PREFÁCIO

Tanto no Brasil como além de nossas fronteiras é conhecido o grande número de pessoas que apresentam sintomas de Dispepsia Funcional e necessitam atenção.
Foi com grande satisfação que constatamos através do artigo **Erradicação do *Helicobacter pylori* na Dispepsia Funcional**, publicado em 2011, na conceituada revista **Archives of Internal Medicine** (grupo **JAMA)**, os relevantes resultados apresentados pelo Dr. Luiz Edmundo Mazzoleni e sua brilhante equipe.
Estes importantes estudos definem novas perspectivas que conduzem à prevenção e tratamento deste problema.

A RenyLab Química e Farmacêutica além de congratular-se com os grandes pesquisadores, sente-se muito feliz e honrada em saber que o teste de urease **RenyLab URETEST®** foi utilizado pela equipe para identificar pacientes urease positivos de maneira rápida, segura e confiável em sua eficácia na constatação da existência do *Helycobacter pylori*.

Publicação original: Revista de Medicina Interna **Archives of Internal Medicine** do grupo **JAMA (The Journal of the American Medical Association)** de 28 de novembro de 2011. Também citada pela **Associação Americana de Gastroenterologia,**

WWW.ARCHINTERNMED.COM
ARCH INTERN MED/VOL 171 (NO. 21), NOV 28, 2011

CME available online at
www.jamaarchivescme.com
and questions on page 1877

Helicobacter pylori Eradication in Functional Dyspepsia

HEROES Trial

Luiz Edmundo Mazzoleni, MD, PhD; Guilherme Becker Sander, MD, PhD; Carlos Fernando de Magalhães Francesconi, MD, PhD; Felipe Mazzoleni, MD; Diego Mendonça Uchoa, MD; Laura Renata De Bona, BSc; Tobias Cancian Milbradt, BSc; Pâmela Schitz Von Reisswitz, MsC; Otavio Berwanger, MD, PhD; Mathias Bressel, PhD; Maria Isabel Edelweiss, MD, PhD; Stela Scaglioni Marini, MD; Cynthia Goulart Molina, MD; Luciano Folador, MD; Roberta Perin Lunkes, MD; Renata Heck, MD; Oscar Augusto Birkhan, MD; Bianca Michel Spindler, MD; Natan Katz, MD; Bruno da Silveira Colombo, MD; Pedro Proença Guerrieri, MD; Luiza Brusius Renck, MD; Elisa Grando, MD; Bianca Hocevar de Moura, MD; Franciele Darsie Dahmer, MD; Juliano Rauber, MD; João Carlos Prolla, MD, PhD

Background: Eradication of *Helicobacter pylori* in patients with functional dyspepsia continues to be a matter of debate. We studied eradication effects on symptoms and quality of life of primary care patients.

Methods: *Helicobacter pylori*–positive adult patients with functional dyspepsia meeting the Rome III International Consensus criteria were randomly assigned to receive omeprazole, amoxicillin trihydrate, and clarithromycin, or omeprazole plus placebo for 10 days. Endoscopy and H pylori tests were performed at screening and at 12 months. Outcome measures were at least 50% symptomatic improvement at 12 months using a validated disease-specific questionnaire (primary end point), patient global assessment of symptoms, and quality of life.

Results: Werandomly assigned 404 patients (78.7% were women; mean age, 46.1 years); 201 were assigned to be treated with antibiotics (antibiotics group) and 203 to a control group. A total of 389 patients (96.3%) completed the study. The proportion of patients who achieved the primary outcome was 49.0% (94 of 192) in the antibiotics group and 36.5% (72 of 197) in the control group (P=.01; number needed to treat, 8). In the patient global assessment of symptoms, 78.1% in the antibiotics group (157 of 201) answered that they were better symptomatically, and 67.5% in the control group (137 of 203) said that they were better (P=.02). The antibiotics group had a significantly larger increase in their mean (SD) Medical Outcomes Study 36-Item Short Form Health Survey physical component summary scores than the control group did (4.15 [8.5] vs 2.2 [8.1]; P=.02).

Conclusion: *Helicobacter pylori* eradication provided significant benefits to primary care patients with functional dyspepsia.

Trial Registration: clinicaltrials.gov Identifier: NCT00404534

Arch Intern Med. 2011;171(21):1929-1936

DYSPEPTIC SYMPTOMS affect up to 40% of the adult population in the Western world.[1] The costs of dyspepsia to society are substantial.[2] Dyspepsia accounts for 8.3% of visits to primary care physicians.[3] Most

See Invited Commentary at end of article

affected individuals do not have structural or biochemical abnormalities that can explain their symptoms and thus are classified as having functional or nonulcer dyspepsia.[4] Its underlying pathophysiologic mechanism is complex and involves changes in gastric motility, visceral hypersensitivity genetic susceptibility, psychosocial factors, and *Helicobacter pylori* infection.[5,6]

CME available online at www.jamaarchivescme.com and questions on page 1877

At least 50% of the world's population is infected by *H pylori*.[7] Previous trials that focused on the symptomatic benefits of eradicating *H pylori* infections in patients with functional dyspepsia[8-16] have yielded conflicting results. The last Cochrane review[17] about the role of *H pylori* eradication in functional dyspepsia selected 21 trials, and only 6 showed positive results from eradication. Recently published consensus statements from the United States

Author Affiliations are listed at the end of this article. Group Information: The authors listed constitute the HEROES (*Helicobacter* Eradication Relief of Dyspeptic Symptoms) Trial Investigators.

and Europe also have discordant recommendations. While the American College of Gastroenterology states [18(p1808)] "whether to test for *H pylori* in patients with functional dyspepsia . . . remains controversial," the Maastricht III Consensus Report recommends it. [19]

Since 1999, it has been suggested that studies should be undertaken in primary care patients whose symptoms may be less resistant to treatment,[10,12,20] but none of the major clinical trials [8,12] were performed in this setting. Given that a large uncertainty remains, we designed a large, randomized, double-blind, placebo-controlled clinical trial to study the effects of *H pylori* eradication on the symptomatic responses and quality of life (QOL) of community and primary care patients with functional dyspepsia.

METHODS

STUDY DESIGN

The HEROES (*Helicobacter* Eradication Relief of Dyspeptic Symptoms) Trial was a randomized double-blind, placebocontrolled clinical trial. The study was conducted in a single academic hospital, the Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil. The local institutional review board approved the trial protocol. Written informed consent was obtained from all patients prior to enrollment.

STUDY POPULATION

Community and primary care patients were recruited through newspaper, radio, and television advertising as well as through invitation in primary care clinics. In Brazil, access to health care facilities is difficult. When free health care is advertised, patients who come are not "nonconsulting" but rather patients in the queue for a primary care visit. So, we considered community or primary care as part of the same population, because these patients had not been previously treated and were not resistant to a first-line treatment, as were the patients included in most of the previous trials, which had been conducted at tertiary centers. Patients of either sex were enrolled in the study if they were 18 years or older and had a diagnosis of *H pylori* infection and functional dyspepsia according to the Rome III International Consensus criteria.[4]

We excluded patients with predominant symptoms of heartburn or irritable bowel syndrome; alarm symptoms; history of peptic ulcer, upper gastrointestinal tract surgery, or biliary colic; previous treatment for eradication of *H pylori*; known allergies to study medication; serious comorbidities; or alcohol or drug abuse. Use of antibiotics or bismuth during the 4 weeks before enrollment, proton pump inhibitors during the 2 weeks before enrollment, or treatment with histamine-2 receptor blockers in the week before enrollment were not permitted. We also excluded women of childbearing potential; patients unable to answer the study questionnaires; patients with endoscopic findings other than gastritis, duodenitis, or hiatal hernia; and patients unwilling or unable to provide consent.

RANDOMIZATION AND ALLOCATION CONCEALMENT

Eligible patients were randomly assigned to receive either treatment with omeprazole, 20 mg twice daily; amoxicillin trihydrate, 1000 mg twice daily; and clarithromycin, 500 mg twice daily (Omepramix;Ache´ Laboratórios Farmacêuticos SA, São Paulo, Brazil) for 10 days (antibiotics group) orome prazole, 20 mg twice daily, plus placebo antibiotics (control group). The randomization list was generated by the manufacturer of the treatment drugs using a computer-generated randomization list (in a 1:1 ratio) in blocks of 8. Randomization was stratified by the presence of erosions and/or use of nonsteroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid, which, in a post hoc analysis of a previous trial that we conducted,[16] were predictive of poor symptomatic response. AnNSAIDs/acetylsalicylic acid userwasconsidered to be a patient who took this class of drugsat least once a week or a daily user of low dosage of acetylsalicylic acid. The allocation concealment was guaranteed using an automated, central computer-based randomization system so the allocation sequence was totally unpredictable to the investigators who enrolled patients in this study.

STUDY PROCEDURES

Patients were randomized at baseline and returned for follow-up visits at 4, 8, and at least 12 months (last visit) after. Upper gastrointestinal tract endoscopies were performed at screening and at the end of follow-up by 2 endoscopistswhowere blinded to treatment allocation. Endoscopic findings were classified according to the Sydney System.[21] Three biopsy specimens were obtained from the body of the stomach, 3 from the antrum, and 2 from the incisura angularis. One specimen from each anatomical region was used for the urease test, and the others were used for histologic examination by 2 pathologists (D.M.U. and J.R.) who were unaware of patients' allocation (stains: Giemsa and hematoxylin-eosin). The severity of histologic gastritis was graded according to the updated Sydney System.[22] *Helicobacter pylori* status was defined when urease test and histopathologic results were both negative or positive for infection. In the case of a disagreement, a third pathologist (M.I.E.) was consulted.

URETEST RenyLab Química e Farmacêutica LTDA. Barbacena - MG Brasil

Patients received medication as needed for postprandial discomfort (metoclopramide chloridrate, dimethicone, andpepsin) and famotidine for epigastric pain (Digeplus and Famox [Aché Laboratórios Farmacêuticos SA], respectively) during the 12 months of follow-up. Patients' consumption of the rescue medication was recorded in a diary. NSAIDs/acetylsalicylic acid use was allowed so that we could study the interaction between their use and *H pylori* eradication.

Compliance with study medications was assessed by pill count of returned medication. Patients were considered to be compliant if they had taken at least 80% of prescribed medications for *H pylori* eradication.

BLINDING

Patients, investigators, caregivers, and outcome assessors were blinded to the allocation group until the study was completed. Both the active and placebo study medications were given orally and were identical in appearance, shape, and weight. Patients recorded adverse events in diaries to keep the researchers blinded to the adverse effects of the antibiotics, which could have unmasked the study groups. These diaries were returned in sealed envelopes and were opened only after the study was completed.

OUTCOME MEASURES

The primary end point was the proportion of patients with at least a 50% decrease in the dyspeptic symptoms score at 12 months compared with their baseline score. The dyspeptic symptoms score was evaluated at all visits by trained investigators using the Porto Alegre Dyspeptic Symptoms Questionnaire (PADYQ).[23] This questionnaire is a unidimensional instrument that has been shown to have high levels of internal consistency, reproducibility, responsiveness, face validity, dis-

criminant validity, and concurrent validity. This 11-question instrument assesses the frequency, duration, and intensity of dyspeptic symptoms during the preceding 30 days. The score ranges from 0 (no symptoms) to 44 (severe symptoms). Secondary end points included the proportion of patients reporting complete improvement of symptoms, the mean decrease in the symptoms score, the use of rescue medications in the 30 days preceding the last visit, patient global assessment of symptoms, and QOL. Patient global assessment was evaluated at 12 months with the use of the global scale with the following 3 grades: symptoms improved, did not change, or deteriorated. Quality of life was assessed at baseline and last study visit using the validated Portuguese version of the Medical Outcomes Study 36-Item Short Form Health Survey, version 2.0 (SF-36v2).[24]

SAMPLE SIZE

For the primary end point the sample size was calculated based on a previous study by our group16 in which the response rate to antibiotics was 35% and the response rate to placebo was 21%. Assuming a 15% missing data rate, the HEROES Trial was designed to enroll 202 patients per group to provide a statistical power of 80% with a 2-sided significance level of P=.05. At the same time, in an exploratory analysis of the previous study in patients without gastric erosions or use of NSAIDs/acetylsalicylic acid, the response to antibiotics was 40%, and the response rate to placebo was 15%. If this is true, the stratum of patients without gastric erosions or use of NSAIDs/acetylsalicylic acid should have at least 170 patients to provide a statistical power of 90% with a 2-sided significance level of P=.03 (used to correct to multiple measurement).

STATISTICAL ANALYSIS

All analyses were performed by intention to treat. The population for analysis included all eligible patients who completed follow-up. No eligible patient was excluded from the analysis because of protocol deviation. Continuous variables were expressed as means (SDs) and were analyzed using the t test for independent samples. Qualitative variables were expressed as percentages and were compared using Fisher exact test. All variables that had P values that were less than .20 on univariate analysis were included in a forward stepwise logistic regression to assess their effect on the primary outcome. Comparisons between groups, regarding the number of symptomatic drugs that were used, were performed using the Mann-Whitney test. All 2-tailed P values less than .05 were considered to be statistically significant. No interim analysis was conducted. All analyses were performed using PASW Statistics software (version 18.0; Chicago, Illinois).

RESULTS

STUDY POPULATION

From November 2006 through June 2008, a total of 1151 patients were screened, and 407 were randomized into the study. The flow of patients through trial and the reasons for exclusion are presented in **Figure 1**. Three ineligible patients were randomly allocated in error andwere excluded from the analysis. A total of 201 patients were assigned to omeprazole and antibiotics (antibiotics group) and 203 to omeprazole and placebo (control group). A total of 188 and 216 patients were allocated to strata of participants with and without erosions and/or use of

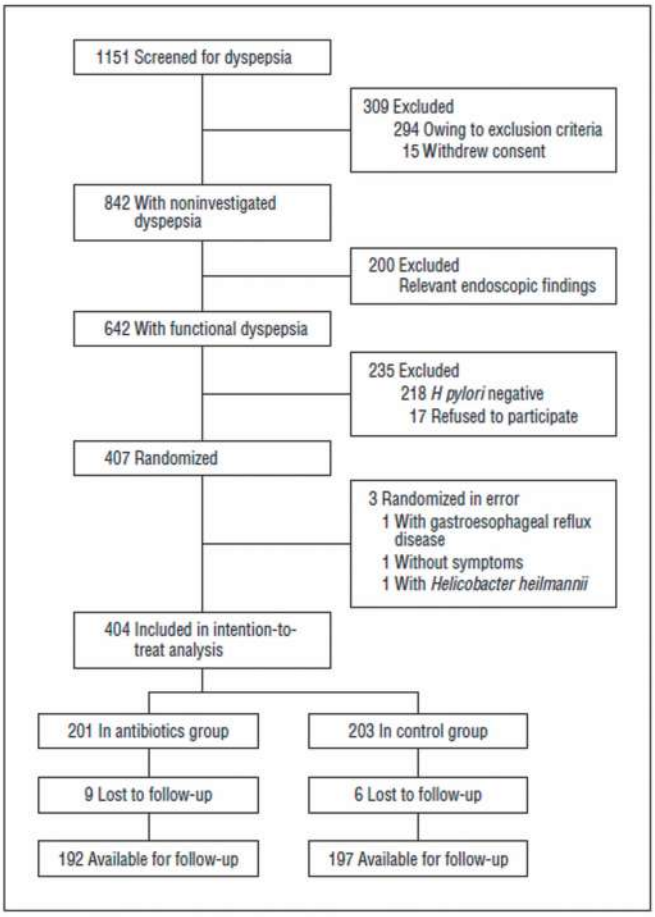

Figure 1. Flow of participants through the trial.

NSAIDs/acetylsalicylic acid, respectively. Data from the PADYQ and patient global assessment of symptoms were available for 389 patients at the final visit, resulting in a loss to follow-up rate of 3.7%. The baseline characteristics were similar between the 2 groups (**Table 1**).

RESPONSE TO TREATMENT

Primary End Point

The rates of treatment success are shown in **Table 2** and **Figure 2**. The proportion of patients with symptomatic improvement of 50% or more was 49% (94 of 192) in the antibiotics group and 36.5% (72 of 197) in the control group (absolute difference between groups, 12.5%; 95% CI, 2.1%-22.7%; P=.01). The number needed to treat (NNT) to achieve the primary outcome was 8. Even after considering all patients who were lost to follow-up as nonresponders, the differences in the rate of achievement of the primary end point remained significant (P=.03).

Other End Points

The proportions of patients reporting improvement in the patient global assessment of symptoms were 78.1% (157 of 201) in the antibiotics group and 67.5% (137 of 203) in the control group (P=.02), and the mean decrease in symptom scores were -10.47 and -7.76 (P=.008), respectively. The rate of complete resolution of symptoms did not differ significantly between the groups (Table 2). The im-

Table 1. Baseline Characteristics of the Study Patients, Stratified According to Treatment Group

Variable	Patients, No. (%)	
	Antibiotics Group (n=201)	Control Group (n=203)
Age, mean (SD) [range], y	46.1 (12.4) [18-75]	46.0 (12.2) [18-81]
>50 y	86 (42.8)	78 (38.4)
Female sex	154 (76.6)	164 (80.8)
White race	162 (80.6)	153 (75.4)
Education >10 y	81 (40.3)	91 (44.8)
Smoking status		
Never smoked	110 (54.7)	123 (60.6)
Current/former	91 (45.3)	80 (39.4)
Alcohol consumption		
No consumption	170 (84.6)	174 (85.7)
Current/former	31 (15.4)	29 (14.3)
Coffee drinker	132 (65.7)	134 (66.0)
Use of NSAIDs or acetylsalicylic acid[a]		
Yes	38 (18.9)	31 (15.3)
PADYQ score, mean (SD)[b]	23.2 (7.7)	21.9 (7.4)
Score >20 points	127 (63.2)	119 (58.6)
Duration of dyspepsia >5 y	92 (45.8)	103 (50.7)
Rome III International Consensus dyspepsia subtypes[c]		
Epigastric pain syndrome	156 (77.6)	145 (71.4)
Postprandial distress syndrome	186 (92.5)	188 (92.6)
Upper gastrointestinal tract endoscopy		
Erosive gastritis/duodenitis	72 (35.8)	78 (38.4)
Histologic characteristics		
Moderate/severe inflammatory activity (Antrum)	87 (43.3)	93 (45.8)

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; PADYQ, Porto Alegre Dyspeptic Symptoms Questionnaire.
[a]Use of NSAIDs or acetylsalicylic acid at least once a week or daily low-dose acetylsalicylic acid.
[b]Scores range from 0 (no symptoms) to 44.
[c]See article by Tack et al. [4]

provement in SF-36v2 scores at month 12 was significantly greater in the antibiotic group for the physical component summary compared with the control group (4.15 and 2.20, respectively; P=.02). However, the 2 groups did not differ on the mental component summary (1.29 and2.9, respectively; P=.18) (Table 2).

To examine the influence that several potentially important prognostic factors had on symptomatic improvement, the following factors were first examined individually by univariate analysis for the 2 treatment groups combined: sex, age, race, years of education, basal PADYQ score, type of dyspepsia, presence of erosions at endoscopy, antral inflammatory activity, NSAIDs/acetylsalicylic acid use, coffee and alcohol consumption, smoking, and duration of dyspepsia. Allocation group and onset of dyspepsia were included in the multivariate analysis. Antibiotic group (odds ratio [OR], 1.63; P=.01) and recent dyspepsia (OR, 1.51; P=.048) were retained in the final stepwise logistic regression analysis model as predictors of symptomatic improvement. **Figure 3** shows the effect that these factors had on the primary end point according to baseline characteristics. Prespecified subgroup analysis showed that neither the presence of erosive gastritis nor NSAIDs/acetylsalicylic acid use affected patients' response to *H pylori* eradication.

According to the intention-to-treat analysis, after 1 year, tests for 88.6% of the patients in the antibiotics group (164 of 185) were negative for *H pylori*, compared with 7.4% of patients in the control group (14 of 189) (P<.001) (Table 2). Patients in the antibiotics group did exhibit a significant improvement in both the inflammatory pattern (lymphocytic infiltrate) and the degree of inflammatory activity (polymorphonuclear infiltrate) compared with the control group (P<.001).

Safety, Compliance, Rescue Treatment, and Development of Peptic Ulcers

Data on compliance, adverse effects of study drugs, use of rescue medications, and the development of peptic ulcer are shown in Table 2. There were no serious adverse events in either group until 30 days after they had completed their treatment course. Endoscopy was performed at 12 months in 374 of 404 patients (92.6%), and findings revealed that peptic ulcers had developed in 13 of 374 patients (3.5%) (Table 2).

COMMENT

This large, single-center study demonstrates a statistically significant benefit in symptomatic improvement among *H pylori*–positive functional patients with dyspepsia treated with omeprazole and antibiotics in comparison with those treated with omeprazole and placebo. Symptomatic improvement was demonstrated by measuring the primary outcome (50% symptomatic improvement on the PADYQ) and supported by the improvement in the patients' global assessment of symptoms as well as by the mean reduction in the PADYQ score. We also observed a significant improvement in the SF- 36v2 physical component summary score and a favorable trend toward a reduction in the use of rescue medications (P=.06). The antibiotic group experienced more

Table 2. Summary of Trial Results

Variable	Patients, No. (%) Antibiotics Group (n=201)	Control Group (n=203)	*P* Value
Completed follow-up	192 (95.5)	197 (97.0)	.44
Primary end point			
Symptomatic improvement ≥50%[a]	94 (49.0)	72 (36.5)	.01
Secondary end points			
Complete symptoms relief[a]	35 (18.2)	28 (14.2)	.34
Improvement of patient global assessment of symptoms	150 (78.1)	133 (67.5)	.02
Change in symptoms score, mean (SD)[a]	−10.47 (10.56)	−7.76 (9.35)	.008
Change in SF-36v2 physical component summary, mean (SD)[b]	4.15 (8.5)	2.20 (8.1)	.02
Change in SF-36v2 mental component summary, mean (SD)[b]	1.29 (11.94)	2.90 (11.08)	.18
Rescue medication use, median[c]	4	8	.06
Other results			
Compliance with treatment[d]	159 (95.8)	159 (97.0)	.77
H pylori eradication[b]	164 (88.6)	14 (7.4)	<.001
Adverse events[e]			
Any adverse event	172 (93.0)	146 (82.0)	.002
Abnormal taste	80 (43.2)	6 (3.4)	<.001
Diarrhea	55 (29.7)	12 (6.7)	<.001
Malaise	30 (16.2)	5 (2.9)	.001
Peptic ulcer at 12 mo of follow-up[b,f]	4 (2.2)	9 (4.8)	.26

Abbreviations: *H pylori*, *Helicobacter pylori*; SF-36v2, Medical Outcomes Study 36-Item Short Form Health Survey, version 2.0.
[a] Assessed by Porto Alegre Dyspeptic Symptoms Questionnaire. Scores range from 0 (no symptoms) to 44.
[b] Available data for 185 of 201 patients in the antibiotics group (92.0%) and 189 of 203 in the control group (93.1%) (P=.83).
[c] Median rescue medication in the last month of follow-up. Available data for 152 of 201 patients in the antibiotics group (75.6%) and 144 of 203 patients in the control group (70.9%) (P=.34).
[d] Available data for 166 of 201 patients in the antibiotics group (82.6%) and 164 of 203 patients in the control group (80.8%) (P=.73).
[e] Showed events with a statistically significant different incidence between groups. Available data for 185 of 201 patients in the antibiotics group (92.0%) and 178 of 203 in the control group (87.7%) (P=.20).
[f] In the antibiotics group all ulcers were negative for *H pylori* and in the control group all were positive for *H pylori*.

adverse events, but these were mild and short lived. The prespecified subgroup analysis showed that neither erosive gastritis nor NSAIDs/acetylsalicylic acid use influenced patients' response to H pylori eradication. As a matter of fact, we did not find any subgroup with statistically better response to eradication.

Weadhered strictly to the Rome III International Consensus recommendations for clinical trials on functional dyspepsia, assuring that we included a population of patients with true functional dyspepsia. All 25 recommendations of the CONSORT statement were followed, and to our knowledge, the HEROES Trial is the first large clinical trial on this topic that has focused on primary care patients and that had an a priori primary outcome definition registered at ClinicalTrials.gov. One strength of this study is the definition of the primary end point. As Axon [25(piv53)] stated, it is unreasonable to expect "total relief of symptoms" in a condition with so many physiopathologic mechanisms and so many symptoms. Other studies[13-16,26-28] included in the Cochrane review did use a 50% or partial reduction as the main outcome in symptoms as a valid outcome. In this study, 93.4% of the patients who experienced the primary end point reported improvement in the patient global assessment of symptoms, suggesting that achieving a 50% symptomatic improvement is a clinical relevant cutoff. Another major strength of this study is that its loss to follow-up rate was less than 4%. Considering the number of eligible patients with complete follow-up in each treatment arm, to our knowledge the HEROES Trial is the largest clinical trial of *H pylori* eradication in functional dyspepsia that has ever been performed on this topic. It

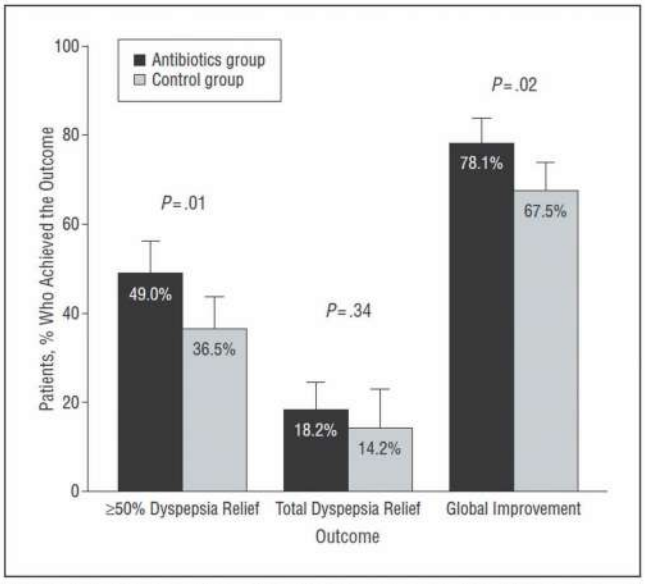

Figure 2. Proportion of patients who achieved response in qualitative outcomes.

is relevant to emphasize that this study did use a locally validated questionnaire that has been shown to have high degrees of reproducibility, validity, and responsiveness. One weakness of our study is that it was conducted in a single center, a characteristic that may limit its external validity. There are no data in the literature, to our knowledge, however, that support the concept that *H pylori* functional dyspepsia is a clinically distinct disorder in different countries. Another point is that a minimum symptomatic score could have been used. Our point of

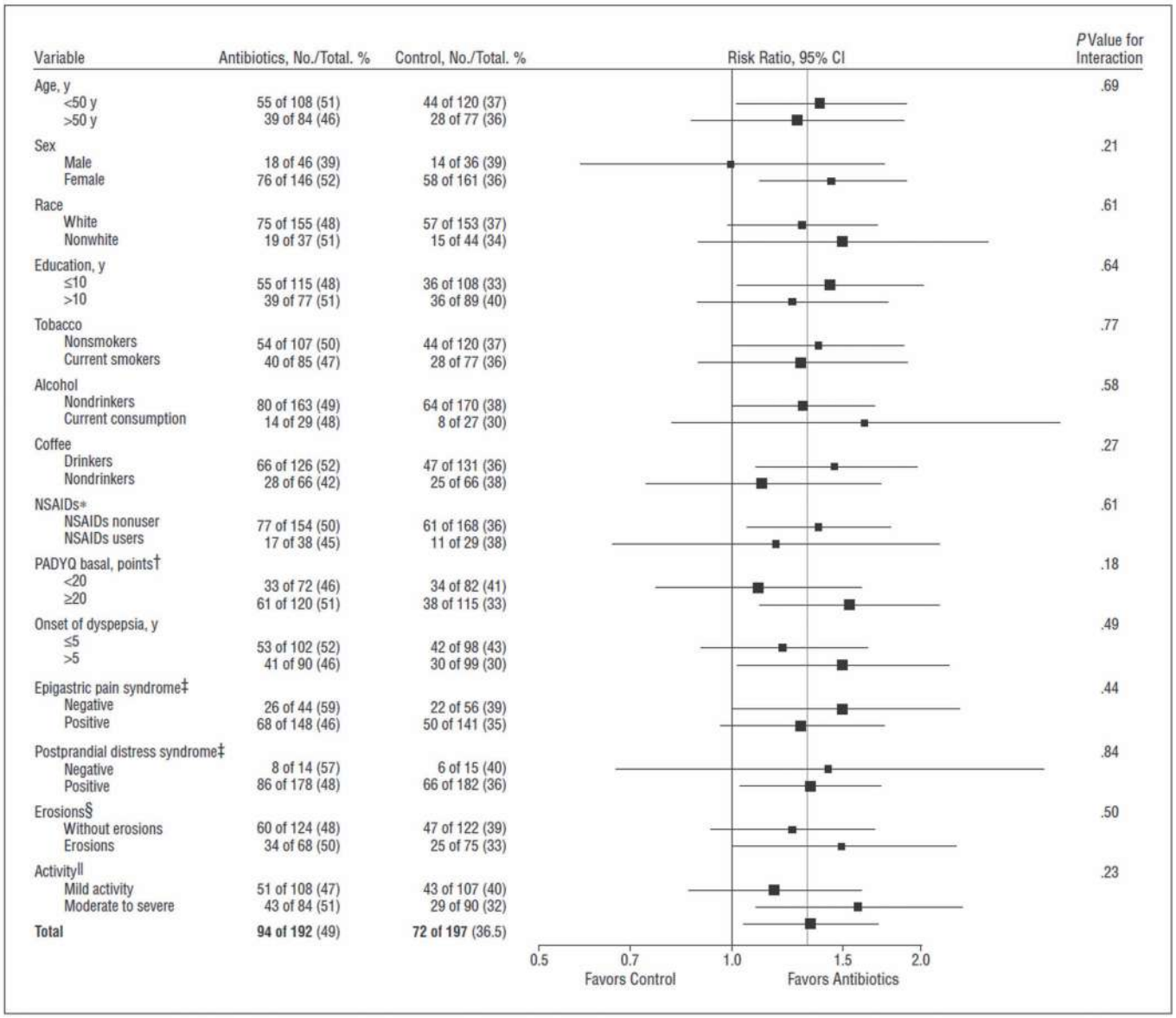

Figure 3. Primary study outcome 12 months after treatment, stratified according to baseline characteristics and treatment groups (intention-to-treat analysis). Scores range from 0 (no symptoms) to 44. *Use of nonsteroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid at least once a week or daily low-dose acetylsalicylic acid. †PADYQ, Porto Alegre Dyspeptic Symptoms Questionnaire. ‡According to Rome III International Consensus Criteria. §Erosive gastritis or erosive duodenitis. ||Polymorphonuclear infiltrate on antral histologic findings.

view is that if this is a bias, it is a conservative one. As presented, patients with high symptom scores did better than those receiving placebo.

Conflicting findings on the effect of *H pylori* eradication in functional dyspepsia have been observed in clinical trials, meta-analyses, and consensus [8-19,29,30] statements. Most of the trials included secondary and tertiary care patients who were likely to have more resistant symptoms and who were not representative of most patients with functional dyspepsia.[10] None of the studies included in the last Cochrane review demonstrated that *H pylori* eradication improved patients' QOL.[17] We showed that patients who were treated with antibiotics exhibited improvements in the physical component summary score of SF-36v2. The improvement in QOL and the trend toward less use of rescue medication that we observed in this study will surely contribute to the adaption of economic models of *H pylori* eradication to primary care populations.

The relatively small patient benefit that we observed as a result of *H pylori* eradication is comparable with the benefit of long-standing proton pump inhibition, an approach that has been shown to be 10% more effective than placebo in patients with ulcerlike dyspepsia.[31] Eradication has a similar magnitude of benefit, it is not restricted to any subtype of dyspepsia, and it has the advantage of being a short-term treatment. Some authors advocate using a test-and-treat strategy in the initial treatment of patients with dyspepsia.[32] However, this strategy is applicable for only 32% of patients with dyspepsia, specifically those who are young and do not have alarm symptoms.[33] Accordingly, our data suggest that the remaining patients, who undergo endoscopy and in whom a diagnosis of functional dyspepsia is established, should undergo H pylori testing and subsequent treatment.

In conclusion, our data support the concept that *H pylori* eradication improves symptoms in primary care pa--

tients with functional dyspepsia with an NNT of 8. We suggest that these data should be considered by investigators who are performing cost-utility studies on the economics of *H pylori* eradication in primary care patients with functional dyspepsia.

Accepted for Publication: August 15, 2011.
Author Affiliations: School of Medicine (Drs L. E. Mazzoleni, Sander, Francesconi, Edelweiss, Molina, Folador, Lunkes, Heck, Birkhan, Spindler, Katz, Colombo, Guerrieri, Renck, Grando, deMoura, Dahmer, and Prolla and Ms Von Reisswitz), and School of Medicine, Postgraduate Program of Medical Science (Mr Milbradt), Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; Departments of Gastroenterology (Drs L. E. Mazzoleni, Francesconi, and Marini and Ms De Bona), Internal Medicine (Dr F. Mazzoleni), and Pathology (Drs Uchoa, Edelweiss, Rauber, and Prolla), Drug and Therapeutics Committee (Dr Sander), and Postgraduate and Research Group (Dr Bressel), Hospital de Clinicas de Porto Alegre, Porto Alegre; and HCor, Research Institute, São Paulo, Brazil (Dr Berwanger).

Correspondence: Luiz Edmundo Mazzoleni, MD, PhD, Department of Gastroenterology, Hospital de Cli´nicas de Porto Alegre, Rua Ramiro Barcelos 2350, 90035-903, Porto Alegre, Rio Grande do Sul, Brazil (lemazzoleni@yahoo .com.br).

Author Contributions: The investigators are fully responsible for the study design, statistical analysis plan, performing the investigation, data analysis, and manuscript preparation. All authors vouch for the completeness and accuracy of the data presented. *Study concept and design:* L. E. Mazzoleni, Sander, Francesconi, F. Mazzoleni, Uchoa, Von Reisswitz, Berwanger, Edelweis, Rauber, and Prolla. Acquisition of data: L. E. Mazzoleni, Sander, F. Mazzoleni, Uchoa, Von Reisswitz, Edelweis, Marini, Molina, Folador, Lunkes, Heck, Birkhan, Spindler, Katz, Colombo, Guerrieri, Renck, Grando, de Moura, Dahmer, and Rauber. *Analysis and interpretation of data:* L. E. Mazzoleni, Sander, Francesconi, De Bona, Milbradt, Berwanger, Bressel, and Prolla. *Drafting of the manuscript:* L. E. Mazzoleni, Sander, Francesconi, F. Mazzoleni, Uchoa, De Bona, Milbradt, Von Reisswitz, Berwanger, Edelweis, Molina, Folador, Lunkes, Heck, Birkhan, Spindler, Katz, Colombo, Guerrieri, Renck, Grando, de Moura, Dahmer, and Rauber. *Critical revision of the manuscript for important intellectual content:* L. E. Mazzoleni, Sander, Francesconi, Berwanger, Bressel, Marini, and Prolla. Statistical analysis: L. E. Mazzoleni, Sander, and Bressel. *Obtained funding*: L. E. Mazzoleni. *Administrative, technical, and material support:* De Bona and Milbradt. Study
supervision: L. E. Mazzoleni, Sander, and Francesconi.

Financial Disclosure: None reported.

Funding/Support: The study drugs and a gastroscope were obtained through unrestricted donation from the Ache´ Laborato´ rios Farmacêuticos SA, São Paulo, Brazil. No member of the research team received grants to conduct this study.

Previous Presentation: This study was presented at the American Gastroenterology Association's Digestive Disease Week; May 3, 2010; New Orleans, Louisiana.

REFERENCES

1. Jones RH, Lydeard SE, Hobbs FD, et al. Dyspepsia in England and Scotland. *Gut*. 1990;31(4):401-405.
2. Agre´us L, Borgquist L. The cost of gastro-oesophageal reflux disease, dyspepsia and peptic ulcer disease in Sweden. *Pharmacoeconomics*. 2002;20(5):347-355.
3. Maconi G, Tosetti C, Stanghellini V, Bianchi Porro G, Corinaldesi R. Dyspeptic symptoms in primary care: an observational study in general practice. *Eur J Gastroenterol Hepatol*. 2002;14(9):985-990.
4. Tack J, Talley NJ, Camilleri M, et al. Functional gastroduodenal disorders. *Gastroenterology*. 2006;130(5):1466-1479.
5. Mertz H, Fullerton S, Naliboff B, Mayer EA. Symptoms and visceral perception in severe functional and organic dyspepsia. *Gut*. 1998;42(6):814-822.
6. Mimidis K, Tack J. Pathogenesis of dyspepsia. Dig Dis. 2008;26(3):194-202.
7. Pounder RE, Ng D. The prevalence of *Helicobacter pylori* infection in different countries. *Aliment Pharmacol Ther*. 1995;9(suppl 2):33-39.
8. McColl K, Murray L, El-Omar E, et al. Symptomatic benefit from eradicating *Helicobacter pylori* infection in patients with nonulcer dyspepsia. *N Engl J Med*. 1998; 339(26):1869-1874.
9. Blum AL, Talley NJ, O'Mora´in C, et al; Omeprazole plus Clarithromycin and Amoxicillin Effect One Year After Treatment (OCAY) Study Group. Lack of effect of treating *Helicobacter pylori* infection in patients with nonulcer dyspepsia. *N Engl J Med*. 1998;339(26):1875-1881.
10. Talley NJ, Janssens J, Lauritsen K, Ra´cz I, Bolling-Sternevald E; Optimal Regimen Cures Helicobacter Induced Dyspepsia (ORCHID) Study Group. Eradication of *Helicobacter pylori* in functional dyspepsia: randomised double blind placebo controlled trial with 12 months' follow up. *BMJ*. 1999;318(7187):833-837.
11. Talley NJ, Vakil N, Ballard ED II, Fennerty MB. Absence of benefit of eradicating *Helicobacter pylori* in patients with nonulcer dyspepsia. *N Engl J Med*. 1999; 341(15):1106-1111.
12. Malfertheiner P, Mossner J, Fischbach W, et al. *Helicobacter pylori* eradication is beneficial in the treatment of functional dyspepsia. *Aliment Pharmacol Ther*. 2003;18(6):615-625.
13. Koskenpato J, Farkkila" M, Sipponen P. *Helicobacter pylori* eradication and standardized 3-month omeprazole therapy in functional dyspepsia. *Am J Gastroenterol*. 2001;96(10):2866-2872.
14. Bruley Des Varannes S, Fle´jou JF, Colin R, Za¸ˆm M, Meunier A, Bidaut-Mazel C. There are some benefits for eradicating *Helicobacter pylori* in patients with nonulcer dyspepsia. *Aliment Pharmacol Ther*. 2001;15(8):1177-1185.
15. Veldhuyzen van Zanten S, Fedorak RN, Lambert J, Cohen L, Vanjaka A. Absence of symptomatic benefit of lansoprazole, clarithromycin, and amoxicillin triple therapy in eradication of *Helicobacter pylori* positive, functional (nonulcer) dyspepsia. *Am J Gastroenterol*. 2003;98(9):1963-1969.
16. Mazzoleni LE, Sander GB, Ott EA, et al. Clinical outcomes of eradication of *Helicobacter pylori* in nonulcer dyspepsia in a population with a high prevalence of infection: results of a 12-month randomized, double blind, placebo-controlled study. *Dig Dis Sci*. 2006;51(1):89-98.
17. Moayyedi P, Soo S, Deeks J, et al. Eradication of *Helicobacter pylori* for nonulcer dyspepsia. *Cochrane Database Syst Rev*. 2006;(2):CD002096.
18. Chey WD, Wong BC; Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of *Helicobacter pylori infection*. *Am J Gastroenterol*. 2007;102(8): 1808-1825.
19. Malfertheiner P, Megraud F, O'Morain C, et al. Current concepts in the management of *Helicobacter pylori* infection: the Maastricht III Consensus Report. *Gut*. 2007;56(6):772-781.
20. Danesh J, Pounder RE. Eradication of *Helicobacter pylori* and non-ulcer dyspepsia. *Lancet*. 2000;355(9206):766-767.
21. Tytgat GN. The Sydney System: endoscopic division: endoscopic appearances in gastritis/duodenitis. *J Gastroenterol Hepatol*. 1991;6(3):223-234.
22. Dixon MF, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis: the updated Sydney System: International Workshop on the Histopathology of Gastritis, Houston 1994. *Am J Surg Pathol*. 1996;20(10):1161-1181.
23. Sander GB, Mazzoleni LE, Francesconi CF, et al. Development and validation of a cross-cultural questionnaire to evaluate nonulcer dyspepsia: the Porto Alegre Dyspeptic Symptoms Questionnaire (PADYQ). *Dig Dis Sci*. 2004;49(11-12): 1822-1829.
24. Campolina AG, Ciconelli RM. SF-36 and the development of new assessment tools for quality of life [in Portuguese]. *Acta Reumatol Port*. 2008;33(2):127-133.
25. Axon A. Management of uninvestigated dyspepsia: review and commentary. *Gut*. 2002;50(suppl 4):iv51-iv57.
26. Ruiz Garc´a A, Gordillo López FJ, Hermosa Hernán JC, Arranz Martınez E, Villares Rodr´guez JE. Effect of the *Helicobacter pylori* eradication in patients with functional dyspepsia: randomised placebo-controlled trial. *Med Clin* (Barc). 2005; 124(11):401-405.
27. Gisbert JP, Cruzado AI, Garcia-Gravalos R, Pajares JM. Lack of benefit of treating *Helicobacter pylori* infection in patients with functional dyspepsia: randomized one-year follow-up study. *Hepatogastroenterology*. 2004;51(55):303- 308.
28. Froehlich F, Gonvers JJ, Wietlisbach V, et al; Eradication in Dyspepsia (ERADYS)

Study Group. *Helicobacter pylori* eradication treatment does not benefit patients with nonulcer dyspepsia. *Am J Gastroenterol*. 2001;96(8):2329-2336.

29. Jaakkimainen RL, Boyle E, Tudiver F. Is *Helicobacter pylori* associated with nonulcer dyspepsia and will eradication improve symptoms? a meta-analysis. **BMJ**. 1999;319(7216):1040-1044.

30. Laine L, Schoenfeld P, Fennerty MB. Therapy for *Helicobacter pylori* in patients with nonulcer dyspepsia: a meta-analysis of randomized, controlled trials. *Ann Intern Med*. 2001;134(5):361-369

31. Talley NJ, Meineche-Schmidt V, Paré P, et al. Efficacy of omeprazole in functional dyspepsia: double-blind, randomized, placebo-controlled trials (the Bond and Opera studies). *Aliment Pharmacol Ther*. 1998;12(11):1055-1065.

32. McColl KE. Clinical practice: *Helicobacter pylori infection*.N Engl J Med. 2010;362 (17):1597-1604.

33. Bodger K, Eastwood PG, Manning SI, Daly MJ, Heatley RV. Dyspepsia workload in urban general practice and implications of the British Society of Gastroenterology Dyspepsia guidelines (1996). *Aliment Pharmacol Ther*. 2000;14(4):413-420.

INVITED COMMENTARY

Helicobacter pylori Eradication for Functional Dyspepsia

What Are We Treating?

Functional dyspepsia is a major burden to society. Upper gastrointestinal tract symptoms account for 5% of all primary care visits,1 and about 80% of patients with epigastric pain have a normal result from endoscopy.[2,3] The cost of investigating and treating this disorder is significant, and it is estimated that the US health care system spends over $1 billion per year on functional dyspepsia.[1,4] Despite this drain on resources, there are few therapeutic options for patients with functional dyspepsia. A systematic review[4] suggests that prokinetic therapy may have some benefit, but this is driven by small positive studies with the larger studies being negative, and any effect seen in the meta-analysis may be due to publication bias.[5] Acid suppression with proton pump inhibitor therapy has modest efficacy in functional dyspepsia,[6] and thismaybe due to the treatment of atypical gastroesophageal reflux disease.[7] Given the paucity of effective therapies, it is important to establish whether eradicating Helicobacter pylori in those infected will have any benefit in functional dyspepsia.

Mazzoleni et al[8] report the results of a large Brazilian randomized controlled trial (RCT), which suggests that *H pylori* eradication is more effective than placebo with a number needed to treat (NNT) of 9 (95% CI, 5-59) on an intention-to-treat analysis. The authors are to be congratulated because there is a paucity of data from South America, and this is a well-conducted RCT with a low risk of bias. The data are consistent with those from a previous Cochrane systematic review[9] that identified 17 RCTs involving 3566 patients with functional dyspepsia and reported that Hpylori eradication had a statistically significant effect compared with placebo (relative risk [RR] of remaining dyspeptic, 0.90; 95% CI, 0.86-0.94). Adding the current study to this review hardly changes the point estimate or 95% CIs (RR, 0.91; 95% CI, 0.87-0.94) (Figure).[10-26] empha-

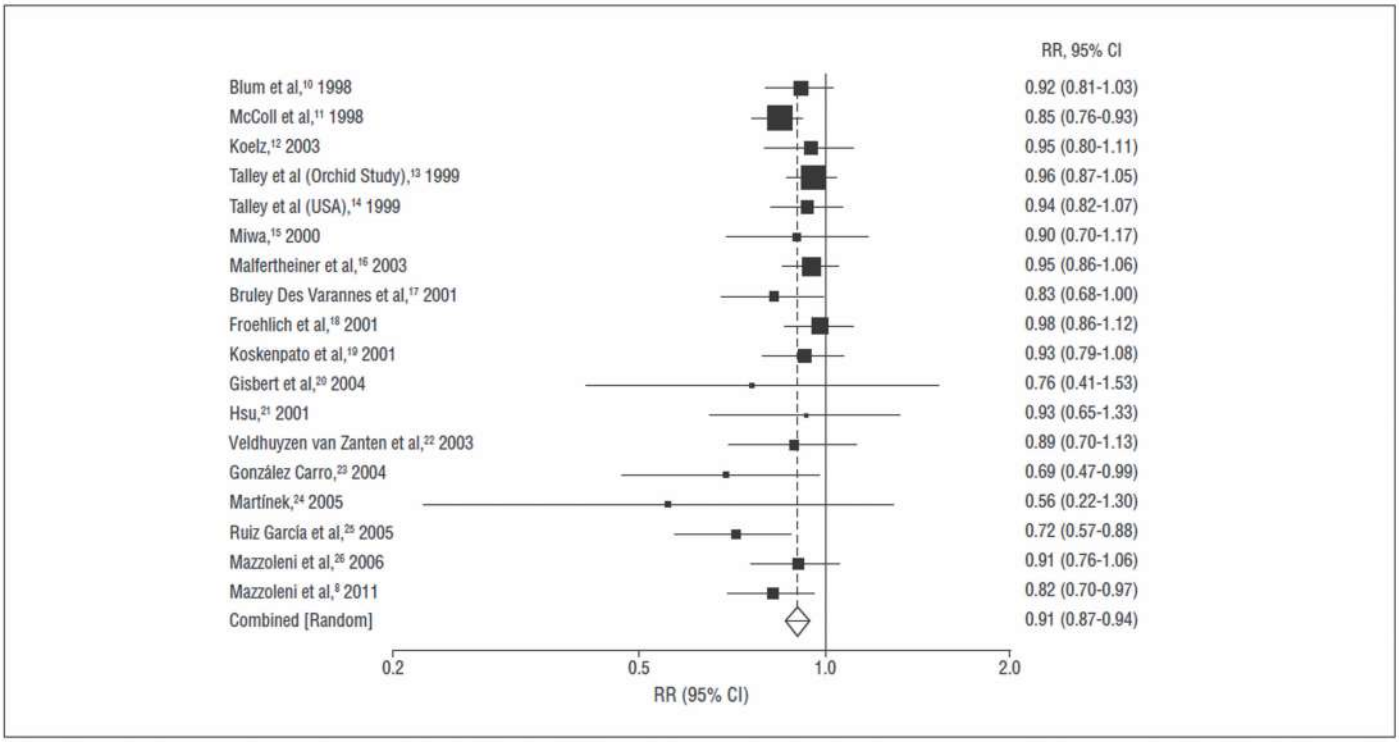

Figure. Forest plot of randomized controlled trials of Helicobacter pylori eradication vs placebo in H pylori–positive patients with functional dyspepsia: outcome relative risk (RR) of remaining dyspeptic. The current study8 is highlighted in red.