

## SUPPLEMENTARY MATERIAL

### Supplementary file S1. Contribution log.

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**Supplementary file S2: Proton pump inhibitor (PPI) categories: low, standard and high acid inhibition [1, 2].**

**Low dose PPI:** ranging from 4.5 to 27 mg omeprazole equivalents, b.i.d. (i.e. 20 mg omeprazole equivalents, b.i.d.).

**Standard dose PPI:** ranging from 32 to 40 mg omeprazole equivalents, b.i.d. (i.e. 40 mg omeprazole equivalents, b.i.d.).

**High dose PPI:** ranging from 54 to 128 mg omeprazole equivalents, b.i.d. (i.e. 60 mg omeprazole equivalents, b.i.d.).

1. Kirchheiner J, Glatt S, Fuhr U, et al. Relative potency of proton-pump inhibitors-comparison of effects on intragastric pH. *Eur J Clin Pharmacol* 2009;65(1):19-31.
2. Graham DY, Lu H, Dore MP. Relative potency of proton-pump inhibitors, *Helicobacter pylori* therapy cure rates, and meaning of double-dose PPI. *Helicobacter* 2019;24(1):e12554.

**Table S1.** Inclusion of patients per country.

<b>Country</b>	<b>Frequency (N)</b>	<b>Percentage (%)</b>
Spain	6313	59
Slovenia	1268	12
Italy	602	5.6
Russia	595	5.6
Ukraine	533	5
Lithuania	225	2.1
Portugal	184	1.7
Greece	178	1.7
Latvia	162	1.5
United kingdom	152	1.4
Norway	136	1.3
Israel	75	0.7
Croatia	51	0.5
Turkey	49	0.5
Romania	47	0.4
France	31	0.3
Hungary	25	0.2
Germany	21	0.2
Bulgary	17	0.2
Ireland	10	0.1
Belgium	5	0.0
Denmark	4	0.0
Serbia	4	0.0
Switzerland	3	0.0
Czech republic	2	0.0
<b>Total</b>	<b>10,692</b>	<b>100</b>

N: total number of patients included.

**Table S2.** Distribution of eradication therapies prescribed according to the statin used.

			Simvastatin	Atorvastatin	Rosuvastatin N	Others
			N (%)	N (%)	(%)	N (%)
Empirical pre- scription	First-line	N included	101 (100)	83 (100)	28 (100)	12 (100)
		PPI+C+A	42 (42)	36 (43)	10 (36)	4
		PPI+C+M/T	11 (11)	9 (11)	5 (18)	2
		PPI+M/T+A	--	1 (1)	--	--
		PPI+Mx+A	1 (1)	--	--	--
		PPI+C+A+M/T (seq)	7 (7)	5 (6)	3 (11)	3
		PPI+C+A+M/T (conc)	3 (33)	20 (24)	6 (21)	3
		PPI+L+A	1 (1)	1 (1)	1 (4)	--
		PPI+C+A+B	2 (2)	5 (6)	--	--
		PPI + single capsule*	2 (2)	6 (7)	2 (7)	--
		PPI+M/T+Tc+B	1 (1)	--	--	--
		PPI+L+A+B	1 (1)	--	--	--
	PPI+A	--	--	1 (4)	--	
	Rescue lines	N included	34 (100)	23 (100)	7 (100)	3 (100)
		PPI+C+A	1 (3)	--	--	--
		PPI+C+M/T	1 (3)	--	--	--
		PPI+L+A	23 (68)	13 (57)	3 (43)	1 (33)
		PPI+Mx+A	1 (3)	1 (4)	--	1 (33)
		PPI+RF+A	--	1 (4)	--	1 (33)
		PPI+M/T+A	1 (3)	--	--	--
		PPI+C+A+M/T (seq)	1 (3)	--	--	--
		PPI+C+A+M/T (conc)	1 (3)	2 (9)	1 (14)	--
PPI+C+A+B		--	1 (4)	--	--	
PPI+L+A+B		1 (3)	--	--	--	
PPI + single capsule*		--	2 (9)	1 (14)	--	
PPI+M/T+Tc+B	2 (6)	2 (9)	--	--		
PPI+M/T+D+B	1 (3)	--	--	--		
Other	1 (3)	1 (4)	2 (28)	--		
Culture-guided prescription	First-line	N included	19 (100)	24 (100)	2 (100)	2 (100)
		PPI+C+A	14 (74)	16 (67)	2 (100)	2 (100)
		PPI+M/T+A	--	1 (4)	--	--
		PPI+RF+A	--	1 (4)	--	--
		PPI+C+A+M/T (seq)	1 (5)	--	--	--
		PPI+C+A+M/T (conc)	1 (5)	4 (17)	--	--
		PPI+C+A+B	1 (5)	2 (8)	--	--
		PPI + single capsule*	2 (2)	--	--	--
	Other	2 (10)	--	--	--	
	Rescue lines	N included	1 (100)	2 (100)	--	--
		PPI+RF+A	--	1 (50)	--	--
		Other	1 (100)	1 (50)	--	--

N: total number of patients included. %: proportion of patients receiving the eradication treatment according to the statin use. Others: includes pravastatin, pitavastatin, lovastatin or fluvastatin. PPI: proton pump inhibitor. C: clarithromycin. A: amoxicillin. M: metronidazole. T: tinidazole. Mx: moxifloxacin. Seq: sequential administration. Conc: concomitant administration. L: levofloxacin. B: bismuth. Single capsule\*: three-in-one single capsule containing bismuth, tetracycline and metronidazole. Tc: tetracycline. RF: rifabutin. D: doxycycline. Others: other minority therapies. --: No patients available.

**Table S3.** Adverse events reported in each group according to severity.

AE	Empirical Prescription				Culture-Guided Prescription			
	First-line		Rescue-line		First-line		Rescue-line	
	Statin-users N (%)	Non-statin users N (%)	Statin-users N (%)	Non-statin users N (%)	Statin-users N (%)	Non-statin users N (%)	Statin-users N (%)	Non-statin users N (%)
<b>Total N</b>	361	1,164	199	438	26	81	8	20
<b>Dysgeusia</b>	112	477	36	104	7	28	2	2
Mild	81 (72)	295 (62)	23 (64)	61 (59)	5 (72)	11 (39)	1 (50)	2 (100)
Moderate	28 (25)	160 (33)	12 (33)	37 (35)	1 (14)	16 (57)	1 (50)	0
Severe	3 (3)	22 (5)	1 (3)	6 (6)	1 (14)	1 (4)	0	0
<b>Diarrhea</b>	126	357	108	187	12	21	0	8
Mild	71 (56)	232 (65)	29 (27)	69 (37)	8 (67)	9 (43)	0	5 (63)
Moderate	51 (41)	115 (32)	79 (73)	111 (59)	4 (33)	11 (52)	0	0
Severe	4 (3)	10 (3)	0	7 (4)	0	1 (5)	0	3 (37)
<b>Nausea</b>	114	395	83	178	6	20	4	5
Mild	61 (53)	247 (63)	40 (48)	84 (47)	5 (83)	13 (65)	3 (75)	3 (60)
Moderate	50 (44)	123 (31)	42 (51)	89 (50)	1 (17)	6 (30)	1 (25)	2 (40)
Severe	3 (3)	25 (6)	1 (1)	5 (3)	0	1 (5)	0	0
<b>Vomits</b>	40	136	44	99	1	6	0	1
Mild	19 (47)	86 (63)	27 (61)	58 (59)	1 (100)	5 (83)	0	1 (100)
Moderate	21 (53)	37 (27)	17 (39)	38 (38)	0	1 (17)	0	0
Severe	0	13 (10)	0	3 (3)	0	0	0	0
<b>Dyspepsia</b>	39	141	35	77	2	11	1	1
Mild	21 (54)	63 (45)	14 (40)	25 (33)	2 (100)	6 (55)	0	1 (100)
Moderate	15 (38)	68 (48)	21 (60)	51 (66)	0	4 (36)	1 (100)	0
Severe	3 (8)	10 (7)	0	1 (1)	0	1 (9)	0	0
<b>Heartburn</b>	18	45	17	22	0	4	0	1
Mild	11 (61)	14 (31)	1 (6)	3 (14)	0	2 (50)	0	1 (100)
Moderate	7 (39)	24 (53)	13 (76)	19 (86)	0	2 (50)	0	0
Severe	0	7 (16)	3 (18)	0	0	0	0	0
<b>Abdominal pain</b>	50	196	24	57	2	17	1	3
Mild	29 (58)	132 (67)	14 (58)	32 (56)	1 (50)	13 (76)	1 (100)	0
Moderate	18 (36)	48 (25)	10 (42)	21 (37)	1 (50)	3 (18)	0	1 (33)
Severe	3 (6)	16 (8)	0	4 (7)	0	1 (6)	0	2 (67)
<b>Asthenia</b>	52	155	41	66	3	7	0	3
Mild	23 (44)	66 (42)	8 (19)	24 (36)	3 (100)	3 (43)	0	1 (33)
Moderate	27 (52)	71 (46)	27 (66)	39 (59)	0	4 (57)	0	2 (67)
Severe	2 (4)	18 (12)	6 (15)	3 (5)	0	0	0	0
<b>Anorexia</b>	28	88	55	72	1	6	2	4
Mild	9 (32)	25 (28)	10 (18)	9 (12)	1 (100)	2 (33)	1 (50)	2 (50)
Moderate	16 (57)	55 (63)	39 (71)	56 (78)	0	2 (33)	1 (50)	2 (50)
Severe	3 (11)	8 (9)	6 (11)	7 (10)	0	2 (33)	0	0

Rescue-lines: embracing therapies prescribed from 2<sup>nd</sup>-6<sup>th</sup> eradication attempt. AE: adverse events. N: total number of patients included. %: proportion of patients included.

**Table S4.** Effectiveness and safety in empirical therapies according to the type of statin used.

			Simvastatin	Atorvastatin	Rosuvastatin	Others	p-value	
First-line (N =224)	Overall	mITT E	N (%)	83 (87)	69 (92)	22 (81.5)	11 (100)	0.278
			95% CI	79-93	83-97	62-94	NA	
	AE		N (%)	15 (15)	10 (12)	5 (18)	2 (18)	0.876
			95% CI	9-23	6-22	6-37	2-52	
	PPI+C+A	mITT E	N (%)	33 (82.5)	26 (90)	7 (70)	3 (100)	0.376
			95% CI	67-93	73-98	35-93	NA	
	AE		N (%)	3 (7)	3 (9)	2 (20)	0 (0)	0.595
			95% CI	2-19	2-23	3-56	--	
	PPI+C+A+M/ T (conc)	mITT E	N (%)	30 (97)	19 (95)	5 (100)	3 (100)	0.875
			95% CI	83-100	75-100	NA	NA	
	AE		N (%)	8 (24)	3 (15)	1 (17)	1 (33)	0.804
			95% CI	11-42	3-38	1-64	1-91	
	PPI+C+M/T	mITT E	N (%)	10 (91)	7 (88)	5 (100)	2 (100)	0.712
			95% CI	59-100	47-100	NA	NA	
	AE		N (%)	3 (27)	2 (25)	2 (40)	1 (50)	0.872
			95% CI	6-61	3-65	5-85	1-99	
	PPI+C+A+M/ T (seq)	mITT E	N (%)	5 (83)	5 (100)	3 (100)	3 (100)	0.532
			95% CI	36-100	NA	NA	NA	
AE		N (%)	0 (0)	0 (0)	0 (0)	0 (0)	NA	
		95% CI	--	--	--	--		
PPI+ single- capsule*	mITT E	N (%)	2 (100)	6 (100)	1 (50)	NA	0.155	
		95% CI	NA	NA	*1-99	NA		
AE		N (%)	0 (0)	0 (0)	0 (0)	NA	NA	
		95% CI	--	--	--	NA		
Rescue lines (N = 67)	Overall	mITT E	N (%)	23 (72)	20 (87)	5 (71)	3 (100)	0.318
			95% CI	53-86	66-97	29-96	NA	
	AE		N (%)	3 (9)	6 (26)	0 (0)	0 (0)	0.104
			95% CI	2-24	10-48	--	--	
	PPI+L+A	mITT E	N (%)	15 (71)	11 (85)	1 (33)	1 (100)	0.297
			95% CI	48-89	55-98	1.91	NA	
AE		N (%)	3 (13)	3 (23)	0 (0)	0 (0)	0.581	
		95% CI	3-34	5-54	--	--		

Only therapies administered to at least 10 patients with the exact statin specified are included. mITT E: modified intention-to-treat effectiveness. AE: adverse events. N: total number of patients included. %: proportion of patients presenting with effectiveness or the adverse event. CI: confidence interval. PPI: proton pump inhibitor. C: clarithromycin. A: amoxicillin. M: metronidazole. T: tinidazole. Single capsule\*: three-in-one single capsule containing bismuth, tetracycline and metronidazole. Conc: concomitant administration. Seq: sequential administration. L: levofloxacin. NA: not applicable. --: No patients available in analysis.

**Table S5.** Effectiveness and safety in culture-guided therapies according to the type of statin used.

				<b>Simvastatin</b>	<b>Atorvastatin</b>	<b>Rosuvastatin</b>	<b>Others</b>	<b>p-value</b>
First-line (N = 47)	Overall	mITT E	N (%)	15 (88)	22 (96)	2 (100)	2 (100)	0.714
			95% CI	64-99	78-100	NA	NA	
	AE	N (%)	0 (0)	4 (17)	0 (0)	0 (0)	0.125	
		95% CI	--	5-39	--	--		
	PPI+C+A	mITT E	N (%)	12 (100)	14 (93)	2 (100)	2 (100)	0.685
			95% CI	NA	68-100	--	--	
AE	N (%)	0 (0)	2 (13)	0 (0)	0 (0)	0.364		
	95% CI	--	2-41	--	--			
Rescue lines (N = 3)	Overall	mITT E	N (%)	1 (100)	1 (100)	NA	NA	NA
			95% CI	NA	NA	NA	NA	
	AE	N (%)	0 (0)	1 (100)	NA	NA	1	
		95% CI	--	NA	NA	NA		

Only therapies administered to at least 10 patients with the exact statin specified are included. mITT E: modified intention-to-treat effectiveness. AE: adverse events. N: total number of patients included. %: proportion of patients presenting with effectiveness or the adverse event. CI: confidence interval. PPI: proton pump inhibitor. C: clarithromycin. A: amoxicillin. NA: not applicable. --: No patients available in analysis.