Helicobacter pylori eradication as the sole treatment for gastric and duodenal ulcers

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Objectives **It is uncertain whether eradication of *Helicobacter pylori* — without a prolonged suppression of acid secretion — is sufficient to allow healing of peptic ulcers. We evaluated whether eradication of *H. pylori* with no following anti-secretory medication then administered is sufficient for treatment of peptic ulcers. We also looked at the impact of non-steroidal anti-inflammatory drug (NSAID) and acetylsalicylic acid (ASA) use on ulcer relapses.**

Methods **The effect of eradication on ulcer healing and relapse rate was analysed in 115 patients, randomly allocated to four treatment groups: (1) quadruple therapy ($n = 28$); (2) dual therapy ($n = 30$); (3) triple therapy ($n = 27$); and (4) lansoprazole and placebo ($n = 30$). Endoscopic assessment was performed at 0, 8, and 52 weeks.**

Results **The ulcer healing rate was 100% [95% confidence interval (CI), 95–100%] in *H. pylori*-negative and 83% (95% CI, 67–94%) in *H. pylori*-positive patients ($P < 0.01$). In patients who used NSAIDs or ASA, the healing rate was 100% (95% CI, 73–100%) and 75% (95% CI, 19–99%) in *H. pylori*-negative (12 patients) and *H. pylori*-positive patients (four patients) (P = not significant). Ulcer relapses occurred in 5% (95% CI, 1–13%) of *H. pylori*-negative and in 36% (95% CI, 19–56%) of *H. pylori*-positive patients ($P < 0.01$). In *H. pylori*-negative patients who used NSAIDs or ASA the ulcer relapse rate was 30% (95% CI, 7–65%), whereas the ulcer relapse rate was 2% (95% CI, 0.4–10%) in patients who did not use NSAIDs or ASA ($P < 0.05$). No difference in ulcer relapse rate in *H. pylori*-positive patients who used or did not use NSAIDs or ASA was found. The eradication rate of *H. pylori* was 93% (95% CI, 76–99%) in the quadruple therapy group, 83% (95% CI, 64–94%) in the dual therapy group, 100% (95% CI, 87–100%) in the triple therapy group, and 0% (95% CI, 0–12%) in the lansoprazole and placebo group.**

Conclusions **Eradication treatment for *H. pylori*-positive gastric or duodenal ulcer is sufficient, with no need to follow it with anti-secretory medication. Cure of the infection reduces ulcer relapses in patients who did not use NSAIDs or ASA. *Eur J Gastroenterol Hepatol* 17:93–101 © 2005 Lippincott Williams & Wilkins**

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Introduction

Although unequivocal evidence supports the causal role of *Helicobacter pylori* infection in the pathogenesis of peptic ulcer disease [1–6], it remains uncertain whether eradication therapy only, without continuing with 2–4 weeks of suppression of acid secretion, is sufficient to permit both duodenal and gastric ulcer healing.

Studies have shown that eradication therapy alone is sufficient for healing of duodenal ulcers, and continuation of anti-secretory drugs after eradication therapy is unnecessary [7–10]. The safety and efficacy of eradication alone in subjects with gastric ulcers, especially in subjects with other risk factors like use of acetylsalicylic acid (ASA) or non-steroidal anti-inflammatory drugs (NSAIDs), has, however, not yet been well documented [11]. The HELP NSAIDs study of *H. pylori* eradication therapy in NSAIDs users has even indicated that healing of gastric ulcers (but not duodenal ulcers) was decreased with *H. pylori* therapy [12]. The same study also showed that *H. pylori* eradication in long-term users of NSAIDs did not affect the rate of peptic ulcer relapse over 6 months [12]. Many physicians therefore use additional ulcer-healing acid-suppressant therapy after *H. pylori* eradication therapy until the ulcer is healed and continue thereafter this therapy in regular NSAID and ASA users. Numerous trials have attempted to define the optimal therapy for *H. pylori* infection. The first experiments performed during the early years after the discovery of *H. pylori* have already

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shown that no single agent alone could achieve its eradication at a sufficient rate. In 1992, a study from Hong Kong showed that bismuth-based quadruple therapy, including a proton pump inhibitor (PPI), bismuth, metronidazole, and amoxicillin, was highly effective even in a population with an assumed high prevalence of primarily metronidazole-resistant *H. pylori* strains [13]. Thereafter, simpler therapies were developed to improve compliance, and of these dual therapies (combination of PPI or bismuth with one antimicrobial agent) gave promising primary results [14]. Dual therapies have thereafter been abandoned because of their inconsistent eradication results [15]. First-line eradication therapy in treatment of *H. pylori* is now triple therapy, which combines two antimicrobials and a PPI [15,16]. Problems with various eradication therapies include patient compliance, side-effects, and antibiotic resistance.

The aim of this randomized trial was to determine whether eradication therapy without any continuation of anti-secretory medication is sufficient for healing *H. pylori*-positive peptic ulcers. The secondary objective was to clarify the impact of NSAIDs or ASA use on ulcer relapse in patients with and without successful *H pylori* therapy.

Materials and methods

Patients

A total of 115 consecutive *H. pylori*-positive non-complicated peptic ulcer patients were enrolled in a prospective, randomized multicentre study. All these patients had endoscopically proven gastric or duodenal ulcer. The patients were recruited in 1996–1997 from Helsinki University Central Hospital (64 patients) and from four other local hospitals (a total of 51 patients).

Inclusion criteria

Patients of both sexes between 18 and 85 years old had to have endoscopically proven duodenal or gastric ulcer and had to be *H. pylori*-positive by urease test and histological evaluation. All were volunteers, and their mental and physical condition was such that they were considered capable of communicating with the investigator, reliably taking oral medication, and remaining compliant for the duration of their treatment and assessment. Fertile females had to use contraception during the study medication.

Exclusion criteria

Patients who needed urgent surgery, such as for severe pyloric stenosis or continuous bleeding, or who had undergone partial gastrectomy were excluded, as were patients suffering from any other major disease that would have an impact on life expectancy during the study period or having any condition associated with poor patient compliance. Pregnant and lactating women and patients with known hypersensitivity or any drug reaction to any agent structurally related to the compounds investigated were also excluded. Use of NSAIDs or ASA was not an exclusion criteria.

Endoscopy, histology, and *H. pylori* diagnosis

Patients were studied by upper gastrointestinal endoscopy after overnight fasting at their pre-entry visit and after 8 and 52 weeks. The study design is shown in Fig. 1. If, during the study, any clinical doubt arose as to the complication such as bleeding or perforation, prolonged healing or reappearance of peptic ulcer, endoscopy was always reassessed.

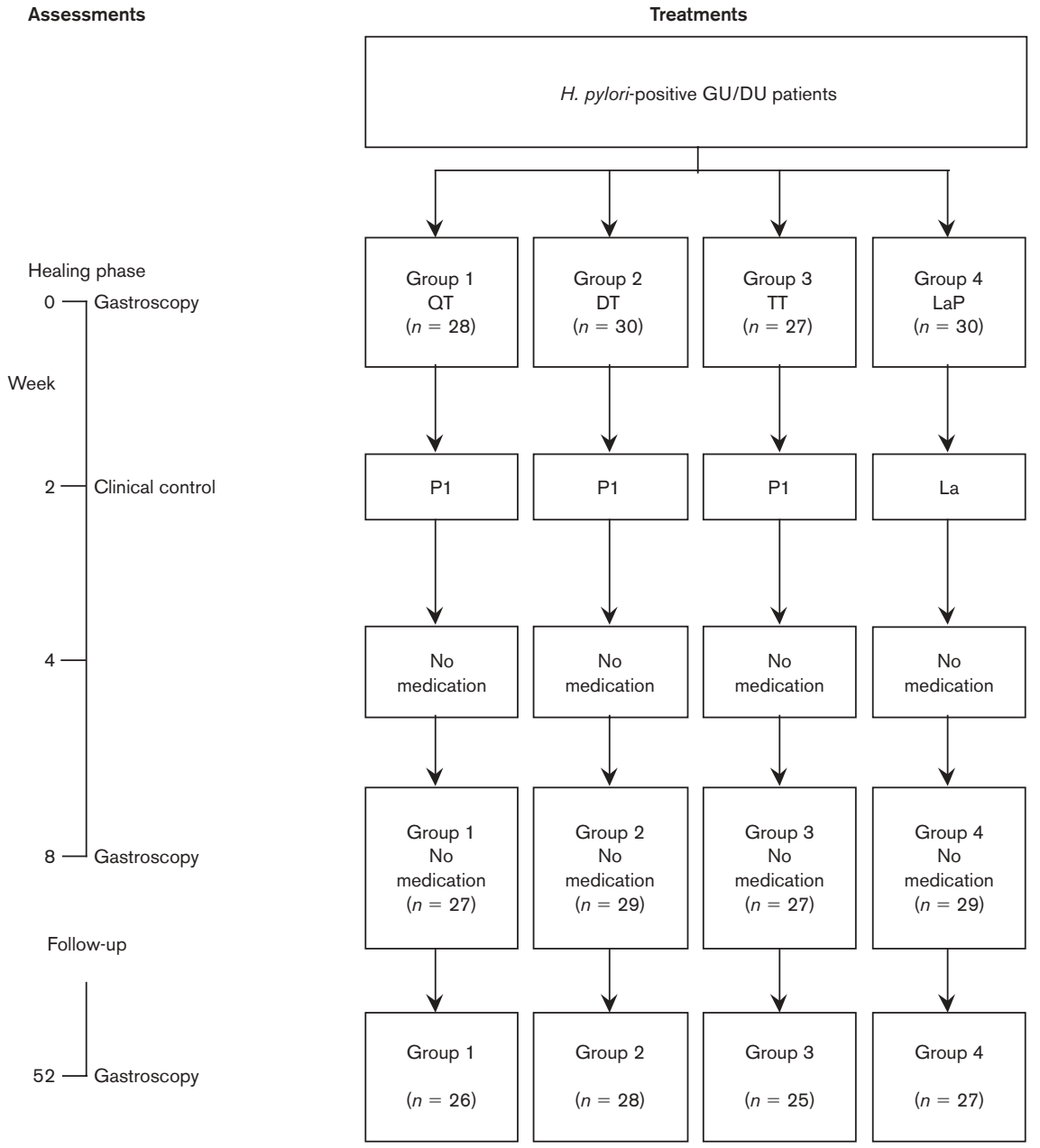
Endpoints were initial ulcer healing and ulcer relapse during 52 weeks. Peptic ulcer was defined as a circumscribed mucosal break at least 5 mm in diameter or 10 mm^2 with a well-defined ulcer crater. Ulcers were classified into gastric and duodenal types. The gastric type included single gastric ulcers (type I, located on the lesser curvature) and those in other parts of the corpus or in the antrum. The duodenal type included ulcers in the duodenum or in the prepyloric area (less than 3 cm from the pylorus) and also gastric ulcers, if these were found in association with the duodenal ulcer.

At baseline endoscopy, at least three biopsy specimens from both the antrum and the corpus in addition to biopsies of gastric or duodenal ulcers were taken with sterilized biopsy forceps. One specimen from the antrum and another from the corpus were used for a rapid urease test (Jatrox® -H.p.-Test; Procter & Gamble Pharmaceutical, Darmstadt, Germany). For histology, two formalin-fixed biopsy specimens from each region were embedded in paraffin and stained with haematoxylin and eosin or with modified Giemsa. The presence of *H. pylori* in these specimens was determined in a blinded manner by an experienced pathologist according to the Sydney system [17]. Serum immunoglobulin G and immunoglobulin A antibodies to *H. pylori* were measured separately with an in-house enzyme immunoassay [18] in 77%, 79%, and 63% of the patients attending the baseline, 8-week, and 52-week follow-up endoscopy.

Gastric biopsies, antrum and corpus together, were cultured for *H. pylori* in 61%, 79%, and 82% of patients attending the baseline, 8-week, and 52-week follow-up endoscopy. Susceptibility of the isolates to metronidazole was tested by disk diffusion as previously described [19].

At the 8-week visit, a patient was regarded as *H. pylori*-negative if rapid urease test, histology, and culture were negative. During follow-up, a patient was regarded as *H. pylori*-negative if both culture and histology were negative and the patient's *H. pylori* IgG antibody titre

Fig. 1



Study design. QT, quadruple therapy (lansoprazole + colloidal bismuth subcitrate + tetracycline + metronidazole); DT, dual therapy (lansoprazole + amoxycillin); TT, triple therapy (lansoprazole + clarithromycin + amoxycillin); LaPl, lansoprazole and placebo therapy; LA, lansoprazole; Pl, placebo; GU/DU.

for the 52-week follow-up serum had decreased by more than 50% of the baseline value.

Treatment design

If the urease test indicated *H. pylori* infection, the patient was randomly assigned to one of the four treatment arms. If the test was negative, the patient was not enrolled until proof of *H. pylori* infection was obtained by histology or culture, or both. Treatment groups were determined by a list of random numbers generated by computer. The endoscopists were blinded for the treatment. The treatment groups were: (1) quadruple therapy (QT), 30 mg lansoprazole (La) twice daily, 120 mg colloidal bismuth subcitrate four times daily, 500 mg tetracycline four times daily, 200 mg metronidazole (two tablets) three times daily for the first 2 weeks and placebo (Pl) once daily weeks 3–4; (2) dual therapy (DT), 30 mg La twice daily, 500 mg

amoxicillin four times daily, two tablets Pl three times daily, and Pl four times daily for the first 2 weeks and once daily weeks 3–4; (3) triple therapy (TT), 30 mg La twice daily, 250 mg clarithromycin (two tablets) three times daily, 500 mg amoxycillin four times daily, and Pl four times daily the first 2 weeks and once daily weeks 3–4; and (4) lansoprazole plus placebo therapy (LaPl), 30 mg La twice daily, two tablets Pl three times daily, Pl four times daily, and Pl four times daily for the first 2 weeks and 30 mg La once daily weeks 3–4. Patients had a compliance visit at week 2, during which they received their medication for the following weeks. Intake of study medication, compliance, and adverse events were determined at weeks 2 and 8.

Ethics

This study was performed in accordance with the principles stated in the Declaration of Helsinki and by the Ethics Committee of the Helsinki University Central Hospital. Patients were informed and aware of the study design and treatment, and they were included after giving their written informed consent.

Statistical analysis

Fisher's exact test, the chi-squared test, and the Bonferroni multiple-comparison test were used to compare the proportions of characteristics between groups. One-way analysis of variance served for continuous variables. Logistic regression analysis served to calculate independent variables affecting clinical outcomes. Calculations were performed with NCSS-2000 software (NCSS Statistical Software, Kaysville, Utah, USA).

Statistical analyses for eradication results of *H. pylori* were performed according to intention-to-treat (ITT) and per protocol (PP) principles. All randomized patients who had taken at least one dose of study medication were included in the ITT analysis. Patients in whom infection status was unknown after treatment were considered treatment failures for purposes of the ITT analysis. Patients with insufficient intake of study drugs were excluded from PP analysis. All patients excluded from the ITT analysis were also excluded from the PP analysis. Differences with $P < 0.05$ were considered statistically significant.

Results

A total of 115 consecutive endoscopically verified peptic ulcer patients with *H. pylori* gastritis were randomly assigned to treatment groups. For their demographic and clinical characteristics, see Table 1. Nine patients had previously undergone unsuccessful *H. pylori* eradication therapy. Of the 115 patients, 18 patients (16%) had used ASA, five patients (4%)

Table 1 Demographic and clinical characteristics of patients and eradication results in different treatment groups

	Study group			
Characteristic	Group 1, QT ($n = 28$)	Group 2, DT ($n = 30$)	Group 3, TT ($n = 27$)	Group 4, LaPl ($n = 30$)
Age (years)				
Mean ± standard deviation	53.4 ± 8.3	52.0 ± 11.4	52.0 ± 11.2	53.4 ± 10.3
Range	41–69	27–74	33–77	36–78
Gender (male/female)				
Female	13 (46)	9 (30)	8 (30)	13 (43)
Male	15 (54)	21 (70)	19 (70)	17 (57)
Use of NSAID				
Yes	2 (8)	2 (8)	2 (7)	2 (7)
No	23 (92)	23 (92)	25 (93)	28 (93)
Use of ASA				
Yes	7 (25)	4 (14)	7 (26)	5 (16)
No	21 (75)	25 (86)	20 (74)	25 (83)
Current smoker				
Yes	12 (43)	15 (50)	18 (67)	14 (47)
No	16 (57)	15 (50)	9 (33)	16 (53)
Use of alcohol				
Yes	22 (79)	24 (83)	18 (72)	24 (80)
No	6 (21)	5 (17)	7 (28)	6 (20)
Largest diameter of index ulcer (mm)				
Mean ± standard deviation	9 ± 5	10 ± 3	10± ± 4	10 ± 4
Range	5–25	5–20	5–20	5–20
Previous peptic ulcer				
Yes	15 (54)	10 (33)	14 (52)	9 (30)
No	13 (46)	20 (67)	13 (48)	21 (70)
Gastric/duodenal/both	3/11/1	1/9/0	4/9/1	0/8/1

Data are the numbers of subjects, with percentages in parentheses for dichotomous variables, and mean and standard deviation in parentheses for continuous variables. The chi-square test and one-way analysis of variance showed no significant differences. No significant differences appeared between groups. QT, quadruple therapy (lansoprazole + colloidal bismuth subcitrate + tetracycline + metronidazole); DT, dual therapy (lansoprazole + amoxycillin); TT, triple therapy (lansoprazole + clarithromycin + amoxycillin); LaPl, lansoprazole and placebo therapy. NSAID, non-steroidal anti-inflammatory drug; ASA, acetylsalicylic acid.

NSAIDs, and five patients (4%) both NSAIDs and ASA at least 1–4 days per week up until the base-line endoscopy. There was no significant difference in use of NSAIDs or ASA between treatment groups. Sixteen patients had previously had a bleeding peptic ulcer and two of these had suffered ulcer perforation.

Number, site and size of ulcers

At the baseline endoscopy, 87 patients (76%) had one peptic ulcer, 23 patients (20%) had two peptic ulcers, three patients (3%) had three peptic ulcers and two patients (2%) had four peptic ulcers. Of the 115 patients, 15 (13%) had the largest gastric type of primary ulcer in the angulus area, one patient (1%) in the gastric corpus, and five patients (4%) in the antrum. Of these 115, 30 patients (26%) had the largest duodenal type of primary ulcer in the prepylorus, and 64 patients (56%) in the bulbus duodeni. Among duodenal ulcer patients, 24 had several peptic ulcers (gastric and duodenal). No difference in location of ulcers between treatment groups existed. The mean ± standard deviation diameter of the largest ulcer was 9.7 ± 4.2 mm, with no difference in size of ulcers between groups.

Eradication results

H. pylori eradication results in different treatment groups are presented in Table 2. No significant difference appeared between active eradication treatment groups. The location of the largest index ulcer did not differ between patients whose eradication was successful and those who remained *H. pylori*-positive. If the placebo group was excluded, no difference in eradication rates appeared in patients with gastric or duodenal types of index ulcer. Metronidazole resistance was 67% (in eight of 12 patients) in the QT group, 53% (in nine of 17 patients) in the DT group, 45% (in five of 11 patients) in the TT group, and 57% (in 12 of 21 patients) in the LaPl group at baseline examination. For two patients of the QT group, eradication therapy failed; *H. pylori* was metronidazole-resistant in one of them at baseline endoscopy; and in the other no culture was performed of the biopsy samples from the baseline endoscopy, but metronidazole-resistant *H. pylori* appeared at the 8-week control endoscopy. In other patients, metronidazole resistance did not influence eradication results.

Peptic ulcer healing rate

The healing rate of peptic ulcers in percentages at the 8-week control gastroscopy was 100% [95% confidence interval (CI), 87–100%], 97% (95% CI, 82–100%), 100% (95% CI, 87–100%), and 83% (95% CI, 64–94%) in the QT, DT, TT, and PLa treatment arms ($P < 0.05$). Symptoms suggesting the complication, prolonged healing or reappearance of peptic ulcer appeared in none of the patients between the baseline and during the 8-week gastroscopy. Successful eradication enhanced the peptic ulcer healing rate (Table 3). For patients who used no NSAIDs or ASA the healing rate was 100% (95% CI, 82–100%) and 84% (95% CI, 67–95%) in *H. pylori*-negative (64 patients) and *H. pylori*-positive patients (32 patients) ($P < 0.01$). During weeks 0–8, eight patients used ASA, five patients used NSAIDs, and four patients used both NSAIDs and ASA. Ibuprofen, naproxen, and ketoprofein were the most commonly used NSAIDs, and their daily doses fell within the normal therapeutic level. The average daily dose of ASA was 390 mg (range, 50–1500 mg) during the first 8 weeks of the study. In patients who used NSAIDs or ASA, the healing rate was 100% (95% CI, 73–100%) and 75% (95% CI, 19–99%) in *H. pylori*-negative (12 patients) and *H. pylori*-positive patients (four patients) (P = not significant).

We used logistic regression analysis to determine independent factors for ulcer healing. *H. pylori* infection, size and location of the primary ulcer, history of previous peptic ulcer, use of NSAIDs or ASA, therapy

Table 2 Cure rate of *Heliobacter pylori* infection for each treatment

Treatment group	*H. pylori*-infection status (*n*)		Eradication rate (%) (95% confidence interval)
	Negative	Positive	
Intention-to-treat			
QT	25	2	93 (76–99)*
DT	24	5	83 (64–94)*
TT	27	0	100 (87–100)*
LaPl	0	29	0 (0–12)
Per protocol			
QT	25	2	93 (76–99)*
DT	22	5	81 (62–94)*
TT	27	0	100 (87–100)*
LaPl	0	29	0 (0–12)

QT, quadruple therapy (lansoprazole + colloidal bismuth subcitrate + tetracycline + metronidazole); DT, dual therapy (lansoprazole + amoxycillin); TT, triple therapy (lansoprazole + clarithromycin + amoxycillin); LaPl, lansoprazole and placebo therapy

*$P < 0.01$ compared with the eradication rate in the LaPl group (two-tailed Fisher exact test).

Table 3 ***Helicobacter pylori*** **status and peptic ulcer healing rate in 112 patients at 8-week follow-up endoscopy**

Study group	Ulcer healed (*n*)		Ulcer healing rate (%) (95% confidence interval)
	No	Yes	
H. pylori-negative	0	76	100 (95–100)*
H. pylori-positive	6	30	83 (67–94)

*$P < 0.01$ compared with *H. pylori*-positive (two-tailed Fisher exact test).

used, patient's age or gender, smoking habits, and use of alcohol were included in the model. None of these parameters was of independent significance in peptic ulcer healing.

Peptic ulcer relapses

The influence of *H. pylori* eradication on cumulative rate of peptic ulcer relapse during the 52-week follow-up is presented in Table 4. Table 5 shows the results according to the use of NSAIDs or ASA in all patients. Tables 6 and 7 include data of ulcer relapses in NSAIDs or ASA users with and without successful *H. pylori* eradication. After the healing phase, 14 patients had used NSAIDs or ASA. The average daily dose of ASA was 287 mg (range, 50–500 mg) during weeks 8–52. Ibuprofen, ketoprofein, and piroxicam were the most commonly used NSAIDs, at their normal recommended daily doses.

Table 4 **One-year follow-up results of cumulative ulcer relapse for 105 patients according to their *Helicobacter pylori* status at 52-week follow-up endoscopy**

Study group	Ulcer relapse (*n*)		Ulcer relapse rate (%) (95% confidence interval)
	No	Yes	
H. pylori-negative	73	4	5 (1–13)*
H. pylori-positive	18	10	36 (19–56)

*$P < 0.01$ compared with *H. pylori*-positive (chi-squared test).

In patients who did not use NSAIDs or ASA, the relapse rate was 2% (95% CI, 0.4–8%) and 28% (95% CI, 10–53%) in *H. pylori*-negative (50 patients) and *H. pylori*-positive (18) patients ($P < 0.01$). The *H. pylori*-negative ulcer relapse patient, who did not use NSAIDs or ASA, smoked 15 cigarettes per day, which may add to the ulcer relapse risk. Histological findings of this patient's antrum and corpus biopsies showed that active gastritis had disappeared and no bacteria was found and so *H. pylori* infection can be considered to be healed. The ulcer relapse rate was 30% (95% CI, 7–65%) in patients on NSAIDs or ASA and whose *H. pylori* eradication was successful (10 patients; see Table 6) and was 25% (95% CI, 0.6–81%) in those who remained *H. pylori*-positive (four patients; see Table 7) (P = not significant). If ASA ($n = 3$) or NSAIDs ($n = 8$) users were analysed separately, no significant difference occurred in ulcer relapse rate versus *H. pylori* status.

The percentage of the relapse rate for the ulcer during 52 weeks was 0% (95% CI, 0–13%), 11% (95% CI, 2–28%), 12% (95% CI, 3–31%), and 29% (95% CI, 13–49%) in the QT, DT, TT, and PLa treatment arms, respectively ($P < 0.05$).

Ten patients had their ulcer relapse in the same region as their index ulcer, which occurred in the duodenal (in six patients), prepyloric (two patients), antral (one patient), and angulus (one patient) regions. One of the patients with the index ulcer in the angulus had ulcer

Table 5 **One-year follow-up results of cumulative ulcer relapse for 87 *Helicobacter pylori*-negative and *H. pylori*-positive patients according to their use of non-steroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid (ASA)**

Study group	Ulcer relapse (*n*)		Ulcer relapse rate (%) (95% confidence interval)
	No	Yes	
NSAIDs or ASA users	10	4	28 (8–58)*
No NSAIDs or ASA users	67	6	8 (3–17)

*$P = 0.05$ compared with patients who did not use NSAIDs or ASA (two-tailed Fisher's exact test).

Table 6 **One-year follow-up results of cumulative ulcer relapse for 65 *H. pylori*-negative patients according to their use of non-steroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid (ASA)**

Study group	Ulcer relapse (*n*)		Ulcer relapse rate (%) (95% confidence interval)
	No	Yes	
NSAIDs or ASA users	7	3	30 (7–65)*
No NSAIDs or ASA users	52	1	2 (0.4–10)

*$P < 0.05$ compared with patients who did not use NSAIDs or ASA (two-tailed Fisher's exact test).

Table 7 One-year follow-up results of cumulative ulcer relapse for 21 *H. pylori*-positive patients according to their use of non-steroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid (ASA)

	Ulcer relapse (*n*)		
Study group	No	Yes	Ulcer relapse rate (%) (95% confidence interval)
NSAIDs or ASA users	3	1	25 (0.6–81)
No NSAIDs or ASA users	13	5	28 (10–53)

relapse in the corpus and one in the duodenum. One patient with the index ulcer in the prepyloric region had the ulcer relapse in the duodenum. Of the 14 patients with ulcer relapse, 12 had one ulcer and two patients had two ulcers at baseline endoscopy. No significant difference existed in risk for ulcer relapse in patients having one, two, three, or four ulcers at baseline endoscopy. The ulcer relapse of the five patients who had received successful eradication therapy for *H. pylori* was located in the same region as the index ulcer in four patients (two patients with ulcer in the bulbus, one with ulcer in the antrum, and one patient with ulcer in the angulus region). Of the five patients with the index ulcer in the antrum, one had the ulcer relapse in the corpus region.

H. pylori status (including open treatment results) was an independent risk factor for ulcer relapse during 52-week follow-up. The odds ratio was 17.2 (95% CI, 1.8–166.5; $P < 0.05$) for *H. pylori*. In the same model, other factors such as use of NSAIDs or ASA, smoking habits, previous ulcer history, location or number of the primary ulcer, or gender did not appear to be independent risk factors for peptic ulcer relapse.

Adverse reactions and withdrawals

Adverse effects appeared in 22 of 115 (19%) patients. Of these, nine patients were in the QT group, five patients in the DT group, seven patients in the TT group, and one patient in the LaPl therapy group. The most common adverse events were diarrhoea/loose stools (in seven patients), taste disturbance (five patients), urticaria/skin rash (five patients), tiredness (two patients), fungal infection (two patients), and aphthous stomatitis (one patient). These adverse events appeared during the first 2 weeks of the study medication. Two patients discontinued therapy (both at day 10 and both in the DT group) as a result of urticaria, whereas others took all the study medication despite these adverse events. Eradication of *H. pylori* was successful in 21 of these subjects with adverse reactions. One patient in the LaPl group had urticaria/skin rash, and her eradication was unsuccessful.

Of the 115, one patient was suspected to have gastric malignancy at the baseline endoscopy, but histology revealed no malignancy. Extra endoscopy was carried out 5 weeks later, and gastric malignancy was then assured by histology; the patient was withdrawn from the study. There were two other dropouts between the baseline and the 8-week endoscopy. One patient stopped the medication after 3 days, because of subjective fear of cardiac adverse reactions due to the medication, and he came neither to the 8-week or 52-week follow-up endoscopy. Another patient was lost from follow-up for an unknown reason.

Of the 115, 107 patients (93%) participated in the 52-week follow-up endoscopy; of the five patients who did not attend the 52-week follow-up endoscopy for unknown reasons, in four the *H. pylori* eradication had been successful.

Open treatment

After 8-week endoscopy, 11 patients received open treatment for persistent *H. pylori* infection, of whom 10 belonged to the LaPl and one to the DT group. Prior to the open therapy, a re-ulceration was found in three and a non-healed ulcer in five of these patients. Attending the 52-week follow-up endoscopy were 107 patients, 93% of the 115 patients at the baseline visit. Active eradication therapy was offered to all patients remaining *H. pylori*-positive at the end of the study. As is clinical practise, serum gastrin was measured for all the patients with recurrent ulcer after successful eradication therapy and after withdrawal of NSAIDs and ASA to find any possible underlying Zollinger–Ellison syndrome, but no such patient was found.

Discussion

The present study shows that, regarding ulcer healing and relapses in patients with gastric or duodenal ulcers, continuation of anti-secretory drug therapy beyond anti-*H. pylori* therapy is unnecessary. Labenz *et al.* [8] have suggested that in patients with duodenal ulcers, such continuation of therapy is actually excessive for relief from dyspeptic symptoms and healing of duodenal ulcers. Sung *et al.* [5] have shown that in patients with *H. pylori* infection and gastric ulcers unrelated to the use of NSAIDs, 1 week of antibacterial therapy without acid suppression heals the gastric ulcers as well as omeprazole does and reduces the rate of their recurrence. The recruitment criteria of the present study did not exclude patients taking NSAIDs or ASA,

and during the study their use was neither recommend nor forbidden, which makes ours differ from most previous studies. Our study also better represents clinical practise and shows that *H. pylori* is an important risk factor for these ulcers.

Successful eradication of infection can be equated with cure of the ulcer disease in most individuals who are not exposed to any other known ulcerogenic agent such as NSAIDs or ASA. The present study confirms the results of numerous earlier studies showing that successful eradication prevents ulcer relapses [2,6,13,20, 21]. Our results also show that the use of NSAIDs or ASA increases the risk of ulcer relapse in *H. pylori*-negative patients. Otherwise in patients who remain *H. pylori*-positive the users and non-users of NSAIDs or ASA have the same risk of ulcers relapse. This points out that the *H. pylori* infection and most probably also the use of NSAIDs or ASA are both independent risk factors for the peptic ulcer relapse. The number of ASA or NSAID users was, however, small and so no final conclusions can be drawn. Regardless of the active eradication treatment given, the recurrence rate of gastric or duodenal ulcers was lower in patients with successful *H. pylori* eradication than in those who continued to be infected. This implies that the successful eradication of *H. pylori* alters the natural history of gastric and duodenal ulcers.

Only therapies that achieve an over 90% cure rate per protocol or over 80% per intention-to-treat should be employed in clinical practice [22,23]. Our study showed that sufficiently high eradication rates could be achieved both by PPI-based quadruple therapy and by triple therapy. Several studies have also shown that high eradication rates for *H. pylori* can be achieved by PPI-based quadruple therapy [24,25]. Although bismuth-based therapies have proven effective for the cure of *H. pylori* infection, the negative impact of pre-treatment metronidazole resistance on eradication rate, and the high rate of side-effects reducing compliance have been the major concerns with this treatment. Better *H. pylori* eradication results have also been achieved with PPI-based triple therapy than with original bismuth-based triple therapy [26]. It is possible that, for these reasons, a regimen including a PPI and a combination of clarithromycin and amoxicillin (PPI/AC therapy) has become the most common first-line treatment for the cure of *H. pylori* infections [16].

The reasons for these high eradication results include the good compliance, and the 2-week duration of the therapy. Although no significant difference appeared between the active treatment groups, quadruple and triple therapies can be recommended also because compliance in all treatment groups was good.

No significant difference in terms of safety profile appeared between the three active treatment arms. Adverse events occurred in 19% of our subjects, but these events were mild and typical of those observed with these drug combinations. Adverse events led to discontinuation of the treatment for only two patients, but this did not worsen these patients' eradication results.

In conclusion, eradication treatment is sufficient, with no following anti-secretory medication needed in *H. pylori*-positive patients with gastric or duodenal ulcer. Cure of the infection reduced ulcer relapses in patients who did not use NSAIDs or ASA.

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Conflicts of interest

None declared.

Authors' contributions

P. Arkkila performed statistical analysis and prepared the manuscript. H. Rautelin and T. Kosunen performed *H. pylori* culture and antibody measurements. P. Sipponen and J. Mäkinen carried out diagnosis of the histology. K. Seppälä and M. Färkkilä were involved in planning the study and making endoscopies.

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