The effect of *Helicobacter pylori* infection and eradication in patients with gastro-oesophageal reflux disease: A parallel-group, double-blind, placebo-controlled multicentre study

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Abstract

Objectives: This study aimed to resolve controversy regarding the effects of *Helicobacter pylori* eradication therapy and *H. pylori* infection in gastro-oesophageal reflux disease.

Design: A randomized, double-blind, multicentre trial was performed in patients presenting with reflux symptoms. *H. pylori*-positive patients were randomized to receive either antibiotics or placebo for 7 days. *H. pylori*-negative patient controls received placebo. All received esomeprazole 20 mg b.d. for 7 days, followed by 40 mg o.d. to complete an 8-week course, and were followed up for 32 weeks by telephone.

Results: In this study, 198/589 (34%) patients were *H. pylori*-positive and 113 *H. pylori*-negative patients served as controls. Baseline endoscopy revealed 63% Los Angeles grade 0A and 37% Los Angeles grade BCD oesophagitis with no difference between patient groups. Symptom improvement on esomeprazole was seen in 89%. *H. pylori* eradication was successful in 82%. *H. pylori* eradication had no effect on symptomatic relapse (hazard ratio 1.15, 95% CI 0.74–1.8; $p = 0.5$). Overall, *H. pylori*-positive patients had a lower probability of relapse compared to *H. pylori*-negative controls (hazard ratio 0.6, 95% CI 0.43–0.85; $p = 0.004$). Relapse hazard was modulated also by oesophagitis grade (BCD vs. 0A, hazard ratio 2.1, 95% CI 1.5–3.0).

Conclusion: Relapse of gastro-oesophageal reflux disease symptoms after a course of high dose acid suppression took longer for *H. pylori*-positive patients than *H. pylori*-negative controls; however eradication therapy had no effect on the risk of relapse; ClinicalTrials.gov number, NCT00574925.

Keywords

H. pylori eradication therapy, esomeprazole, gastritis, gastro-oesophageal reflux disease, *Helicobacter pylori*, oesophagitis, symptomatic relapse

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Introduction

Gastro-oesophageal reflux disease (GORD) is a common medical problem with a spectrum of symptoms and varying degrees of severity. It is estimated that 20–40% of the adult population experiences heartburn or other symptoms related to reflux and this can impact on quality of life and health costs.¹ Moreover, there is a strong relation between acid reflux and the development of oesophageal adenocarcinoma.² These concerns highlight the importance of identifying modifiable risk factors for GORD. One such factor may be gastric *Helicobacter pylori* infection.

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There is an on-going debate about the appropriate management of *H. pylori* infection in GORD. Many authors recommend *H. pylori* eradication prior to the initiation of long-term proton pump inhibitor (PPI) therapy because the combination of *H. pylori* and acid suppression accelerates development of gastric mucosal atrophy and there is some anxiety that this may increase the risk of gastric adenocarcinoma.³ Other experts caution against this approach,^{4,5} as most epidemiological studies indicate that reflux symptoms, mucosal disease, and oesophageal cancer are less common in patients with *H. pylori* infection.^{5–11} Clinical studies show that acid suppression is more profound and the healing of reflux oesophagitis during treatment with PPIs is more rapid in patients with than in patients without gastric *H. pylori* infection.^{12,13} Additionally, two case-control studies report an increased risk of developing GORD after eradication of *H. pylori* in patients with duodenal ulcer,^{14,15} although others find no significant effect.^{16–18} There are concerns, therefore, that treatment of *H. pylori* infection in GORD patients may exacerbate the disease.

Five prospective controlled trials have studied the effects of *H. pylori* infection and eradication in patients with GORD.^{19–23} For patients with reflux symptoms and normal mucosa or grade A oesophagitis on endoscopy, Moayyedi et al.¹⁹ observed no difference in the relapse rate between the antibiotic, placebo, and *H. pylori*-negative control groups for up to 18 months of follow up. Negative results were reported also by Kuipers et al.²¹ in *H. pylori*-positive patients with reflux oesophagitis. In contrast, Schwizer et al. in a study that recruited patients with all grades of endoscopic findings reported that *H. pylori* eradication delayed the time to relapse compared to the placebo group and *H. pylori*-negative controls.²⁰ These divergent findings are likely due to differences in patient populations or the failure to account for the pattern of gastric infection and inflammation in the *H. pylori*-positive treatment groups. The latter point may affect clinical outcomes as antral gastritis is associated with increased acid output, whereas corpus gastritis is associated with reduced acid output.²⁴ Thus, in principle, *H. pylori* eradication may increase or decrease acid secretion and so the likelihood of acid reflux and related symptoms.

This large, multicentre trial is designed to provide more definitive evidence whether *H. pylori* infection impacted on the severity or prognosis of GORD and to inform the clinical decision whether to eradicate *H. pylori* in patients presenting with reflux symptoms. Subjects are stratified according to the presence and grade of reflux oesophagitis at baseline to assess whether the impact of *H. pylori* eradication, if any, is observed across the spectrum of GORD. Additionally, gastric biopsies obtained before and after treatment assess

whether the severity or pattern of gastritis, mucosal thickness, or parietal cell numbers is related to clinical outcome.

Methods

Erastrat is a randomized, controlled, double-blind, multicentre clinical trial of *H. pylori* eradication therapy in patients presenting with typical reflux symptoms of at least moderate severity as defined by a score of >25 on the Eraflux questionnaire.^{20,25} Three parallel groups are studied. Patients in the randomized groups were *H. pylori*-positive and assigned to eradication treatment or placebo. Patients in the non-randomized control group were *H. pylori*-negative and received placebo. Patients were stratified by endoscopic classification of reflux disease according to the Los Angeles (LA) system.²⁶

Patient recruitment

A total of 19 hospital- and office-based gastroenterology practices participated in the study, from Austria ($n = 2$), Germany ($n = 10$) and Switzerland ($n = 7$). Patients aged above 18 that met the inclusion criteria were recruited: (i) present with heartburn or acid regurgitation; (ii) at least 8 weeks duration; (iii) at least three times a week; and (iv) with at least moderate intensity, corresponding to mild impairment in daily life and need for medication. Exclusion criteria include history of previous oesophageal or gastric surgery, alcohol or drug abuse, severe organic or psychiatric disease, pregnancy or lactation, women with child-bearing potential without contraceptive measures, allergy or contra-indication to study medications, or need for concomitant medication. Prior knowledge of *H. pylori* status and previous treatment with PPIs were not exclusion criteria. The trial was approved by ethical committees at each centre and written informed consent was obtained.

Study participants underwent endoscopy. Patients with Barrett oesophagus, malignancy, or peptic ulceration on endoscopy were excluded. Endoscopy and biopsy were repeated at the end of the study. *H. pylori* status was assessed by a ¹³C urea breath test at recruitment and at the end of the study.²⁷ Gastric biopsies (author MV) and breath test samples (author AL) were forwarded to reference laboratories. Local investigators remained blind to the *H. pylori* status throughout the study.

Randomization

Computer-controlled inclusion and randomization of patients were operated by an independent study monitor (PharmaPart, Thalwil, Switzerland). Patients that met

entry criteria were randomized by a dynamic, centralized procedure that ensured blinding to *H. pylori* status and treatment group allocation. Probability of rejection was computed such that the projected fraction of patients in each group was constant at each point in time during the study. This system ensured that the appropriate numbers of patients with LA grade 0, AB, or CD oesophagitis on endoscopy were recruited and that a balanced sample of patients was entered at each site.

Patients with evidence of *H. pylori* infection on ^{13}C urea breath test were randomized either to the antibiotics group for eradication or placebo (gastric histology was not considered). *H. pylori*-negative control patients all received placebo. Because of the higher prevalence of *H. pylori*-negative compared to *H. pylori*-positive patients, a computerized early random rejection scheme was applied that accepted one-third initially and was dynamically adjusted to ensure balanced recruitment throughout the entire study. Prior to transferring data for analysis, monitors removed all information on drug randomization and *H. pylori* status from the database.

Study protocol

Once the centralized system had rejected or accepted the patient, the local investigator was informed by

fax. If accepted, study medication was dispensed and a central call centre was informed so that telephone interviews could be arranged (no clinical details were transferred). As outlined in the flow chart (Figure 1), patients were contacted by the call centre to assess symptom severity before and after 8 weeks treatment with esomeprazole and subsequently at 2-week intervals until recurrence of reflux symptoms on two subsequent occasions (relapse) or the completion of 32 weeks of follow up. At the end of the study (i.e. relapse or 32-week follow up), the patient underwent repeat endoscopy and ^{13}C urea breath test. Further management decisions were based on clinical discretion.

Study medications

For *H. pylori* eradication, patients were randomized to receive either amoxicillin 1000 mg, and clarithromycin 500 mg, administered twice daily for the first 7 days (antibiotics group), or identical placebo tablets (placebo group). Treatment of GORD with esomeprazole (Nexium; AstraZeneca, Zug, Switzerland) was not randomized. All patients received 20 mg b.d. for 7 days from study start, followed by 40 mg o.d. for 49 days to complete an 8-week course of esomeprazole. This management has been proven effective for *H. pylori* eradication,²⁸ oesophagitis healing, and

Figure 1. Schematic flow chart of Erastrat study procedures. PPI, proton pump inhibitor.

symptom resolution.²⁹ After acid suppression was withdrawn, patients were provided with an alginate preparation (Gaviscon; Reckitt Benckiser, Slough, UK) as rescue medication for recurrent symptoms.

Symptom assessment

The Eraflux questionnaire measures the frequency, duration, and intensity of reflux symptoms: heartburn, regurgitation, chest or retrosternal pain, and dysphagia.²⁰ Relapse was defined as recurrence of GORD symptoms to an Eraflux score of 25 at two consecutive interviews.²⁵ The day of the first interview was taken as date of relapse.

Outcome measures

The primary objective of this study was to assess whether *H. pylori* eradication treatment extends the time to symptomatic relapse after withdrawal of PPI therapy in patients with a clinical diagnosis of GORD. In addition, the time to relapse in the two *H. pylori*-positive study groups with the non-randomized *H. pylori*-negative control group was compared. Data analysis was performed with patients stratified according to oesophagitis grade at inclusion. Secondary objectives were to compare the effect of *H. pylori* infection and eradication on reflux oesophagitis and to compare the pattern of gastric inflammation and atrophy in the two *H. pylori*-positive treatment groups with the *H. pylori*-negative control group at relapse. Outcome data was analysed by 'intention-to-treat' (ITT) and 'as treated', defined by *H. pylori* status at relapse or the end of the study (eradicated, non-eradicated, negative control).

Histology

Biopsies were obtained from the oesophagus, gastric antrum, and corpus (midportion at the greater curvature) with standard forceps at recruitment and at the end of the study. Specimens were fixed in 10% neutral

buffered formalin and stained with haematoxylin and eosin and Alcian blue periodic Schiff. Histology was assessed by independent investigators (MV, RG) for determination of *H. pylori* infection, presence of gastritis, mucosal thickness, and density of parietal cells. *H. pylori* gastritis and mucosal atrophy were graded according to the Sydney System.³⁰ Histologists were not aware of clinical and endoscopic findings or treatment allocation.

Data analysis

Clinical data was entered manually into an on-line database. Data from early dropouts within the first 8 weeks (i.e. during treatment with esomeprazole) were not used. Data from dropouts during the 32-week follow up (off treatment) are censored to the date of the last telephone interview. Statistics were computed with R.³¹ Two-sided tests were used throughout the study; results are reported as significant for $p < 0.05$. Cross-tabulations were tested with a χ^2 test. Cox-proportional hazard regression was used for estimation and comparison of survival curves and to test the effect of covariates.³² 95% confidence intervals (CI) of estimates were calculated. To test the hypothesis that reduced inflammation in the gastric corpus is related to reduced relapse hazard, a three-level variable was defined for each patient, with 0 for no change, 1 for improvement, and -1 for deterioration, and was analysed by a generalized linear model.

The ITT analysis contained all patients who took at least one medication tablet. The as-treated subgroup included patients with complete information from gastric biopsies and ¹³C breath test at recruitment and at the end of study. No gender-specific effects were present at baseline (Table 1). No breakdown for smoking, alcohol, or non-steroidal antiinflammatory drugs (NSAID) consumption was done, because the numbers of patients that smoked, consumed >20 g alcohol/day or took NSAID were too low. To assess the effect of oesophagitis on outcomes, subjects were stratified by

Table 1. Baseline characteristics of patients recruited into Erastrat study

		<i>n</i>	Min	Q1	Median	Q3	Max
Placebo	Age (years)	98	21	39	50	60	81
	BMI (kg/m ²)	97	19	24	27	30	39
Antibiotics	Age (years)	100	20	40	49	57	75
	BMI (kg/m ²)	100	19	25	27	30	36
Control	Age (years)	113	19	41	50	61	71
	BMI (kg/m ²)	112	18	24	26	30	41

There were no differences in demographic or clinical parameters between *H. pylori*-positive and -negative patients. BMI, body mass index.

oesophagitis grade. A secondary analysis compared outcome of patients with LA grade 0A and BCD endoscopic findings. This grouping was based on findings of longitudinal studies of GORD natural history and to allow direct comparison to previous publications.^{19,33}

The sample size was based on a Monte Carlo resampling of the patients enrolled in the Eraflux study.²⁰ These calculations determined that with 60 patients in each study group and a hazard ratio (HR) of symptomatic relapse of 1.5 between the patient groups, a test power of 0.9 at an type I error rate of 0.05 can be achieved for the primary endpoint. Based on these calculations and allowing for a 40% dropout rate, the study aimed to recruit 318 patients.

Results

This multicentre trial involved eight teaching hospital- and 11 office-based practices or district hospitals. The median number of patients assessed and recruited per type of centre was 18 and 10 patients, respectively. When terminated because of time constraints, 589 patients had been assessed of whom 581 were eligible. After randomized exclusion of excess *H. pylori*-negative patients, 311 were recruited (62% from office-based practices or district hospitals).

Study population

The baseline statistics of 311 patients included in the ITT analysis are in Table 1. In the study, 169 females

and 142 males (54 and 46%) participated. Median age was 50 years (range 19–81), and six patients were older than 70 years. At study entry, endoscopy revealed LA grade 0 (41%, $n=127$), A (23%, $n=71$), B (25%, $n=77$), and CD (11%, $n=36$) reflux oesophagitis.

Patient progression

Of 581 eligible patients, 198 (34%) were *H. pylori*-positive on ¹³C urea breath test. Of 383 *H. pylori*-negative patients, 113 were randomly selected to serve as controls. The progress of the 311 patients recruited through the Erastrat study is detailed in Figure 2. Initial treatment with 8-week esomeprazole did not improve reflux symptoms in 35 (11%) patients. There was no indication that the likelihood of treatment failure was influenced by oesophagitis grade, baseline *H. pylori* status or allocation to study treatment. Adverse events were reported by 76 patients (antibiotics 25, placebo 23, control 28), leading to the withdrawal of 20 patients. Of these 13 were considered due to the study medication, most commonly nausea or diarrhoea during *H. pylori* eradication therapy. Following withdrawal of esomeprazole, in the 223 patients that had an initial response to acid suppression and continued in the study, symptomatic relapse was reported by 134 patients (60%) during the 32-week follow-up period. The success of *H. pylori* eradication was 82% by ¹³C urea breath test at time of relapse or at 32-week follow up. At the end of the study (as treated), 84 patients were *H. pylori*-positive (placebo and failed eradication), 55

Figure 2. CONSORT diagram of Erastrat study: ITT analysis.

Hp, *H. pylori*; RanEx, *H. pylori*-negative patients randomly excluded from study; No result, dropouts during treatment phase, treatment failures, and dropouts on follow up.

Figure 3. Cox regression.

The proportion of patients with sustained remission of reflux symptoms after 8 weeks of PPI therapy was similar in *H. pylori*-positive patients irrespective of treatment allocation to antibiotic (Anti) or placebo (Pla), but greater in the *H. pylori*-negative control (Con) group.

were *H. pylori*-negative (successful eradication), and 59 were *H. pylori*-negative controls.

Effect of *H. pylori* status and eradication therapy on relapse of reflux symptoms

Patients in the two *H. pylori*-positive groups had a similar rate of relapse at 32-week follow up (Figure 3). *H. pylori* eradication therapy had no effect on relapse hazard during the 32-week follow up (HR antibiotic vs. placebo 1.15, 95% CI 0.74–1.8; $p=0.5$). *H. pylori*-positive patients, treated by antibiotics or placebo, had a lower probability of relapse compared to the *H. pylori*-negative control group (HR 0.6, 95% CI 0.43–0.85; $p=0.004$). Subgroup analysis showed that the non-randomized *H. pylori*-negative control group had an increased risk of relapse compared to both *H. pylori*-positive groups (HR against placebo 1.79, 95% CI 1.18–2.70; against antibiotics 1.54, 95% CI 1.03–2.33). This result is not altered by correction for age and sex. Time to relapse from the smaller as-treated subset of patients is not different from that of the ITT subset.

Effect of oesophagitis status on relapse of reflux symptoms

Stratification of time to relapse analysis by endoscopic findings reveals two distinct patterns (Figure 4, Table 2).: All patients in the *H. pylori*-negative control group and patients with moderate-severe oesophagitis

Figure 4. Cox regression stratified according to endoscopic findings.

The proportion of patients with sustained remission of reflux symptoms after 8 weeks of PPI therapy. *H. pylori* status had important effects on the risk of relapse in patients with endoscopy-negative reflux disease or LA grade-A reflux oesophagitis; however *H. pylori* status had no effect on the relatively high risk of relapse in patients with more severe, LA grade BCD reflux oesophagitis.

Table 2. Probability of relapse at 32 weeks by degree of oesophagitis and patient group

Oesophagitis LA grade	Treatment	Symptomatic relapse at 32 weeks
0 or A	<i>H. pylori</i> + antibiotics	50 (37–65)
	<i>H. pylori</i> + placebo	45 (32–60)
	<i>H. pylori</i> – control	77 (64–88)
B, C or D	<i>H. pylori</i> + antibiotics	74 (58–88)
	<i>H. pylori</i> + placebo	71 (53–87)
	<i>H. pylori</i> – control	72 (58–85)

Values are % (95% CI).

LA, Los Angeles.

(LA grade BCD) had a probability of relapse at 32 weeks of 71% or above. In contrast, irrespective of eradication ($p=0.6$), *H. pylori*-positive patients without oesophagitis or with mild oesophagitis (grade A) had 50 and 45% probability of relapse, respectively (Table 2). The HR for relapse between patients with oesophagitis BCD compared to 0A was 2.1 (95% CI 1.5–3.0). Increased time to relapse in non-eradicated *H. pylori*-positive compared to *H. pylori*-negative controls was observed for patients with LA OA (HR 0.41, 95% CI 0.23–0.71; $p=0.002$), but not those with LA BCD (HR 0.97, 95% CI 0.52–1.80).

In the patient group with oesophagitis, repeat endoscopy at the end of the study revealed that LA grade had

improved for 59 (34%), deteriorated for 22 (13%) patients, and was unchanged for 91 patients (53%). The improvement was greater in the patients with severe reflux oesophagitis. Comparing patients with and without a symptomatic relapse, those that remained symptom free tended to have a greater improvement in oesophagitis grade at the end of the study ($p=0.089$).

Histology

All 311 patients enrolled into the study had biopsies obtained from the oesophagus, gastric antrum and gastric corpus at baseline, and 173 (56%) had histology samples also taken at the end of the study.

Oesophageal histology reveals no difference at baseline between *H. pylori*-positive and -negative patients in terms of inflammation, dilated intracellular spaces, length of regenerative papillae, or thickness of the basement membrane (all $p > 0.1$). Neutrophilic ($p=0.093$) and eosinophilic ($p=0.011$) infiltration increased with severity of reflux oesophagitis. Oesophageal histology did not predict primary treatment outcome (i.e. response of reflux symptoms to 8 weeks of esomeprazole treatment).

At baseline moderate or marked gastritis defined by the Sydney Classification was much more prevalent in *H. pylori*-infected patients than in *H. pylori*-negative controls (143/198, 72%, vs. 4/103, 4%; $p < 0.0001$) and the gastric mucosa was thicker (difference 130.9 μm , 95% CI 27.2–158.1 μm ; $p=0.0063$). There was no difference in the number of parietal cells per high-powered field (hpf) between *H. pylori*-positive and -negative patients (difference 5.3/hpf, 95% CI –1.9 to 3.4/hpf; $p=0.56$). After successful *H. pylori* eradication and 8 weeks of esomeprazole, the number of patients with moderate or marked gastritis fell from 77% to none, whereas 66% had persistent gastritis in those *H. pylori*-positive patients that either failed eradication or received placebo ($p < 0.001$). There was a trend between the improvement in gastritis following *H. pylori* eradication and the risk of symptomatic relapse ($p=0.09$) but there was no evidence that the number of parietal cells per high-powered field is a predictor of relapse ($p=0.39$).

Discussion

This large, multicentre trial evaluated the effect of *H. pylori* infection and eradication on reflux symptoms and endoscopic findings in patients presenting with symptoms of GORD. Patients received *H. pylori* eradication therapy or placebo with esomeprazole followed by 8 weeks of PPI therapy using methodology of proven efficacy,^{28,29} which is consistent also with guidelines for treatment of these conditions.^{1,34} At the end of

this treatment period, effective relief of reflux symptoms was achieved in 89% of patients and a repeat ¹³C urea breath test confirmed successful *H. pylori* eradication in 82%, both consistent with previous reports from similar populations.^{28,29} The primary outcome of the randomized controlled trial is that *H. pylori* eradication therapy has no effect on the relapse hazard (i.e. cumulative probability of relapse) for reflux symptoms during 32 weeks of follow up after withdrawal of acid suppression (Figure 3). The risk of symptomatic relapse is reported as 50 and 45% in the antibiotic and placebo groups, respectively, with no difference between groups (HR 1.15, 95% CI 0.74–1.8; $p=0.5$). This result was not altered by correction for age, sex, or other potential confounding factors included in the analysis.

Important additional information was obtained when patients were stratified according to grade of oesophagitis (Figure 4). For patients with endoscopy-negative reflux disease or mild oesophagitis (grade 0 or A, $n=196$), the relapse hazard in the *H. pylori*-negative control group was significantly greater than that of the eradicated patients (HR 2.13, 95% CI 1.23–3.70; $p=0.006$), with a relapse hazard at 32 weeks of 77 and 50%, respectively. Whereas for patients with moderate to severe oesophagitis (grade B, C, or D, $n=115$), symptomatic relapse was rapid and *H. pylori* status had no effect on relapse hazard (HR 0.93, 95% CI 0.52–1.69; $p=0.8$). The findings were not altered by *H. pylori* eradication in either subgroup. Thus, the presence of *H. pylori* infection prolongs the time to symptomatic relapse in patients with absent or mild endoscopic disease, but other factors, likely related to disruption of the oesophago-gastric junction and high levels of oesophageal acid exposure,¹ determine the natural history of disease in patients with more severe reflux oesophagitis.

These findings are in agreement with epidemiological reports that the risk of reflux symptoms and mucosal disease is reduced in *H. pylori*-positive patients. Raghunath et al.⁹ undertook a systematic review of 20 studies including more than 4000 patients and found that the odds ratio for *H. pylori* prevalence in GORD patients was 0.60 (95% CI 0.47–0.78). However, the results differ from previous randomized controlled trials which report little or no difference in time to relapse between the *H. pylori*-positive and -negative groups.^{19,20} The current study had a similar design but important strengths. First, a much larger study population. Second, inclusion of patients across the spectrum of GORD allowed stratification of results with severity of oesophagitis. Third, recruitment of patients with typical reflux symptoms from multiple centres, with the majority from office-based practices and district hospitals. Patients presenting to tertiary care have a high rate of somatization and psychosocial

morbidity and these factors may be more closely related to treatment outcomes than disease activity.³⁵ The excellent response (~90%) to initial PPI therapy and the high 'ongoing remission' rate at 32 weeks (~50%) off medication in the current study is higher than that reported by previous randomized controlled trials based in tertiary care and may be more representative of those sampled in epidemiological and community-based studies in which similar effects of *H. pylori* infection in GORD were found.

The biological mechanism underlying the relatively rapid relapse of reflux symptoms in *H. pylori*-negative controls compared to *H. pylori*-positive patients is not established. One explanation for the 'protective' effect of *H. pylori* infection in GORD is persistent reduction in gastric acid secretion. Rebound acid hypersecretion and reflux symptoms have been reported in healthy *H. pylori*-negative subjects and also *H. pylori*-negative reflux patients after discontinuation of omeprazole;^{36,37} in contrast, many *H. pylori*-positive patients show persistent acid suppression after eradication.³⁶ Direct measurements of acid secretion were not performed; however, the results are consistent with these observations. *H. pylori* status has no effect on the success of initial PPI therapy and yet, during 32 weeks of follow up after withdrawal of acid suppression, *H. pylori*-negative patients have a higher risk of relapse than *H. pylori*-positive patients irrespective of allocation to eradication therapy or placebo. Histology shows a dramatic improvement in gastritis in *H. pylori*-positive patients following successful eradication therapy and resolution of corpus inflammation is associated with a trend to symptomatic relapse. Over time, recovery of acid-secreting capacity may occur in patients with gastric mucosal atrophy as parietal cell mass recovers;^{38,39} however, in this study, very few *H. pylori*-positive patients had mucosal atrophy and there was no difference in mucosal thickness or parietal cell numbers between *H. pylori*-positive and -negative patients at baseline or at the end of the study. These results imply that the reduction in acid secretion with *H. pylori* infection is caused by other mechanisms; for example, downregulation of parietal cell H,K-ATPase expression in gastric mucosa by *H. pylori cag* gene products that significantly inhibiting acid secretion.^{40,41}

The study population was under 70 years old. It is possible that results may be different in an older population with a greater proportion of gastric atrophy, and also in specific patient groups, such as those with duodenal ulcer^{14,15} and with strains of *H. pylori* infection or host inflammatory responses (e.g. interleukin 1 β) that powerfully inhibit acid secretion.⁴² Patients were diagnosed and recruited on the basis of typical reflux symptoms rather than ambulatory pH-impedance

monitoring; however, symptom-based diagnosis and the response to therapeutic trials are considered acceptable surrogates in most clinical settings.³⁴ Overall, slightly less patients entered the study than planned (311/318, 98%); however, sufficient numbers were attained for a robust ITT analysis of primary and secondary endpoints. Nevertheless, it should be noted that the confidence intervals of the ITT analysis are fairly wide, thus a small effect of eradication therapy on treatment outcome cannot be excluded or could become apparent with longer follow up. Findings from the as-treated analysis were not qualitatively different; however, the differences between groups were less pronounced because repeat ¹³C breath tests and gastric histology were available for only 56% of the total study population. Incomplete data collection also reduced the statistical power to determine the effects of changes in histological biomarkers following *H. pylori* eradication on relapse hazard.

In conclusion, *H. pylori* eradication therapy has no impact on the success of PPI therapy for GORD or the risk of symptomatic relapse after withdrawal of acid suppression. Instead, the presence of *H. pylori* infection at study entry decreases the risk of symptomatic relapse, especially in patients with absent or mild mucosal disease. This is the first time that the protective effect of *H. pylori* infection in GORD described by epidemiologists has been demonstrated in a prospective, clinical study.

These findings have direct implications for practice. Clinicians and patients can be reassured that the short-to mid-term management of GORD patients can be focused on symptom control, independent of the decision to investigate and treat *H. pylori* infection. Indeed, it will often be easier to discontinue PPI therapy in reflux patients with *H. pylori* infection. If long-term PPI therapy is required, then *H. pylori* infection can be identified and eradication therapy prescribed; however, again, this can be performed without undue concern that this will exacerbate GORD symptoms or mucosal disease.

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Conflict of interest

The authors declare that there is no conflict of interest.

Clinical Trial registration

NCT00574925

Full trial protocol

The full trial protocol is available at <http://menne-biomed.de/uni/ERASTRATStudyProtocol.zip>.

References

1. Fox M and Forgacs I. Gastro-oesophageal reflux disease. *BMJ* 2006; 332: 88–93.
2. Lagergren J, Bergstrom R, Lindgren A, et al. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 1999; 340: 825–831.
3. Kuipers EJ, Uytterlinde AM, Pena AS, et al. Increase of *Helicobacter pylori*-associated corpus gastritis during acid suppressive therapy: implications for long-term safety. *Am J Gastroenterol* 1995; 90: 1401–1406.
4. Richter JE, Kahrilas PJ, Johanson J, et al. Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. *Am J Gastroenterol* 2001; 96: 656–665.
5. Graham KS and Graham DY. *Helicobacter pylori*, gastroesophageal reflux disease, Barrett's esophagus, and adenocarcinoma of the distal esophagus. In: *Contemporary diagnosis and management of Helicobacter pylori-associated gastrointestinal diseases*, 2nd ed. Newtown: Pennsylvania, 2002, pp. 128–147.
6. Newton M, Bryan R, Burnham WR, et al. Evaluation of *Helicobacter pylori* in reflux oesophagitis and Barrett's oesophagus. *Gut* 1997; 40: 9–13.
7. Hackelsberger A, Schultze V, Gunther T, et al. The prevalence of *Helicobacter pylori* gastritis in patients with reflux oesophagitis: a case-control study. *Eur J Gastroenterol Hepatol* 1998; 10: 465–468.
8. Csendes A, Smok G, Cerda G, et al. Prevalence of *Helicobacter pylori* infection in 190 control subjects and in 236 patients with gastroesophageal reflux, erosive esophagitis or Barrett's esophagus. *Dis Esophagus* 1997; 10: 38–42.
9. Raghunath A, Hungin AP, Wooff D, et al. Prevalence of *Helicobacter pylori* in patients with gastro-oesophageal reflux disease: systematic review. *BMJ* 2003; 326: 737.
10. Chow WH, Blaser MJ, Blot WJ, et al. An inverse relation between cagA+ strains of *Helicobacter pylori* infection and risk of esophageal and gastric cardia adenocarcinoma. *Cancer Res* 1998; 58: 588–590.
11. Whiteman DC, Parmar P, Fahey P, et al. Association of *Helicobacter pylori* infection with reduced risk for esophageal cancer is independent of environmental and genetic modifiers. *Gastroenterology* 2010; 139: 73–83. quiz e11–e12.
12. Labenz J, Tillenburger B, Peitz U, et al. *Helicobacter pylori* augments the pH-increasing effect of omeprazole in patients with duodenal ulcer. *Gastroenterology* 1996; 110: 725–732.
13. Holtmann G, Cain C and Malfertheiner P. Gastric *Helicobacter pylori* infection accelerates healing of reflux esophagitis during treatment with the proton pump inhibitor pantoprazole. *Gastroenterology* 1999; 117: 11–16.
14. Labenz J, Blum AL, Bayerdorffer E, et al. Curing *Helicobacter pylori* infection in patients with duodenal ulcer may provoke reflux esophagitis. *Gastroenterology* 1997; 112: 1442–1447.
15. Fallone CA, Barkun AN, Friedman G, et al. Is *Helicobacter pylori* eradication associated with gastroesophageal reflux disease? *Am J Gastroenterol* 2000; 95: 914–920.
16. Vakil N, Hahn B and McSorley D. Recurrent symptoms and gastro-oesophageal reflux disease in patients with duodenal ulcer treated for *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2000; 14: 45–51.
17. McColl KE, Dickson A, El-Nujumi A, et al. Symptomatic benefit 1–3 years after H. pylori eradication in ulcer patients: impact of gastroesophageal reflux disease. *Am J Gastroenterol* 2000; 95: 101–105.
18. Malfertheiner P, Dent J, Zeijlon L, et al. Impact of *Helicobacter pylori* eradication on heartburn in patients with gastric or duodenal ulcer disease results from a randomized trial programme. *Aliment Pharmacol Ther* 2002; 16: 1431–1442.
19. Moayyedi P, Bardhan C, Young L, et al. *Helicobacter pylori* eradication does not exacerbate reflux symptoms in gastroesophageal reflux disease. *Gastroenterology* 2001; 121: 1120–1126.
20. Schwizer W, Thumshirn M, Dent J, et al. *Helicobacter pylori* and symptomatic relapse of gastro-oesophageal reflux disease: a randomised controlled trial. *Lancet* 2001; 357: 1738–1742.
21. Kuipers EJ, Nelis GF, Klinkenberg-Knol EC, et al. Cure of *Helicobacter pylori* infection in patients with reflux oesophagitis treated with long term omeprazole reverses gastritis without exacerbation of reflux disease: results of a randomised controlled trial. *Gut* 2004; 53: 12–20.
22. Wu JC, Chan FK, Wong SK, et al. Effect of *Helicobacter pylori* eradication on oesophageal acid exposure in patients with reflux oesophagitis. *Aliment Pharmacol Ther* 2002; 16: 545–552.
23. Pilotto A, Perri F, Leandro G, et al. Effect of *Helicobacter pylori* eradication on the outcome of reflux esophagitis and chronic gastritis in the elderly. A randomized, multicenter, eight-month study. *Gerontology* 2006; 52: 99–106.
24. Graham DY. *Helicobacter pylori* infection in the pathogenesis of duodenal ulcer and gastric cancer: a model. *Gastroenterology* 1997; 113: 1983–1991.

25. Menne D. *Eraflux score*. Tuebingen: Menne Biomed, 2010.
26. Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999; 45: 172–180.
27. Leodolter A, Dominguez-Munoz JE, von Arnim U, et al. Validity of a modified ¹³C-urea breath test for pre- and posttreatment diagnosis of *Helicobacter pylori* infection in the routine clinical setting. *Am J Gastroenterol* 1999; 94: 2100–2104.
28. Tulassay Z, Kryszewski A, Dite P, et al. One week of treatment with esomeprazole-based triple therapy eradicates *Helicobacter pylori* and heals patients with duodenal ulcer disease. *Eur J Gastroenterol Hepatol* 2001; 13: 1457–1465.
29. Kahrilas PJ, Falk GW, Johnson DA, et al. Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: a randomized controlled trial. The Esomeprazole Study Investigators. *Aliment Pharmacol Ther* 2000; 14: 1249–1258.
30. Dixon MF, Genta RM, Yardley JH, et al. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. *Am J Surg Pathol* 1996; 20: 1161–1181.
31. R Development Core Team. *R: a language and environment for statistical computing*. 2.0.1 ed. Vienna, Austria: R Foundation for Statistical Computing, 2011.
32. Cox D. Regression models and life tables. *Journal of the Royal Statistical Society* 1972; 34: 187–220.
33. Labenz J, Nocon M, Lind T, et al. Prospective follow-up data from the ProGERD study suggest that GERD is not a categorical disease. *Am J Gastroenterol* 2006; 101: 2457–2462.
34. National Institute of Health and Clinical Excellence. *Dyspepsia: managing dyspepsia in adults in primary care*. London, Newcastle on Tyne: NICE, North of England Dyspepsia Guideline Development Group, 2004.
35. Dorn SD, Hernandez L, Minaya MT, et al. Psychosocial factors are more important than disease activity in determining gastrointestinal symptoms and health status in adults at a celiac disease referral center. *Dig Dis Sci* 2010; 55: 3154–3163.
36. Gillen D, Wirz AA, Ardill JE, et al. Rebound hypersecretion after omeprazole and its relation to on-treatment acid suppression and *Helicobacter pylori* status. *Gastroenterology* 1999; 116: 239–247.
37. Sandgren JE, McPhee MS and Greenberger NJ. Narcotic bowel syndrome treated with clonidine. Resolution of abdominal pain and intestinal pseudo-obstruction. *Ann Intern Med* 1984; 101: 331–334.
38. Gutierrez O, Melo M, Segura AM, et al. Cure of *Helicobacter pylori* infection improves gastric acid secretion in patients with corpus gastritis. *Scand J Gastroenterol* 1997; 32: 664–668.
39. Koike T, Ohara S, Sekine H, et al. *Helicobacter pylori* infection inhibits reflux esophagitis by inducing atrophic gastritis. *Am J Gastroenterol* 1999; 94: 3468–3472.
40. Saha A, Backert S, Hammond CE, et al. *Helicobacter pylori* CagL activates ADAM17 to induce repression of the gastric H, K-ATPase alpha subunit. *Gastroenterology* 2010; 139: 239–248.
41. Saha A, Hammond CE, Beeson C, et al. *Helicobacter pylori* represses proton pump expression and inhibits acid secretion in human gastric mucosa. *Gut* 2010; 59: 874–881.
42. Chourasia D, Achyut BR, Tripathi S, et al. Genotypic and functional roles of IL-1B and IL-1RN on the risk of gastroesophageal reflux disease: the presence of IL-1B-511*T/IL-1RN*1 (T1) haplotype may protect against the disease. *Am J Gastroenterol* 2009; 104: 2704–2713.