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ORIGINAL ARTICLE

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Probiotic supplementation with Lactobacillus plantarum and Pediococcus acidilactici for *Helicobacter pylori* therapy: A randomized, double-blind, placebo-controlled trial

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Abstract

Objective: To evaluate the safety, tolerability and efficacy of a probiotic supplementation for *Helicobacter pylori (H. pylori)* eradication therapy.

Design: Consecutive adult *naive* patients with a diagnosis of *H. pylori* infection who were prescribed eradication therapy according to clinical practice (10-day triple or nonbismuth quadruple concomitant therapy) randomly received probiotics (1×10^9 colony-forming units each strain, *Lactobacillus plantarum* and *Pediococcus acidilactici*) or matching placebo. Side effects at the end of the treatment, measured through a modified De Boer Scale, were the primary outcome. Secondary outcomes were compliance with therapy and eradication rates.

Results: A total of 209 patients (33% triple therapy, 66% non-bismuth quadruple therapy) were included [placebo (n = 106) or probiotic (n = 103)]. No differences were observed regarding side effects at the end of the treatment between groups (β −0.023, *P* 0.738). Female gender (*P* < 0.001) and quadruple therapy (*P* 0.007) were independent predictors of side effects. No differences in compliance were observed, regardless of the study group or eradication therapy. Eradication rates were similar between groups [placebo 95% (95% confidence interval (CI), 89% to 98%) vs probiotic 97% (95% CI, 92% to 99%), *P* 0.721]. There were no relevant differences in cure rates (>90% in all cases) between triple and quadruple concomitant therapy.

Conclusion: Probiotic supplementation containing *Lactobacillus Plantarum* and *Pediococcus acidilactici* to *H. pylori* treatment neither decreased side effects nor improved compliance with therapy or eradication rates.

KEYWORDS

H. pylori, *Lactobacillus plantarum*, *Pediococcus acidilactici*, probiotics, randomized clinical trial

Adrian G. McNicholl and Javier Molina-Infante equally contributed to the development of the project and to the analysis and drafting of the manuscript.

1 | INTRODUCTION

Helicobacter pylori infection is associated with several clinical conditions, such as chronic gastritis, peptic ulcer disease, and gastric cancer, and therefore requires adequate eradication therapy.[1,2] The efficacy of standard triple therapy (ie, a regimen containing proton-pump inhibitor [PPI], clarithromycin and amoxicillin or metronidazole) has notably decreased over the past decade, although with geographical variations.[1,2] Rising antimicrobial resistance and antibiotic-related side effects are the most important factors explaining this decreasing efficacy.[1] Increasing PPI doses or the length of treatment, switching to quadruple regimens by adding an antibiotic, performing susceptibility testing prior to antibiotic therapy or probiotic supplementation have all been suggested as adjuvant interventions to increase the efficacy of triple therapy.[3,4]

Because many of the gastrointestinal side effects related to the use of eradication therapy are likely associated with the modification of the gastrointestinal microbiota, restoration with adjuvant probiotics may be an alternative to reduce these side effects, theoretically improving treatment compliance and, ultimately, eradication rates.[1] A number of recent meta-analyses have shown that several probiotic strains (including *Lactobacillus*, *Bifidobacterium*, *Saccharomyces boulardii*, fermented milk and bovine lactoferrin) may increase eradication rates compared to placebo in children and adults.[5-18] However, the impact of probiotics on antibiotic-associated adverse effects and tolerability is more heterogeneous, with meta-analyses showing no significant differences in the occurrence of side effects,[6-8,12] a positive impact limited to diarrhea [9,13,14] or no differences in compliance.[17]

Lactobacillus plantarum and *Pediococcus acidilactici* are two probiotic strains that exhibit in vitro activity against *H. pylori*.[19,20] However, clinical information on their use as adjuvant treatment for eradication therapy is lacking. The aim of this randomized, double-blind, placebo-controlled study was to evaluate the effect of a probiotic supplement containing *Lactobacillus plantarum* and *Pediococcus acidilactici* on the occurrence of side effects of *H. pylori* eradication therapy. We also evaluated the effect of this adjuvant therapy on compliance with therapy and *H. pylori* eradication rates.

2 | METHODS

2.1 | Participants

Between January 2013 and April 2014, 17 Spanish centers (including hospital outpatient clinics, primary care centers and private clinics) recruited patients under these inclusion criteria: aged 18-70 years; diagnosed with *H. pylori* infection within 12 months of study entry by ^{13}C-urea breath test, rapid urease test or histological examination; presented an otherwise good general health status but requiring eradication therapy according to the investigators' judgment; ability to understand the study requirements; and provided written informed consent. Patients were excluded if they met any of the following criteria: history of gastrointestinal surgery (except for appendectomy or herniorraphy), allergy to penicillin or any contraindication to the eradication therapy prescribed, pregnant or lactating women, prior eradication therapy for *H. pylori*, and history of any severe disease or condition that might interfere with the study objectives. Patients were also excluded if they had taken any probiotic, antibiotic, or investigational product during the week, month, or trimester prior to inclusion, respectively.

The study was approved by the Ethics Committee of each participant site and was conducted in accordance with the principles of Good Clinical Practice and those contained in the Declaration of Helsinki. Every subject provided a written informed consent.

2.2 | Study design

Physicians prescribed an eradication therapy according to their routine clinical practice. Eradication regimens used in the study were 10-day triple therapy (PPI at standard doses (eg, omeprazole 20 mg b.d. or equivalent), clarithromycin 500 mg and amoxicillin 1 g, all taken twice daily), or 10-day nonbismuth quadruple concomitant therapy (PPI at standard doses, clarithromycin 500 mg, metronidazole 500 mg, and amoxicillin 1 g, all taken twice daily for 10 days). All medications were taken concurrently after breakfast and dinner.

This was a randomized, parallel-group, double-blind and placebo-controlled study. After prescription of one of the aforementioned eradication regimens, patients were randomly allocated in a 1:1 ratio to receive either the investigational product or placebo along with *H. pylori* therapy. The randomization sequence was generated using SAS ® 9.1.3 (SAS Institute Inc., Cary, NC, USA) and was stratified by site and type of eradication therapy prescribed. The treatment was assigned centrally by a clinical research organization, assuring the concealment of randomization.

The investigational product consisted of a probiotic formula combining two bacterial strains (1×10^9 colony-forming units [CFU] for each strain, *Lactobacillus plantarum* CETC7879 and *Pediococcus acidilactici* CETC7880), which were included in a capsule. To maintain the blinding, patients in the control group received placebo included in identical capsules. Both groups had to take 1 capsule every day after breakfast. Use of antibiotics other than those included in the eradication therapy and other probiotics distinct from the investigational product were forbidden during the study. Compliance with antibiotic therapy and the investigational product was evaluated by means of a patient's diary and product accountability, while compliance with eradication therapy was evaluated through a questionnaire.

2.3 | Study evaluations and outcomes

Patients were evaluated at 4 visits: screening (10-30 days before the baseline visit), baseline, end of treatment/efficacy (10-15 days after the baseline visit) and follow-up (6 ± 2 weeks after treatment completion). A detailed timeline of the study is summarized in Figure 1.

Patients were diagnosed with one (or more) of three validated methods, ^{13}C-urea breath test, rapid urease test or histology, depending on the clinical situation of the patient (if endoscopy was, or not, required due to alarm symptoms, age or desire of the patient) following national recommendations on the management of dyspepsia. Eradication confirmation test was also performed following standard recommendations: ^{13}C-urea breath test more than 4 weeks after treatment, unless a follow-up endoscopy was indicated for ulcer healing, or other risk indications.

Patients who had filled in at least 80% of baseline symptoms and type of stools on the baseline modified De Boer scale and baseline Bristol Stool Chart (see below) were prescribed an eradication therapy and randomized to receive the investigational product or placebo. Patients were also provided a new diary with the above-mentioned scales and instructed to record the date and time when the investigational product was taken, to fill out a daily questionnaire on adherence to eradication therapy and to record whether they had experienced any adverse event. At the efficacy visit, diaries and unused investigational product were collected, leftover eradication treatment drugs were counted, and adverse events were recorded. At the follow-up visit (ie, a routine visit scheduled by the clinic), a ^{13}C-urea breath test was performed and recorded.

The primary outcome was the mean total score of the modified De Boer scale at the end of treatment.[21] The modified version of the De Boer scale is a validated scale for assessment of *H. pylori* therapy-related side effects, comprising 7 items that are rated using a 4-point Likert scale (not present, mild, moderate and severe). The seven evaluated symptoms are taste disturbance, diarrhea, abdominal pain, constipation, bloating, nausea and vomiting.

Secondary outcomes included the mean final score of the individual items of the modified De Boer scale, proportion of patients with occurrence or worsening of any of the symptoms included in the modified De Boer scale and the frequency of spontaneously reported adverse events. Symptom worsening or novel symptoms during treatment were classified as treatment-emergent adverse events. Other secondary outcomes were the percentage of compliance with the eradication therapy and the proportion of patients who reached eradication status (ie, a negative ^{13}C-urea breath test at the follow-up visit).

Constipation was defined as having more than 25% of the bowel movements with a score below 3 in the Bristol Stool Chart during the treatment period and/or had less than 3 depositions per week. Diarrhea was defined as more than 3 depositions with a score above 4 during at least 1 day.

2.4 | Statistical analysis

Sample size calculation was based on detecting a difference in the total score of the modified De Boer scale between the two study groups of 2.5 points, assuming a mean score at the endpoint in the control group of 8.95 points and a mean score in the intervention group of 6.45 points, with a standard deviation of 5.81 in both groups. The expected score in the control group and the standard deviation were based on the results of a previous randomized clinical trial on the effect of supplementation with probiotics on the tolerance of eradication therapy.[15] Assuming these figures, for a 5% significance level and a power of 80%, a sample size of 96 patients per group was necessary, given an anticipated 10% drop-out rate.

All efficacy analyses were performed in the intention-to-treat population, defined as all randomized patients; these analyses were also performed in the per-protocol population, defined as all randomized patients who completed the treatment and were not considered to have a major protocol deviation such as treatment compliance below 80% with eradication therapy and/or the investigational products, taking prohibited medication, not filling out the De Boer scale for at least 8 days, or having 20% or more missing items in the De Boer scale at baseline. All safety analyses were

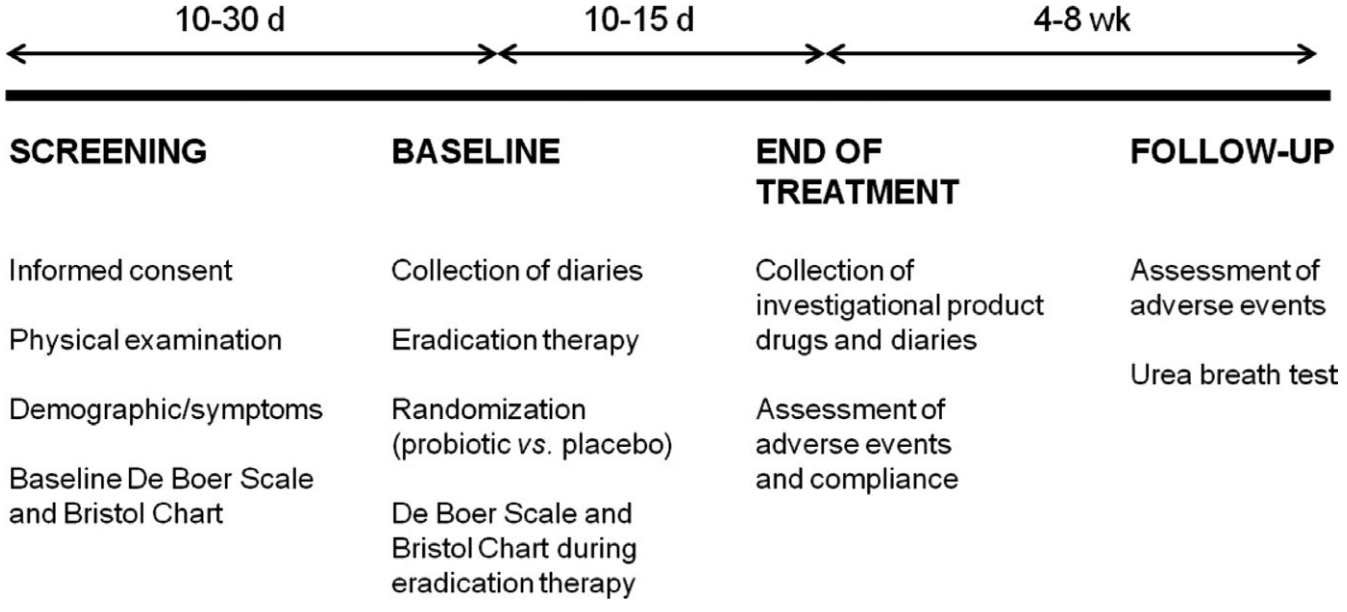

FIGURE 1 A timeline summarizing the phases of the study

performed in the tolerability and safety population, defined as all randomized patients who received at least one dose of the investigational products.

The 95% confidence interval (95% CI) was calculated for categorical variables and the mean ± standard deviation for quantitative variables. Primary efficacy analysis was performed using a multivariate linear regression model with total score of the modified De Boer scale at the endpoint as the outcome; covariates or factors were selected by the univariate comparison and a subsequent stepwise procedure from the variables age, sex, smoking status, alcohol habits, type of eradication therapy, patient' adherence to the eradication therapy, patient's adherence to the investigational product, use of forbidden medication and the interaction between investigational treatment and adherence to investigational treatment. Other efficacy analyses for continuous outcomes were performed using the same final model as for the primary outcome. Binary outcomes (eg, eradication rates) were compared using the Fisher exact test.

3 | RESULTS

3.1 | Patient disposition and characteristics

Among the 234 patients screened, 209 were randomly assigned to receive placebo (n = 106) or probiotic (n = 103) (Figure 2). Patients were middle-aged, predominantly Caucasian and with a slight predominance of women (Table 1). Treatment groups were comparable regarding demographic and clinical characteristics, with the exception of *H. pylori* diagnosis (Table 1). Two-thirds of the patients were prescribed nonbismuth quadruple eradication therapy and one-third triple therapy.

3.2 | Side effects

The mean total scores of the modified De Boer scale at the end of treatment were almost identical in the placebo and probiotic group (Table 2). For the primary efficacy analysis, only age, gender and type of eradication therapy were significantly associated with the occurrence of adverse effects included in the De Boer Scale in the univariate analysis (data not shown). Female gender and type of eradication therapy (quadruple therapy) were independent predictors of these side effects in the multiple linear regression model (Table 3). Using this model, there were no significant differences between the two study groups in the mean total score of the modified De Boer scale. Similarly, there were no significant differences in the mean final score of any of the individual symptoms of the scale, except for constipation, which showed a significantly higher score in the probiotic group compared to the placebo group (1.18 ± 0.47 vs 1.09 ± 0.27, $P = 0.049$) (Table 3). Worsening of at least one symptom of the modified De Boer scale occurred in 88.3% (95% CI, 80.7% to 93.2%) of the placebo-treated patients and 87.6% (95% CI, 79.6% to 92.8%) of the probiotic-treated patients, a difference that was not statistically significant ($P = 1.000$).

At least one treatment-emergent adverse event (TEAE) was reported by 103 (49.8%) subjects, including 30 (14.5%) subjects who had at least one TEAE with the eradication therapy (19 [18.3%] subjects in the placebo group and 11 [10.7%] in the probiotic group) and one (0.5%) subject who had at least one TEAE related with the investigational product, who belongs to the placebo group. Once again, no relevant differences were observed regardless of eradication therapy or the investigational product/placebo. The most frequent were (placebo vs probiotic) as follows: headache (36.5% vs 29.2%), dizziness (17.3% vs 4.9%), dry mouth (3.9% vs 4.9%), dyspepsia (3.8% vs 5.8%), abdominal distension (3.8% vs 1.0%), aphthous stomatitis (3.9% vs 0.0%) and asthenia (6.7% vs 2.9%). One patient in the placebo group took an overdose of the product, causing no symptoms. Neither deaths nor other serious adverse events were reported during the study.

There were no significant differences between the two study groups regarding in other secondary efficacy outcomes, such as number of bowel movements per day, mean score of the stools and mean score of the stools per day according to the Bristol chart (Table 4).

3.3 | Compliance

Adherence to eradication therapy was high and identical in both study groups (94.3% and 94.1% [$P = 1.000$]) of the placebo-treated and probiotic-treated patients, respectively, were considered compliers). Treatment adherence with the investigational products, probiotic and placebo was also high and almost identical in both study groups (96.1% vs 95.3% [$P = 1.000$]).

3.4 | Eradication rates

Eradication rates were also similar in both study groups (95.2% [95% CI, 89.2% to 97.9%] vs 97.0% [95% CI, 91.6% to 99.0%], for the placebo and probiotic group, respectively; $P = 0.721$) and did not differ according to the type of eradication therapy received (Table 5). The results for all efficacy analyses performed in the per-protocol population (data not shown) were similar to those reported above for the intention-to-treat population.

4 | DISCUSSION

In this randomized, double-blind, placebo-controlled trial, addition of a probiotic supplement containing *Lactobacillus plantarum* and *Pediococcus acidilactici* to triple or quadruple concomitant eradication therapy was not associated with a reduction in the side effects. Furthermore, this probiotic formula did not increase compliance with therapy or *H. pylori* eradication rates. This is the first study evaluating this probiotic formula for *H. pylori* infection, and any probiotic concurrently with a nonbismuth quadruple concomitant regimen. vOverall, our results strongly advise against its use as a generalized coadjuvant treatment for eradication regimens.

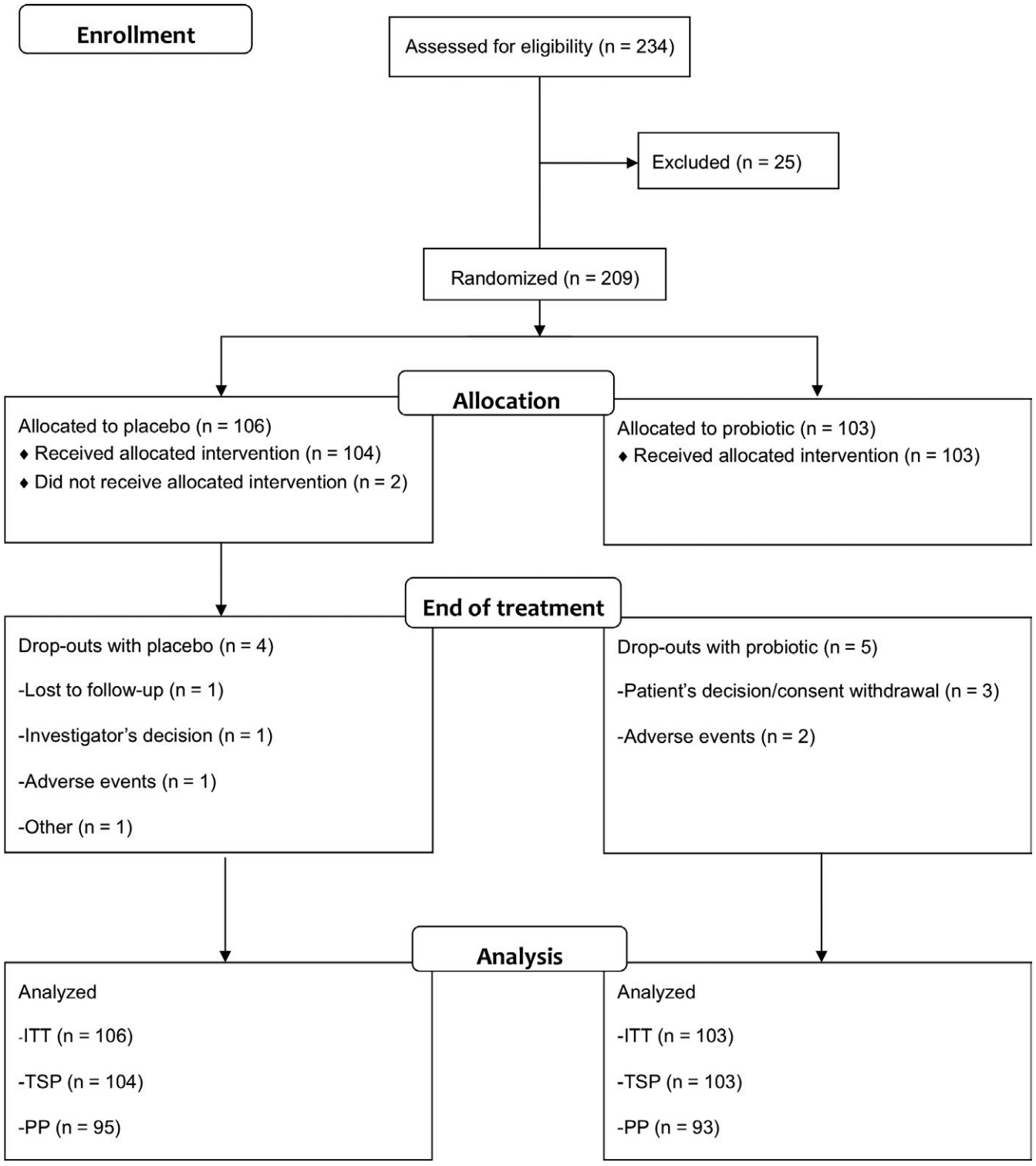

FIGURE 2 Flowchart of patients throughout the study. ITT, intention-to-treat population; PP, per-protocol population; TSP, tolerability and safety population

Regarding the primary outcome of the study (side effects), it has been suggested that probiotic supplementation in patients receiving eradication therapy for *H. pylori* may be especially effective for reducing nausea, vomiting, diarrhea and taste disorders.[22] This is likely the most relevant therapeutic target of probiotics, as dropping eradication rates with standard triple therapy necessarily have paved the way for better-optimized therapies, such as bismuth and nonbismuth quadruple therapies. These treatments are burdened with a higher rate of side effects due to increasing number of antibiotics.

TABLE 1 Demographics and clinical characteristics of patients included in the study

Characteristic	Placebo N = 106	Probiotic N = 103	*P*-value
Age (y), mean ± SD	45 ± 13	47 ± 13	0.278
Sex, % of females	65	60	0.478
Ethnicity, % Caucasian	92	87	0.439
Smoking status, % smokers	24	21	0.859
Alcohol intake, % yes	22	23	0.869
Helicobacter pylori diagnosis, %			
Urea breath test	55	63	0.161
Rapid urease test (biopsy)	18	19	0.860
Histological (biopsy)	27	18	0.099
Eradication therapy, %			
Triple therapy	34	34	-
Quadruple therapy	66	66	-

TABLE 2 Comparison of the scores of the modified De Boer scale after eradication therapy between groups

Score (mean ± SD)	Placebo N = 106	Probiotic N = 103	*P*-value*
Total	9.66 ± 2.19	9.48 ± 2.52	0.738
Constipation	1.09 ± 0.27	1.18 ± 0.47	**0.049**
Abdominal pain	1.48 ± 0.58	1.43 ± 0.60	0.575
Diarrhea	1.35 ± 0.56	1.35 ± 0.59	0.877
Vomiting	1.06 ± 0.21	1.05 ± 0.21	0.968
Nausea	1.27 ± 0.49	1.25 ± 0.48	0.875
Bloating	1.46 ± 0.65	1.41 ± 0.67	0.673
Taste disturbance	1.96 ± 0.80	1.81 ± 0.75	0.241

*All *P*-values are from a multiple linear regression analyses adjusted for the same variables as the primary efficacy outcome. Bold numbers represent significant p values ($p < 0.05$).

Unfortunately, we could not identify significant differences between groups after a thorough assessment of side effects, even though nonbismuth quadruple concomitant therapy was prescribed in two-thirds of patients. A reason for this might be that eradication therapies in the present trial were quite well tolerated, as demonstrated by the low frequency of treatment-emergent adverse events, the high compliance with the eradication therapy and the low rate of treatment discontinuations. The mean number of bowel movements per day after eradication therapy is consistent with the absence of diarrhea in the majority of patients. One can speculate that more relevant differences could have been observed with a qualitative rather than a quantitative assessment of gastrointestinal adverse effects, through the modified De Boer Scale. Our results, however, are consistent with the literature, with conflicting or heterogeneous results regarding a positive impact of probiotics on side effects.[6-8,12-14,17] By far, the most common non-gastrointestinal side effect was headache, present in a third of patients. Extradigestive side effects, which may clearly jeopardize adherence with therapy, cannot likely be improved with a probiotic formulation.

As for eradication rates, it is conceivable that the bacterial strains included in this probiotic supplementation (*Lactobacillus plantarum* CETC7879 and *Pediococcus acidilactici* CETC7880) may not be effective in vivo against *H. pylori*. We lack previous data to compare with. This therapeutic benefit has been suggested to be stronger with alternative probiotic strains (eg *Lactobacillus*, *Bifidobacterium*, multistrain probiotics),[15,16] but no comparative studies between probiotics have been conducted so far. Unexpectedly, triple therapy in the present trial achieved excellent cure rates (>90%) comparable to those obtained with nonbismuth quadruple concomitant therapy. The choice of eradication therapy was left up to the researchers, according to routine clinical practice. As such, we can speculate triple therapy was prescribed in centers where it still achieves acceptable cure rates. Although uncommon in our geographical area,[23,24] cure rates >90% for triple therapy were still observed in 25% of participant centers in a multicenter Spanish trial.[25]

Excellent to good cure rates for both eradication regimens in the present study may have limited our capacity to identify the differential effect of the probiotic formula. This hypothesis is supported by the results of a recent meta-analysis comprising thirty-three randomized clinical trials involving a total of 4459 patients with probiotic supplementation for *H. pylori* therapy.[15] It was reported that

TABLE 3 Multiple linear regression of the total score of the modified De Boer scale after eradication therapy between groups

	Nonstandard coefficient		Standard coefficient		
	B	Error	Beta	t	*P*-value
Constant	6.038	0.899		6.714	**<0.001**
Treatment group (placebo)	−0.106	0.315	−0.023	-0.335	0.738
Gender (male)	1.315	0.329	0.270	3.993	**<0.001**
Type of eradication therapy (triple)	0.924	0.337	0.185	2.745	**0.007**

Reference categories appear in parentheses. Bold numbers represent significant p values ($p < 0.05$).

TABLE 4 Other secondary continuous outcomes measured during eradication therapy

Outcome	Placebo	Probiotic	*P*-value*
Number of bowel movements per day	1.4 ± 0.6	1.5 ± 0.6	0.476
Mean score of the stools according to the Bristol chart	4.7 ± 1.1	4.7 ± 1.2	0.858
Mean score of the stools per day according to the Bristol chart	4.7 ± 1.1	4.7 ± 1.2	0.947

*All *P*-values are from a multiple linear regression analysis adjusted for the same variables as the primary efficacy outcome.

probiotic supplementation was most useful in the less effective antibiotic therapies. When eradication rate was <60%, pooled relative risk (RR) was 1.28; when the eradication rate was 6%-69%, RR was 1.18; when the eradication rate was 70%-79%, RR was 1.11; finally, if the eradication rate was over 80%, the supplementation was useless (pooled RR = 1.01). In this large meta-analysis, probiotics only demonstrated therapeutic benefit if the eradication rates in the control groups were relatively low. Similarly, when meta-analyses proving a therapeutic benefit for probiotics have reported pooled eradication rate for the control group, it was always <80%.[5,13,15-18]

Overall, our results hint at the lack of usefulness of probiotic to increase cure rates when eradication schemes achieve themselves good eradication rates. Several tools different from probiotic supplementation (increasing PPI doses, prolonging the length, increasing antibiotic doses or shortening the interval dose, changing antibiotics, addition of bismuth) can effectively increase cure rates up to a successful threshold without necessarily using probiotics.[4]

Of note, we observed that female gender and quadruple therapy were independent predictors of eradication therapy-associated side effects. Identifying predictors for adverse events during eradication therapy may be clinically useful to select the best candidates to benefit from their use. Further studies should definitely elucidate this question, as we definitely cannot use a one-size-fits-all approach with probiotics. They are over-the-counter drugs, subsequently rising the cost of eradication therapy and add even more complexity to increasingly complex quadruple therapies, therefore putting at risk compliance with therapy.[26]

The present study has a number of limitations to acknowledge. The sample size was designed to detect differences in side effects through the modified De Boer Scale, which is a quantitative measurement, but the main eradication therapy-related gastrointestinal side effects were not qualitatively measured. This might have affected the magnitude of the primary outcome. In line with this argument, the sample size of the study is relatively small to detect differences in eradication rates, probably due to the higher than expected eradication rates achieved. In this regard, it is important to state that in treatments offering high eradication rates, the aim of probiotic supplementation is side effects reduction and improved tolerability, and the potentially corresponding increase in treatment adherence and subsequent efficacy. As discussed, the results from the present study were unable to demonstrate these effects. It is important to clarify that these negative results may be strain (or dose or dose-timing) specific and cannot be extrapolated to other available strains.

In conclusion, the supplementation of the eradication therapy with a probiotic containing *Lactobacillus plantarum* and *Pediococcus acidilactici* in our study neither decreased side effects nor improved compliance with therapy or eradication rates.

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DISCLOSURES OF INTEREST

Carlos Badiola is employee of the sponsor of the study. Ángel Callejo works for the sponsor of the study as external project manager. Dr. Gisbert has served as a speaker, a consultant and advisory member for or has received research funding from Almirall, Nycomed, AstraZeneca, Casen Recordati, Mayoly and Allergan. Dr. Serra has served as a speaker, a consultant and advisory member for or has received research funding from Casen Recordati, Almirall, Norgine and Reckitt Benckiser. Dr. Calleja has served as a speaker and consultant for Casen Recordati. Dr. Molina-Infante

TABLE 5 Eradication rates, overall and by eradication therapy prescribed

	Placebo		Probiotic		
	n/N	% (95% CI)	n/N	% (95% CI)	*P*
Overall	99/104	95.2 (89.2-97.9)	98/101	97.0 (91.6-99.0)	0.721
Triple therapy	32/34	94.1 (80.9-98.4)	31/34	91.2 (77.0-97.0)	1.000
Nonbismuth quadruple therapy	67/70	95.7 (88.1-98.5)	67/67	100.0 (94.6-100.0)	0.245

CI, confidence interval; n, number of patients reaching the eradication status; N, number of evaluable patients.

has served as a consultant for Casen Recordati. Dr. McNicholl has been a speaker in formative actions by Allergan and MSD.

AUTHORS' CONTRIBUTIONS

A.G. McNicholl has coauthored the manuscript, made substantial contribution to the study design, to the analysis and interpretation of the data, and has critically revised the manuscript and given approval to the submitted and final versions. J. Molina-Infante has coauthored the manuscript, made substantial contribution to the study design, to the analysis and interpretation of the data and has critically revised the manuscript and given approval to the submitted and final versions. He has also contributed to the inclusion of patients and acquisition of data. A.J. Lucendo, J.L. Calleja, A. Pérez-Aisa, I. Modolell, X. Aldeguer, M. Calafat, L. Comino and M. Ramas have included patients and acquired the data, have critically reviewed and approved the manuscript. A. Callejo and C. Badiola have made a substantial contribution to the study design, analysis and interpretation of the data and have critically revised the manuscript and given approval to the submitted and final versions. J. Serra has made substantial contribution to the study design and to the analysis and interpretation of the data and has critically revised the manuscript and given approval to the submitted and final versions. He has also contributed to the inclusion of patients and acquisition of data. J.P. Gisbert has made substantial contribution to the study design, to the selection of collaborators and to the analysis and interpretation of the data and has critically revised the manuscript and given approval to the submitted and final versions. He has also contributed to the inclusion of patients and acquisition of data. He has acted as scientific coordinator of the project. As secondary contributors, the following persons have participated in the inclusion of patients, acquisition of data and/or coordination of activities at the participating sites: CAP Can Gibert del Pla - Girona (Silvia Torrent, Elena Fuentes, Ketty Torres, Sonia Castro, Pilar Font, Anna Refils, Emma Alcivar and Leticia Traspo), Hospital Germans Trias i Pujol-Badalona (Fausto Riu, Betty Morales, Ingrid Marín and Vicente Lorenzo-Zúñiga), Hospital Josep Trueta-Girona (René Louvriex, Silvia Virolés, Esther Font and David Busquets), Hospital Puerta de Hierro-Majadahonda (Virginia Matallana, Mª Juana Gómez, Luis Rodríguez, José Santiago and Marta Hernández), Hospital Ramón y Cajal-Madrid (C. Martín de Argila and Daniel Boixeda), Hospital La Princesa-Madrid (Maria José Casanova), Hospital Costa del Sol-Marbella (Nuria Fernández), Hospital Arnau Vilanova-Valencia (Miguel Bixquert, José M. Gonzalvo, and Rafael Gil), Hospital de Barbastro-Barbastro (Javier Alcedo), CAP Sant Pere i Sant Pau-Tarragona (José Mª Sabate), CAP Jonquera-Girona (Montse Mallol, Jordi Isart, Yolanda Macau and Francesca Ruiz), Hospital de Sanchinarro-Madrid (Magdalena García and Norberto Mañas), Hospital de Tomelloso-Tomelloso (Mª Teresa Angueira and Sonia González).

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