to check the impact of generic drugs or different brands. The major drawback of our study is that culture was not performed, and therefore information on the prevalence of antibiotic resistance is lacking. Additionally, the impact of antibiotic resistance to clarithromycin in the prescribed therapy could not be evaluated. Resistance of *H pylori* to clarithromycin is increasing worldwide, mainly in countries with a high consumption of these drugs. A recent multicenter study investigated the rate of primary antibiotic resistance of *H pylori* in 2008 and 2009 in 18 European countries and found the rate for clarithromycin to be 14% in Spain.[4] More recently, this figure has been increased up to 18% in this country.[37] In any case, readers should be aware that the potential beneficial effect of bismuth addition, and lengthening treatment or increasing inhibitory potency, will have lower impacts in regions were basal treatment obtains high eradication rates (ie, in low-resistance areas).

In summary, bismuth coadministrated with antibiotics against *H pylori* can have an additive or synergistic effect on antibiotics and, consequently, improve the efficacy of eradication treatment. Our study shows that, especially in patients without antibiotic susceptibility testing, the combination of bismuth plus a standard clarithromycin-containing triple therapy, especially if given for 14 days and with high-dose PPI, is an effective and safe empirical strategy in countries with intermediate to high clarithromycin resistance rates.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2019.03.048.

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Conflicts of interest
These authors disclose the following: Adrian G. McNicholl has received wages from Allergan for formative actions. Ángeles Pérez-Aisa has served as a speaker; and has received wages from Allergan, Norgine, and Casen-Recordati for formative actions and advisory for Shionogi. Javier Molina-Infante has served as a speaker; and has received wages from Allergan, Almirall, and Casen Recordati for formative actions. Javier Alcedo has received wages from Allergan, Almirall, and Casen Recordati for formative actions. Javier P. Gisbert has served as a speaker, a consultant, and advisory member for or has received research funding from Almirall, Nycomed, AstraZeneca, Casen Recordati, and Allergan. The remaining authors disclose no conflicts.